NATIONAL GOOD PRACTICE GUIDELINES FOR THE DIAGNOSIS, TREATMENT AND FOLLOW UP OF MALIGNANT DISEASES IN CHILDREN AND ADOLESCENTS, IN ROMANIA

RODICA VOICHIȚA COSNAROVICI
DANA MICHAELA CERNEA
(COORDINATORS)

Reviewers: Anne Grete Bechensteen
Eva Widing
Translator: Cornelia Banghea

NATIONAL GOOD PRACTICE GUIDELINES FOR THE DIAGNOSIS, TREATMENT AND FOLLOW UP OF MALIGNANT DISEASES IN CHILDREN AND ADOLESCENTS, IN ROMANIA

RODICA VOICHIȚA COSNAROVICI
DANA MICHAELA CERNEA
(COORDINATORS)

Cluj-Napoca
2021

The National Good Practice Guidelines for the Diagnosis, Treatment and Follow up of Malignant Diseases in Children and Adolescents was elaborated through the project: "Increasing performance in the diagnosis and treatment of childhood cancers, by improving the technical equipment, by purchasing modern equipment, by training the medical staff and by developing recommendations" within the program Challenges in the Public Health at European level, funded by the EEA Financial Mechanism 2014-2021.
We would like to thank the Norwegian Public Health Institute and the Norwegian Health Directorate for the guidance and support throughout the project.

Project participants and partners:

The Ministery of health: Program Operator

The Cluj Oncology Institute "Prof.Dr. Ion Chiricuță": Project Promoter

The Timisoara Clinical Children's Emergency Hospital "Louis Țurcanu" : Partner

The Iasi Regional Oncology Institute: Partner

The Bucharest Oncology Institute "Prof. Dr. Alexandru Trestioreanu": Partner

The Norwegian Directorate of Health: Project partner, Donor

TABLE OF CONTENTS

1. FOREWORD 7
2. INTRODUCTION 9
3. EPIDEMIOLOGY 11
4. SCREENING, EARLY DIAGNOSIS, PATHWAYS 13
5. DIAGNOSIS PRINCIPLES IN CHILDHOOD CANCERS 15
   5.1. GENERAL SYMPTOMATOLOGY 15
   5.2. INVESTIGATIONS AT DIAGNOSIS 17
      5.2.1. COMMON LABORATORY TESTS 17
      5.2.2. IMAGING 17
   5.3. PATHOLOGY 20
      5.3.1. MALIGNANT HAEMOPATHIES 20
      5.3.2. SOLID TUMORS 21
6. GENETICS IN CHILDHOOD CANCER 23
7. PRINCIPLES OF ONCOLOGICAL TREATMENT IN CHILDHOOD CANCERS 29
   7.1 PRINCIPLES OF SURGICAL TREATMENT 29
   7.2 PRINCIPLES OF CHEMOTHERAPY 31
   7.3 GENERAL PRINCIPLES OF RADIATION THERAPY IN THEPEDIATRIC ONCOLOGY 34
   7.4 ONCOLOGICAL EMERGENCIES IN CHILDHOOD CANCER 37
   7.5 LYMPH NODE ENLARGEMENT 44
   8.1 MALIGNANT HEMOPATHIES 46
      8.1.1 ACUTE LYMPHOBLASTIC LEUKEMIA 46
      8.1.2 ACUTE NONLYMPHOBLASTIC LEUKEMIA 57
      8.1.3 CHRONIC MYELOID LEUKAEMIA 66
      8.1.4 JUVENILE CHRONIC MYELOMONOCYTIC LEUKEMIA 73
      8.1.5 NON-HODGKIN'S LYMPHOMA 78
      8.1.6 HODGKIN'S LYMPHOMA 88
      8.1.7 HISTIOCYTOSIS 93
   8.2 PRIMARY TUMOURS OF THE CENTRAL NERVOUS SYSTEM 101
      8.2.1 EPENDYMOMA 101
      8.2.2 HIGH GRADE GLIOMA (HGG) 111
      8.2.3 LOW GRADE GLIOMA 116
      8.2.4 MEDULLOBLASTOMA 124
      8.2.5 EMBRYONAL BRAIN TUMOURS 132
      8.2.6 GERM CELL BRAIN TUMOURS 137
      8.2.7 PRIMARY BRAIN LYMPHOMA 144
      8.2.8 CRANIOPHARYNGIOMA 147
      8.2.9 BENIGN TUMOURS OF THE CENTRAL NERVOUS SYSTEM 151
      8.2.10 METASTASES OF THE CENTRAL NERVOUS SYSTEM 158
   8.3 SOFT TISSUE SARCOMAS 161
   8.4 BONE TUMOURS 169
      8.4.1 OSTEOSARCOMA 169
      8.4.2 EWING SARCOMA OF BONE 175

8.4.3 BENIGN BONE TUMORS OF ONCOLOGICAL IMPORTANCE 181
8.5 KIDNEY TUMOURS 184
8.6 NEUROBLASTOMA 195
8.7 LIVER TUMOURS 212
8.8 GERM CELL TUMOURS 219
8.9 RETINOBLASTOMA 226
8.10 RARE CHILDHOOD CANCERS 241
8.11 HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN 248
8.11.1 AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION 248
8.11.2 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION 252
9. SUPPORTIVE TREATMENTS 259
9.1 MANAGEMENT OF INFECTIONS 259
9.2 GROWTH FACTOR TREATMENT (G-CSF) 264
9.3 TRANSFUSION INDICATIONS 266
9.4 PAIN MANAGEMENT 271
9.5 PSYCHOLOGICAL SUPPORT 274
9.6 TERMINAL CARE 277
10. LEGISLATIVE PROVISIONS 281
11. VACCINATION IN CHILDHOOD CANCER 283
12. FOLLOW-UP OF CHILDREN WITH CANCER, SIDE EFFECTS OF ONCOLOGICAL THERAPIES 293
12.1 ACUTE TOXICITY OF ONCOLOGICAL TREATMENTS 293
12.2 LATE SIDE EFFECTS OF ONCOLOGICAL TREATMENT 302
12.3 LONG – TERM FOLLOW-UP OF SURVIVORS 306
13. THE ELABORATION OF THE GUIDE FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP OF CHILDHOOD CANCERS 307
ABBREVIATIONS 309
AUTHORS 315

1. FOREWORD

The elaboration of the first guide for diagnosis, treatment and follow-up in childhood cancers is an initiative of the Paediatric Oncology community in Romania. Its development is possible within the program Challenges in the Public Health at European level, funded by the EEA Financial Mechanism 2014-2021, through the project: **"Increasing performance in the diagnosis and treatment of childhood cancers, by improving the technical equipment, by purchasing modern equipment, by training the medical staff and by developing recommendations"**.

The activity was carried out with the support and under the guidance of paediatric oncology specialists from paediatric oncology centres in Norway, as well as from medical specialists within the Norwegian Directorate of Health. (1)

The guide for diagnosis, treatment and follow-up during and after therapy in childhood cancers is meant to offer guidance to healthcare professionals who work in paediatric oncology departments, to the specialists in any field that is related to the children with cancer, to the young doctors in training.

The guide is a concise presentation of the current knowledge and therapeutic possibilities at a given moment in time, for each clinical situation and for each disease. The main goal is to help physicians choose the best management strategies for each patient, based on concrete evidence provided by clinical trials. Only the protocols showing good therapeutic results and those who are applicable in Romania are proposed.

Other protocols are being proposed for line 2 and 3 treatments, so that the attending physician can choose the most appropriate option for a given case.

The therapeutic decision is always made in a responsible manner by the attending physician. The guidelines cannot overpass the individual responsibility of health professionals to make appropriate decisions based on the particularities of each patient, while consulting with the child's parent or guardian. The guide is just a point of reference that will enable to determine the best therapeutic options, in order to provide the best chances of long-term survival for each patient.

It is very important that the therapeutic attitude should be unitary, for all the specialists in the country, so that the chances offered to children with cancer are equal, regardless of the medical institution in which they are to be treated. Adopting these guidelines at the national level would reduce the efforts and risks of delaying treatment, caused by the need to obtain a second opinion in other specialized institutions, as well as the risks of patient complaints in case of therapeutic failure.

The guide for the diagnosis, treatment and follow-up of children with cancer will be one of the important elements to be considered when allocating resources and planning public health actions.

The selected experts in the field performed a detailed review of the published evidence for diagnosis, treatment and follow-up for each of the conditions, taking into consideration the

experience of each centre of paediatric haematology and oncology in the country and the knowledge and observations of other collaborators.

A critical evaluation of the diagnostic and therapeutic procedures was performed, including the evaluation of the risk-benefit ratio. The authors declare no conflict of interest.

The task of developing the guide also includes the creation of educational tools and programs for implementing the recommendations. The safest method to verify the implementation of these guidelines in the current practice is to evaluate the data reported in the National Childhood Cancer Registry.

The strategies proposed by the guide will be reviewed and updated periodically, as the results research papers and clinical trials will bring new information, in order to improve the long-term survival of paediatric oncology patients in Romania

Each of the experts who elaborated the recommendations will represent the Romanian Society for Paediatric Oncology and Haematology within the European Society for Paediatric Oncology. This will be the way we stay anchored in the ever-changing realities of the paediatric oncology.

The guide for diagnosis, treatment and follow-up in childhood cancers will be finalized on September 1, 2021. Starting with this date, it will be made available to the Romanian Ministry of Health and to the general public. Access will be provided on the website of the Ministry of Health and from the website of the Romanian Society for Paediatric Oncology and Haematology.

Bibliography

1. Norwegian National Action programme with guidelines for the diagnosis, treatment and follow-up of cancer in children, third edition, 1/2017

2. INTRODUCTION

Cancer in children is a rare disease, but it is an important mortality cause, being the second leading cause of death for the 1-14 years age group, following the death by accidents.

The number of children with cancer is far lower than that of the adults with cancer, representing about 1% of all adult malignancies. There are significant differences between cancers in children and cancers in adults.

Thus:

- Cancers in adults are often defined by the name of the organ of origin, while in children the disease is defined by the morphological type or by the type of the involved tissue.

- In adults, the carcinomas are the most prevalent, while embryonic tumours and sarcomas are dominant in children. The most common paediatric cancers are the haematologic cancers (leukaemias, lymphomas) and tumours of the central nervous system.

- And even when the morphological type is similar, there may be significantly different biology in adult and childhood cancer, and treatment also has to be different in such cases.

- The prognosis of the disease is considerably better in paediatric oncology patients, as about 70-80% of children are long-term survivors, if the disease is diagnosed on time and if it is treated correctly. (1)

- The main therapeutic weapon in childhood cancer is chemotherapy; chemotherapy is often associated with other therapeutic tools, such as: surgery, radiation therapy or high-dose chemotherapy with stem cell rescue; adults benefit especially from surgery and radiation therapy.

In Romania, children with cancer are treated in 13 Paediatric Oncology departments, according to established protocols, recommended by SIOP, ESMO or NCCN. Only protocols showing good therapeutic results and for which there are conditions of being applied in Romania are selected. Most protocols are today used as best available treatment (BAT). There are also patients included in clinical trials, in compliance with the current legislation. The application of these protocols guarantees that every child in the country receives treatment in accordance with the applicable international norms. Exercising correct and appropriate therapeutic strategies is the responsibility of each attending physician and each paediatric oncology centre.

Cancer in children is par excellence a multidisciplinary disease. That is the reason why it is unrealistic to expect a single person, with a single qualification, to possess the skills and opportunities to make a full assessment and to establish competent interventions in all these areas. The decisions concerning the diagnosis and treatment of the disease are done by a specific tumor board – multidisciplinary team.

The multidisciplinary team involved in the care of children with cancer consists of:

• Paediatric Oncologist

• Surgeon trained in paediatric oncology (general, neurosurgeon, orthopaedist, urologist, ENT specialist)

- Radiation oncologist
- Anaesthesiologist, cardiologist, endocrinologist, neurologist, psychiatrist
- Nurses specialized in the chemotherapy treatment in children
- Caregiver/ nursing assistant trained to care for a child with cancer
- High performance laboratory
- High-performance radiological diagnostic service
- High-performance nuclear medicine service
- High-performance pathology laboratory
- Ambulatory care doctor - family doctor/general physician
- Psychotherapist, Psychopedagogue
- Social workers, support groups, school
- Physical therapist
- Pharmacist
- Dietician
- Priest
- Family

The complete care of the child with cancer involves the efficient contribution of each member of the multidisciplinary team to the general care plan.

Each of the paediatric oncology centres in Romania has the ability to treat most of the diseases. Of course, in the case of the diseases that are usually treated with radiation therapy, the hospitals specializing in radiation therapy in children are preferred. The two bone marrow transplant departments are: the Paediatric Clinical Section of the "Fundeni Clinical Institute", Bucharest and the "Luis Țurcanu Emergency Clinical Hospital for Children", Timișoara. Rare cancers are preferably treated in large departments (over 50 new cases diagnosed/ year), due to the broad expertise in these particular situations, and smaller centres should refer such patients to larger centres.

Palliative care is an integrated part of all active childhood cancer treatment from the time of diagnosis. Palliative care and end-of-life care are not properly implemented in the legislation in force for the moment. There is a need for a national program concerning treatment strategy when curative therapy no longer is a realistic aim. See also chapters 9.4 and 9.6. Patients are cared for in the departments where they have received the curative therapy. There are also several specialized centres (in Bucharest, Brașov, Timișoara), but there is no national coverage.

All cases of childhood cancers should be reported to the National Childhood Cancer Registry in Romania (RNCCR). The RNCCR was established on September 1, 2009. The reports are made through an electronic system, using the international classification of oncological diseases, the 3rd edition (ICD-0-3) and the Toronto staging system, specifying the treatment protocol.

Bibliography

1. Childhood cancer survival in Europe 1999-2007 Results of EUROCARE-5 – a population-based study

3. EPIDEMIOLOGY

The National Childhood Cancer Registry in Romania is a relatively recent data recording system (September 1, 2009), undergoing constant improvement and development. . The reporting initially encountered some difficulties, however at the present time, all 13 paediatric oncology centres in the country successfully participate in collecting data.

So far, the recording system shows that 400 children and young people (aged 0-14 years) are diagnosed and treated every year in paediatric oncology departments in Romania. Each paediatric oncology centre reports according to the methodology of registration required by the system: new cases upon diagnosis, events in the evolution of the disease (recurrence, relapses), death. During 2010-2017, 5000 notifications were registered for 3000 new cases. A total of 10% of the cases had a documented the circuit through two or more paediatric oncology centres in the country. The overall incidence and sites are shown in Table 1. (1)

Table 1: Standardized incidence rate 0-19

Sites	2010	2011	2012	2013	2014	2015	2016	2017
All the sites	**4.05**	**3.93**	**3.88**	**3.87**	**4.16**	**3.75**	**4.06**	**4.17**
Leukaemia	1.17	1.30	1.21	1.38	1.35	1.34	1.00	1.48
Lymphomas	0.74	0.57	0.56	0.52	0.68	0.52	0.54	0.61
CNS tumour	0.55	0.44	0.66	0.56	0.56	0.56	0.51	0.49
Neuroblastoma	0.22	0.30	0.30	0.16	0.27	0.27	0.37	0.27
Retinoblastoma	0.11	0.07	0.08	0.01	0.11	0.05	0.07	0.06
Renal tumours	0.30	0.23	0.18	0.09	0.24	0.11	0.27	0.26
Liver tumours	0.03	0.05	0.05	0.06	0.06	0.08	0.08	0.07
Bone tumours	0.26	0.29	0.30	0.21	0.25	0.23	0.33	0.26
Soft tissue sarcomas	0.29	0.30	0.20	0.21	0.27	0.26	0.33	0.26
Germ cell tumours	0.14	0.16	0.16	0.14	0.19	0.12	0.28	0.15
Epithelial tumours	0.14	0.19	0.16	0.20	0.19	0.18	0.28	0.25
Other tumours (Rare tumours)	0.11	0.03	0.02	0.00	0.01	0.02	0.00	0.00

As it results from the table, the incidence of children with cancer treated in Romania seems to be much lower than in the other European countries. (2) It is most likely a false conclusion. The causes that determine this error are the following:

- The annual number of new cases is evaluated in relation to the last census in Romania (2011), despite the fact that the number of people aged 0-19 years has most probably decreased significantly.

- Romania is facing the largest population migration in the country's history, a large number of children live abroad and, in case of illness, they are treated in the countries of residence.

- There are children treated in adult sections that do not yet report cases to the registry

- We believe that there are sick children who are not addressed to health services

All these are shortcomings under the attention of epidemiologists and solutions are being sought.

The therapeutic outcomes, as it results by the recorded data, show an overall survival of 68%, with better results in different types of leukaemia, lymphomas, and kidney cancers. The results were poorer in soft tissue and bone sarcomas as well as in brain tumours and rare tumours.

The aetiology of childhood cancer is still poorly understood. Environmental factors have little influence. Inbreeding, common in some communities, may be a contributing factor in some cases (eg. retinoblastoma). The current oncologic treatments may be the cause of secondary malignancies. Certain inherited conditions increase the risk of childhood cancer. Of these, Down syndrome and type 1 and 2 neurofibromatosis are well known and common in paediatric oncology patients.

Bibliography

1. Registrul Național al Cancerelor la Copil în România, 2009-2019 (National Childhood Cancer Registry in Romania, 2009-2019)

2. Eva Steliarova-Foucher, Charles Stiller, Brigitte Lacour, and Peter Kaatsch. International classification of childhood cancer. Cancer, 103(7):1457–1467, 2005.

4. SCREENING, EARLY DIAGNOSIS, PATHWAYS

At the present time, there are no efficient screening techniques available worldwide for detecting childhood malignancies. Attempts have been made, such as screening infants for neuroblastoma, but they have proven themselves ineffective.

Diagnosing childhood cancers at the earliest possible stage, should be the primary goal of all healthcare professionals involved in diagnosing and treating this particular patient group.

The first step consists of educating the general population towards recognizing the first signs of illness in a child and understanding the need for seeing a doctor. Parents should be encouraged to understand that a child's symptoms should not be neglected, especially if they worsen or refuse to subside under standard treatments conducted by general practitioners or pediatricians.

We will consider initiating awareness campaigns through the media, internet, schools, training programs for family doctors, regularly.

The pathway of the sick child, suspected of suffering from a malignant disease, must be very precise, starting from the family doctor, to the paediatrician and in the shortest time to the paediatric oncologist. Any delay in guiding the patient to the upper level may compromise the therapeutic results. Monitoring the chain of medical decisions that lead to the full and correct diagnosis, is one of this guides main objectives.

The collaboration and the communication between those involved in diagnosis, treatment, follow-up and social reintegration are of utmost importance.

The guide for diagnosis, treatment and follow-up in childhood cancers will be finalized on September 1, 2020. Starting with this date, it will be made available to the Romanian Ministry of Health and to the general public. Access will be provided thorugh the website of the Ministry of Health and from the website of the Romanian Society for Paediatric Oncology and Haematology.

5. DIAGNOSIS PRINCIPLES IN CHILDHOOD CANCERS

5.1. GENERAL SYMPTOMATOLOGY

Malignant diseases in children have typical a short history (from weeks in acute leukaemia to sometimes up to several months in solid tumours); the rapid onset of the disease is their characteristic (weeks - a few months). However, the diagnosis of malignant diseases in children might sometimes be delayed, as the initial clinical manifestations can be extremely varied, most often being non-specific symptoms, which also can be encountered in (a) several benign conditions. Symptoms can appear suddenly (bone pain, vision problems, bleeding) or insidiously (intermittent headache), they can be general and nonspecific (fever, pallor, asthenia) or localized (palpable tumour masses). Usually the child is brought to the doctor for various symptoms that alarm the parents: fever, anorexia, weight loss, lymphadenopathy, hemorrhagic signs. Sometimes it is about accidental clinical and paraclinical findings that determine the completion by the doctor of the investigations in order to specify the aetiology. It is important to interpret these symptoms in the context of other elements that emerge from the child's history and clinical examination, especially if the patient repeatedly has the same symptom or if the symptomatology persists.

"Alarming" symptoms that are suggestive for a possible oncological pathology in children include the following: weight loss, pallor, anorexia, asthenia, fatigue, prolonged fever of unknown cause, adenopathy, hepatomegaly, splenomegaly, palpable tumour masses, unexplained bone or joint pain, persistent headache, vomiting in the morning, acute vision disorders, hemorrhagic syndrome (ecchymosis, purpura, petechiae), neurological signs of outbreak, hypertension.

The main types of cancer in children (0-14 years) are, in order of frequency: acute lymphoblastic leukaemia, tumours of the central nervous system (CNS), malignant lymphomas, neuroblastoma, nephroblastoma.

The clinical manifestations in acute leukaemia are caused by the change in the bone marrow with deregulation of the normal production of various blood cells and by the infiltration with blasts. Most commonly, leukaemia can be manifested by anaemic syndrome (pallor, asthenia, fatigue, tachycardia, dyspnoea), hemorrhagic syndrome (epistaxis, purpura, ecchymosis, petechiae, gingival bleeding), prolonged fever of unknown cause, severe or recurrent infections. To these there may be added lymphadenopathy, hepatosplenomegaly, bone or osteoarticular pain, intracranial hypertension syndrome.

CNS tumours, intracranial and spinal tumours, can occur at any age and the symptoms vary depending on the sites of the tumour and the age of the child at onset. In infants, there are no symptoms of intracranial hypertension because the skull grows alongside the extension of the tumour, so that the increase in cranial circumference and bulging of the fontanelle may

be the main suggestive clinical sign at this age, along with irritability and loss of appetite. In the older child, the predominant element is the intracranial hypertension syndrome (headache, vomiting in the morning) with a chronic, progressive characteristic. The headache that awakens the child from sleep must draw attention to the possibility of the presence of an intracranial space occupying process. Other symptoms reflect focal neurological deficits: diplopia, eyelid ptosis, seizures, speech or sensory disorders. Sometimes endocrine disorders may be present (diabetes insipidus, growth disorders), behavioural changes, impaired school performance. Spinal tumours occur in the older child, the most common symptomatology being spinal pain or spinal compression phenomena (gait disorders, decreased muscle strength, sensory deficits, lack of sphincter control).

Depending on the sites, the lymphomas may have different symptoms. Most commonly, it begins as painless supraclavicular or lateral cervical tumour masses, of firm consistency. Patients with mediastinal masses, have a persistent, unexplained cough, dyspnoea, superior vena cava syndrome. Other symptoms are axillary and inguinal lymphadenopathy, abdominal pain, intestinal invagination (in the child over 5 years), hepato-splenomegaly, palpable abdominal masses. About one third of the children with Hodgkin's lymphoma may have general symptoms ("B" signs of illness): fever, weight loss, night sweats and itching.

In the case of neuroblastoma, the symptoms vary depending on the site of the tumour: abdominal (anorexia, abdominal pain, palpable abdominal tumour masses, diarrhea), thoracic (respiratory distress, Horner syndrome, superior vena cava syndrome), paravertebral (spinal cord compression syndrome - pain, motor and sensory deficits, sphincter disorders). Bone metastasis causes bone pain with various sites. Tumour infiltration of periorbital bones typically produces (usually unilaterally) periorbital ecchymosis, eyelid ptosis, exophthalmos.

Nephroblastoma is the most common form of kidney cancer in children, especially affecting the young children. Most children display palpable abdominal mass, generally without other associated symptoms. If present, they consist of abdominal pain, macroscopic hematuria, fever, high blood pressure. There are several genetic conditions that are associated with development of Wilms tumour (WAGR syndrome, Beckwith-Wiedemann syndrome, aniridia,). Children with these conditions should be offered a surveillance program for detecting tumours early and the examination of patients with Wilms tumour should include the assessment of possible associated abnormalities such as aniridia, hemihypertrophy and genitourinary abnormalities.

Recommendations

- Typically the cancers in children have a short history (days-weeks-months)
- Children with cancer may experience a variety of the signs or symptoms, depending on the type of disease
- Symptoms are often general and uncharacteristic. The differential diagnosis of malignancy should be considered when there is unfavourable progression under conventional, non-oncological treatment and if new symptoms are developing.

5.2. INVESTIGATIONS AT DIAGNOSIS

When there is a clinical suspicion of malignancy, the confirmation of the diagnosis by testing procedures is mandatory. The investigations in paediatric oncology must include conventional laboratory testing (haematological, biochemical, immunological), investigations by imaging, pathological, immunohistochemical and genetic tests, using a multidisciplinary approach.

These tests aim to specify the site and extension of the tumour (primary tumour and distant metastasies), the cellular or histological type of cancer, staging and inclusion in a risk group, as well as the assessment of the anatomical and functional consequences of the malignancy on the body. Depending on the oncological diagnosis, based on the protocol specific for each type of disease, additional investigations will be performed for a complete evaluation, choosing the optimal therapeutic plan and monitoring the evolution of the disease and of the response to treatment.

5.2.1. COMMON LABORATORY TESTS

Tests used to evaluate the child with malignant disease include: complete blood count, peripheral blood smear (allow the numerical and qualitative assessment of blood elements), inflammatory tests, biochemical tests (evaluation of liver function, serum electrolytes), virological and bacteriological testing, tumour markers detection tests (HCG, AFP, NSE, LDH, ferritin), urine tests (hematuria, proteinuria, urinary catecholamines), cerebrospinal fluid analysis.

5.2.2. IMAGING

Imaging tests have a significant importance in the diagnosis and treatment of paediatric oncological diseases, bringing significant contributions in establishing the positive diagnosis, the staging and the tumour extension, that are necessary for the inclusion in risk groups and in making the optimal therapeutic decision. These investigations allow, at the same time, to evaluate the response to antineoplastic therapy, as well as to monitor the occurrence of possible relapses and/or complications related to the disease or treatment.

The use of these diagnostic methods must be made in stages. Initial investigations should be limited to first-line ones, which are essential in supporting the suspicion of a diagnosis of malignancy. Thus, in the case of detecting an abdominal mass, the abdominal ultrasound is sufficient as an initial method of imaging evaluation, leaving it to the paediatric oncologist to recommend and ensure the imaging tests necessary for the final diagnosis. Using the same approach, in the case of intrathoracic or bone tumours, the first-line imaging investigation should be the conventional radiological examination.

Diagnostic imaging methods

- **The Ultrasonography**

The ultrasonography is a valuable diagnostic tool in paediatric oncology, being an excellent method for assessing the abdomen, pelvis, thyroid, breasts and testis in children and can determine tumour sites and relationship with surrounding organs, allowing the differentiation of solid structures from those with liquid content. It can also be used to guide the needle during aspiration or biopsy. The Doppler ultrasound allows the evaluation of the tumour vascularization, invasion or compression of large vessels and the detection of the intravascular tumour thrombus. Ultrasound diagnosis is relatively quick and inexpensive, it does not use ionizing radiation, it has no known side effects, and it usually does not require sedation or anaesthesia. The major disadvantages of conventional ultrasonography are: the lower resolution compared to CT or MRI testing, the limited visual field and the interference of bone or gas structures with the image production, limiting the usefulness of ultrasound in many anatomical areas.

- **The Radiography**

The conventional radiography continues to play an important role in the assessment of malignancies in children. Conventional radiographies are fast and technically easy to perform, they are inexpensive, they do not require anaesthesia or sedation, and they provide a much lower radiation dose to radiation-sensitive tissues than the computed tomography. The conventional chest X-ray allows the identification of primary thoracic tumours and lung metastases (the tiny ones shows only on CT/MRI), the detection of pleural or pericardial fluid collections, the airways compression in association with a mediastinal mass, and the identification of lung infections. Conventional radiographies are generally less sensitive than the bone scintigraphy or MRI for assessing the neoplastic involvement of the skeleton. However, in most patients with symptomatic primary bone tumours, the skeletal radiographies show significant changes and should represent the first-line imaging testing in a paediatric patient with localized bone pain.

- **The Magnetic Resonance Imaging**

MRI is the preferred imaging testing. MRI is superior in assessing soft tissue tumours of the trunk and extremities and it is preferred for imaging the head and neck. MRI is superior to CT in the detection of CNS tumours, especially in the posterior fossa, it is also the method of choice for evaluating a possible spinal cord compression or intraspinal tumor invasion. MRI is increasingly used to evaluate tumours located in the retroperitoneum, abdomen and pelvis. The patient's lack of exposure to ionizing radiation makes it an important method to be use in paediatrics. The disadvantages of MRI include its relatively high cost, limited availability, and limited ability to assess lung parenchyma and bone cortex. The quality of the MRI image is affected by cardiac and respiratory movements, intestinal peristalsis and vascular pulsations, a disadvantage that is further aggravated by the slower acquisition of the image by MRI compared to CT. In addition, the patient's movements substantially compromise the quality of the MRI image. Consequently, children who would not require sedation for other imaging modalities, including CT, often require sedation for MRI investigation.

- **The Computed Tomography**

It is one of the most valuable diagnostic methods, used for diagnosing, staging and monitoring solid tumours and tumour metastases, providing detailed images of bones, organs and tissues. Computer tomography can be used to determine the size and volume of the tumour. It also brings important information regarding the therapeutic response. The use of contrast agents increases the quality of the details. The disadvantages of the CT include high costs, the risk of adverse reactions to the contrast agent, the need for sedation/general

anaesthesia in some patients, and the relatively high dose of ionizing radiation, but the benefits of using this imaging technique overcome the risks.

- **PET/CT**

It provides additional information compared to conventional imaging methods. It provides both anatomical information (CT) and metabolic activity of the examined structures (increased activity in malignant tumours). PET/CT imaging test is recommended for early diagnosis of tumours, if the symptoms or the paraclinical tests indicate a neoplastic disease, but this cannot be demonstrated by other imaging methods, for accurate identification of the tumour site, staging, evaluation of the therapeutic response, for evaluation of residual formations or suspicion of recurrence (highlighted by other imaging methods), diagnosis of rare tumours.

5.2.3 ORGAN SPESIFIC BASELINE EVALUATIONS PRIOR TO PLANNED TREATMENT

Some of the treatment we plan to offer might cause short or long term toxicity to organs at risk. Some protocols and treatment regimens require that we do base line testing before start of treatment. These examinations might be relevant: endocrinology, hearing, vision, EEG, cognition, kidney, cardiology, ECG, and others.

Recommendations

- In paediatric oncology, the imaging testing by ultrasound, MRI, CT, PET-CT are recommended according to the protocol for the type of cancer, the organ to be examined, the patient's condition
- Some investigations of patients must be carried out in general anaesthesia to secure as good quality as possible for evaluation of the malignancy (young age, uncooperative patient).
- The use of ionizing radiation should always be strictly limited to avoid future late effects. We therefore recommend to avoid unnecessary examinations.

5.3. PATHOLOGY

There are two main categories of cancers: malignant haematological diseases and solid tumours with various sites. For their complete diagnosis, as well as for staging, classification into risk groups for choosing the therapy, the pathological diagnosis is mandatory. This includes morphological, immunohistochemical and genetic investigations.

5.3.1. MALIGNANT HAEMOPATHIES

Morphological diagnosis

In the case of leukaemia, the examination of the peripheral blood smears or medullary aspirate allows the diagnosis and the morphological type to be established according to the FAB classification, but a number of additional tests are needed to classify the disease (immunophenotyping, cytogenetics, molecular biology), having a major influence on the prognosis and on the choice of the appropriate therapy and these analyses are crucial to monitor minimum residual disease (MRD) .

In rare cases, the bone marrow aspirate is inconclusive, requiring a bone marrow biopsy. The initial assessment also includes the analysis of the CSF in order to identify the presence of blasts at the CNS level.

Immunophenotyping

Determining the immunophenotype of the neoplastic cell population is essential for the proper classification of the malignant hematologic diseases. The flow cytometry and the immunohistochemistry are the two most commonly used immunophenotypic methods. The immunophenotyping by flow cytometry is performed on samples in fluid cell suspensions prepared from blood or solid tissue samples. Therefore, it is a preferred method for immunophenotyping of peripheral blood and bone marrow aspiration and may be useful in some lymphomas. Peripheral blood and/or bone marrow cells examined using flow cytometry allow the detection of antigens both on the surface and inside the cells, which is a particularly useful method for analyzing several antigens on a given cell and rapidly evaluating a very large number of antigen cells. This method is indispensable for the diagnosis, classification, and staging of malignant haematological diseases, as well as their monitoring in order to detect the MRD or possible recurrences. It is also used for establishing the DNA index. The immunohistological examination of the bone marrow biopsy is no longer necessary if the leukaemia has been satisfactorily classified using flow cytometry.

Still, a bone marrow biopsy at diagnosis is mandatory since sometimes there might be diagnostical challneces like “dry tap”, bone marrow fibrosis, dilution of the bone marrow by blood, and when the diagnosis is not leukaemia (MDS/aplastic anaemia) - a biopsy is essential .

Cytogenetics and molecular genetics

Most types of leukaemia and lymphomas have changes in the number of chromosomes (ploidy) or in the specific structure of the chromosomes (rearrangements). Thus, karyotyping of tumour cells in order to identify chromosomal abnormalities acquired using conventional and molecular cytogenetics (FISH) in patients with various hematologic neoplasms has become increasingly important in the management of these diseases. It provides essential information related to prognosis and to their proper classification. The optimal source of cells is the bone marrow. The chromosomal changes observed after performing the tumor karyotyping in patients with malignant hematological diseases are varied, multiple and they affect most human chromosomes: translocations, inversions, duplications, trisomies, monosomies, deletions, isochromosomes, ring chromosomes, etc. A wide variety of molecular genetic methodologies are now available, including polymerase chain reaction (PCR) and other amplification methods. Molecular genetics tests allow the evaluation of malignant hematologic diseases, the identification of occult cytogenetic aberrations and the detection of MRD; these molecular genetics techniques are also used to identify specific mutations in order to develop targeted antineoplastic molecular therapy. Both immunophenotyping and PCR are tools crucial for monitoring of MRD.

5.3.2. SOLID TUMORS

Morphological diagnosis

Solid tumours are evaluated histologically based on the pathological examination of the sample obtained through biopsy. There are several different types of biopsies, depending on the execution technique: excisional biopsy, incisional biopsy, aspiration biopsy with fine or thick needle, endoscopic biopsy. Some tissue segments are embedded in paraffin after processing, while others are frozen for subsequent immunohistochemical and genetic examinations.

The immunohistochemical test

The immunohistochemical test is a widely used method that can specify a series of intrinsic characteristics of the tumour (presence of receptors, specific cellular abnormalities), combining histological techniques with the immunological and biochemical techniques in order to identify specific tissue components by an antigen-antibody reaction (tumour markers). These investigations are used to determine the precise type of cancer, as well as the most effective therapeutic method (individualization of cancer treatments).

The genetic tests

In the case of solid tumours, genetic tests (cytogenetics or molecular genetics) serve two purposes: they can be used diagnostically to demonstrate genetic aberrations characteristic for a particular entity. In addition, there are a number of genetic mutations (usually amplifications or deletions) that have a prognostic significance and therefore contribute to the determination of the treatment choice.

Recommendations

- The definitive diagnosis of cancer implies the pathological examination in the case of solid tumours, the cytological examination of the bone marrow for leukaemia
- In leukaemia, the cytological examination is completed with the immunophenotyping (usually by flow cytometry), cytogenetics and molecular genetics testing; the purpose of performing these investigations is to establish the risk group, thus providing the opportunity to choose the appropriate therapy
- In solid tumors, excisional biopsy/ incisional biopsy/ fine or thick needle aspiration biopsy/ endoscopic, ultrasound or CT guided biopsy are performed
- The immunohistochemistry must complete the classic histopathological examination
- Genetic investigations (cytogenetics or molecular genetics) have the role of confirming the diagnosis, establishing the prognosis and choosing the appropriate therapy

6. GENETICS IN CHILDHOOD CANCER

Cancer is considered to be a multifactorial disease in which the genetic modifications are an important etiological factor. The modifications in gene expression cause the alteration of the homeostasis that regulates cell division, cell apoptosis and the migration of cells from one area of the body to another, regardless of the needs of the body at that time.

During carcinogenesis:

- Some genes are activated in such a way as to increase the cell division and/or to decrease the cell apoptosis (activation of oncogenes with a positive effect on cell proliferation), the mutation of an allele being sufficient in order to induce uncontrolled cell growth;

- Some genes are inactivated so that they cannot stop these multiplication processes and induce apoptosis (e.g. tumour suppressor genes that negatively control cell proliferation by inhibiting the cell cycle process and inducing apoptosis, in which case one functional allele is sufficient to provide these functions). These genes are inactivated by three mechanisms: by mutations that result in the loss of normal gene function, by complete loss of the gene, or by epigenetic mechanisms that cause the gene to "fall asleep." Epigenetic alterations are changes in gene expression or cell phenotype caused by mechanisms other than the changes in the DNA sequence, such as: abnormal DNA methylation, histone post-translational modifications, modifications in the organization and composition of chromatin.

- The genes that control the DNA stability and the DNA repair genes do not directly regulate cell proliferation, but the lack of the normal function increases the risk of mutations, resulting in an increased risk of cancer. (1)

In most of the cancer- prone syndromes, the tumor suppressor genes are inactivated. In less than 10% of the cases, the oncogenes cause the cancer. (1)

The hereditary nature of cancer has been known for over a century and the aspects of the inheritance of the susceptibility to cancer are studied extensively in the last decades, but also taking into account the fact that in the same family the environmental factors (tobacco, pollution, etc.) and the lifestyle (alcohol, tobacco, red meat, obesity, hormonal factors, etc.) can contribute to the prevalence of multiple cancers. (2)

The study of the hereditary nature of cancer started with and was based on observations on families with:

- Several individuals affected by rare types of cancer that sometimes were associated with other phenotypic changes;

- Typical family associations of different cancers;

- A large number of "common" cancers at a young age (3)

It was thus concluded that the occurrence of cancer in one of the members of a family increases the risk of occurrence of the same type of cancer or "related" cancers in close relatives. The observation according to which some cancers are diagnosed in close relatives led

to the discovery of the genes that cause monogenic disorders with the predisposition to develop cancer. Some of these syndromes or disorders only increase the predisposition to develop a certain type of cancer, others also associate particular phenotype changes (facial dysmorphism, neurological disorders, mental retardation, etc.). Although the genetic cancer predisposition syndromes are rare in general and they represent only 1-10% of cancers in children that are secondary to these syndromes, the study of these cases has led to a better understanding of the pathogenesis of cancer in children. (3)

Thus, when confronted with a new case of childhood cancer, the attending physician has the obligation to look for the causes that determined the disease and to identify the presence of a possible genetic syndrome that predisposes to cancer, as it may have subsequent implications for the entire family of the patient.

The occurrence of cancer in children without the genetic predisposition to develop cancer is due to the development of genetic mutations in somatic cells causing imbalances between the proliferation, the differentiation and the cell apoptosis through the same mechanisms described in the text above. (4)

The hereditary predisposition to developing cancer is due to genetic mutations present in the germline, inherited from parents and which increase the chances of developing cancer when compared to the general population. To date, more than a hundred genetic mutations have been described that increase the predisposition to develop cancer. (4)

In 1969, Li and Fraumeni reported a wide variety of family cancers in children and young adults (soft tissue tumours, osteosarcomas, premenopausal breast cancers, brain tumours, different types of leukaemia, pancreatic cancers) and they collected biological samples from the members of these families, which, with the help of the technology that was developed in the field of genetics in 1990, allowed the identification of a mutation in the germline of the TP53 tumour suppressor gene. Subsequently, somatic mutations of the TP53 tumour suppressor gene have been observed in some cases of cancer in the general population.

The TP53 gene is the most commonly mutated gene in cancer. The mutation of the TP53 gene in the DNA binding sites causes cancer in 73% of the males and in 100% of the females with these germline mutations.. The presence of the germline mutation associates the risk of developing cancer before the age of 30 to 21% for men and 49% for women, respectively. The somatic mutations in this gene are associated with low survival rates, resistance to chemotherapy and high recurrence rates. (3)

There are at present multiple other examples documented of germline mutations associated with high risk of developing cancer. Some of the most common and well-known examples will be presented below.

The mutations in the BRCA1 and BRCA2 genes are associated with 10-20-fold increase in the risk of developing breast cancer and ovarian cancer. The presence of these mutations requires close monitoring of young women in those families starting from adolescence. (2)

The mutations in the DNA repair genes MLH1, MSH2, MSH6 (present in cases of hereditary non-polypoid colorectal neoplasm) are associated with an increased risk of developing colon cancer and endometrial adenocarcinoma in young adults. (2)

The biallelic mutations in the ATM gene that are present in patients with ataxia-telangiectasia (a rare autosomal recessive neurological disorder) are associated with a predisposition to develop types of leukaemia and lymphomas. The presence of heterozygous mutations in the ATM gene in women descending from families with ataxia-telangiectasia increases the risk of developing breast cancer without increasing the risk of malignant lymphoproliferative disorders. (2) (Breast cancer is also increased in mothers of AT pts (they are heterozygote) who have increases susceptibility to chromosome alterations from

irradiation as in mammografi, and they are informed to avoid mammografi and go for MRI as surveillance.)

The patients with Fanconi Anaemia, a rare genetic disease with recessive transmission, have an increased risk of developing acute myeloblastic leukaemia or squamous cell cancer of the neck, vulva, oesophagus, liver or brain.

Multiple endocrine neoplasia (MEN) comprises a group of familial syndromes that associate endocrine gland cancers (MEN1, MEN2A, MEN2B). In MEN1, there are mutations of the tumour suppressor gene MEN 1, and in MEN2A and MEN2B there are mutations of the RET proto-oncogene. In the case of MEN1 carriers up to the age of 15, 28% of patients show clinical and biological modifications, thus justifying early endocrinological screening in families with MEN1. In the case of MEN2, 100% of patients with RET mutation develop medullary thyroid cancer, so in 100% of cases these patients benefit from prophylactic thyroidectomy from early childhood. (5)

In the juvenile polyposis syndrome, a rare autosomal dominant disorder associated with the presence of numerous hamartomatous polyps in the colon, patients have germline mutations in the SMAD4 and BMPR-1A genes. These patients require colonoscopy surveillance from the age of 15 for the early detection of colon adenocarcinoma. (4)

Xeroderma pigmentosum is an autosomal recessive disorder that leads to increased risk of skin cancer, increased sensitivity to ultraviolet (UV) and degenerative neurological manifestations. These patients are up to 10,000 times more likely to develop skin cancer compared to the general population. (4)

One quarter (we have 1/3 - 40%) of all retinoblastoma cases are caused by germline mutations in the RB1 gene (tumour suppressor gene associated with an increased risk of melanomas, sarcomas). (4) The presence of the germline mutation explains the characteristics of the congenital retinoblastoma: early onset, bilateral involvement, increased risk of developing other malignancies later in life (osteosarcomas, soft tissue sarcomas, melanomas, tumours of the epithelial cells in the bladder, lung or breast) compared to the general population or survivors with non-congenital retinoblastoma. (4) Non-congenital retinoblastoma accounts for 75% (we have 60%) of retinoblastoma cases and it is determined by the presence of sporadic mutations of both RB1 genes in the somatic cells, causing unilateral damage and the late onset of the disease.

Neurofibromatosis (NF) type 1, 2,and 3 are associated with three genetic modifications that increase the predisposition to develop cancer, especially gliomas and peripheral nerve tumors. Thus in NF type 1 the patients develop benign tumours (neurofibromas) of the peripheral nerves, in NF type 2 patients characteristically develop schwanomas of the vestibulocochlear nerve and in NF type 3 schwannomas of the cranial, peripheral and spinal nerves occur. NF type 1 is characterized by the presence of autosomal dominant mutations in the NF1 gene that is responsible for regulating cell division by inactivating RAS-GTP, resulting in uncontrolled cell proliferation and inhibition of cell apoptosis. In half of the cases of NF type 1, the mutations are sporadic, in these cases there is no family history of NF. (4)

Down syndrome (trisomy 21) is the most common human aneuploidy. Children with Down syndrome have an up to 500 times higher risk of developing acute leukaemia. Thus, 1% of all children with Down syndrome develop transient abnormal myelopoiesis (TAM), acute myeloblastic leukaemia (AML) or B-cell acute lymphoblastic leukemia. The associated mutations are diverse, among them the GATA1 mutation that is frequent in TAM and AML, in patients with AML this being associated with an increased response rate to treatment. In B-ALL, patients with Down syndrome have deletions of IKZF1 and mutations in tyrosine kinase JAK2, thus making it possible to apply specific targeted therapies in these situations. (4)

However, these mutations are too rare to be the only ones involved in the aetiology of the large number of cancer cases in children. Multiple modifications such as somatic deletions, translocations, inversions, etc. have been identified in many cases of childhood cancer. Many of them are used for classification into risk groups and thus the adaptation of chemotherapy treatment to the form of the disease, for monitoring the response to chemotherapy treatment and long-term disease follow-up. These modifications are described for each disease in which they are present.

It is important to identify the cases where the inherited genetic modifications in childhood cancer are suspected because:

- Different treatment regimens are sometimes required (for example: radiation therapy is not included in the treatment regimen of congenital retinoblastoma, the intensive chemotherapy used in other cases of AML is contraindicated in AML in Fanconi Anaemia patients);
- The prognosis is different if there are inherited genetic modifications;
- The risk of developing another type of cancer or tumour is higher in some cancers with inherited genetic modifications (for example: congenital retinoblastoma may be associated with an increased risk of developing sarcomas or melanomas, requiring appropriate and long-term post-therapeutic follow-up; in patients with Fanconi Anaemia, the average age of cancer is 16 years and they have a 500 times higher risk of developing squamous cell carcinoma of the head or neck and a 75% risk of developing a malignant disease by the age of 45); (4)
- The genetic evaluation of other members of the patient's family who are at risk of developing cancer, the periodic monitoring and screening adapted to the type of the disease for the early detection of the onset of the disease, which leads to increased survival rate in these cases. Thus, the genetic screening is recommended in asymptomatic siblings of patients with Fanconi Anaemia, knowing that 25% of them may have genetic modifications. In cases of MEN2, the prophylactic thyroidectomy is recommended at a young age (less than 1 year) to prevent the occurrence of medullary thyroid carcinoma. In NF type 1, an annual ophthalmological examination is recommended for the early detection of optic nerve glioma and blood pressure monitoring for the diagnosis of the pheochromocytoma and in NF type 2 the annual audiogram screening,
- The possibility to perform prenatal genetic diagnosis or even embryonic preimplantation in the case of parents with one or more sick children.

The germline mutations can occur dominantly or recessively, can have varying levels of penetration, thus causing different ages at which the diseases occur (early or late) and various manifestations of the diseases. Somatic mutations are not found in siblings; however they may be transmitted to the patient’s offspring’s. In the case of the recessive mutations, the risk is higher for siblings (25%) and lower for the patient's descendants. Increased attention is paid to families with Fanconi Anaemia in which the parents are heterozygous and they are at risk of developing ovarian cancer, being carriers of the BRCA2 gene.

In the future, the use of new genetic screening technologies for children with cancer and their families will lead to the identification of other genetic mutations associated with increased predisposition to develop cancer at an early age.

If there is a suspicion of the diagnosis of hereditary cancer, it is recommended to perform genetic tests both on the child and on the family in specialized centres in the country or even abroad in case they cannot be done in the country.

Recommendations

Warning signs for suspected hereditary cancer are:

- The diagnosis of a single type of cancer with dominant transmission (for example: retinoblastoma, Wilms tumour, etc.) in several members of the same family;
- The occurrence of a case of sarcoma in a child and a case of breast cancer in a young woman in the same family raises the suspicion of a Li Fraumeni syndrome;
- The occurrence of cancer in cases of previously known patients with various developmental abnormalities (for example: Beckwith-Wiedemann syndrome, neurofibromatosis, MEN2, etc.);
- The occurrence of cancer in patients who have had, since childhood, syndromes known to be associated with various cancers in adults (for example: familial adenomatous polyposis (FAP));
- The presence of the homozygous mutations in the BRCA2 or MMR gene in children is associated with the presence of a heterozygous mutation in their parents, who have an increased risk of ovarian or breast cancer. The children develop Fanconi Anaemia and have an increased risk of malignant haemopathies, sarcomas. In these cases, the identification starts with the child with " cafe au lait " spots similar to patients with neurofibromatosis;
- The presence of cancers that are not characteristic for their age in some children;
- The presence of cancers that affect the paired organs in some children;
- The presence of two types of cancer in the same child;
- A diagnosis of cancer in two or more children in the same family.
- Inferior response to anticancer treatment and more than expected intolerance to chemotherapy or irradiation (Fanconi anemia, AT)

The genetic testing by DNA analysis has been available for certain monogenic diseases since 1985. Nowadays, new genetic study technologies (NSG- Next Generation Sequencing) have greatly increased the accuracy of genetic diagnoses, allowing for a large number of tests to be performed simultaneously, thus reducing the importance of a previous diagnostic orientation. Thus, the chances of diagnosing the patients with rare genetic abnormalities increased and new genetic diseases were discovered.

Bibliography

1. Stephen B. Baylin, Peter A. Jones. Epigenetic determinants of cancer. Cold Springs Harbor Perspectives Biology 2016; 8: a019505

2. Federica Turati, Eva Negri, Carlo La Vecchia. Family history and risk of cancer genetic factors influencing multiple cancer sites. Expert Rewiew of Anticancer Therapy, 14:1, 1-4, DOI: 10.1586/14737140.2014.863713

3. Clare Turnball, Shirley Hodgson. Genetic predisposition to cancer. Clinical Medicine 2005;5:491-8

4. Federica Saletta, Luciano Dalla Pozza, Jennifer A. Byrne. Genetic causes of cancer predisposition in children and adolescents. Translational Pediatrics 2015; 4(2):67-75

5. Brigitte Strahm, David Malkin. Hereditary cancer predisposition in children: Genetic basis and clinical implications. Int. J. Cancer:119, 2001-2006

7. PRINCIPLES OF ONCOLOGICAL TREATMENT IN CHILDHOOD CANCERS

The multimodality approach, which integrates surgery and radiation therapy (for the local management of the disease) with chemotherapy (for systemic-metastatic disease control) is the standard treatment for childhood cancer.

The therapeutic plan is established by the multidisciplinary team. The goal of the therapy is to induce and maintain complete remission.

7.1 PRINCIPLES OF SURGICAL TREATMENT

The surgical treatment is an essential component of cancer treatment for solid tumours in children. It should be performed preferably in specialized centres of surgery/ paediatric orthopaedics/paediatric neurosurgery.

The surgeon is a member of the multidisciplinary team that coordinates the treatment for each case. It should be taken into account the fact that the application of the first therapeutic method has a major impact on the prognosis of the disease.

For brain tumours, surgery is usually the first therapeutic intervention. The other therapeutic methodsare applied later, according to the specific therapeutic protocols.

For solid tumours,the surgical treatment has the following indications:

- Establishing the diagnosis - biopsy
- Primary tumour surgery (as the first stage of treatment or after neoadjuvant chemotherapy)
- Surgery for metastasis (the timing of the intervention being determined according to the protocol)
- Cytoreductive surgery
- Reconstruction and rehabilitation surgery
- Vascular access surgery
- Surgery for oncological emergencies
- Palliative surgery
- Staging or restaging surgery (“second-look surgery”) (1)

The techniques for obtaining tumour sample are:

- Percutaneous biopsy - fine needle aspiration biopsy (FNAB – the least invasive technique), Core needle biopsy

- Minimally invasive incisional biopsy (laparoscopy, thoracoscopy)
- Open incisional biopsy - laparotomy, thoracotomy (1)

Recommendations

- The timing and type of surgery is determined within the multi disciplinary team.
- A specialized paediatric oncology service is preferred.
- The correct application of the first therapeutic method has a major impact on the prognosis.

Bibliography

1. Geiger JD, Barnhart DC: Biopsv Techniques for children with Cancer. In GrosfeldJL, O'Neill AJ, Fonkalsrud EW, Coran AG Pediatric Surgery – Sixth Edition volume One, 2006 Mosby, pp 437-44

7.2 PRINCIPLES OF CHEMOTHERAPY

The majority of childhood cancers are chemosensitive (due to the rapidly proliferating nature of the tumour and the ability to undergo apoptosis), and thus chemotherapy is a key element in their treatment. The chemotherapy is largely responsible for the therapeutic successes in the treatment of childhood cancers, but the pathologies that are refractory to this type of treatment, are oftentimes problematic (brain tumours, metastasis, high-risk leukaemia). Treatment related toxicity, both long- and short- term, is also one of the major concerns related to chemotherapy. (1)

In various types of leukaemia, chemotherapy is the only method of treatment. In acute lymphoblastic leukemia (ALL) the treatment is long-term, lasting 2-3 years, and consists of a multidrug combination. It amounts to 4 phases: induction of remission, consolidation, reinduction and maintenance treatment (aiming to eradicate the minimum residual disease) In acute myeloblastic leukemia (AML) the treatment is shorter, with 4-5 blocks of extremely intensive chemotherapy.

In solid tumours, the chemotherapy is adapted to the diagnosis, stage and risk group, and it can begin before or after the tumour resection; it may be associated with radiation therapy.

Polychemotherapy is preferred (regimens that combine several cytostatic agents - with different action and resistance mechanisms that do not have cumulative or similar side effects). The chemotherapyprograms are used according to international protocols (they will be described later in each chapter). The therapeutic protocols are established by large paediatric cancer study groups, and are designed to provide maximum chances of survival with minimum risks and side effects.

Methods of administration of cytostatic agents

- Intravenous route (preferably through long life catheter - Port-a-Cath or Hickman/ Broviac).
- Oral route (usually tablets / capsules; it may be complicated for the treatment to be administered and dosed due to lack of specific paediatric formulas - suspension/syrup)
- Trough naso-gastric tube
- Intrathecal - in leukaemia and lymphomas for the prophylaxis/in CNS tumours as treatment of dissemination (monotherapy - methotrexate, or combined - methotrexate, cytarabine, cortisone)
- Subcutaneous, intramuscular - less used
- Local therapy-rarely used (intraarterial, intraperitoneal, intrapleural, intrapericardial) (2,3)

Dosage in children – it generally refers to the body surface area (BSA); however, in infants and young children (<1 year, <10 kg) it is preferred to administer it according to body weight (BSA / W ratio being significantly increased at this age and the dose being overestimated by BSA).

Due to the immaturity of the clearance mechanisms, further dosage adjustments of cytostatic agents (up to 50-75% of the calculated dose) may be required at young ages / small weights. (3, 4)

Types of chemotherapy: (2, 5)

- **Neoadjuvant** - administered before surgery, in order to reduce the tumour size and facilitate surgery (prototype - osteosarcoma, nephroblastoma);
- **Adjuvant** - administered after surgery, it helps to achieve optimal local control, it treats undetectable micrometastasis;
- **Induction** - usually in leukaemia - intensive treatment, aiming to induce remission;
- **Maintenance** - long-term oral chemotherapy, monotherapy or a combination of drugs in a patient who is in remission;
- **Salvage chemotherapy** - potentially curative chemotherapy, administered to a patient with no response or with recurrence after the initial treatment; high dose regimens are used;
- **High dose chemotherapy** - involves the administration of high doses (myeloablative therapy) of cytostatic agents, followed by reinfusion with stem cell or autologous bone marrow transplant. It is a treatment indicated in metastatic/advanced/refractory solid tumours (Ewing's sarcoma, neuroblastoma, brain tumours, lymphomas), respectively in refractory leukaemia or after induction therapy in patients at high risk of relapse;
- **Metronomic chemotherapy** - involves oral, chronic administration of cytostatic agents (cyclophosphamide, etoposide, vinorelbine) in low doses, with minimal toxic effects, with antiangiogenic and antitumoral effects;
- **Palliative** - in patients with evolving disease, without curative purpose, for symptom control and to prolong life.

Recommendations

- Chemotherapy is the main therapeutic weapon in childhood cancers;
- Strict compliance to the protocol involves adhering to the doses, sequences and rhythm, to the extent that the clinical situation allows it;
- In young or underweight children, the dosage should be calculated according to the body weight, and not the BSA;
- In case of significant toxicity physicians should consider calculating the dosage the same way;
- The vast majority of protocols contain classical cytostatic agent;
- Aggressive chemotherapy is often mandatory;
- Megadoses must be followed by stem cell rescue;
- Cytostatic agents are administered according to a complex program (hydration, electrolyte intake, alkalinisation, protective therapy (MESNA) sometimes also with rescue therapy (leucovorin calcium, depletive/diuretic treatment, prophylactic antiemetic);
- The patient must be monitored during the time when the risk of acute toxicity is present.

Bibliography

1. Vassal G, Geoerger B, Pein F: Chimiothérapie des cancers de l'enfant. In Kalifa C, Pein F, Oberlin O, Hartmann O, Lemerle J - Cancers de l'enfant, 2008 Flammarion SA, pp321-326

2. Verschuur A, Zwaan M: Chemotherapy: current knowledge and new perspectives. In Stevens MCG, Caron HN, Biondi A, red. Cancer in children: clinical management. 6th edition, Oxford: Oxford University Press; 2012, pp 49-65

3. Adamson PC, Bagatell R, Balis FM, Blaney SM: General principles of chemotherapy In: Pizzo PA, Poplack DG, eds.: Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams and Wilkins, 2011, pp 279-343

4. Ceja ME, Christensen AM, Yang SP. Dosing considerations in Pediatric Oncology, US Pharm 2013;(38) (Oncol suppl):8-11

5. Pavlidis N: Principles of chemotherapy in cancer , ESMO/ESO course Valencia 2019

6. Makin G. Principles of chemotherapy. Paediatrics and Child Health: Volume 28, Issue 4, 157-208

7.3 GENERAL PRINCIPLES OF RADIATION THERAPY IN THEPEDIATRIC ONCOLOGY

The radiation therapy plays an important role in the treatment of cancers in children. The decision to use radiotherapy in addition to other therapeutic methods is made within a multidisciplinary committee, according to treatment protocols in use.

The overall survival of children with cancer is constantlyincreasing, exceeding 80% in developed countries. The increasing number of long-term survivors emphasize the importance of identification of acute and late effects of radiotherapy, due to their impact on the somatic and psychosomatic development and the socio-economic life of the future adultlongtime survivors.

Theymay appear years, even decades aftertreatment, they may be progressive and they are more important for younger patients.

The most common complications are:

- Growth disorders
- Various functional disorders: hearing, vision, neurocognitive, vascular and endocrine abnormalities
- Second cancer
- Cosmetic effects

The appearance of these effects is related to:

- The patient's age, sex, genetic predisposition, associated diseases
- The invasion of the tumour in surrounding tissues and organs, compression of the organs (spinal cord - spinal cord compression, kidney - kidney failure)
- The radiotherapy parameters

The principles of radiation therapy in children follow the general principles of radiation therapy. The most important parameters are:

- The time of the radiotherapy in the general context of the multidisciplinary treatment
- The irradiated volume
- Total dose administered
- Dose per fraction
- Total time of radiation treatment
- Total dose at organs at risk
- Concomitant chemotherapy
- Type of chemotherapy (methotrexate, cisplatin)
- The association of surgery

Strategies to reduce the incidence of late effects of radiation therapy are:

- To postpone the radiotherapy beyond the age of 3 years (especially for brain tumours);
- Decreasing the total dose administered (medulloblastoma, Hodgkin's lymphoma, Wilms'tumour);

- Decreasing the doses at the level of the organs at risk and at the normal tissues by using advanced radiotherapy techniques (IMRT, heavyparticles-proton beam therapy);

- Giving up radiotherapy for patients in favourableprognostic groups (leukaemia, Hodgkin's lymphoma, total lung irradiation in Wilms' tumour).

The familymust be informed in advance by the attending physician regarding the need of radiotherapy, on its benefits in the general context of the treatment, but also on the acute and/or late effects of the radiotherapy.

The first contact of the radiation oncologist and/or their team with the patient (child) should be made in a friendly atmosphere, if possible in a special dedicated space that allows the presence of the family, but also to allocate sufficient time to explain the details regarding theprocedures of the radiotherapy. These meetings can be repeated as many times as they are needed.

It is good to prepare the child for radiotherapy together with the paediatric oncologist, the paediatric psychologist and the family and is important to:

- Explain the procedures of radiotherapyas clearly as possible (simulation, positioning, manufacturing of immobilizationdevices)

- Getting the child familiar with the radiotherapy department:

  - The surroundings of the simulation device, the immobilization tools and the way they are made, their utility;
  - Theradiation treatment room and how the linear accelerator is working
  - Thecontrol room and the way in which the permanent supervision is done during the treatment, the possibility of audio contact during the treatment with the dedicated staff and/or with the parent, if the child wishes; audio means (stories, music) to help the child overcome fear and have confidence.

- The presentation of the team of radiotherapists who will perform the treatment.

When the child's compliance is not possible, it is necessary to put the child under anaesthesia, both during the simulation and throughout the treatment.

During the treatment, different procedures can be used to reduce the child's fear as much as possible: light, music, stories. If necessary, the mother or the person accompanying the child can talk to him from the control room to reassure the child.

Due to the particularities related to the patient’s age, the treatment’s complexityor the need of specialtechniques, there is a need for a team composed byradiation oncologist, physicists, radiotherapists, who are specialized in radiotherapy in children.

Target volume delineation is done taking into account all the relevant diagnostic examinations. The tumour volume and the organs at risk will be outlined with high precision. The verification ofpatient's position will be done daily online and/or offline.

The parameters of the radiotherapy (total dose, dose/fraction, total treatment time) are decided according to the treatment protocol specific to each site, in concordance with the national and/or international protocols.

If there are clinical situations that cannot be included in these protocols, it is recommended toconsult with national and/or international specialized centres.

Patient’s follow-up is important. During the treatment, the patient will be monitored by the radiation oncologist at least once a week, or whenever it is needed. The acute effects and their intensity will be registered; their treatment will be established together with the paediatric oncologist. After the completion of the radiotherapy, the patient will be monitored for possible late effects.

Recommendations

- Theradiation therapy for the treatment of cancers in children will be made following a decision taken by a multidisciplinary committee for therapeutic indications, according tonational and/or international protocols.
- Radiotherapy must be performed in centres that can ensure the existence of a team specialized in the preparation and treatment's administration.
- The radiation of young children (especially under 3 years old) should usually be avoided in order to prevent unwanted late complications. In some situations focal proton beam treatment may be justified also in younger children
- For young children or those who do not cooperate, it is necessaryto use sedation, on a daily basis for several weeks. If this is not possible, the child will be sent to another national or international centre to ensure the safe administration of the radiotherapy.
- Children who require special techniques that cannot be administered in the country will be sent abroad. This is generally the casefor small children, children with tumours in the vicinity of organs at riskwhich require high doses and that can be cured with protons and/or other heavy particles, or techniques that are unavailable in the country.

Bibliography

1. National action programmewith guidelinesfor the diagnosis, treatment and follow-up of cancer in children, Third edition; The Norwegian Directorate of Health; Jan 2017

2. Good practice guide for paediatric radiotherapy, Second edition; The Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine, Children's Cancer and Leukaemia Group; August 2018; www.rcr.ac.uk

3. Janssens GO; TimmermannBeate; Laprie Anne et al; Recommendations for theorganisation of care in paediatricradiationoncologyacross Europe: a SIOPE-ESTRO-PROS-CCI-Europe collaborative project in theframework of the JARC; European Journal of cancer 114 (2019) 47-54

4. Recommendations for Paediatric RadiotherapyProgrammes, Minimal Requirements of Quality; Paediatric RadiationOncology: BridgingtheGapVienna, 18-21 June 2013

7.4 ONCOLOGICAL EMERGENCIES IN CHILDHOOD CANCER

The child with cancer has an increased risk of occurrence of various life-threatening situations, situations that occur due to structural and metabolic changes generated by the cancer itself, or by its metastases. The emergencies can occur at any point during the evolution of the malignant disease, sometimes being its initial manifestation. They should be assessed and treated as early as possible in order to minimize the morbidity and mortality of these patients. Therefore, all the physicians who provide care for a child with cancer must be able to recognize life-threatening situations and treat them rapidly and appropriately.

The paediatric oncologic emergencies can be classified into two categories, according to their origin. The first category includes emergencies secondary to complications caused by the tumour mass expansion, and the second includes emergencies secondary to complications caused by the disease itself and its treatment (metabolic, haematological complications). (1, 2)

Neurological emergencies

- Increased intracranial pressure (ICP)

Brain tumours can lead, by exerting the mass effect or by the obstruction of the normal circulation of the cerebrospinal fluid (CSF), to an increase in the intracranial pressure, sometimes in a relatively short time, and can be a major emergency. The occurrence of the intracranial hypertension syndrome is due to the expansive processes (hematoma, tumours), increased of the brain volume (oedema, tumours) or increased fluid volume (hydrocephalus). If this increase of the intracranial pressure is significant, the phenomenon of cerebral herniation may occur. (1)

ICP symptoms differ depending on the patient's age and the site of the tumour. Behavioural disorders, lethargy, irritability, vomiting, loss of motor skills, seizures, coma may occur in infants and young children. The clinical examination may reveal an increase in the skull circumference, fontanelle bulging, sutures separation, epicranial collateral circulation, ("setting sun" sign), strabismus. In older children, the main sign is the headache, initially intermittent, later persistent and rebellious to treatment. It occurs mainly in the morning, typically with occipital location, it may be accompanied by projectile vomiting (which alleviates headache), worsened by changes in position, effort, cough. Other symptoms may include vision problems (diplopia), behavioural disorders, deteriorating school performance, seizures, coma. The clinical examination may reveal strabismus, nystagmus, cranial nerve palsy, esotropia, dysarthria, ataxia, hemiparesis, stiff neck, and, in the late stages, areactive pupils, spasticity, positive Babinski sign, decerebrate posture. The cerebral herniation is the end result of a progressive ICP syndrome or a sudden drop in CSF pressure in case of lumbar puncture. Clinical symptoms depend on the type of the involvement, ranging from mydriasis, hemiplegia / tetraplegia, to bradycardia, coma and respiratory arrest. (1, 3)

The early diagnosis is important to prevent the occurrence of a significant ICP syndrome that can cause life-threatening complications. The paraclinical examinations help to confirm the diagnosis of ICP syndrome. The ophthalmologic examination of the fundus of the eye reveals papillary stasis, papillary oedema, retinal haemorrhage in advanced stages, optic nerve atrophy. In case of suspicion of ICP syndrome, the cerebal examination by magnetic

resonance (MRI) is indicated. The MRI is the standard, allowing to identify the aetiology: hydrocephalus, edema, tumour, haemorrhage. If this is not possible, a CT scan of the brain is acceptable). (1, 4)

The treatment of the patients with ICP signs consists in the administration of corticosteroids (dexamethasone), cerebral depletion with mannitol, diuretics, preventing seizures, neurosurgical intervention (CSF drainage, tumour excision).

- Spinal cord compression syndrome

The spinal cord compression occurs in 3-5% of childhood cancers, sometimes representing the modality of onset. The spinal cord compression is usually secondary to the extension of infiltrative paravertebral tumours, tumours of the vertebral body or, more rarely, compressive metastases in the spinal cord parenchyma. The involvement of the spinal cord can occur in virtually any type of malignancy, the most common being the tumours of the central nervous system, sarcomas, neuroblastomas, lymphomas, but also leukaemia, and nephroblastomas. The spinal cord compression syndrome is an emergency that, unrecognized and untreated in time, can lead to irreversible neurological damage).

The main symptom is the pain, localized or radiating, followed by motor and sensory deficit, sphincter disorders, being a progressive process. The diagnosis must be confirmed as soon as possible and it involves a multidisciplinary approach (neurologist, neurosurgeon, orthopaedist, paediatric oncologist). To clarify the diagnosis, the imaging method of choice is the MRI examination of the spine; if it is not available in a timely manner, the CT examination is an acceptable alternative.

The treatment should be started immediately. The goals of the treatment in spinal cord compression syndrome are the recovery and the maintenance of the normal neurological function, the local tumour control, the spine stabilization, and the pain control. Glucocorticoids and mannitol are used to reduce interstitial oedema. The definitive therapeutic options include the surgical resection, the radiotherapy and/or the chemotherapy, the optimal therapeutic decision being preferably established by a multidisciplinary team.

- Other oncologic emergencies in the neurological field are represented by posterior reversible encephalopathy syndrome (PRES) (5), stroke, cerebral palsy, convulsions, altered mental status, requiring specialized diagnosis and treatment. (1, 3)

Thoracic emergencies

- Superior vena cava syndrome and superior mediastinal syndrome

Bulky tumours located in the anterior mediastinum can cause compression to the structures from this level, causing obstruction of the airways or of the cardiovascular system. The superior vena cava syndrome (SVCS) refers to the signs and symptoms that result from the compression or the obstruction of the superior vena cava. Superior mediastinal syndrome (SMS) is due to the compression of the trachea or main bronchus. The main cause is the compression by mediastinal tumours: lymphomas, leukaemia, germ cell tumours, neuroblastomas, sarcomas. The prolonged use of central venous catheters (CVC) during the antineoplastic therapy increases the risk of venous thrombosis and obstruction of the superior vena cava (SVC). The main clinical symptoms are dyspnea, cough, dysphagia, orthopnea, dysphonia, edema of the face, neck, thorax and upper limbs, cyanosis of the face, collateral venous circulation, headache, chest pain, worsened by clinostatism and having a usually rapid evolution (days). The anxiety, altered mental status, lethargy, visual disturbances may be less common. Left untreated, the SVCS can lead to intracranial hypertension, cerebral haemorrhage, syncope or severe airway obstruction, death. (1, 2)

The diagnosis and the treatment should be performed in centres that have intensive care units that can provide orotracheal intubation and ventilator support. In case of a suspicion

of a malignant disease, obtaining a biopsy for diagnostic purposes is the standard, but often, the severity of the symptoms requires the urgent initiation of a treatment aimed at reducing the tumour mass. The initial investigations should be as minimally invasive as possible, being limited to clinical examination, imaging tests (radiography or chest CT examination), laboratory investigations (complete blood count, catecholamine urine test, tumour markers), bone marrow aspirate or biopsy under local anaesthesia. Any procedure that requires sedation or general anaesthesia will be avoided as they may aggravate the patient's condition. (6, 7)

It may be necessary for empirical therapy to precede the etiological diagnosis in severe cases. The emergency treatment requires, in addition to the general measures (semi-sitting position, oxygen therapy, diuretics), the administration of the chemotherapy (corticosteroids, cyclophosphamide, anthracyclines, vincristine) or decompression radiotherapy (with doses of 3–5 fractions of 12–20 Gy, per tumour volume), generally followed by a significant reduction of the tumor mass. In case of an intravenous thrombus occlusion, it may be necessary to proceed to an anticoagulant or thrombolytic treatment followed by removal of the CVC or of the implantable port.

• Other cardio-thoracic emergencies include pericarditis, cardiac tamponade, pleural effusions that will require specific therapy, including fluid evacuation, insertion of a drain tube, intracavitary administration of cytostatic agents. (1, 3) The puncture and the evacuation of a pleural or pericardial collection can have a double benefit, both diagnostic and therapeutic one.

Abdominal emergencies

The abdominal emergencies often occur as a result of the complications associated with paediatric cancer: esophagitis, hemorrhagic gastritis, typhlitis, pancreatitis, mechanical or paralytic ileus, cholestasis syndrome, acute abdomen. The abdominal emergencies in children with cancer are due to inflammation, immunosuppression, mechanical obstruction, haemorrhage and perforations. The anamnesis and the clinical examination, the laboratory tests, the imaging and endoscopic investigations establish the diagnosis accurately and they allow the selection of the cases that require surgical intervention. The treatment will aim to correct the primary cause that led to the occurrence of the digestive tract complications. (1)

• Gastrointestinal bleeding

The child with cancer has an increased predisposition for the occurrence of upper digestive tract bleeding (oesophageal, gastro-duodenal) due to haematological disorders (thrombocytopenia, DIC), uncontrollable vomiting from ICP syndrome (Mallory-Weiss syndrome), stress ulcers, Cushing ulcers, etc. The treatment involves the administration of gastric antacids and anti-secretory drugs (proton pump inhibitors), correction of the thrombocytopenia and of the coagulation disorders, the surgical therapy, as appropriate. The causes of lower gastrointestinal tract bleeding are enteral infections, intestinal invagination, abscesses, gastrointestinal perforation. The treatment addresses the primary cause of the bleeding. (4, 7)

• Intestinal obstruction

The intestinal obstruction can have extraluminal or intraluminal causes: tumour formations (lymphomas, sarcomas, ovarian, adrenal tumours, etc.), adhesions and postoperative structures in patients who have undergone abdomino-pelvic surgery. The main symptoms are severe abdominal pain and vomiting. Imaging investigations (ultrasound, abdominal radiography, CT examination) as well as surgical consultation are necessary to clarify the diagnosis. The initial management involves stopping the oral intake, stopping the medication with intestinal toxicity, placing a nasogastric tube followed by surgical resolution, as appropriate. (1, 7)

• The typhlitis is the inflammation of the intestinal wall of the cecum, caused by bacterial or fungal invasion secondary to neutropenia (in leukaemia). It is most often manifested by abdominal pain, fever, tenderness to palpation, diarrhea, in a child with malignancy associated with neutropenia. The most commonly involved bacterial species are Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus and Clostridium difficile, while Candida and Aspergillus are the main fungi correlated with neutropenic enterocolitis. The ultrasound or the abdominal CT usually indicates the thickening of the cecum wall (> 3 mm), intestinal pneumatosis, the presence of the peritoneal fluid. The treatment involves broad-spectrum antibiotics and the surgical evaluation. Most patients can be treated conservatively with broad-spectrum antibiotics effective on gram-negative pathogens, clindamycin or metronidazole for anaerobes, and antifungals. (7)

Haematological emergencies

• Hyperleukocytosis is defined as an increase in the number of leukocytes above 100,000 / mmc in the peripheral blood, most commonly found in patients with leukaemia, affecting about 10% of cases of acute lymphoblastic leukaemia (ALL), 5-20% of cases of acute myeloblastic leukaemia (AML) and almost all the cases of chronic myeloid leukaemia (CML) in the chronic phase. The clinical effects become evident at values of over 200,000/mmc in the case of AML, respectively 300,000/mmc in ALL and due to the hyperviscosity of the blood and to the leukostasis, with the formation of thrombi in the microcirculation. The cerebral and pulmonary vascular sites are most often affected. In case of CNS involvement, there may be present headache, visual disturbances, symptoms associated with a stroke: altered mental status (confusion, delirium, coma), seizures, motor deficits. The lung involvement leads to dyspnea, hypoxia, acute respiratory failure (ARDS - acute respiratory distress syndrome). Intra-abdominal complications (gastrointestinal bleeding, rupture of the spleen) are also possible. In addition to lesions secondary to leukostasis, children with hyperleukocytosis are at increased risk of metabolic complications secondary to tumour lysis syndrome.

The treatment aims to reduce blood viscosity and to correct metabolic and coagulation imbalances. The aggressive hydration is indicated, avoiding the administration of potassium, administration of allopurinol, alkalinization. The erythrocyte transfusions are avoided if the patient is hemodynamically stable; the platelet transfusion is indicated in case of thrombocytopenia <20,000/mmc. Diuretics are also avoided (they increase the blood viscosity). The leukapheresis or the exchange-transfusion (in children under 12 kg) can rapidly reduce the level of leukocytosis and can improve coagulation disorders. The prompt initiation of cytoreductive chemotherapy is essential in the management and the treatment of hyperleukocytosis. (1, 8)

• Thrombosis

The thrombotic manifestations associated with childhood cancer are relatively rare compared to the adult patients, affecting between 2 and 16% of children with malignancy, the incidence varying with age, type of malignancy, tumour site, occurring more frequently in leukaemia, lymphomas, soft tissue sarcomas and less commonly in brain tumours. (9) The aetiology is multifactorial, including congenital coagulation disorders (thrombophilia), factors related to the malignant disease and factors related to the antineoplastic therapy. The cancer induces a procoagulant status by producing cytokines and increasing plasma coagulation factors. The hyperleukocytosis, the mass effect exerted by the solid tumours, and the tumour invasion of the blood vessels promote the venous stasis and the occurrence of thromboembolism. The presence of the central venous catheters (CVC) is the most common predisposing factor of venous thrombosis in children with cancer (5-36%). Anticancer chemotherapy, especially the administration of L-Asparaginase or the corticosteroid therapy, is

in itself an important risk factor in the development of the thromboembolism. (9, 10) Other risk factors cited are prolonged immobilization, infections, blood type (non 0). (11)

The clinical manifestations vary and they depend on the site and size of the thrombus as well as the degree of the venous occlusion (partial or total): neurological (headache, vomiting, motor deficits, visual disturbances, convulsions, dizziness, and coma), respiratory (tachypnea, dyspnoea, hypoxia, chest pain), cardiac (arrhythmias, heart failure), peripheral (local pain, swelling, edema, erythema, vein dilatations). (6, 9) The evaluation of the procoagulant status includes the determination of prothrombin time (PT), activated partial thromboplastin time (aPTT), complete blood count, D-dimer test, fibrinogen, fibrin degradation products, (serum antithrombin III (AT III), protein S and protein C levels). The EchoDoppler, CT, MRI examinations bring information about the site and extent of the thrombus. (12)

The treatment aims at the therapy of the acute episode and the prophylaxis of future thromboembolic accidents, considering the fact that the anticoagulant treatment in children with cancer is a challenge given the coexistence of thrombotic risk with the hemorrhagic risk related to thrombocytopenia and chemotherapy-induced coagulopathy. It is recommended to use low molecular weight heparin and vitamin K antagonists in regular doses, with platelet count monitoring and platelet transfusion if their number falls below 30,000/mmc. (9)

- Disseminated intravascular coagulation

Childhood cancer can be complicated by the onset of disseminated intravascular coagulation syndrome (DIC), characterized by the excessive activation of the coagulation and consecutive consumption of coagulation factors, leading to concomitant hemorrhagic and thrombotic manifestations. The most common situations in the paediatric oncological pathology that may be associated with DIC are acute non-lymphoblastic leukaemia (especially acute promyelocytic leukaemia), generalized metastases, and sepsis. The clinical signs and symptoms are varied and complex, from subclinical forms to thrombotic and hemorrhagic phenomena refractory to treatment: petechiae, ecchymosis, purpura, pallor, multiple localization bleeding, hematuria, melaena, hemoptysis, altered mental state, confusion, lethargy (intracranial haemorrhage). Recognizing this process in its early stages will help improve the prognosis of the affected patient. (6. 12). The laboratory diagnosis is difficult, none of the available tests being specific for DIC. They evaluate the pathophysiological processes underlying DIC: consumption of the coagulation factors and platelets, increased fibrin production and increased fibrinolysis. The platelets are typically low (below 100,000/mmc), fibrinogen may be low, TP, aPTT and thrombin time (TT) are increased, the level of D-dimer and fibrin degradation products is increased, the level of coagulation factors (V, VIII) is low, schizocytes are present in the peripheral smear. The treatment must target the underlying pathology that led to the onset of DIC, being doubled by supportive therapy measures: platelet transfusion, fresh frozen plasma (FFP), cryoprecipitate, coagulation factors, erythrocyte mass. The heparin anticoagulant therapy, although controversial, can be used in the treatment of thrombotic events. (5, 12, 13, 14) The antifibrinolytic agents (tranexamic acid) are not routinely recommended. The antifibrinolytic agents are useful in cases of DIC secondary to hyperfibrinolysis associated with acute promyelocytic leukaemia and other cancers. (13, 14)

Metabolic emergencies

The tumour lysis syndrome (TLS)

It is an oncological emergency characterized by hyperuricemia, hyperkaliemia, hyperphosphatemia with secondary hypocalcemia, acidosis, and acute renal failure. The TLS is generated by the lysis of the malignant cells in tumours with rapid cell turnover. TLS can occur in any malignancy with a high tumour load and rapid turnover of the malignant cells. It is most commonly found in acute leukaemia, especially in acute T-cell lymphoblastic leukaemia and in

highly aggressive lymphomas, such as Burkitt's lymphoma. TLS may be present before the start of the chemotherapy or it occurs after the first doses of cytostatic agents, when large amounts of degradation products are released rapidly (maximum risk in the first 12-72 hours, but it lasts up to 7 days).

TLS will be aggravated by renal failure, which may be caused by preexisting renal disease, dehydration, precipitation of calcium-phosphate salts or uric acid or xanthine crystals in the kidneys, renal leukemic infiltration, uretheral compression by enlarged lymph nodes or leukemic infiltrates, and nephrotoxic drugs. Hyperphosphatemia is a common precipitating factor behind acute renal failure. Life-threatening cardiac arrhythmias may be caused by both hyperkaliemia and hypocalcemia, and the latter may in addition cause muscle cramps and tetany. In addition, many patients experience nausea, vomiting, lethargy, edema, fluid overload and congestive heart failure, seizures, and sudden death.

Clinical and paraclinical monitoring of the patients include: daily weighing, fluid balance, heart and blood pressure monitoring, blood count, frequent tests of blood and urine electrolytes, serum biochemistry (LDH, uric acid, creatinine, urea, bicarbonate), urine test, ECG test. The prophylaxis and the treatment of TLS require adequate hydration, the alkalinization of the urine, preferably before the initiation of chemotherapy. In case of TLS, it is recommended to administer adjuvant therapy (control of hyperuricemia with allopurinol or rasburicase, treatment of hyperkalemia with kayexalate (sodium polystyrene sulfonate), insulin, calcium gluconate, dialysis in case of renal failure. (1, 3, 7)

Recommendations/summary:

- The oncological emergencies can occur at any time during the evolution of the malignant disease, sometimes being its initial manifestation
- All oncological emergencies can also occur at any stage during treatment. Specific attention awareness should be given in the initial treatment of patients with large tumor burden (leukemia/lymphoma) with high risk of developing TLS.
- The oncological emergencies imminently endanger the life of the child with cancer, thus they must be recognized and treated rapidly and appropriately.
- Sometimes it is necessary to have the support of the intensive care specialists.

Bibliography

1. Fisher MJ, Rheingold SR. Oncologic Emergencies. In Pizzo PA, Poplack DG (Eds.). Principles and practice of pediatric oncology 6th Edition. Philadelphia: J.B. Lippincott, 2011: 1125-1152

2. Handa A, Nozaki T, Makidono A et al. Pediatric oncologic emergencies: Clinical and imaging review for pediatricians. Pediatr. Int.2019;61: 122–39.

3. Jefferson MR, Fuh B, Perkin R. Pediatric oncologic emergencies. Pediatr Emerg Med Rep 2011; 16(5):57-72.

4. Rapkin L. Pediatric Oncologic Emergencies. https://www.cancertherapyadvisor.com /home /decision-support-in-medicine / critical-care-medicine/pediatric-oncologic-emergencies/

5. Esther V. Hobson, Ian Craven, and S. Catrin Blank, Posterior Reversible Encephalopathy Syndrome: A Truly Treatable Neurologic Illness, Perit Dial Int. 2012 Nov-Dec; 32(6): 590–594 doi: 10.3747/pdi.2012.00152

6. Mullen E, Gratias E. Oncologic emergencies. In: Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE. Nathan and Oski´s hematology and oncology of infancy and childhood. 8 ed. Philadelphia: Elsevier-Saunders, 2015: 2267-91.

7. Prusakowski MK, Cannone D. Pediatric Oncologic Emergencies. Emerg Med Clin N Am 32 (2014) 527–548

8. Kühne T. Chap. 18. Emergencies in Pediatric Oncology in Imbach P, Kühne T, Arceci R (Eds.). Pediatric Oncology. A Comprehensive Guide. Springer-Verlag Berlin Heidelberg 2006: 193-204

9. Ko RH, Thornburg CD. Venous Thromboembolism in Children with Cancer and Blood Disorders. Frontiers in Pediatrics. 2017: Volume 5, Article 12

10. Athale UH, Yang JYK, Chan AKC. Thromboembolism in children with cancer. UpToDate 2020. https://www.uptodate.com/contents/thromboembolism-in-children-with-cancer/print

11. Athale UH et al. Impact of baseline clinical and laboratory features on the risk of thrombosis in children with acute lymphoblastic leukemia: A prospective evaluation. Pediatr Blood Cancer. 2018;65(5):e26938. Epub 2018 Jan 15

12. Rhodes V, Manzullo E. Oncologic Emergencies. 1995. Available at: www.cancernetwork.com/ articles/oncologic-emergencies.

13. Thachil J, Falanga A, Levi M, Liebman H, Di Nisio M. Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH. J Thromb Haemost 2015; 13: 671–5

14. Wong W., Glader B. Disseminated intravascular coagulation in infants and children. UpToDate 2020. https://www.uptodate.com/contents/disseminated-intravascular-coagulation-in-infants-and-children/print

7.5 LYMPH NODE ENLARGEMENT

Lymphadenopathy is defined as an enlargement or a change in the character of a lymph node, greater than 10 mm. The exception to this rule is represented by the epitrochlear and inguinal lymph nodes which are considered to be pathological if their size is more than 5 mm and more than 15 mm, respectively. (1)

Pathologic lymphadenopaty is usually a symptom of benign diseases, especially of infections. The adenopathy can also be a sign of malignant diseases, such as leukaemia, lymphoma, histiocytosis, neuroblastoma and germ cell tumours. It rarely occurs in soft tissue sarcoma and bone tumours. The site of the enlarged lymph node and the age of the patient may offer clues for a possible etiology.

Suggestive signs of the malignant nature of the adenopathy. (2)

- The epitrochlear and supraclavicular localization (malignant in 75-80% of the cases)
- Association with adenopathies in other sites or generalized lymphadenopathy
- Painless nodes, of hard or firm consistency, fixed nodes
- Lymph nodes > 1 cm in the neonatal period
- Adenopathy with a diameter > 2 cm that tends to grow or does not respond to antibiotic therapy lasting 2 weeks
- General symptoms: weight loss (>10% of body weight), fever, night sweats
- Associated hepatosplenomegaly
- Abnormal chest radiograph
- Modified blood count (presence of atypical cells or cytopenia affecting more than one cell line), constantly increased ESR / PCR values

It is important to avoid corticosteroid therapy before final diagnosis; it covers the signs of leukaemia, lymphoma, histiocytosis and it delays the diagnosis.

Etiology

The causes of a generalized adenopathy may be:

- Infectious causes (viral infections: Epstein-Barr, cytomegalovirus, herpes-, varicella-, adeno-virus, rubella, measles, hepatitis B, HIV; fungal infections: coccidioidomycosis, blastomycosis, histoplasmosis; bacterial infections: beta-hemolytic streptococcus, brucellosis, leptospirosis, tularemia; Spirochaetes: syphilis, borrelia burgdorferi; Parasites: toxoplasmosis, malaria)
- Non-infectious causes (leukaemia, lymphomas, histiocytosis, solid tumour metastases, metabolic diseases, drugs side effects, immune diseases, sarcoidosis, Castleman's disease, Rosai-Dorfman, hyperthyroidism, etc.).

Localized adenopathy is caused by infections of the drained site or by neoplasm.

Assessment of the adenopathy (3)

Anamnesis, paying attention to the interval of the onset, general physical examination and examination of the affected adenopathy. The examination of the lymph nodes determines whether the lymphadenopathy is localized or generalized, the size, the consistency, the fixation/adhesion, presence or absence of Celsius signs.

Useful laboratory tests are: blood count, peripheral blood smear; acute phase reactants: ESR, PCR; biochemical examinations: uric acid, LDH; bacteriological and serological examinations for viral, parasitic infections, specific examinations for immune diseases, tuberculin test; cytological examination of the bone marrow in case of suspected leukaemia.

The imaging investigations have the role of detecting other lymphadenopathy, hepatosplenomegaly, tumour formations.

Lymph node biopsy - is indicated in the presence of suggestive signs of malignancy. The biopsy is performed in specialized centres. For the biopsy, choose the lymph node that seems most suspicious for malignancy. Open biopsy or lymph node removal is preferred to aspiration, especially in case of suspected lymphoma.

Empirical antibiotic therapy

This may be a diagnostic and therapeutic intervention in the case of the localized lymphadenopathy or of unspecified etiology, in the absence of suspicious signs of cancer. The antibiotic therapy can be initiated even in the absence of the infection signs, because the localized adenopathy (except for supraclavicular ones) is frequently caused by infections. The initial empirical treatment usually treats the streptococcus and staphylococcus. The result is verified after 3 to 7 days of treatment: in case there is no response, the antibiotic range is widened.

Biopsy

Performing the biopsy depends on certain factors. Thus, supraclavicular and inferior cervical lymphadenopathy point towards malignant diseases such as leukaemia, lymphomas, neuroblastoma, histiocytosis and germ cell tumours. The biopsy is indicated early. The axillary and inguinal lymphadenopathy is often caused by infection (watch out for Bartonella henselae infection). The biopsy is recommended after 2-3 weeks of persistence of the symptoms (max. 4 weeks) in case of a lack of response to anti-infective treatment. The cervical lymphadenopathy, in case of obvious infection, is treated according the diagnosis. If the lymph node is smaller than 2 cm and there are no obvious signs of infection, the patient is observed for 10-14 days. If the lymph node is bigger than 2 cm and there are no signs of infection, opt for early biopsy. The epitrochlear lymphadenopathy is often associated with malignant haemopathy.

The mediastinal adenopathy is sometimes diagnosed incidentally during an X-ray performed for other reasons or in symptomatic patients. The evaluation of the mediastinal lymphadenopathy is done by chest radiograph, thoracic CT scan, e.g. MRI, PET / CT.

Depending on the other examinations, the biopsy may be indicated early.

Recommendations

- Lymph node biopsy is indicated if the lymph node enlargement persists beyond 2-3 weeks (max. 4 weeks) in case of a lack of response to anti-infective treatment
- Biopsy is indicated early in situations that are suspicious for malignancy:

- supraclavicular, inferior cervical, epithrochlear sites
- the size of the lymphadenopathy is bigger than 2 cm, with no obvious signs of infection
- the association of symptoms-signs-investigations suspicious of cancer

Bibliography

1. McClain KL, Kaplan SL, Mahoney DH et al.: Peripheral lymphadenopathy in children: Evaluation and diagnostic approach. UpToDate

2. Oguz A, Karadeniz C, Temel EA et al.: Evaluation of peripheral lymphadenopathy in children. PediatrHematol Oncol 2006; 23:549.

3. Healy CM, Drutz JE, Isaacson G C et al.: Cervical lymphadenitis in children: Diagnostic approach and initial management.

8.1 MALIGNANT HEMOPATHIES

Acute leukaemias (AL) are a heterogeneous group of hematopoietic stem cell malignancies characterized by the proliferation and accumulation of immature (blastic) cell clones. Depending on the origin of the malignant clone, there are two major categories of acute leukaemias: lymphoblastic and myeloid.

8.1.1 ACUTE LYMPHOBLASTIC LEUKEMIA

According to the definition of the National Cancer Institute (NCI), the acute lymphoblastic leukaemia (ALL) is a rapidly progressive neoplasm that originates in the hematopoietic tissue such as the bone marrow, causing a large number of malignant cells to enter the bloodstream.

Epidemiology

With approximately 3.3 occurrences/100,000 inhabitants under the age of 15, ALL represents about 30% of all cancers in the paediatric population and it is therefore the most common malignancy in children. The average age at onset is 4.7 years with a peak incidence between 2 and 5 years. In Romania, the standardized incidence rate for males was 1.46 and for females 0.97 (data from the National Cancer Registry 2017, unpublished).

Classification

The classification is done based on morphological criteria (FAB classification), cytochemical, immunophenotypic, cytogenetic and molecular biology criteria. At the same time, there is a WHO classification based strictly on cytogenetic and molecular biology criteria.

Diagnosis

Symptomatology

Symptoms due to bone marrow infiltration: pallor, fatigue, tachycardia or dyspnoea, caused by anaemia; fever, infections, canker sores secondary to neutropenia, petechiae and ecchymosis, bleeding in the mucous membranes, cerebral haemorrhage due to thrombocytopenia. (1, 2)

Symptoms due to extramedullary invasion: lymphadenopathy, hepatomegaly, splenomegaly. The symptoms of the central nervous system (CNS) involvement can be headache, morning vomiting, cranial nerve palsy, papillary edema, seizures, outbreak signs, ataxia, etc. Sometimes patients may experience diabetes insipidus due to posterior pituitary infiltration or polyphagia in the case of hypothalamic invasion. Blastic infiltration of the testicles can be shown by unilateral or bilateral swelling of the testicles. Priapism is due to leukemic infiltration of the sacral nerve roots, corpus cavernosum or dorsal veins. Patients can often suffer from joint swelling, bone pain, and the bone pain is usually in the calves, due to invasion of the periosteum or expansion of the bone marrow invaded by blasts. Hematuria,

hypertension and renal failure may be due to the invasion of the renal parenchyma or tumour lysis syndrome. Infiltrative skin lesions are of the leukemia cutis type. (3)

Initial paraclinical investigations and investigations during the treatment

Specific laboratory investigations (complete characterization of the type of ALL):

- Blood count (automatic)

- Cytomorphological examination of the peripheral blood and of the bone marrow aspirate. The morphological characterization of ALL is done by microscopy according to the FAB classification (French-American-British) in the L1, L2, L3 types. If bone marrow aspiration is not possible (dry tap or impossibility to perform immunophenotyping) it is recommended to perform bone marrow biopsy (BMB) with immunohistochemical examination, which then always should be performed at diagnosis to ensure enough diagnostic material. In case of hyperleukocytosis, analysis of lymphoblasts in the peripheral blood smear may be sufficient. It is preferable for the smear to be from native blood / bone marrow and not from a test tube containing EDTA or heparin, using MGG panoptic stain. (2, 3)

- The cytochemical / cytoenzymatic examination has lost its importance with the introduction of immunophenotyping. However, in certain dilemmas / impossibility of immunophenotyping, the cytochemical examination may guide the diagnosis.

- The immunophenotyping from bone marrow aspirate (or peripheral blood) is also essential and it is performed by flow cytometry. The expression of surface lymphatic antigens or intracellular antigens by at least 10% of blasts is considered relevant. The antibody panel used in the diagnosis of ALL is based on the consensus of the AIEOP-BFM group (Table 1). (4)

Table 1. Antibody panel for immunophenotyping in ALL

Antibody Type	**Markers (each combined with CD45)**
Intracellular	iCD3, iCD22, iCD79a, iIgM (μ-chain), iLysozyme, iMPO
Surface	CD2, CD3, CD5, CD7, D10, CD19, CD20, CD11c, CD11b, CD13, CD14, CD15, CD33, CD64, CD65, CD117, CD34, (CD45), CD56, HLA-DR For T-ALL: CD1a, CD4, CD8, TCRαβ, TCRγδ if B-IV ALL suspected: κ-chain,λ-chain
Optional / Recommended	All cases: NG2, CD371 If BCP-ALL: CD11a, CD22, CD24, CD38, CD44, CD58, CD66c, CD123, CRFL2 If T-ALL: CD99, iTdT If BAL: CD24, iTdT

Based on the panel described in Table 1, the assignment to the dominant lineage leukemia will be differentiated according to the antigenic expression described in Table 2. (4)

Table 2. Immunophenotypic expressions of acute leukemia (dominant lineage)

Lineage	**Positivity**	**Antigens**
BCP-ALL (B-cell precursor ALL)	≥2 positive of:	CD19, CD10, (i)CD22, iCD79a
T-ALL	all 3 of:	(i)CD3, CD7, iMPO negative or weak
AML	≥2 positive of:	CD13, CD33, CD64, CD65, CD117, iMPO and BCP-/T-ALL criteria not met

Depending on the antigen expression, several subtypes of ALL are defined (Table 3). (4)

Table 3. Immunophenotypic subclasses in ALL

Subtype	Discriminators	Remarks
B-I (pro-B)	$CD10^{neg}$	BCP-ALL lineage criteria fulfilled
B-II (common B)	$CD10^{pos}$	-
B-III (pre-B)	$iIgM^{pos}$	$CD10^{neg\ or\ weak\ pos}$ may occur
B-IV (mature B)	Kappa- or lambda ^{pos}	may occur with FAB L1/L2 morphology
T-I (pro-T)	only $iCD3^{pos}$ and $CD7^{pos}$	T-ALL lineage criteria fulfilled
T-II (pre-T)	≥1 of: $CD2^{pos}$, $CD5^{pos}$, $CD8^{pos}$	Surface (s) $CD3^{weak\ pos}$ allowed
T-III (cortical T)	$CD1a^{pos}$	$sCD3^{weak}$ may occur
T-IV (mature T)	$CD1a^{neg}$ and $sCD3^{pos}$	$sCD3^{strong}$, or $sCD3^{weak\ pos}$ with TCR^{pos}
ETP (only additive to T-I or T-II)	$CD1a^{neg}$, $CD8^{neg,}$ de usually $CD5^{neg\ or\ weak\ pos}$, and $\geq 1^{pos}$ of HLADR, CD11b,13,33,34,65,117	If $CD5^{strong\ pos}$; $\geq 2^{pos}$ of HLADR, CD11b,13,33,34,65,117; $sCD3^{weak\ pos}$ may occur

Particular immunophenotypic expressions

- ALL with co-expression of myeloid markers characterized by ALL immunophenotype and co-expression of up to 2 myeloid markers (≥10% of blasts express CD13, CD15, CD33, CD65 or CD66c);

- AML with co-expression of lymphoid markers characterized by AML immunophenotype and co-expression of lymphatic antigens (≥10% of blasts express CD2, CD4, CD7, CD19, CD56, iCD79a or TdT);

- Mixed-phenotype acute leukaemia, representing 3-5% of the total acute leukemias (MPAL - according to the WHO classification 2008), previously known as biphenotypic acute leukemia (BAL according to the EGIL classification). The variants are: a) co-expression of ALL and AML specific antigens on an otherwise homogeneous blastic population; b) the coexistence of two independent blastic populations (one with ALL and one with AML phenotype); c) MPAL genetically defined with t(9; 22) (q34; q11)/BCR-ABL 1 or t(v; 11q23)/MLL; d) leukaemia that changes the lineage during treatment ("lineage switch"); e) undifferentiated acute leukaemia (4, 5, 6)

Cytogenetics and molecular genetics

For a complete characterization of the ALL type, both conventional and biomolecular cytogenetic analysis is required. By karyotyping (high-resolution G banding), hyperdiploid forms (with a favourable prognosis) and hypodiploid forms (unfavourable prognosis) can be diagnosed. Using fluorescent in situ hybridization (FISH), the translocations with prognostic value can be highlighted. Using the polymerase chain reaction (PCR), the molecular equivalents of the translocations (fusion genes) can be highlighted. Currently, genetic abnormalities can also be identified by spectral karyotyping (SKY) or by comparative genomic hybridization (CGH). It is recommended to identify the following translocations with the respective fusion genes: t(9; 22) (q34; q11.2) with the BCR-ABL1 fusion gene; t(4; 11) with the MLL-AF4 fusion gene (old classification) or KMT2Ar (new classification); t(12; 21) (p13; q22) with TEL-AML1 fusion gene (old classification) or ETV6-RUNX1 (new classification); t(1; 19) with the fusion gene E2A-PBX1 (old classification) or TCF-PBX1 (new classification) (1, 5, 6, 7)

Revised WHO Classification of ALL (2016) (8)

- B-Cell Acute lymphoblastic leukaemia/ B-Cell lymphoblastic lymphoma

- B-Cell Acute lymphoblastic leukaemia / B-Cell lymphoblastic lymphoma, NOS (not otherwise specified)

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma, with recurrent genetic abnormalities

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with t(9; 22) (q34; q11.2); BCR-ABL1

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with t(v; 11q23); KMT2A rearrangement

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with t(12; 21) (p13; q22); ETV6-RUNX1

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with hyperdiploidy

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with hypodiploidy

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with t(5; 14) (q31; q32); IL3-IGH

- B-Cell Acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with t(1; 19) (q23; p13.3); TCF3-PBX1

- Provisional entity: B-cell acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma, BCR-ABL1-like

- Provisional entity: B-cell acute lymphoblastic leukaemia / B-cell lymphoblastic lymphoma with iAMP21

- T-cell acute lymphoblastic leukaemia / T-cell lymphoblastic lymphoma

- Provisional entity: ALL with early T-cell precursor

- Provisional entity: NK cell acute lymphoblastic leukaemia / NK cell lymphoma

General diagnosis of the extramedullary involvement: (2, 3, 9)

- detailed anamnesis

- complete physical examination

- lumbar puncture (see CSF analysis below) always with concomitant administration of MTX

- chest radiograph (PA and latero-lateral incidence)

- radiograph of the left hand in dorso-volar projection

- radiograph of the spine in lateral projection

- ultrasound of the neck, abdomen, testicles

- lumbar puncture with CSF analysis (recommended before starting any cytoreductive therapy)

- in case of suspicion: MRI/CT for the chest and/or abdomen

- in case of suspected or proven CNS involvement: brain CT/MRI

- cardiological consultation (with ECG and Eco)

- neurological consultation (with EEG)

- fundus of the eye examination

CSF analysis is performed by analysis of the cellular elements (e.g. SYSMEX analyzer) cytomorphological examination of the CSF sediment after its centrifugation (CYTOSPIN examination). Total protein of CSF is also determined. CNS involvement is classified into 3 statuses (CNS-1 status defined by <5 leukocytes/mm^3 without detectable blasts, CNS -2 status defined by <5 leukocytes/mm^3 with detectable blasts, CNS-3 status defined by ≥5 leukocytes/mm^3 with detectable blasts, brain mass or involvement of the cranial nerves). See ALLIC-BFM protocols 2002 and 2009 for details. (6, 9, 10)

The diagnosis of testicular involvement does not necessarily require testicular biopsy.

Other laboratory investigations include: full haematogram, CRP, procalcitonin, transaminases, LDH, urea, creatinine, uric acid, ionogram, blood glucose, immunogram, aPTT,

PT, fibrinogen, D-dimer, electrolytes and viral screening (AgHBs, anti-HBs, anti-HCV, CMV, EBV, HIV) (2)

Minimum residual disease (MRD)

It will be performed by flow cytometry at the beginning of the disease and at specific time points according to protocol during the treatment in order to assess the response to treatment (FC MRD). The evaluation of MRD is also a major criterion for prognosis and stratification in the risk groups. Molecular genetics (PCR) techniques have now been developed for the evaluation of MRD: genetic rearrangements of T lymphocyte receptors (T-ALL) and immunoglobulin genes (BCP-ALL). The NCCN guideline recommends that the MRD test be determined from the first bone marrow aspirate, just before the one intended for morphological analysis, and that the evaluation of MRD during bone marrow aplasia be repeated after hematopoietic reconstitution. (2, 6, 7) MRD can be monitored either by flowcytometry or by PCR or both. PCR evaluation of MRD cannot be routinely performed at present in our country. Evaluating T-ALL MRD by flowcytometry has challenges, and PCR is the preferred choice of MRD monitoring in T-ALL.

TREATMENT

Treatment of newly diagnosed BCP-ALL

The principles of the newly diagnosed BCP-ALL treatment are:

ALL treatment in children is based on the principle of stratification based on the prognostic factors: number of leukocytes at onset, age, ploidy highlighted by karyotyping, the presence of molecular genetic changes that characterize blasts (specific translocations with molecular transcripts), immunophenotype, response to therapy. (6, 7, 11, 12)

Therapy is dependent upon the protocol used and at the moment consists of the following elements: induction 5 weeks + early intensification 4 weeks; consolidation (extracompartmental therapy) 8 weeks; reinduction 7 weeks, maintenance up to a total of 2 years from diagnosis. (2, 6, 10, 12)

The ALL treatment with B and T-ALL precursors newly diagnosed in children will follow the recommendations of the ALL IC-BFM 2009 protocol, a protocol applicable in our country at present in all onco-hematology centres and considered as the "best available treatment". (9) The treatment will be applied according to the stratification of patients into risk groups, using the following criteria:

- **Standard Risk Group (SR):**

-blasts on day 8 <1,000/mm^3 in PB and
- age at diagnosis between 1-6 years old and
- onset leukocytes <20,000/m^3 and
-FC MRD <0.1% or M1/M2 marrow on day 15 and
-M1 marrow on day 33

- **Intermediate risk (IR) group - includes all patients who are not in the SR or HR group**
- **High risk group (HR)** - at least 1 criterion must be met:

-initial inclusion in the intermediate group (IR) and FC MRD> 10% or M3 marrow on day 15
-SR group and MRD group ≥10% on day 15
-blasts on day 8 ≥ 1,000/mm^3
-M2/M3 marrow on day 33
-t(9; 22) [BCR-ABL] or t(4; 11) [MLL-AF4]
-hypodiploidy ≤ 45 chromosomes

Chemotherapy is performed according to the risk group of the ALL-IC-BFM 2009 protocol (9)

- **Induction** (64 days of treatment) consists of protocol I with the 2 phases, IA (I'A for SR) and IB for all patients.

- Protocol IA (days 1-33)

- Protocol I'A is intended for the SR group and, compared to protocol IA, it has only two VCR + DNR administrations.

- Protocol IB (early intensification): days 36-64

- **Consolidation** (56 days of treatment) consists of the protocol mM for the SR and IR group with BCP-ALL and the protocol M for patients with T-ALL (SR or IR). For the patients in the IR group with BCP-ALL the protocol provided a randomization (mM vs M). Patients in the HR group will follow the consolidation blocks, 2 x (HR1'- HR2'- HR3').

- **Reinduction** (49 days of treatment) consists of Protocol II.

- **Maintenance** will be performed starting 2 weeks after the completion of the protocol II for all patients with BCP-ALL or T-ALL except for patients in the HR group undergoing an allogeneic HCT if they have an HLA-compatible family donor. The total duration of treatment in ALL patients who do not have HCT is 104 weeks after diagnosis. Prophylaxis of CNS involvement will be done by 4 weekly administrations of intrathecal MTX for BCP-ALL and CNS 1/2 status and by 6 intrathecal administrations for T-ALL with leukocytes <100,000/mm^3.

- **Radiotherapy (RT)** (3, 7, 9)

-Prophylaxis RT of the CNS is addressed to patients in the High risk group and T-ALL with leukocytes≥100,000/mm.

-Therapeutic RT of the CNS is addressed to all patients with CNS involvement.

- **Hematopoietic stem cell transplantation (HSCT)**

It is indicated in the first complete remission only in case of an increased risk of relapse, if there is a related HLA-compatible donor or, under certain conditions, according to the protocols, even unrelated donor and it is performed within 3-4 months after obtaining the remission.(5) (Table 4)

Table 4. Indications for hematopoietic stem cell transplantation (according to the protocol ALL IC-BFM 2009) (9)

CRITERION		**HSCT INDICATION with related donor**
non-remission on day 33		yes
ALL with PPR	+ T-ALL	yes
ALL with PPR	+ pro-B ALL	yes
ALL with PPR	+ leukocytes > 100,000/mm^3	yes
ALL with PPR	+ t(9;22)	yes
ALL with PPR	+ t(4;11)	yes
ALL with PGR	+ t(9;22)	yes
HR Group	+ M3 marrow on day 15	yes

Abbreviations: PGR, prednisone good response; PPR, prednisone poor response

Other applicable protocols for the treatment of newly diagnosed BCP-ALL are: ALL IC-BFM 2002, AIEOP-BFM ALL 2009, DCOG-ALL10, UKALL 2011

Treatment of mature B-ALL

Mature B-ALL represents 1-2% of all cases of ALL in children. The cells have L3 type morphology in the FAB classification, immunophenotypic expressing surface immunoglobulins. The treatment is identical to that of Burkitt's lymphoma. (2, 7, 13)

Ph+ ALL treatment

The incidence of Ph+ ALL is between 3-5%. Although the presence of t(9; 22) / BCR-ABL1 is considered an unfavourable prognostic factor, with indication of HSCT in the first complete remission, the introduction of tyrosine kinase inhibitors (TKI) along with chemotherapy treatment has considerably improved the prognosis.

The studies of the European consortium EsPhALL, and also of the COG have shown that most patients with Ph+ ALL can be effectively treated with the combination of TKI plus chemotherapy, without the need for HSCT. (7, 13) The international study EsPhALL2017/COG is currently underway, and it aims at optimizing the prognosis under the combination therapy TKI + chemotherapy/HSCT by trying to reduce treatment-related toxicity without negative impact on the relapse rate. The treatment is done according to the risk group.

• **Induction**

- protocol I (phase IA) + initiation of IMATINIB starting with day 15, after MRD evaluation, and continuing throughout the chemotherapy period as follows:

- Early intensification (phase IB) + IMATINIB (until day 28 of phase IB)

• **Consolidation** with blocks HR1, HR2, HR3 + IMATINIB

• **Reinduction** (protocol II) + IMATINIB

• **Interim maintenance** with 6-MP and oral MTX + IMATINIB + 18 Gy cranial radiation therapy

• **Second reinduction** (protocol II) + IMATINIB

• **Maintenance**, concomitantly with IMATINIB with a total duration of up to 104 weeks after the diagnosis.

The unfavourable risk group will undergo a HSCT (from compatible family or non-family donor, 10/10 or 9/10, or haploidentical donor) after the consolidation blocks. In contrast, the published data to date show that patients in the favourable risk group can be treated according to the standard chemotherapy arm without requiring HSCT. (14, 15)

ALL treatment in infants (0-1 year)

The prognosis of infants with ALL is pessimistic compared to ALL in children over 1 year. This is due to genetic factors, especially KMT2A rearrangements (MLL in the old classification). The partner genes involved in gene rearrangements together with KMT2A in ALL in infants are: AF4, ENL, AF9, AF10. These rearrangements are found in 93% of infants with ALL. In contrast, the wild-type KMT2A (MLL) gene, present in approximately 20% of infants with ALL, is associated with a better prognosis. (16, 17). In Europe, the treatment of ALL in infants is carried out according to the INTERFANT 06 protocol (18) as follows: (18)

Patients are stratified based on the presence of a wild-type MLL gene (germline MLL) or of a MLL rearrangement at diagnosis, on the age at diagnosis, on the response to PRD, and leukocyte count.

Risk groups:

-LR group (low risk): all patients with germline MLL, including those with prednisone good response

-HR group (high risk): patients with MLL rearrangement + age <6 months + (leukocytes> 300,000/mm^3 or prednisone poor response).

-The MR group includes patients who are neither LR nor HR.

Treatment:

-LR group: induction, protocol 1B, MARMA, OCTADAD, maintenance up to 104 weeks.

-MR and HR group: same as for LR group with the mention that patients with MRD>10^{-4} before the OCTADAD block will undergo HSCT after the MARMA block or during the OCTADAD block, but not later than 8 months after the diagnosis, if they are in complete remission. The conditioning regimen will be of the BU-Flu-TT type.

Treatment of ALL relapse

Currently, about 15-20% of patients have a recurrence of the disease. With the help of intensive chemotherapy followed by an allogeneic HCT in patients at high risk, 30-50% of relapsed patients can be cured. (19) An attempt will be made to obtain a new remission of the disease by means of a new induction therapy. Patients with unfavourable prognostic factors (early/very early bone marrow relapse, T-ALL or those with MRD+ after induction) will also require a HSCT. In case of CNS / testicular relapse, radiotherapy of these involvements will be performed (5, 7, 20).

Definitions of ALL relapse are dependent on the timing of the recurrence (according to the ALL-Rez BFM 2002 protocol):

-Late relapse: ≥6 months after completion of the first-line therapy

-Early relapse: ≥18 months after the first diagnosis and <6 months after completion of the first-line therapy

-Very early relapse: <18 months after the first diagnosis and <6 months after the completion of the first-line therapy

Table 5. Definitions of relapse in ALL depending on the site of the recurrence (according to the ALL-Rez BFM 2002 protocol)

% blasts marrow		**<5%**	**5% - 25%**	**≥25%**
Extramedullary involvement	NO	No relapse	Needs reassessment	Isolated bone marrow relapse
	YES	Isolated extramedullary relapse	Combined bone marrow relapse	

The best available treatment protocols recommended and applicable in Romania for the treatment of ALL relapse are:

BFM ALL-Rez Protocol 2002 (21)

The study demonstrated the superiority of using the II-IDA protocol for the consolidation phase compared to the R2 - R1 - R2 blocks. (22)

The risk groups S1 to S4 are defined considering the time point and the site of the relapse, as follows:

- Treatment group S1: patients with late (> 6 months after completion of primary therapy), isolated extramedullary relapse.

- Treatment group S2: patients with early (>18 months after primary diagnosis and <6 months after completion of primary therapy) or very early (<18 months after primary diagnosis and <6 months after completion of primary therapy) isolated extramedullary relapse, late bone marrow relapse of non-T ALL or patients with combined early or late relapse of non-T ALL.

- Treatment group S3: patients with early isolated bone marrow relapse of a non-T ALL.

- Treatment group S4: patients with very early combined or isolated bone marrow relapse, patients with bone marrow relapse of T-ALL.

Therefore, the following therapeutic sequences of treatment blocks are recommended:

- S1 Group: F1 - F2 - Prot II-IDA - R1 - R2 - R1 - maintenance

- S2 Group (MRD negative after block F2): F1 - F2 - Prot II-IDA - R1 - R2 - R1 - R2 - R1-maintenance (with VP-16 pulse blocks)

- S2 Group (MRD positive after block F2): F1 - F2 - Prot II-IDA - R1 - R2 - allogeneic bone marrow transplant

- S3/S4 Groups: F1 - F2 - Prot II-IDA - allogeneic bone marrow transplant

Patients with CNS or testicular involvement benefit from local radiation therapy.

Other protocols used in Europe are the IntReALL SR 2010 and IntReALL HR 2010 protocols.

The ALL-IC study group is currently conducting the Childhood ALL 1st relapse guidance study. ALL-IC study group, 2016 "ALL-IC REL 2016".

Other therapeutic options for relapsed/refractory BCP-ALL:

- BLINATUMOMAB (BLINCYTO®) is a bispecific monoclonal antibody for the binding of CD3 + T lymphocytes directed against the CD19 antigen expressed by the BCP-ALL blasts. It has been shown to be superior to chemotherapy in various studies both in EFS, OS and in the response rate and in the eradication of minimal residual disease. The potential severe and characteristic side effects such as the cytokine release syndrome (CRS) are to be taken note of. BLINATUMOMAB is indicated as monotherapy for the treatment of adolescents and children that are at least 1 year old with BCP-ALL and Philadelphia chromosome negative, CD19 positive, refractory or relapsed after at least two previous treatments or relapsed after allogenic HCT. (7,11,19)

- CAR T-CELL IMMUNOTHERAPY (KYMRIAH®) is an immunocellular therapy containing tisagenlecleucel, autologous T-cells, genetically modified ex vivo, using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). CAR T-cell treatment usually serves as a bridge to HCT. The procedure consists of the genetic manipulation of one's own T lymphocytes to generate a response to an antigen expressed by lymphoblasts (CD19). Kymriah is indicated in paediatric and young adult patients up to 25 years of age with refractory BCP-ALL, post-transplant relapse, second relapse or subsequent relapses. Among the side effects there are CRS as well as macrophage activation syndrome. (7, 11, 19)

- CLOFARABINE is indicated in paediatric patients with refractory / relapsed ALL. It can be used alone or in combination with cyclophosphamide and etoposide or with cytarabine. These new and targeted treatment options put a new and increased focus and awareness on severe side effects.(7)

Other therapeutic options for relapsed/refractory T-ALL

NELARABINE is indicated for the treatment of patients with acute T-cell lymphoblastic leukaemia (T-ALL) and T-lymphoblastic lymphoma (T-LBL) who have not responded or have relapsed following treatment with at least two lines of chemotherapy.

Supportive treatment during chemotherapy

- transfusions of blood and/or plasma derivatives;
- infection prophylaxis, curative treatment of infections/sepsis;
- ensuring proper nutrition (enteral or parenteral feeding);
- symptomatic therapy (against pain, antiemetic);
- care of mucous membranes (prophylaxis and treatment of mucositis) and skin;
- ensuring central venous access (central venous catheter or implantable port);
- psycho-social support.

Follow-up of the disease and long-term side effects

The follow-up of the disease at short intervals is necessary up to 5 years after diagnosis, then at increasing intervals, through clinical and biological re-evaluations. After 5 years, the evaluation is done annually. It is necessary to monitor long-term side effects until the age of 18 in a pediatric medical service (up to 25 years in some centers), so that later on these patients could be registered in the records of hematology centers for adults. (5, 7)

The following potential side effects will be monitored:

- neurological (development of CNS and cognition, stroke, sensory, coordination or motor deficits); CT / MRI evaluations and neurocognitive tests are recommended;
- endocrinological (thyroid, obesity, DM, gonadal dysfunction, growth and reproductive disorders);
- cardiac (mainly due to the use of anthracyclines);
- immunological (increase in the rate of infections in survivors);
- secondary cancers (brain tumors, hematological malignancies).

Recommendations

- ALL is the most common malignancy in children
- Specific laboratory investigations will completely characterize the ALL form, for correct assessment of the risk group, with specific therapy
- Treatment of BCP-ALL and T-ALL will follow the recommendations of the ALL IC-BFM 2009 protocol, currently applicable in our country in all onco-hematology centres and considered as the "best available treatment"
- Ph+ ALL has an unfavourable prognosis, with indication of HCT in the first complete remission for the unfavourable risk group but the use of TKI has considerably improved the prognosis, and HCT might therefore be avoided in the lower risk groups.
- ALL treatment in infants is performed according to the INTERFANT 06 protocol
- For the treatment of ALL relapse, the ALL-Rez BFM 2002 protocol is recommended and applicable in Romania
- New and promising therapeutic strategies and approaches are being studied in order to treat ALL relapses.

BIBLIOGRAPHY

1. Gutierrez A, Silverman LB. Chapter Acute Lymphoblastic Leukemia. In: Stuart H. Orkin, David E. Fisher, A. Thomas Look, Samuel E. Lux, IV, David Ginsburg, David G. Nathan Nathan and Oski's Hematology of Infancy and Childhood, Elsevier, Eighth Edition 2015; 1527-1554

2. Schrappe M, Harbott J, Riehm H. Akute lymphoblastische Leukamien. In: Gadner H, Gaedicke G, Niemeyer Ch, Ritter J. Padiatrische Hamatologie und Onkologie. Springer 2006; 656-689

3. Leukemias. In: Lanzkowsky Philip, Jeffrey Lipton, Jonathan Fish. Manual of pediatric hematology and oncology, Elsevier, Fifth Edition, 2011; 518-549

4. Dworzak M, Buldini B, Gaipa G, Ratei R, Hrusak O, Luria D, Rosenthal E, Bourquin J- P, Sartor M, Schumich A, Karawajew L, Mejstrikova E, Maglia O, Mann G, Ludwig W- D, Biondi A, Schrappe M, Basso G. AIEOP-BFM Consensus Guidelines 2016 for Flow Cytometric Immunophenotyping of Pediatric Acute Lymphoblastic Leukemia. Cytometry B Clin Cytom.2018 Jan;94(1):82-93

5. Escherich G, Schrappe M, Creutzig U. Akute lymphoblastische Leukamie – ALL – im Kindesalter. In: AWMF online. Das Portal der wissenschaftlichen Medizin. GPOH Ped Guidelines. S1-Leitlinie 025/014: Akute lymphoblastische- (ALL) Leukämie im Kindesalter

6. Roganovic J. Acute Lymphoblastic Leukemia in Children. Chapter 2, 2013. https://www.intechopen.com/books/leukemia/acute-lymphoblastic-leukemia

7. NCCN Guidelines Version 2.2020 Pediatric Acute Lymphoblastic Leukemia. *https://www.nccn.org/professionals/physician_gls/pdf/ped-all.pdf*

8. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau M, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20): 2391-2405

9. ALL IC-BFM 2009. A Randomized Trial of the I-BFM-SG for the Management of Childhood non-B Acute Lymphoblastic Leukemia

10. Jan Stary, Martin Zimmermann, Myriam Campbell, Luis Castillo, Eduardo Dibar, Svetlana Donska, Alejandro Gonzalez, Shai Izraeli, Dragana Janic, Janez Jazbec, Josip Konja, Emilia Kaiserova, Jerzy Kowalczyk, Gabor Kovacs, Chi-Kong Li, Edina Magyarosy, Alexander Popa, Batia Stark, Yahia Jabali, Jan Trka, Ondrej Hrusak, Hansjorg Riehm, Giuseppe Masera, and Martin Schrappe. Intensive Chemotherapy for Childhood Acute Lymphoblastic Leukemia: Results of the Randomized Intercontinental Trial ALL IC-BFM 2002. J Clin Oncol 2014;32:174-184,

11. Locatelli F, Schrappe M, Bernardo ME, Rutella S. How I treat relapsed childhood acute lymphoblastic leukemia. Blood 2012;120(14):2807-2816

12. Cooper SL, Brown PA. Treatment of Pediatric Acute Lymphoblastic Leukemia. Pediatr Clin North Am. 2015 February; 62(1): 61–73

13. Horton TM, Steuber C. Overview of the treatment of acute lymphoblastic leukemia/ lymphoma in children and adolescents. Literature review current through: Jan 2020. | UpToDate

14. EsPhALL. An open-label study to evaluate the safety and efficacy of IMATINIB witH chemotherapy in pediatric patients with Ph+/BCR-ABL+ acute lymphoblastic leukemia (Ph+ALL). https://www.skion.nl/workspace/uploads/EsPhALL_Amendment-2_01102015_final_1.pdf

15. International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones. EsPhALL2017/COGAALL1631.https://www.skion.nl/voorprofessionals/behandelrichtlijnen/protocollen/3355/esphall2017-cogaall1631

16. Brown P, Pieters R, Biondi A. How I treat Infant Leukemia. Blood 2019;133(3):205-214

17. Van der Linden MH, JudithM.Boer, Schneider P, Willekes M, Seslija L, De Lorenzo P, Valsecchi MG, Cazzaniga G, Biondi A, den Boer ML, Pieters R, Stam RW. Clinical and molecular genetic characterization of wild-type MLL infant acute lymphoblastic leukemia identifies few recurrent abnormalities. Haematologica 2016;101:e95-e98

18. INTERFANT-06. International collaborative treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukemia. https://www.skion.nl/workspace/uploads/Interfant-06_version-17_6april2017.pdf

19. AIEOP-BFM ALL 2017. International collaborative treatment protocol for children and adolescents with acute lymphoblastic leukemia. A randomized phase III study conducted by the AIEOP-BFM study group. Protocol version 1.5. https://clinicaltrials.gov/ct2/show/NCT03643276

20.Henze G, v.Stackelberg A, Eckert C. ALL-REZ BFM – The Consecutive Trials for Children with Relapsed Acute Lymphoblastic Leukemia. Klin Padiatr 2013; 225 (Suppl. 1): S73–S78

21. ALL-REZ BFM 2002. Protocol for the Treatment of Children with Relapsed Acute Lymphoblastic Leukemia . Treatment Optimization Study using Chemotherapy and Radiotherapy by the Society of Pediatric Oncology and Hematology (GOPH).https://clinicaltrials.gov/ct2/show/NCT00114348

22. ALL-REZ BFM Beobachtungsstudie und Biobank für Rezidive einer akuten lymphoblastischen Leukämie im Kindes – und Jugendalter. Fassung vom 20.09.2012. https://www.kinderkrebsinfo.de/sites/kinderkrebsinfo/content/e1676/e9032/e68518/e5358/download122069/ALLREZ_BFM_Beobachtungsstudie_Protokoll_ger.pdf

8.1.2 ACUTE NONLYMPHOBLASTIC LEUKEMIA

There are also rare cases of biphenotypic leukaemia. Acute myeloid leukaemia (AML) is diagnosed in the presence of at least 20% myeloblasts in the bone marrow. (1, 2, 3)

Epidemiology, Etiology

Acute leukaemia is the most common malignancy in children. The overall incidence is about 45 new cases/million under the age of 16, with a peak in the period of 2-5 years old. According to the National Register of Cancer Patients, approximately 300 new cases of childhood cancer are diagnosed in Romania each year, 31% being represented by leukaemias. (4) A percentage of 15-20% of leukemias are represented by AML. The disease occurs especially in very young children.

Causes: idiopathic, secondary to other haematological conditions, exposure to chemicals, drugs, ionizing radiation, parental consumption of alcohol, tobacco and drugs, association with some viral infections, hereditary genetic causes (e.g. Down, Bloom, Schwachman, Klinefelter syndromes; neurofibromatosis , ataxia-telangiectasia, family aggregation). (5-6)

Diagnosis

The correct diagnosis should include a careful medical history and clinical examination. (7-8)

General signs, lasting a few days - weeks, rarely months:

- fever, asthenia, fatigue, weight loss

Signs caused by the bone marrow infiltration syndrome

- anemia: pallor, tachycardia, systolic murmur
- neutropenia: fever, viral, bacterial or fungal infections (associated with a variable number of leukocytes)
- thrombocytopenia: bleeding in the mucous membranes, petechiae, ecchymosis

Signs caused by the extramedullary infiltration syndrome:

- organomegaly: hepatomegaly, splenomegaly, isolated/confluent lymphadenopathy
- cardiorespiratory: enlarged mediastinum, pleurisy, pulmonary infiltrates, dyspnoea, heart involvement
- urogenital: renal involvement, priapism, testicular edema
- other signs: gingival hypertrophy, neurological signs, skin lesions, chloromas, bone pain (rare in AML), etc.

Paraclinical examinations

Type of investigation	Moment of investigation
- blood count	- daily during treatment; 1/week or 1/month in maintenance
- peripheral blood smear	- at onset; 1/week during treatment until the blasts disappear; 1/month in maintenance
-reticulocyte count, IPF	- at onset; as indicated
- group, Rh, phenotype	- at onset
- transaminases, total and indirect bilirubin, LDH, creatinine, urea, uric acid, alkaline	- at onset; 2-3 times/week during treatment or more often, as indicated; 1/month in

phosphatase, blood glucose, sideremia, ionogram (Na, K, Ca, Cl, P), CRP, ESR, procalcitonin	maintenance or more often, as indicated
-acid-base balance	- as indicated
-hemostasis: APTT, fibrinogen, PDF, D-dimer test, PT, AP, INR, etc.	- at onset; 2-3 times/week or more often, as indicated; 1/month in maintenance
-HLA typing - in the patient and in potential stem cell donors	- as indicated
-bone marrow -morphological examination / cytochemistry (Sudan black, peroxidase) -immunophenotyping / flow cytometry: HLA-DR, CD2, CD7, CD9, CD11b, CD11c, CD13, CD14, CD15, CD19, CD34, CD33, CD41, CD56, CD61, CD64, CD65, CD117, MPO (9) -cytogenetics / FISH ratio	- at onset; repeated according to the evaluations presented in the treatment protocol used - at onset; repeated according to the evaluations presented in the treatment protocol (MRD monitoring) - at onset; repeated according to the evaluations presented in the treatment protocol used, if an initial marker has been identified
-osteo-medullary biopsy	-in case of dry tap or inconclusive puncture
-molecular biology: -mutations NPM1, FLT3 (-ITD), c-KIT, RAS, BAALC, AFIq, etc. -exceptionally, other molecular markers may be indicated in individual cases to confirm or refute an inconclusive cytogenetic examination -next generation sequencing (not implemented in Romania)	- at onset; during treatment and maintenance, if a quantifiable initial marker has been identified (MRD monitoring)
-lumbar puncture	-according to the protocol
-imaging: -abdominal ultrasound, chest radiography -cardiac / testicular ultrasound, computed tomography, magnetic resonance imaging	- at onset - as indicated
-bacteriology:-nasal and pharyngeal exudates, digestive microbial bearing, urine culture -blood culture, stool test, urine test, Galactomannan test	- at onset; as indicated - as indicated (in a febrile episode)
-virology: Ag HBs, Ac HBs, Ac VHC, HIV, IgM and IgG EBV, IgM and IgG CMV, etc.	-at onset; as indicated
-constants: -height, weight -blood pressure, pulse, respiratory rate, oxygen saturation, diuresis	-at onset; as indicated -at onset; daily during treatment; at indicated
interdisciplinary examinations: ophthalmological, ENT, cardiological, neurological, etc.	-at onset
In case of relapse, repeat the diagnosis investigation protocol.	

Differential diagnosis:
-acute lymphoblastic leukaemia
-chronic granulocytic leukaemia / chronic juvenile myelomonocytic leukaemia
-leukemoid reactions
-infections
-aplastic anemia
-immune thrombocytopenia
-medullary infiltration of other malignancies
-juvenile rheumatoid arthritis (10)

Classification

The WHO classification takes into account the morphological, cytogenetic and molecular biology criteria. However, the FAB (French-American-British) morphological classification is still used, especially in cases where cytogenetic/molecular examinations could not be performed. (5, 11)

• WHO 2016 classification
^ AML with genetic abnormalities -t(8,21) (q22, q22.1), RUNX1-RUNX1T1
- inv (16) (p13,1q22) or t(16,16) (p13.1, q22), CBFB-MYH11
- PML-RARA
- t(9.11) (p21.3, q23,3) MLLT3-KMT2A
- t(6.9) (p23, q34.1), DEK-NUP214
- inv (3) (q21.3, q26.2) or t(3,3) (q21.3, q26.2), GATA2, MECOM
- megakarioblastic with t (1,22) (p13.3, q13.3), RBM15-MKL1
- BCR-ABL1
- NPM1 mutated
- CEBPA with biallelic mutations
- RUNX1 mutation
^ AML with myelodysplastic changes
^ Drug-induced AML
^ AML -with minimal differentiation
- without maturation
- with maturation
- myelomonocytic
- monocytic
- pure erythroid keukaemia
- megakarioblastic
- basophilic
- panmyelosis with myelofibrosis
^ Myeloid sarcoma
^ Myeloid proliferations related to Down syndrome - transient abnormal myelopoiesis
-AML associated with Down syndrome

• FAB classification

- M0 = cytologically unidentifiable; belonging to the myeloid line, it can be established only by immunophenotypic analysis
- M1 = myeloblastic without differentiation
- M2 = myeloblastic with differentiation (over 10% maturing granulocyte component)
- M3 = promyelocytic
- M3v = promyelocytic, hypogranular variant

- M4 = myelomonoblastic: monocyte component (monoblasts- monocytes)> 20% in the bone marrow

- M4Eo = variant with eosinophilia

- M5 = monoblastic: monocyte component> 80%

- M5a = monoblastic: monoblasts> 80% of the monocyte component

- M5b = monoblastic with differentiation: monoblasts <80% of the monocyte component

- M6 = acute erythroleukemia: erythroblasts represent> 50% of medullary cells; myeloblasts> 30% of non-erythroid medullary cells

- M7 = megakaryoblastic AL (or acute myelofibrosis); the megakaryoblasts can only be accurately identified by highlighting immunological or ultrastructural platelet markers

FAB Subtype of AML	Immunologic Surface Marker										
	HLA-DR	CD11b	CD13	CD14	CD15	CD33	CD34	Glycophorin	CD41	CD42	CD61
M1/M2	+				+	+	+				
M3/M3V		+	+		+	+	+				
M4/M5	+	+	+	+	+	+	+				
M6	+		+			+	+	+			
M7	+		+			+	+		+	+	+
M0			+			+	+				

Risk groups, prognostic factors

Patients are included in temporary risk groups based on the characteristics from the diagnosis and then in definitive risk groups according to the response to treatment, assessed at the end of the induction. This prevents over- or under-treatment of patients. (12)

- Standard risk group: AML3, AML in Down syndrome, AML1, 2, 4Eo if the assessment on day 15 shows less than 5% blasts.

- High risk group: AML4, 5, 6, 7 and AML1, 2, 4Eo if at the assessment on day 15 there is over 5% blasts, any patient with FLT3-ITD.

Prognostic factors:

- Favourable: the age under 1 year, t (15.17), inv 16, t(8.21), t(1.11), Down syndrome

- Unfavourable: (-7, -5, t (6.9), complex karyotype, AML after myelodysplastic syndrome, persistent/refractory disease after induction).

Supportive Treatment

• During the chemotherapy and until immune recovery (after 6-12 months), it is recommended to stop vaccination.

• General hygienic-dietary measures

- Isolation
- Avoid placing patients with contagious infections in the same ward as patients with AML.
- Maintain personal hygiene - training of patients and staff
- Stop the tooth brushing. Replacement with mouthwashes and gargles with antiseptic solutions
- Avoid food brought from outside the section. Avoid raw products.
- Installation of a peripheral venous approach, subsequently of a central venous catheter (two lumens)

• Transfusions

• Antibiotics (liberal use of broad spectrum antibiotics and also antifungal treatment in case of infections)

• Growth factors NOT routinely recommended! The dose is 5-10 μg/kg/day, they will be added if the used protocol specifies this (as in the FLAG regimen)

• Supportive, symptomatic

De novo AML treatment protocol

a) AML-BFM 2004

It is the protocol of the German working group and is widely adopted in Romania. (12-13)

• Cytoreductive pre-phase: can be used in patients with more than $50x10^9$ leukocytes/L at diagnosis or with significant organomegaly, with a maximum duration of 7 days

• Induction: AIE regimen

• Only for high-risk patients: HAM regimen

• Consolidation I: AI regimen

• Consolidation II: haM regimen

• Intensification: HAE regimen (in patients without stem cell transplantation)

- Its start at 2-4 weeks after the haM regimen, if the patient's condition allows it

NB1: high doses of ARA-C are adjusted according to the age of the patient

NB2: the rest of the cytostatic agents are adjusted in patients less than 1 year of age or smaller than 10 kg

NB3: the dose of ARA-C administered intrathecally is adjusted according to age; In case of CNS involvement at onset, it should be administered weekly until CSF is negative, at least 3 times

• Radiotherapy

- in Romania, the radiotherapy is used only in selected cases, after consulting the committee of therapeutic indications. The current recommendations are to reduce as much as possible the indications for radiotherapy in children under 3 years old, due to the late effects on the somatic and intellectual development of the children.

• Maintenance

- It starts 4 weeks after the HAE regimen, if the patient's condition allows it (concomitantly with

CNS radiotherapy); it lasts 1 year

https://clinicaltrials.gov/ct2/show/NCT00111345

b) *AIEOP LAM 2002/01-02*

It is the protocol of the Italian working group, it uses the same drugs as the previous protocol, but in other doses and other combinations, it does not apply to patients with Down syndrome, with LAM3, secondary AML. (14)

https://pdfs.semanticscholar.org/4317/26aa229805ff9a4c5aad9444d4cebfb3cfc1.pdf

c) *"Guideline for acute myeloid leukaemia in children and young adults"*

It was published in 2016 by the English group. (15) https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/Acute_Myeloid_Leukaemia_January_2016_FINAL.pdf

Acute Promyelocytic Leukemia (APL) protocol

a) *AML-BFM 2004*

It follows the standard arm to which all-oral trans-retinoic acid (ATRA) is added. (12, 13) https://clinicaltrials.gov/ct2/show/NCT00111345

b) *PETHEMA LPA 2005*

It is a protocol for adults, but can be adapted to children; it derives from the AIDA protocol, the changes occurring especially in the high-risk group. (16)

It contains induction, several consolidation courses and the maintenance period, depending on the risk group in which the patient was placed in based on the blood count at the onset. Idarubicin, Mitoxantron, Cytarabine and Purinethol are used in low doses, in addition to oral ATRA. (17)

www.hovon.nl›trials›trials-by-type›aml

c) *ICC APL STUDY 01*

It is the study of the AIEOP Italian group, derived from AIDA and intended for paediatric patients, being similar to the previous one (18).

https://www.skion.nl/workspace/uploads/protocollo-v_01_del_14-02-082_1.pdf

Refractory/relapse AML

- Relapsed AML 2001/01

It contains two induction courses and two consolidation courses, consisting of Fludarabine, ARA-C, VP16, 6-TG, ± Liposomal Dauno and intrathecal chemotherapy. (18)

- Refractory/relapsed LAP

In the case of LAP r/r, arsenic trioxide (ATO) can be added alone or in combination with other cytostatic agents (19). ATO is not available in Romania.

Ongoing studies and clinical trials

There are a number of ongoing studies aimed at increasing the survival of patients with AML, reducing the risk of relapse or refractory disease, and minimizing the drug toxicity. (20)

- Paediatric Relapsed AML 2010/01, initiated in 2013 by the German Society of Paediatric Haematology and Oncology
- DB AML 01, initiated in 2010 by the Dutch-Belgian group, based on the NOPHO AML 2004 study
- NOPHO DBH AML 2012, started in 2013
- AIEOP LAM 2013, started in 2015
- ICC APL STUDY 02 for acute promyelocytic leukaemia.

Also, a series of studies are undergoing for AML r/r, which use new agents, these being associated with chemotherapy: Quizartinib, Volasertib, Gemtuzumab ozogamicin, Clofarabine, CPX-351, Midostaurin, Sorafenib, Ivosidenib, Enaseidenib, Gilteritinib, Pirarubicin (in patients with Down syndrome in order to reduce the cardiotoxicity caused by classical anthracyclines), infusion with natural killer cells in consolidation, etc. (20)

Hematopoietic stem cell transplantation

Allogeneic stem cell transplantation: It is indicated:

- in the first complete remission, as soon as possible after obtaining it, in all patients <60 years, with a compatible donor, with the following exceptions:
  - AML with favourable karyotype / molecular genetics:
  - t(8; 21) (q22; q22) - AML-ETO
  - inv16 (p13.1q22) or t (16; 16) (p13.1q22) - CBFB-MYH11
  - t(15; 17) (q22; q12) - PML-RARA
  - Mutant CEBPA
  - NPM1 mutant in the absence of association with FLT3-ITD
- relapsed AML (in the second complete remission) and in the cases with molecular karyotype-genetics listed above

Autologous stem cell transplantation: there are no data to show any benefits in AML.

Particular forms of AML

- AML in Down syndrome

It is found in many children between 0-4 years diagnosed with Down syndrome, being usually preceded by cytopenias. The risk of developing AML in patients with Down syndrome is 14-20 times higher than in the general population. The prognosis is very good, exceeding 85% overall survival (5). The cytostatic treatment is adapted, using lower doses of chemotherapeutics, indications broadly specified in the BFM AML protocol (12).

Transient myeloproliferative disorder in children with Down syndrome usually goes into remission after 10 days. If treatment is required, use low doses of ARA-C 0.5-1mg/kg/day for 4 -7 consecutive days.

- Secondary AML

It is the most common malignancy that appears after the treatment of other hemato-oncological diseases (for example: myelodysplastic syndrome, solid tumours), with an unfavourable prognosis. Different treatments can be tried (ADxE and HAM, Relapsed AML 2001/01 protocol), then stem cell transplantation.

Complications of the disease

- Acute complications

Examples: leukostasis (dyspnea to acute respiratory failure, neurological manifestations), tumor lysis syndrome, nausea, vomiting, mucositis, alopecia, neutropenia, anemia, thrombocytopenia, fever, infections, electrolyte disorders, bleeding/ thrombosis, allergic reactions, blood transfusion accidents, reversible posterior encephalopathy syndrome, typhlitis, pancreatitis, veno-occlusive disease, etc.

Complications that occur during the chemotherapy are managed according to the national/local procedures in force.

If the patient is in serious condition and he/she cannot be stabilized at the ward, it is required to transfer the patient to an intensive care unit.

- Specific complications in AML3, as follows:

a) Disseminated intravascular coagulation / hyperfibrinolysis

Clinical: cutaneous-mucous haemorrhages, but also deep haemorrhages (hematomas, internal haemorrhages), sometimes associated with thrombosis

Paraclinical: thrombocytopenia, prolongation of TQ / APTT, decrease in fibrinogen, increase in D-dimers. Treatment: platelet and plasma transfusion, prompt initiation of ATRA/ATO treatment

b) Differentiation syndrome (DS)

It is also known as ATRA syndrome, it can occur in 10-25% of patients treated with ATRA and/or ATO. It consists of acute respiratory distress, with dyspnea, cough, micronodular pulmonary infiltrates, pleural effusion. DS coincides with the beginning of the process of maturation (differentiation) of leukemic promyelocytes and it is sometimes associated with an explosive increase in the number of leukocytes.

Clinical: dyspnea, cough, hemoptysis, oedema, respiratory failure (occurring 7-12 days after starting ATRA/ATO)

Imaging: interstitial pulmonary infiltrates, pleurisy, pericarditis

Hematologic: sometimes a rapid increase in the number of leukocytes

Treatment: - adding IDA at the onset of ATRA decreases the risk of DS

- Dexamethasone 0.5-2mg/kg at the first respiratory symptoms suggestive of DS
- chemotherapy with Hydroxyurea in case of hyperleukocytosis
- diuretics, if there is no hypotension

- Chronic complications

Examples: cardiotoxicity, neurological, endocrine, gastrointestinal, musculoskeletal, pulmonary, ENT, ophthalmic, fertility, psychological and psychiatric disorders, secondary malignancies, posttransplant complications of stem cells.

AML survivors need to be monitored for a long time in order to be able to diagnose these possible late complications early on. The collaboration of the paediatric hemato-oncologist with the doctor of the adult patients, in order to register the patient after the age of 18, is mandatory.

Evolution, prognosis

- overall survival = 70%
- event-free survival = 50% (21)
- complete remission (80-85% of patients): asymptomatic patient, without lymphadenopathy / organomegaly, neutrophils >1,5x10^9/L, platelets >100x10^9/L, haemoglobin > 10g/dl, without peripheral blood blasts, bone marrow blasts <5%, without cytogenetic or molecular abnormalities
- risk of relapse (30-40% of patients): after a complete documented remission, recurrence of at least 10% medullary blasts or evidence of leukemic infiltration at other sites
- early relapse: occurred in the first year after the initial diagnosis
- late relapse: occurred after the first year after the initial diagnosis
- refractory disease (non-responder patient): over 20% medullary blasts after 1-2 courses of chemotherapy and/or documentation of the presence of leukemic cells in other sites after 2 courses of chemotherapy.

Recommendations

- Use of the protocol of the German BFM group in the case of acute myeloblastic leukaemia at onset, except for the promyelocytic form.
- Use of the PETHEMA or AML-BFM 2004 protocol in case of acute promyelocytic leukaemia
- Use of the RELAPSED AML protocol in case of relapsed/refractory acute myeloblastic leukaemia
- Referral of patients with an indication for stem cell transplantation as soon as possible after obtaining complete remission to a bone marrow transplant centre.

Bibliography

1. Lanzkowsky P. Acute myeloid leukemia. In Manual of Pediatric Hematology and Oncology. Elsevier. 2011; 550-562

2. Childhood Leukemia, a Practical Handbook (editors Reaman GH, Smith FO). Springer. 2011

3. Clark JJ, Berman JN, Look AT. Myeloid leukemia, myelodysplasia and myeloproliferative disease in children. In Oncology in Infancy and Childhood (editors Orkin SH, Fisher DE, Look AT, Lux SE, Ginsburg D, Nathan DG). Saunders Elsevier. 2009; 332-374

4. Registrul Național al Cancerelor la Copil. https://www.daruiestearipi.ro/wp-content/uploads/2019/04/Raport_RNCCR_-1-feb-2019.pdf

5. Derwich K, Mitkowshi D, Skalska-Sadowska J. Acute myeloid leukemia in pediatric patients: a review about current diagnostic and treatment approaches. In Myeloid leukemia (editor Lasfar A). Rutgers, USA. 2018

6. Kean LS, Arceci RJ, Woods WG. Acute myeloid leukemia. In Pediatric Hematology (editors Arceci RJ, Hann IM, Smith OP). Blackwell Publishing. 2006; 360-384

7. Creutzig U, van den Heuvel-Eibrink MM, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood. 2012; 120 (16): 3187-3205

8. Part I – Acute myeloid leukemia. In Hematologic Malignancies: Acute Leukemias (editors Estey EH, Faderl SH, Kantarjian H). Springer. 2008; 8-77

9. Buldini B, Maurer-Granofszky M, Varotto E, Dworzak MN. Flow-Cytometric Monitoring of Minimal Residual Disease in Pediatric Patients With Acute Myeloid Leukemia: Recent Advances and Future Strategies. Front Pediatr. 2019; 7: 412

10. Childhood Leukemias (editor Pui CH). Cambridge University Press. 2006

11. Basso G, Silvestrino R (coordonatori). Basi scientifiche per la definizione di linee-guida in ambito clinic per I tumori dell'eta pediatrica. 2008. http://old.iss.it/binary/lgac/cont/2008TESTO PEDIATRIAFINALE.1222954230.pdf

12. AML-BFM 2004 protocol. https://clinicaltrials.gov/ct2/show/NCT00111345

13. Rasche M, Zimmermann M, et al. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. Leukemia. 2018; 32(10): 2167–2177

14. Pession A, Masetti R, et al. Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia. Blood. 2013; 122 (2): 170-178

15. Guideline for acute myeloid leukaemia in children and young adults. Childrens Cancer and Leukaemia Group. Childhood Leukaemia Clinicians Network (CLCN), 2016. https://www.cclg.org.uk /write/MediaUploads/Member%20area/Treatment%20guidelines/Acute_Myeloid_Leukaemia_January_20 16_FINAL.pdf

16. Lo-Coco F, Avvisati G, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood. 2010; 116(17): 3171-9

17. PETHEMA LPA 2005 protocol. www.hovon.nl › trials › trials-by-type › aml

18. Creutzig U, Zimmermann M, et al. The prognostic significance of early treatment response in pediatric relapsed acute myeloid leukemia: results of the international study Relapsed AML 2001/01. Haematologica. 2014; 99(9): 1472–1478

19. ICC APL STUDY 01. https://www.skion.nl/workspace/uploads/protocollo-v_01_del_14-02-082_1.pdf

20.https://clinicaltrials.gov/

21. Im HJ. Current treatment for pediatric acute myeloid leukemia. Blood Res. 2018; 53(1): 1–2

8.1.3 CHRONIC MYELOID LEUKAEMIA

The chronic myeloid leukaemia (CML) is a malignant haematological condition characterized by the significant proliferation of hematopoietic stem cells (HSC), predominantly granulocyte series, at all stages of maturation and the presence of the Philadelphia chromosome (Ph1) and / or BCR-ABL rearrangement. Regarding its evolution, CML has 3 phases: the chronic phase, the accelerated phase and the blast phase. (1, 2)

Epidemiology

The chronic myeloid leukaemia is responsible for about 2-3% of all types of childhood leukaemia. The incidence of positive Philadelphia chromosome leukaemia in children is reported to be less than 1 in 100,000 cases and it is less common in the under-2 age group compared to other age groups. In children, the disease is characterized by the same molecular, cytogenetic, clinical and morphological characteristics as in the case of adults. More than 90% of all patients with CML have a Philadelphia chromosome. In 5-10% of the cases in which the Philadelphia chromosome is not identified by the conventional cytogenetic test, BCR-ABL rearrangement is detectable by the molecular test in half of these patients. This proves a clinical evolution similar to that in which the Philadelphia chromosome is present. (3, 4)

Symptomatology

In the chronic phase of the disease, children and adolescents show more serious symptoms compared to adults. The clinical manifestations are generally insidious, the disease being discovered by chance, during the chronic phase, with evidence of a hyperleukocytosis accompanied by a significant splenomegaly. The most common symptoms are: fatigue, asthenia, anorexia, abdominal discomfort, weight loss, excessive sweating. The clinical examination will reveal splenomegaly, hepatomegaly, pallor. (3, 4)

Some of the less common symptoms are: night sweats, acute gouty arthritis, priapism, headache, tinnitus caused by the associated hyperleukocytosis; rarely neutrophilic infiltrate in the dermis.

In patients who are in the accelerated phase or the blast phase, the main symptoms are bleeding and cutaneous and mucosal hemorrhagic syndrome, associated with lymphadenopathy, skin nodules. The symptoms and the splenomegaly progress rapidly. (3, 4)

Initial paraclinical examinations and examinations during the treatment (2)

- Mandatory investigations to establish the diagnosis:
- Complete blood count, peripheral blood smear
- Complete biochemistry: AST/ ALT, uric acid, urea, creatinine, LDH, glycemia, albumin, total protein, sideremia, total bilirubin, direct bilirubin, inflammatory markers: CRP, procalcitonin, ESR
- Coagulation tests: AP, APTT, PT, INR, fibrinogen, D-Dimer test, platelet aggregation, thromboelastogram
- Bone marrow aspiration with morphological analysis and cytogenetic examination (karyotype, FISH analysis for t (9; 22) (q34; q11) identification)
- Molecular biology tests to identify the BCR-ABL transcript
- Bone marrow biopsy - to assess the degree of fibrosis, cellularity, blastic transformation - if other investigations do not confirm the diagnosis

- Immunophenotyping test - if the patient is diagnosed in the blast phase
- Leukocyte alkaline phosphatase
- Abdominal ultrasound to measure the size of the spleen and liver
- Virology: CMV, EBV, hepatitis virus B / C, HIV, VZV
- **Recommended investigations during treatment:**
- Complete blood count, peripheral blood smear
- Complete biochemistry: AST, ALT, uric acid, urea, creatinine, LDH, glycemia, albumin, total protein, ferritin, total bilirubin, direct bilirubin, inflammatory markers: CRP, ESR
- Coagulation tests: AP, APTT, PT, INR, fibrinogen
- Abdominal ultrasound to measure the size of the spleen and liver
- **Recommended investigations to monitor the response to treatment:**
- Complete blood count, peripheral blood smear
- Complete biochemistry: AST, ALT, uric acid, urea, creatinine, LDH, glycemia, albumin, total protein, sideremia, total bilirubin, direct bilirubin, inflammatory markers: CRP, ESR
- Coagulation tests: AP, APTT, PT, INR, fibrinogen
- Bone marrow aspirate with morphological analysis and cytogenetic examination (karyotype, FISH analysis for t (9; 22) (q34; q11) identification) every 6 months until complete cytogenetic response is obtained
- Molecular biology tests for monitoring the response to treatment (RT BCR-ABL1) - monthly for the first 3 months, then every 3 months

Diagnosis, classification, staging

The differential diagnosis is made taking into account other diseases accompanied by hyperleukocytosis: severe infections, congenital heart disease, malignancies with secondary determinations. The diagnosis of juvenile chronic myelomonocytic leukaemia (JMML) should be excluded in young children. JMML is common in children under 2 years of age, while CML occurs predominantly in children over 6 years of age. The clinical profile is different: macular erythematous rash and lymphadenopathy are common signs in JMML, but rare in the chronic phase of CML, and voluminous splenomegaly is suggestive of CML. The characteristics of the laboratory tests are also distinct. In JMML, the number of leukocytes is below 100 x 10^9/L, with monocytosis, thrombocytopenia and an elevated fetal hemoglobin. The differential diagnosis is usually resolved by the morphological examination of the bone marrow aspirate, but the absence of the Philadelphia chromosome in some cases of CML may lead to an uncertain diagnosis in some situations. (5, 6, 7)

The differential diagnosis in the chronic phase excludes other Ph negative chronic conditions (2):

- chronic myelomonocytic leukemia (CMML); myelodysplastic / myeloproliferative neoplasms, differs from CML by the presence of dysplastic features, more pronounced cytopenias, increased monocytes and lack of basophils.
- chronic neutrophilic leukemia (CNL) can be taken for CML in rare cases with the BCR-ABL p230 transcript; cytogenetic examination differentiates between them.
- Exceptionally, patients with CML may have isolated thrombocytosis without leukocytosis, and in these situations the problem of the differential diagnosis with essential thrombocythemia (ET) arises. Basophilia is often used as a diagnostic sign. Cytogenetic and molecular biology tests are essential in these situations. For staging, see Table 1. (3, 4, 5)

Table 1 Staging

Disease stage	Definition of WHO
Chronic phase	Blast cells < 10% in the peripheral blood and bone marrow
Accelerated phase	Blast cells 10-19% in the peripheral blood and/or bone marrow Myeloblasts and promyelocytes in the peripheral blood ≥30% Basophils ≥20% Persistent thrombocytopenia (<100 × 10^9/L) that is not related to the treatment or Persistent thrombocytosis (> 1000 × 10^9/L) unresponsive to treatment Leukocytosis and splenomegaly unresponsive to treatment Additional cytogenetic abnormalities
Blast phase	Blast cells ≥ 20% in peripheral smear or bone marrow Extramedullary blast infiltrates Blasts identified by the bone marrow biopsy

Treatment

Management during the diagnosis:

- Transfusion support, treatment of infections, hydration 3l/m^2
- Allopurinol 10 mg/kg (WBC >20 x 10^9/l)
- Hydrea 25-50 mg/kg/day, if applicable
- Initiation of TKI treatment after confirmation of the diagnosis
- Leukapheresis in severe cases: priapism, pulmonary infiltrates, severe retinopathy, papillary edema

The goals of TKI treatment are

- Complete hematological response: PLT < 450 x 10^9/L, WBC < 10 x 10^9/L, peripheral: no immature granulocytes, basophils <5%; impalpable spleen
- Complete cytogenetic response (0% cells with Philadelphia chromosome positive)
- Major molecular response - MR4, MR5

Recommended treatment: Table 2

- First generation TKI: Imatinib: the dose in children is 340 mg/m^2/day and the dose capping is 400 mg/day (adult dose) Table 3
- Second generation TKI: Dasatinib, Nilotinib, Ponatinib: Table 4

Table 2. Treatment recommendations according to ELN [1]

Treatment line	Description		TKI, standard dose					TCSH				
Chronic phase												
			Imatinib 400 mg/day	Nilotinib 300 mg/bid	Dasatinib 100 mg/day	Bosutinib 500 mg/day	Pomatinib 45 mg/day	Searched		ALLO TCSH		chemotherapy
								HLA id fam	Unrelated donor	indicated	recommended	
1st	Baseline		x	X	x			x[2]				
2nd	Intolerance to TKI		Any first-line TKI									
	1st Failure	Imatinib		x[8]	x	X	x	x				
		Nilotinib			x	X	x	x	x	x		
		Dasatinib		x[8]			x	x	x	x		
3rd	Intolerance /Failure 2 TKI		any non administered TKI so far								x	
Any	T315I mutation						x	x	x	x		
Accelerated / blast phase												
New cases without TKI therapy	Initial		x[3]		x[4]			x	x			
	No response, blast phase										x[7]	x[5]
Patients previously treated with TKI			Any TKI				x[6]				x[7]	x[5]

[1] choice of TKI based on tolerability and safety; [2] in case of baseline warnings (high risk, CCA/Ph+); [3] 400 mg/bid, [4] 70 mg/bid or 140 mg/day; [5] before TCHS for disease control; [6] in the case of T315I mutation, [7] only patients eligible for allo TCSH, not in the case of resistant forms, resistance in the blast phase; [8] 400 mg bid

Table 3. Response criteria for first generation TKI (1)

Assessment	Optimal response	Warning	Treatment failure
Diagnostic phase		High risk CCA/Ph+	
3 month	BCR-ABL ^{IS} ≤ 10% Ph+ ≤ 35% (PCyR)	BCR-ABL ^{IS} > 10% Ph+ 36-95%	No complete hematological response Ph+>95%
6 month	BCR-ABL ^{IS} ≤ 1 % Ph+ 0 % (PCyR)	BCR-ABL ^{IS} 1 – 10 % Ph+ 1-35%	BCR-ABL ^{IS} > 10% Ph+>35%
12 month	BCR-ABL ^{IS} ≤ 0.1 % (MMR)	BCR-ABL ^{IS} 0.1 – 1 %	BCR-ABL ^{IS} > 1% Ph+ > 0%
> 12 month	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of complete/cytogenetic/molecular hematological response Additional mutations CCA/Ph+

Table 4. Response criteria to second generation TKI, in case of failure of Imatinib (ELN table)[1]

Assessment	Optimal response	Warning	Treatment failure
baseline		- no complete hematological response - Loss of complete hematological response under Imatinib - no cytogenetic response after the first line of TKI -increased risk	
3 month	BCR-ABL ^{IS} ≤ 10% Ph+ ≤ 65% (PCyR)	BCR-ABL ^{IS} > 10% Ph+ 65-95%	- no complete hematological response, or -Ph+>95% or additional mutations
6 month	BCR-ABL ^{IS} ≤ 10 % Ph+ < 35 % (PCyR)	BCR-ABL ^{IS} < 10 % Ph+ 35-65%	BCR-ABL ^{IS} > 10% Ph+>65% Additional mutations
12 month	BCR-ABL ^{IS} ≤ 1 % Ph + 0 (CcyR)	BCR-ABL ^{IS} 1 – 10 % Ph+ 1-35%	BCR-ABL ^{IS} > 01% Ph+ > 35% Additional mutations
> 12 month	MMR or better	CCA/Ph- (-7, or 7q-) BCR-ABL ^{IS} >0.1%	Loss of complete hematological response/ complete or partial cytogenetic/molecular response Additional mutations CCA/Ph+

Table 5. Cytogenetic / molecular monitoring recommendations[1]

At diagnosis	-e.g. cytogenetic in MO, FISH if Ph-, qualitative PCR for transcript identification
During treatment	-RT-PCR every 3 months until MMR is obtained, then every 3-6 months and/or -e.g. cytogenetic at 3, 6 and 12 months until obtaining CCyR, then annually -after obtaining CCyR, FISH can be performed from the peripheral blood smear
Failure or progression of the disease	-RT-PCR, analysis of additional mutations, e.g. cytogenetic -immunophenotyping in the blast phase
Warning	-cytogenetic tests and molecular biology - to be performed at shorter intervals -e.g. cytogenetic in case of myelodysplasia or CCA / Ph-

Before the introduction of TKI, HCT transplantation was the only curative option for patients with CML, and indications are currently very limited (see Table 2).

Side effects of TKI Imatinib (7, 8, 9):

- haematological toxicity:

- anaemia - preferably transfusion support

- neutropenia < 1 x 10^9/l → stop TKI for up to 2 weeks, resume when neutrophils > 1,5 x 10^9/l; if it persists - G-CSF (chronic phase only), resume full dose if neutropenia <2 weeks, otherwise reduce dose by 20%

- -thrombocytopenia < 50 x 10^9/l : STOP, treatment is resumed when PLT > 100 x 10^9/l; recurrent thrombocytopenia → 20% reduction

- non-haematological toxicity:

- edema, fluid retention, oral diuretic; in case of severe pleurisy → thoracentesis and corticosteroids

- muscle cramps: Calcium / Magnesium supplements

- bone pain <10% of children: nonsteroidal anti-inflammatory drugs (NSAIDs)

- skin rash: local topical steroid

- diarrhea, nausea, vomiting: symptomatic

- lethargy, weight gain, very rare: liver toxicity

Monitoring of long-term side effects (7.8.9)

- monitoring of the growth in length and weight - annual endocrinological examination

- monitoring of the bone osteodensitometry - annual endocrinological examination

- monitoring of the thyroid function - TSH, fT4 at 4-6 weeks after initiation of TKI treatment, biannually or annually thereafter

- monitoring of gonadal function: periodic Tanner staging, gonadotropin level

Recommendations

- First-line treatment in CML in children is Imatinib therapy, similar to adults
- There are second-line tyrosine kinase inhibitors available: Dasatinib, Nilotinib, Ponatinib
- Before the use of TKI's, CSH transplant was the only curative option for patients with CML, currently the indications are very limited.

Bibliography

1. ELN Guide
2. NCCN Guidelines v3. 2020
3. de la, Fuente, J., Baruchel, A., Biondi, A., de, Bont, E., Dresse, M.-F., Suttorp, M., Millot, F. and (2014), Managing children with chronic myeloid leukaemia (CML). Br J Haematol, 167: 33-47. doi:10.1111/bjh.12977
4. Hijiya, N., Schultz, K. R., Metzler, M., Millot, F., & Suttorp, M. (2016). Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood*, *127*(4), 392–399. https://doi.org/10.1182/blood-2015-06-648667
5. Nobuko Hijiya, Meinolf Suttorp; How I treat chronic myeloid leukemia in children and adolescents. Blood 2019; 133 (22): 2374–2384. doi: https://doi.org/10.1182/blood.2018882233
6. EBMT Handbook
7. Hijiya N, Millot F, Suttorp M. Chronic myeloid leukemia in children: clinical findings, management, and unanswered questions. Pediatr Clin North Am. 2015;62(1):107-119.
8. Millot F, Guilhot J, Suttorp m, et al. advanced phases at diagnosis of childhood chronic myeloid leukemia: the experience of the International Registry for Chronic Myeloid Leukemia (CML) in Children and Adolescents (I-CML-Ped Study) [abstract]. Blood. 2017;130(suppl 1). Abstract 316.
9. Suttorp M, Schulze P, Glauche I, et al. Frontline imatinib treatment in children and adolescents with chronic myeloid leukemia: results from a phase III trial. Leukemia. 2018; 32(7):1657-1669

8.1.4 JUVENILE CHRONIC MYELOMONOCYTIC LEUKEMIA

The juvenile chronic myelomonocytic leukemia (JMML) is a rare, aggressive condition that accounts for 2-3% of all hematologic malignancies in children. It is characterized by excessive proliferation of the granulocyte and monocytic series. Somatic or germline mutations are present in 90% of patients: PTPN-11, K-RAS, N-RAS, CBL or NF1. Hematopoietic stem cell transplantation (HCT) is the therapy of choice for most patients with JMML, noting that HCT is a standard indication in patients with PTPN-11-, K-RAS-, or NF1 mutations.

Some patients relapse after transplant. In this case a second HCT procedure is recommended. (1) Recent studies have shown the efficacy of Azacitidine, a hypomethylating agent, in obtaining molecular remission prior to transplantation.

Epidemiology

The annual incidence of JMML is 1.2 cases per 1 million people, most cases occurring in children under 3 years and 2 times more frequently in boys.

Diagnosis (See Table 1)

The patients present non-specific symptoms such as: fever, cough, tachypnea, infections.

Possible signs are: hepatomegaly, splenomegaly, lymphadenopathy, skin lesions (erythematous papules, eczematous plaques, juvenile xanthogranulomas, cutaneous-mucosal hemorrhagic syndrome, "cafe-au-lait" spots in patients with NF1)

The paraclinical tests show:

- leukocytosis (usually values < 50 x 10^9/l, occasionally > 100 x 10^9/l), with monocytosis (>1 x 10^9/l is mandatory for diagnosis)
- anemia,
- moderate → severe thrombocytopenia
- increased fetal hemoglobin (HbF)
- hypercellular bone marrow, with myeloid hyperplasia and blasts <20%
- monosomy 7 occurs in 25% of patients

Table 1 Diagnosis criteria in JMML

Mandatory criteria	**Additional criteria (at least 1 criterion)**	**Further criteria (patients without genetic testing must meet these criteria in addition to the mandatory ones)**
Clinical and haematological criteria	Genetic tests	other criteria
Absence of *BCR-ABL1*	KRAS, NRAS, or PTPN11 somatic mutations (germline mutations should be excluded)	Monosomy 7 or other chromosomal abnormality, or at least 2 of the following criteria:
>1 × 10^9/L circulating monocytes	Clinical diagnosis of NF1 neurofibromatosis or presence	Circulating myeloid / erythroid precursors

<20% blasts in the peripheral blood and bone marrow	CBL germline mutation with loss of CBL heterozygosity	High Hb F
Splenomegaly		Hyperphosphorylation STAT5
		Hypersensitivity GM-CSF

Genetic characteristics (2)

Uncontrolled activation of the RAS/MAPK pathway plays a very important role in the pathogenesis of JMML. Over 90% of patients will have mutations in one of the 5 genes: NF1, PTPN11, NRAS, KRAS and CBL.

Patients who show NF1 and later develop JMML represent 10-15% of all JMML cases. The only treatment for these patients is HCT.

Noonan syndrome is characterized by general developmental delay and other clinical signs similar to those in patients with NF1. In Noonan Syndrome there is an increased incidence of JMML and JMML - like transient myeloid myeloma proliferation. Transient myeloproliferative disorder in Noonan syndrome usually occurs in early childhood, and the evolution is not clonal, unlike JMML. Most patients will have a spontaneous regression of symptoms, and only 10% will progress to JMML, as a result of a new cytogenetic abnormality. PTPN11 germline mutations have been identified in most patients with Noonan Syndrome, more frequently in patients with JMML, the sporadic form (in 35% of cases).

Studies have shown that most SHP2 mutations associated with JMML have more pronounced "gain-of-function" effects than those seen in patients with Noonan Syndrome, which may explain the transient nature of Noonan Syndrome / Transient myeloproliferative disorder (NS/TMD). JMML associated with PTPN11 mutations leads to death without HCT.

NRAS and KRAS mutations were identified in up to 20-25% of JMML cases. Most mutations occur in codons 12, 13 or 61, which leads to the activation of the RAS-GTP pathway.

JMML that associates NRAS or KRAS mutations is very aggressive and requires emergency HCT.

Germline or somatic mutations in CBL were identified in almost 10% of patients with JMML. Unlike myeloproliferative disorder, germline CBL mutations cause skeletal malformations, with developmental delay and cryptorchidism, a phenotype similar to Noonan Syndrome. Some of these patients with JMML and germline CBL mutations may have spontaneous regression of leukaemia, but usually have several vasculitic phenomena during lifetime. HCT in this category of patients is oriented towards immune reconstitution and it is indicated only if a rapid evolution of the disease occurs. Patients with somatic mutations in CBL do not have specific particularities, but in this case JMML tends to evolve extremely aggressively.

Exome sequencing identified mutations in the SETBP1 and JAK3 genes in 17% of patients with JMML, however, they are apparently secondary mutations that do not generate additional events. ASXL1 mutations are identified in a minority of patients with JMML, but mutations in IDH1/2, TET2, EZH2, DNMT3A, SRFS2, U2AF1 and SF3B1 have not been described in this category of patients. The discovery of genetic mutations and cytogenetic changes associated with JMML have been incorporated into the new recommended diagnosis criteria for JMML, which is more specific compared to the existing WHO 2008 criteria (Table 2). Diagnosis tests such as the GM-CSF hypersensitivity of myeloid precursors involve techniques that are difficult to reproduce and they are therefore only available in specialized centres. Newer tests, such as GM-CSF hyperphosphorylation of STAT5 protein by flow cytometry, look promising, but they are not yet approved for clinical use.

Prognostic factors (2)

JMML is a genetically and phenotypically heterogeneous entity. Some patients may experience spontaneous regression, while others have an unfavourable course. Patients showing NS/TMD will most likely experience spontaneous regression of the disease and this is also true for the vast majority of patients with germline CBL mutations. Analysis of a subset of JMML patients with RAS G12S mutations proved that they showed spontaneous hematological improvement with minimal therapy, but other studies have shown a lack of genotype-phenotype correlation in JMML patients with RAS mutations.

Negative prognostic factors include higher age at onset (> 1.4–4 years), increased fetal hemoglobin (Hb F> 40%), decreased platelet count (<33,000/ µL), monosomy 7, and PTPN1 mutation.

Diagnosis

- Complete blood count, peripheral blood smear
- Complete biochemistry: AST, ALT, uric acid, urea, creatinine, LDH, glycemia, albumin, total protein, ferritin, total and direct bilirubin
- Coagulation tests: AP, APTT, PT, INR, fibrinogen, D-Dimer test, platelet aggregation, thromboelastogram
- Inflammatory markers: CRP, procalcitonin, ESR
- Bone marrow aspirate with morphological analysis and cytogenetic examination (karyotype, FISH analysis 5q- / 7q-)
- Molecular biology tests for the exclusion of BCR-ABL
- Bone marrow aspirate and biopsy - if other investigations do not confirm the diagnosis
- Immunophenotyping
- Hemoglobin electrophoresis
- Abdominal ultrasound to measure the size of the spleen and liver
- Genetic tests to identify mutations - if accessible

Recommended investigations during hospitalization

- Complete blood count, peripheral blood smear
- Complete biochemistry: AST, ALT, uric acid, urea, creatinine, LDH, glycemia, albumin, total protein, ferritin, total and direct bilirubin
- Coagulation tests: AP, APTT, PT, INR, fibrinogen
- Inflammatory markers: CRP, ESR
- Virology examinations: CMV, EBV, hepatitis virus B / C, HIV, VZV
- Abdominal ultrasound to assess the size of the spleen and liver

Treatment (1)

HCT is the only curative treatment for most patients with JMML (Table 3). However, in order to establish a correct therapeutic approach, genetic tests are necessary in order to identify genetic mutations.

Studies to date have not shown major benefits of standard chemotherapy. Recent studies have shown that the administration of pre-transplant Azacitidine may induce clinical, haematological, cytogenetic and molecular remission in some patients with JMML.

In the event of relapse or progressive mixed chimerism in a transplant patient, a second HCT procedure should be considered.

Detailing of HCT in JMML according to molecular subtypes

- Investigations to be performed before transplantation for the initial assessment, then repeated before the procedure
  - Bone marrow aspirate to assess the percentage of blasts
  - karyotype for identifying anomalies
  - skin biopsy for cryopreservation of fibroblasts
- Criteria for selecting the donor
  - family HLA-identical donor (sibling) BM / PBSC / CB - typing HLA-A, HLA-B, HLA-C, HLA-DRB1.
  - HLA-identical twin: HLA-A, HLA-B, HLA-C, HLA-DRB1 typing
  - unrelated BM / PBSC donor: identical or with antigenic / allelic mismatch - typing HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1.
  - cord donor cells: 6/6 or 5/6 compatibility using HLA-A, HLA-B, HLA-DRB1 typing.
- The source of the stem cells can be:
  - bone marrow
  - peripheral blood
  - cord cells
- Graft characteristics:
  - Bone marrow (BM) graft without manipulation of CD34 > 3.5 x 10^8 nucleated cells/kg
  - Peripheral blood graft between 4 x 10^6 CD34/kg and 10 x 10^6 CD34/kg or < 5 x 10^7 CD3/kg
  - Cord cells graft - at least 3.5 x 10^7 nucleated cells/kg.
- Conditioning regimen for patients with NF1, PTPN11 / NRAS somatic mutations

Busulfan iv, 4 doses/day, 4 consecutive days (-7→-4) – 0.8 – 1.2 mg/kg, depending on weight

Cyclophosphamide 60 mg/kg/day, 2 consecutive days (-3→-2)

Melphalan 140 mg/m2, in z-1

- Conditioning regimen for patients with KRAS somatic mutations or without genetic mutations

Thiotepa 8 mg/kg/day iv in z-7

Fludarabine 40 mg/m2, day, 4 consecutive days (-6→-3)

Treosulfan 10-14 g/m2/day, 3 consecutive days (-6→-4)

- Prophylaxis of the graft versus host reaction
  - r-ATG in patients with unrelated donor: 10 mg/kg/day, 3 consecutive days (-4→-2)
  - for related donor, with BM / peripheral blood / cord cell source and patient <4 years with BM <20% blasts: CSA 2mg/kg/day
  - for related donor, with BM / peripheral blood / cord cell source and patient > 4 years with BM> 20% blasts: CSA 1mg/kg/day
  - for unrelated donor, with BM / peripheral blood / cord cell source and patient <4 years with BM <20% blasts: CSA 2mg/kg/day, in combination with MTX 10 mg / m2 - 3 doses (+1, +3, + 6)
- Post-transplant patient monitoring will be done by analyzing chimerism after 3 months, 6 months, 9 months, 12 months and then annually.

Table 2. JMML treatment according to the associated mutations.

	PTPN11	**K-RAS**	**N-RAS**	**NF1**	**CBL**
Germline mutations	Noonan Sdr. *W&W*	Noonan Sdr. *W&W*	Noonan Sdr. *W&W*	NF type 1 *HCT*	CBL Sdr. *W&W* *HCT in case of progression*
Somatic mutations	*HCT*	*HCT*	*HCT for the majority*	-	-

W&W – watch and wait

Recommendations

- JMML is a rare, aggressive condition that occurs in young children (under 4 years of age)
- Genetic mutations can be identified in 90% of all patients.
- It frequently accompanies type 1 Neurofibromatosis and Noonan Syndrome.
- There are cases of spontaneous regression.
- HCT is the therapy of choice for most patients with JMML, and in patients with PTPN-11-, K-RAS-, or NF1 mutations; it is a standard indication.
- Recent studies have shown the effectiveness of Azacitidine in achieving molecular remission before transplantation.
- In case of a recurrence a second transplant procedure should be performed.

Bibliography:

1. Guidelines for Hematopoietic Stem Cell Transplantation (HSCT) in Childhood MDS and JMML for Patients enrolled in EWOG-MDS Studies

2. Franco Locatelli, Charlotte M. Niemeyer; How I treat juvenile myelomonocytic leukemia. Blood 2015; 125 (7): 1083–1090. doi: https://doi.org/10.1182/blood-2014-08-550483

8.1.5 NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's Lymphoma (NHL) is a malignancy of the lymphatic system, resulting from the proliferation of B, T or NK lymphocytes.

Epidemiology

Non-Hodgkin's Lymphoma accounts for about 5% of all cancers in children, occurring more commonly until the age of 14. It is rare in children under the age of 3, its frequency increasing with age, so that up to 19 years the number of cases is equal to that of Hodgkin's Lymphoma (HL). It is 2-3 fold more common in boys and it is predominant in the caucasians. Significant progress has been made in the survival of pediatric patients, with mortality being 50% lower now than in the 1970s. The 5-year overall survival is 87% in those under 15 and 82% in 15 to 19 year olds. (1)

Signs and symptoms (2, 3)

- Lymph nodes (painless, laterocervical, supraclavicular, axillary, mediastinal or intra-abdominal sites)
- Increase in volume of the abdomen due to lymphadenopathy or ascites; when there is intestinal invasion, paralytic ileus may occur accompanied by pain, nausea, vomiting
- Intra-abdominal lymphadenopathy can cause compression of the ureters causing oliguria, fatigue, loss of appetite, nausea or peripheral edema
- Sensation of early satiety (by gastric compression) in case of splenomegaly
- Dyspnoea or cough when the site is in the mediastinum, by compression of the trachea
- Superior vena cava syndrome, being a life-threatening situation, it is associated with an unfavorable prognosis
- Fever, shivering
- Weight loss
- Night sweats
- Fatigue
- In cases where there is involvement of the central nervous system or cervical spine, headaches, nausea, speech or visual disturbances may occur, NHL in these sites has an unfavorable prognosis
- In case of skin involvement, there are subcutaneous nodules, pruritus, erythema (anaplastic large cell NHL, ALK neg, when occuring exclusively cutaneous it has a very good prognosis)
- Severe and frequent infections
- Ecchymosis or bleeding from minor injuries
- Fatigue and cutaneous-mucous paleness

Risk factors, causes (3, 4) A number of immunodeficiencies have been involved in the occurrence of NHL:

- Wiskott-Aldrich syndrome
- SCID (severe combined immunodeficiency disease)
- Ataxia-telangiectasia
- Common variable immunodeficiency
- X-linked lymphoproliferative syndrome

- Organ transplant with immunosuppressive treatment, in most cases caused by the reactivation of Ebstein-Barr virus

- HIV infection

- Exposure to radiation, especially in the intrauterine life or after radiotherapy to treat another malignancy

- Ebstein-Barr virus infection and malaria account for over 95% of Burkitt's lymphoma cases in Africa

- Other possible risk factors are: family history of lymphoma or children from older mothers

The cause of Non-Hodgkin's Lymphoma is unknown, but researchers have shown that certain mutations in DNA (especially translocations) can cause the activation of an oncogene or the inhibition of a suppressor gene. In general, mutations are congenital, but there are also cases in which they occur during lifetime, either de novo or secondary to radiation exposure.

Diagnosis (2, 5, 6)

- The detailed anamnesis is an essential element in establishing the diagnosis
- Clinical: in general, lymphadenopathy is the reason for seeing a doctor
- Biopsy: when malignancy is suspected:
  - Surgical: excisional or incisional biopsy
  - Aspiration with an aspiration needle – is usually not sufficient and should mostly not be performed
  - Bone biopsy and bone marrow aspiration to determine bone marrow involvement
  - Lumbar puncture: in order to establish the presence of malignant cells in the CSF
  - Thoracocentesis or paracentesis in the case of pleurisy / ascites
- Laboratory tests:
  - Complete blood count, LDH, biochemistry, coagulation, ESR
  - Virology (HIV, EBV, HBV, CMV, Toxoplasma)
  - Flow cytometry
  - Immunohistochemistry
  - Cytogenetics: karyotype and FISH (fluorescent in situ hybridization) - assessment of the presence of translocations
  - CRP
- Imaging:
  - Abdominal and soft tissue ultrasound
  - Pulmonary radiography
  - CT
  - MRI (useful in case of bone invasion or CNS)
  - PET-CT

Histopathological diagnosis, classification

The WHO (World Health Organization) classification is the most widely used and includes the immunophenotypic and molecular characteristics of pediatric NHL. (7) (Table 1)
Table 1

WHO Classification	Immuno-phenotyping	Clinic	Chromosomal abnormalities	Affected genes
Burkitt's lymphoma	Mature B cells	Intra-abdominal (sporadic), cephalic extremity and cervical region (sporadic), maxillary (endemic), bone marrow, CNS	t(8;14)(q24;q32), t(2;8)(p11;q24), t(8;22)(q24;q11)	MYC, TCF3, ID3, CCND3, TP53
Burkitt-like lymphoma with 11q aberration	Mature B cells	Nodal	11q aberrations	MYC, TCF3, ID3, CCND3, TP53
Large B cell lymphoma with IRF4 rearrangement	Mature B cell	Nodal (typical for the cervical region and cephalic extremity)	Cryptic rearrangement IRF1 with IGH locus	IRF4
Diffuse large B-cell lymphoma	Mature B cells	Nodal, abdominal, bone, primary CNS (associates an immunodeficiency), mediastinal	No genetic abnormalities identified	
Primary mediastinal (thymic) large B-cell lymphoma	Mature B cells frequent CD30+	Mediastinal, but possibly also affecting other lymph nodes or extranodal regions (abdominal, often kidney)	9p and 2p	CIITA, TNFAIP3, SOCS1, PTPN11, STAT6
Large B cell lymphoma ALK-pozitive		Generalized lymphadenopathy, bone marrow involvement 25%	t(2;5)(p23;q35); translocation variants of ALK	ALK, NPM
T-cell lymphoblastic lymphoma	Ly T (TdT, CD2, CD3, CD7, CD4, CD8)	Mediastinal mass, bone marrow		
B-lymphoblastic leukemia/lymphoma	Ly B (CD19, CD79a, CD22, CD10, TdT)	Skin, soft tissues, bone, lymph nodes, bone marrow		
Pediatric-type follicular lymphoma	Mature B cell	Nodal (typical for the cervical region and cephalic extremity)		TNFRSF1, MAP2K1
Pediatric nodal margin al zone lymphoma	Mature B cell	Nodal (typical for the cervical region and cephalic extremity)		

CNS = central nervous system; TdT = deoxynucleotidyl transferase terminal; + = positive.

Other types of lymphoma: non-anaplastic peripheral large T-cell lymphomas - including T/NK lymphomas, cutaneous and indolent B-cell lymphomas (e.g. follicular and marginal zone lymphoma) are found in adults, but exceptionally in children too. The most recent WHO

classifications have classified pediatric types of follicular and nodal marginal zone lymphoma as distinct entities.

Staging

St. Jude Children's Research Hospital staging is used. (Murphy) (8)

The bone marrow involvement is defined by the presence of ≥ 5% malignant cells, but <25%. Patients with lymphoblastic lymphoma who have more than 25% malignant cells in the bone marrow are considered to have leukemia and treated according to the specific protocols.

CNS involvement in lymphoblastic lymphoma has the same criteria as in leukemia: over 5 cells/µl in CSF. The BFM group showed a prevalence of CNS involvement in NHL of 6%.

Prognostic factors (4, 9, 10)

- Response to treatment: The response to early treatment is correlated with prognosis as illustrated by Burkitt's lymphoma, where unfavorable response to early treatment is associated with a survival of 20%; and in patients with anaplastic large cell lymphoma (ALCL) where negative MRD after induction treatment is associated with a risk of relapse of only 20% and with an OS of 90%, while patients with positive MRD have a relapse rate of 80% with OS of 65%.
- Disease stage at diagnosis / MDD (Minimal Disseminated Disease): patients in the early stages (extra-abdominal / extrathoracic single tumor or completely resectable tumor) have an excellent prognosis (5-year 90% survival) regardless of the histological type. (11) MDD is defined as submicroscopic bone marrow invasion at onset, but positive by flow-cytometry tests (patients with more than 5% tumor cells in the bone marrow are classified as stage IV disease). In the case of Burkitt's lymphoma, the role of MDD in the evolution of the disease is not yet very well defined, but in lymphoblastic T-cell lymphoma it was shown that patients with MDD below 1% had an EFS of 91%, compared to 68% in cases with MDD above 1%, and 52% in cases with MDD over 5%. In patients with MDD anaplastic large cell lymphoma determined by RT-PCR for the NPM-ALK gene transcription, it was present in 57% of cases and it was associated with a relapse rate of 46%, compared to 15% in patients without bone marrow invasion. Patients who obtained negative MRD after the first course of treatment had an EFS rate of 69%, compared to patients with negative MDD (82%) and those with MDD and positive MRD (19%).
- Site of the disease at diagnosis: in pediatric NHL, some sites of the disease have prognostic value. Bone marrow and CNS require more aggressive treatment regimens with an unfavorable prognosis. Mediastinal involvement is also associated with an unfavorable prognosis, studies showing a 3-year EFS of 50-70% in pediatric patients. Bone and skin site (ALK neg) is associated with a good prognosis, while involvement of various organs or testis does not influence EFS.
- Age: NHL under the age of 1 year is extremely rare (1% in BFM trials from 1986 to 2002) and has an unfavorable prognosis. Adolescents have a worse prognosis than children under the age of 15, except for those with Burkitt's lymphoma.
- Immune response: highlighted by determination of anti-ALK antibodies titer.
- Comorbidities: children with pre-existing immunodeficiencies have an unfavorable prognosis.

Treatment

In most cases, NHL in children is diagnosed in advanced stages requiring treatment with combinations of chemotherapy. (10) The exception to this treatment strategy is skin-limited peripheral T-cell lymphoma, including ALCL; indolent mature B cell lymphoma, follicular lymphoma - pediatric type, post-transplant lymphoproliferative disease (when immunosuppression can be

safely reduced). Studies have shown that radiotherapy in pediatric patients has no indications in the early stages (I or II), nor prophylactic in the CNS, nor in patients with anaplastic large B-cell NHL with CNS involvement. The only situations in which radiotherapy could be considered are those of patients who have not obtained a complete response with chemotherapy.

Surgery in NHL is useful for confirming the diagnosis by performing a biopsy or for therapeutic purposes in stages I and II (in the case of pediatric, marginal zone lymphoma or cutaneous T-cell lymphoma) in combination with chemotherapy.

Medical emergencies: Mediastinal mass tumors present a vital risk during imaging investigations, during general anesthesia or in deep sedation. That is why less invasive investigations are preferred (biopsy and bone marrow aspiration, diagnostic thoracentesis when there is pleurisy or biopsy of peripheral lymphadenopathy).

Tumor lysis syndrome (TLS): requires prophylactic treatment. Often in case of Burkitt lymphoma, the tumor could be disseminated, and a huge tumor burden is put opon the patient. At diagnosis and shortly after start of treatment all these patient are at risk for developing spontanous and therapy induced TLS, and increased hydration and rasburicase or allopurinol should be given.

<u>Mature B cell NHL:</u>

Risk groups (12):

Risk group 1: macroscopic excision of the tumor

Risk group 2: -Stage I/II: incomplete tumor resection

-Stage III: incomplete tumor resection with LDH <2x normal value

Risk group 3: -Stage III with LDH ≥ 2x normal value but <4x normal value and

-Stage IV/B-ALL with LDH <1000U/L without CNS involvement

Risk group 4: -Stage III disease with LDH ≥ 4x normal value or

-Stage IV/B-ALL with LDH ≥ 4x normal value without CNS involvement

Risk group 4 CNS positive with incomplete tumor resection or stage IV/B-ALL with CNS involvement

Burkitt's lymphoma and Burkitt-like lymphoma are an aggressive form of lymphoma. A variety of B cell markers (CD19, CD20, CD22) are present, most of them being CD10 pos (CALLA).

- The BFM study established differentiated treatment according to the stage (12):

- Localized disease: R1 (fully resected tumor in stage I and abdominal tumor stage II) and R2 (unresected tumor stage II or II and stage III with LDH> 500 IU/L) - NHL-BFM 95 protocol. For R2, patients received cytoreducation treatment followed by 5 cycles of chemotherapy. EFS>95%

- Advanced disease: R3 (stage III disease with LDH 500-999 IU/L or stage IV, > 25% blasts in the bone marrow without CNS involvement with LDH <1000 IU/L) and R4 (stage III, IV with bone marrow involvement with LDH > 1000 IU/L or any stage with CNS involvement) - NHL protocol - BFM 95. EFS=93% and 70% at 3 years for those with CNS involvement.

- FAB/LMB-96 is a treatment alternative, but with inferior long-term results.

- Superior results were highlighted in the case of the R-CHOP protocol 6 cycles at an interval of 21 days. (13)

- Treatment options for recurrent forms: R-ICE (rituximab, IFO, Carbo and VP16) (14), CYVE (HDAra-C and VP16), bone marrow transplantation or bispecific antibodies (anti-CD20 and anti-CD3).

Diffuse large B-cell lymphoma is a very aggressive form, accounting for 10-20% of pediatric NHL. (7) Most pediatric forms have a phenotype characteristic of germinal center B-

cell lymphoma (BCL6 and CD10), one third of cases have rearrangements of the MYC gene, 15% having IRF4 translocation (associated with a favorable prognosis).

The treatment of this type of NHL is similar to that for Burkitt's lymphoma.

Primary mediastinal B-cell lymphoma accounts for 1-2% of cases of NHL in children. It has surface markers similar to those of diffuse lymphoma with large B-cell: CD19, CD20, CD22, CD79s, PAX-5; CD30 pos, mutations of the PTPN11, PDL2 genes, most show JAK2 and IL4R. (1)

The treatment includes R-CHOP (13) or DA-EPOCH-R (dose-adjusted VP16, Doxo, CTX, VCR, PRD, Rituximab), a protocol associated with an EFS rate of 93% and OS of 97%. (15)

Lymphoblastic lymphoma

It is found in 20% of pediatric NHL forms, 75% being T-cell (7, 16, 17)

The treatment protocol administered is EURO-LB 02: PRD, Dexa, VCR, Dauno, L-ASP, CTX, ARA-C, MTX, 6MP and 6TG; MTX it. (19) Radiotherapy should be considered in cases of initial CNS involvement.

In recurrent or refractory forms, therapeutic options include Nelarabine or combinations of cytostatic agents containing Nelarabine, ICE (IFO, Carbo and VP16) and allogeneic bone marrow transplantation.

Anaplastic large cell lymphoma (20, 21)

It represents approximately 10% of all cases of pediatric NHL. All cases of anaplastic NHL in children are CD30 pos and over 90% have rearrangements of the ALK gene, most of them being represented by the NPM-ALK fusion gene. (Table 2)

Table 2 The characteristics of anaplastic large cell NHL

Fusion genes	Chromosomal location	Fusion gene frequency
NPM-ALK	5q36.1	~80%
TPM3-ALK	1p23	~15%
ALO17-ALK	17q25.3	Rare
ATIC-ALK	2q35	Rare
CLTC-ALK	17q23	Rare
MSN-ALK	Xp11.1	Rare
MYH9-ALK	22q13.1	Rare
TFG-ALK	3q12.2	Rare
TPM4-ALK	19p13	Rare
TRAF1-ALK	9q33.2	Rare

Adapted from Tsuyama et al. (21)

Treatment options are ALCL 99 (with a total duration of 5 months and a cumulative dose of Doxo of 150mg/ m^2) (23); APO (Doxo, PRD, VCR) (24); CHOP EG (VP16 and GEM in association with the CHOP protocol). (25)

An option of treatment is the B-NHL BFM 04 protocol, a protocol currently used by many centers in the country; The successor protocol, the most current of the BFM group,

namely B-NHL 2013, is currently underway, in which randomized Rituximab was introduced in combination with the standard arms of the previous B-NHL BFM 04 protocol. (26)

The recurrent/ refractory forms of the disease benefit from other combinations of chemotherapeutic agents: ICE, VBL (they may induce remission even in monotherapy), Brentuximab (studies were conducted on CD30 pos adolescents and adults), Crizotinib (is a kinase inhibitor that blocks the activity of the NPM-ALK fusion gene), allogeneic or autologous bone marrow transplantation**.**

Posttransplant lymphoproliferative disease

PTLD is a spectrum of clinically and morphologically heterogeneous lymphoid proliferations. All PTLDs after HSCT are associated with EBV, but the post-transplantation of solid organs appears the option EBV neg. In most cases there is a proliferation of B cells, in about 10% there is a proliferation of the T line. (9)

Post HCT PTLD is very rare (less than 1.6%). The associated risk factors are HLA incompatibility (those with HLA mismatch - 8/10 or 9/10), TCR depletion graft processing and ATG use in the conditioning protocol. (9)

Posttransplantation of solid organs, a higher risk was identified in cases of seronegative patients for EBV at the time of the transplantation. Other predisposing factors are the intensity and duration of immunosuppression, and tacrolimus poses a higher risk than cyclosporine.

WHO Classification for PTLD (27)

PTLD with early lesions: expansion of the germinal center with normal tissue architecture.

Polymorphic PTLD (B and T / NK cells): shows infiltrations with the T or B cells, change in lymph node architecture and necrosis.

Monomorphic PTLD: histology similar to that of NHL (most commonly similar to the histology characteristic of large B-cell lymphoma, followed by Burkitt / Burkitt-like lymphoma, myeloma or plasmacytoma and Hodgkin / Hodgkin-like PTLD).

The clinical-paraclinical picture may be similar to hepatitis, lymphoid interstitial pneumonia, meningoencephalitis or mononucleosis-like infectious syndrome. PTLD is characterized by lymphomatous lesions, often extranodal (especially at the level of the allograft).

The treatment consists primarily of reducing the dose of immunosuppressant, as far as it is permitted, in combination with chemotherapy according to the R-CHOP protocol (6 courses every 21 days). (13)

Hygienic-dietary treatment: isolation of the patient, rigorous personal hygiene, avoidance of uncooked food (especially during periods of neutropenia), no salt diet (when the therapeutic protocol requires it) and avoidance of food brought from outside the ward, no toothbrushing and replacement with gargling with antiseptic solutions (during periods of thrombocytopenia).

A central catheter is required (especially when aggressive chemotherapy is expected).

The prophylactic treatment is initiated from the beginning of the chemotherapy, in the absence of fever or overt infections:

- antibiotic therapy, antifungal treatment, antiviral treatment - according to the protocols

- In the case of fever (T> 38°C) or hypothermia (T <35°C), broad-spectrum empirical antibiotic therapy is initiated after culture collection. If there are positive cultures, the therapy will change depending on the antibiogram / antifungigram. If the fever persists > 48 hours without positive cultures, the treatment is adapted to local protocols.

Transfusions: only concentrates of blood components are used, not whole blood.

Granulocyte growth factor: in case of severe neutropenia

Supportive / symptomatic treatment: prevention of tumor lysis syndrome, antipyretics, analgesics, antiemetics, laxatives / antidiarrheals, diuretics (indication only), oxygen therapy, parenteral or enteral nutrition.

Vaccinaton is resumed 1 year after the completion of the treatment.

Psychological support: for the patient and their family, continuing schooling with the help of the hospital school, ludotherapy.

Complications

Acute toxicity: tumor lysis syndrome (requires hyperhydration 3l/m^2, Rasburicase or Allopurinol, alkalinization (not if Rasburicase is given)), hydro-electrolyte imbalances, severe neutropenia (with increased susceptibility to severe infections), severe anemia, severe thrombocytopenia (with high risk of bleeding), coagulopathy (disseminated intravascular coagulation) typhlitis, pancreatitis, hypertension, hyperglycaemia, iatrogenic Cushing's syndrome, gastritis, haemorrhagic cystitis, toxic hepatitis, reversible posterior encephalopathy syndrome, nausea, vomiting, mucositis, alopecia, allergic reactions, transfusion accidents, erythroderma, stretch marks, depression, irritability.

Chronic side effects (due to treatment toxicity): heart and vascular involvement, eye damage, musculoskeletal damage (aseptic necrosis, osteoporosis), chronic kidney disease, liver damage (autoimmune hepatitis), lung damage, thyroid dysfunction, infertility, growth retardation, psychiatric disorders behavior, skin damage (stretch marks), dental dystrophy, second malignancy. Rigorous long-term post-therapeutic follow-up allows early identification of these complications.

Post-therapeutic follow-up

Depending on the type of NHL, each protocol provides a certain frequency of the evaluations.

Clinical examination and laboratory tests: monthly in the first year after the end of the treatment, then every 3 months in the second year, every 6 months in the next 3 years, then annually up to 5 years. In the case of lymphoblastic lymphoma, the minimum residual disease is evaluated by flow cytometry, morphological examination of the bone marrow and CNS status every 3 months in the first 3 years, then only the bone marrow is examined every 6 months - 1 year, depending on the evolution of the disease up to 5 years.

Imaging investigations: PET-CT or MRI examination at the end of the treatment and then after 1 year and 2 years.

Evaluation of thyroid, cardiac, gonadal function, respiratory function tests has to be performed.

Recommendations

- NHL is classified histologically according to the WHO classification and is staged according to the St. Jude Children's Research Hospital (Murphy)
- The main prognostic factors are the stage of the disease / MDD, the patient's age, the serum LDH level, the extralymphatic involved sites, the performance status
- There is no chemotherapy protocol unanimously accepted by the centers in Romania, several protocols are used that include similar associations of chemotherapeutic agents, with close response rates (ALCL 99); B-NHL BFM 04, APO, CHOP EG
- Radiotherapy has limited indication

Bibliography

1. Smith MA, Altekruse SF, Adamson PC, et al.: Declining childhood and adolescent cancer mortality. Cancer 120 (16): 2497-506, 2014. [PUBMED Abstract]

2. Link MP, Jaffe ES, Leonard JP. Pediatric Hodgkin and non-Hodgkin lymphomas. In: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017:959-965.

3. Sandlund JT, Onciu M. Childhood lymphoma. In: Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, eds. *Abeloff's Clinical Oncology*. 5th ed. Philadelphia, Pa: Elsevier; 2014:1873–1889.

4. Attarbaschi A, Carraro E, Abla O, et al.: Non-Hodgkin lymphoma and pre-existing conditions: spectrum, clinical characteristics and outcome in 213 children and adolescents. Haematologica 101 (12): 1581-1591, 2016.

5. Howard J. Weinstein, Mlissa M. Hudson, Michael P. Link: *Pediatric lymphomas,* Springer-Verlag Berlin Heidelberg 2007

6. Crump C, Sundquist K, Sieh W, et al. Perinatal and family risk factors for non-Hodgkin lymphoma in early life: A Swedish national cohort study. J Natl Cancer Inst. 2012;104:923–930.

7. Percy CL, Smith MA, Linet M, et al.: Lymphomas and reticuloendothelial neoplasms. In: Ries LA, Smith MA, Gurney JG, et al., eds.: Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, Md: National Cancer Institute, SEER Program, 1999. NIH Pub.No. 99-4649, pp 35-50. Also available online. Last accessed February 05, 2020.

8. Rosolen A, Perkins SL, Pinkerton CR, et al.: Revised International Pediatric Non-Hodgkin Lymphoma Staging System. J Clin Oncol 33 (18): 2112-8, 2015. [PMC free article] [PubMed] [Reference list]

9. Howard J. Weinstein, Mlissa M. Hudson, Michael P. Link: *Pediatric lymphomas,* Springer-Verlag Berlin Heidelberg 2007

10. Kamdar KY, Sandlund JT, Bollard CM. Malignant lymphomas in childhood. In: Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastasi J, eds. *Hematology: Basic Principles and Practice*. 6th ed. Philadelphia, Pa: Elsevier; 2013:1255–1266.

11. Reiter A, Schrappe M, Ludwig WD, et al.: Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: a BFM group report. Blood 95 (2): 416-21, 2000. [PubMed] [Reference list]

12. Reiter A, Schrappe M, Tiemann M, et al.: Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood 94 (10): 3294-306, 1999. [PubMed] [Reference list]

13. R-CHOP chemotherapy: http://www.nwcscnsenate.nhs.uk/files/2114/2305/5439/CMSCN_RCHOP_High.pdf

14. R-ICE chemotherapy: http://www.nwcscnsenate.nhs.uk/files/1114/2658/9185/CMSCN_R_ICE.pdf

15. DA-EPOCH-R chemotherapy: http://nssg.oxford-haematology.org.uk/lymphoma/documents/lymphoma-chemo-protocols/L-66-da-epoch-r-etoposide.pdf

16. Jaffe ES, Harris NL, Stein H, et al.: Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow SH, Campo E, Harris NL, et al., eds.: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: International Agency for Research on Cancer, 2008, pp 157-66. [Reference list]

17. Allen CE, Kamdar KY, Bollard CM, Gross TG. Malignant non-Hodgkin lymphomas in children. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 7th ed. Philadelphia Pa: Lippincott Williams & Wilkins; 2016:587–603.

18. Rabin KR, Margolin JF, Kamdar KY, Poplack DG. Leukemias and lymphomas of childhood. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 10th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2015:1500–1510.

19. EURO-LB 02 chemotherapy: https://www.skion.nl/workspace/uploads/prot-euro-lb-02def-versiejuli1-0amendement.pdf

20. Mann G, Attarbaschi A, Burkhardt B, et al.: Clinical characteristics and treatment outcome of infants with non- Hodgkin lymphoma. Br J Haematol 139 (3): 443-9, 2007. [PUBMED Abstract]

21. Tsuyama N, Sakamoto K, Sakata S, et al.: Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. J Clin Exp Hematop 57 (3): 120-142, 2017. [PMC free article] [PubMed] [Reference list]

22. Sandlund JT, Martin MG. Non-Hodgkin lymphoma across the pediatric and adolescent and young adult age spectrum. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):589–597. doi:10.1182/asheducation-2016.1.589

23. ALCL-99 protocol: https://www.skion.nl/workspace/uploads/alcl-99.pdf

24. APO protocol: https://hemonc.org/wiki/Anaplastic_large_cell_lymphoma

25. Kim, J.G., Sohn, S.K., Chae, Y.S. *et al.* CHOP plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy for patients with peripheral T cell lymphomas. *Cancer Chemother Pharmacol* 58, 35–39 (2006). https://doi.org/10.1007/s00280-005-0136-y

26. B-NHL 2013 https://clinicaltrials.gov/ct2/show/NCT03206671

27. Steven H. Swerdlow, Elias Campo, Stefano A. Pileri, Nancy Lee Harris, Harald Stein, Reiner Siebert, Ranjana Advani, Michele Ghielmini, Gilles A. Salles, Andrew D. Zelenetz, Elaine S. Jaffe; The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127 (20): 2375–2390. doi: https://doi.org/10.1182/blood-2016-01-643569

8.1.6 HODGKIN'S LYMPHOMA

Hodgkin's lymphoma (HL) is a malignant lymphoma originating in the B lymphocytes.

Epidemiology

It is a rare malignancy in the paediatric population, it accounts for about 40% of all childhood lymphomas. It is the most common malignancy in adolescents and young adults. The long term survival rate in children and adolescents with Hodgkin's lymphoma has steadily improved over the years, mainly due to the polychemotherapy and the use of radiation therapy.

The incidence of Hodgkin's lymphoma according to age shows a bimodal distribution. A peak incidence is observed in young adults aged 15 to 34 years; another peak in people over the age of 50. During childhood, there is a slight predominance in males. In Romania, among children and adolescents under 18, approximately 30 new cases are diagnosed each year, with a male / female ratio of 1.4: 1. (1)

Symptomatology

Most patients with Hodgkin's lymphoma (HL) have persistent painless lymphadenopathy, usually cervical and/or mediastinal, with no response to antibiotic therapy. Over 70% of the patients have cervical lymphadenopathy. The patients with mediastinal lymphadenopathy may experience respiratory symptoms: dyspnoea, chest pain, coughing. The presence of an important mediastinal mass can lead to the superior vena cava syndrome. The axillary lymphadenopathy occurs in 25% of all cases; there are also supraclavicular, inguinal and, more rarely, epitrochlear or popliteal sites.

About 25% of the patients have one or more systemic symptoms that are associated with an advanced stage disease and an unfavourable prognosis: fever above 38 degrees C, night sweats, weight loss of more than 10% of the body weight in the last 6 months, pruritus.

The splenomegaly, the hepatomegaly or both may be present. The disease can affect other organs and systems by spreading itself: lungs, bones, bone marrow, and more rarely, CNS.

The immune-mediated paraneoplastic syndromes that may be associated with Hodgkin's lymphoma are: immune thrombocytopenic purpura, autoimmune hemolytic anaemia, nephrotic syndrome. These paraneoplastic syndromes may be present before, after or at the same time as the onset of Hodgkin's disease. (1)

Diagnosis

- Clinical examination: careful evaluation of all lymph node sites, hepatosplenomegaly and involvement of Waldeyer's tissues or tonsils
- Laboratory examinations: blood count with leukocyte picture, ESR, ALP, LDH, CRP, renal and hepatic functional tests, Epstein-Barr antivirus antibodies, HBV, HCV, HIV, CMV, toxoplasmosis serology.
- Imaging examinations:
- PA and lateral chest radiograph, cardio-thoracic index
- Abdominal and pelvic ultrasound
- cervico- thoraco- abdomino- pelvic CT or MRI
- positron emission tomography (PET-CT): initially and after two cycles of treatment

- Cardiologic examination with echocardiography for FEV (pre-chemotherapy, pre-radiotherapy)

- Bone marrow aspirate and/ biopsy in stages IIB, III and IV

- Cytological examination of effusion fluids (ascites, pleural effusion)

Testing during treatment

- blood tests at start of each treatment cycle and / or as needed
- imaging tests PET-CT of other appropriate imaging after 2 courses (ERA) and after courses (LRA), and at end of treatment.

Histopathological diagnosis, classification

The diagnosis is established by means of a lymph node biopsy or the biopsy of an affected tissue with morphological and immunohistochemical examination. (2.3).

The clinical characteristics of different histological subtypes:

- lymph node involvement with predilection in the cervical site, lymph node involvement and contiguous extension to others;

- the lymph node with modified architecture contains a small number of giant mononucleated Hodgkin cells and multinucleated Reed–Sternberg (RS) cells, disseminated in a number of inflammatory cells (lymphocytes, plasma cells, histiocytes, macrophages, neutrophils, eosinophils, fibroblasts and collagen fibres);

Classification: Based on clinical and biological studies, the existence of the two entities of Hodgkin's lymphoma has been established:

I. Nodular lymphocyte predominant Hodgkin lymphoma

II. Classical Hodgkin's lymphoma with the following histological subtypes:

1.Nodular sclerosis HL (NSCHL)

2.Mixed cellularity HL (MCCHL)

3.Lymphocyte rich HL (LRCHL)

4.Lymphocyte depletion HL (LDCHL)

These subtypes differ from each other in regard to clinical features, growth characteristics, the presence of fibrosis, atypia of tumour cells, EBV infection. The genetic aspects and the immunophenotype of the tumour cells are the same in the four subtypes.

I.Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)

- Site: - cervical, axillary, inguinal lymph nodes

- Bone marrow involvement (<1%), rare splenic and mediastinal involvement;

Immunophenotype: positive stains: CD20, CD22, CD79a, CD45, PAX-5

II. Classical Hodgkin's lymphoma: monoclonal lymphoid neoplasm composed of Hodgkin's cells and

Reed-Sternberg (HRS) cells on a background of non-neoplastic cells (small lymphocytes, eosinophils, neutrophils, histiocytes, plasma cells, fibroblasts and collagen fibres)

Lymph node involvement:

- cervical (75%), mediastinal, axillary, paraaortic nodes

- extranodal primary involvement is rare

- mediastinal lymph nodes involvement in the nodular sclerosis type (60%)

- abdominal lymph nodes and splenic involvement in the mixed cellularity type

- splenic involvement (20%) is associated with a risk of extranodal dissemination;

- spinal cord involvement is rare (5%).

Immunophenotype, with subsequent therapeutic implications: positive stains: CD30 (all cases); CD15 (75-85%); CD20 (30-40%); CD79a (10%);

There is a predilection for the clinical presentation of different histological subtypes, as follows:

1. Nodular sclerosis HL (NSCHL): cervical, mediastinal lymph nodes (80%), splenic and/or pulmonary (8-10%), bone (5%), spinal cord and hepatic (2-3%);

2. Mixed cellularity HL (MCCHL): peripheral lymph nodes, cervical and supraclavicular lymph nodes

- mediastinal involvement is unusual
- spleen (30%); bone marrow (10%); liver (3%)

3. Classical lymphocytes rich HL (LRCHL): peripheral lymph nodes (typical); mediastinal involvement (15%), lung (4%), bones (3%), bone marrow (2%), liver (2%), Waldeyer ring

4. Classical lymphocyte depletion HL (LDCHL): retroperitoneal lymph nodes, abdominal organs, marrow (54%); peripheral lymphadenopathy (50%); often associated with HIV;

The two forms described by Lukes and Butler (1966) are included: diffuse fibrosis and the reticular form.

Staging, prognostic factors

The Ann Arbor staging in four stages, A or B, is used to stage Hodgkin's lymphoma and it is the basis of the treatment regimen.

- Favourable prognostic factors (4, 5):
- Small number of affected lymph nodes
- No large tumour volume (less than 5 cm in diameter)
- No B symptoms
- No extra-nodal presence
- Stages I, II A
- Unfavourable prognostic factors (4, 5):
- Advanced stages (IIB, III and IV)
- B symptoms
- High tumour volume
- Pericarditis, pleurisy
- Anaemia, leukocytosis over 11,500 / mmc, accelerated ESR
- Hypoalbuminemia
- Male sex
- Lack of Initial response to chemotherapy
- Adolescents have a less favourable prognosis than children

Treatment (6)

The recommended chemotherapy follows the recommendations of the EuroNet-Pediatric Hodgkin's Lymphoma Group, differentiated according to the therapeutic group and taking into account the response to treatment assessed after the first two cycles of OEPA protocol treatment, in both boys and girls. The assessment of the response to the treatment is completed by a PET-CT scan.

Treatment groups (TG):

- TG-1: stages I A/B and II A: 2X OEPA - RC (PET-CT): complete treatment
- nonRC (PET-CT): RT
- TG-2: stages IEA/B, IIEA, II B or III A: 2X OEPA - (PET-CT) - 2X COPP or 2X COPDAC
    - RC (PET-CT): ends the treatment
    - nonRC (PET-CT): RT
- TG-3: stages IIEB, IIIEA/B, III B or IV A/B: 2X OEPA - (PET-CT) - 4COPP / 4COPDAC
- RC (PET-CT): ends the treatment
- nonRC (PET-CT): RT

Description of the protocols:

- OEPA protocol: PRD, VCR, Doxo, VP16
- COPP protocol: PRD, PCB, VCR, CTX
- COPDAC protocol: PRD, DTIC, VCR, CTX

Other accepted protocols:

Primary: ABVD; COPP; CVPP, MOPP; ChlVPP; COMP; OPPA; OEPA; OPA; BEACOOP; CVPP (with CCNU), MOPP / ABV, STANFORD V

- ABVD: Doxo, Bleo, DTIC, VBL
- COPP: CTX, VCR, PCB, PRD
- MOPP: Mechlorethamine, VCR, PCB, PRD
- ChlVPP: Chlorambucil, VBL, PCB, PRD
- OPPA: VCR, PCB, PRD, Doxo
- OEPA: VCR, VP16, PRD, Doxo
- BEACOPP: Bleo, VP16, Doxo, CTX, VCR, PCB, PRD
- CVPP: CTX, VBL, PCB, PRD

Second-line:

- ICE: IFO, Carbo, VP16
- DHAP: dexa, ARA-C, DDP
- IGEV: IFO, GEM, Vin, PRD
- IEP: IFO, EPI, DDP
- APE: ARA-C, DDP, VP16
- MIED: HD-MTX, IFO, VP16, Dexa
- Rituximab (for CD20-positive patients) alone or in combination with second-line chemotherapy (7).
- Brentuximab vedotin has been proven to be effective in studies for CD30-positive adults and it is being studied in children for post-transplant relapse (8).
- Checkpoint inhibitors therapy (Nivolumab, Pembrolizumab) has been proven to be effective in adult population studies (8).

The doses and cycles of chemotherapy are determined by the stage of the disease, the risk group, the initial response, age, tumour volume, B symptoms, for example:

Stages I-II A, favourable histology: 2-3 cycles of ABVD; 2 OPPA; 2 OEPA; 3 COPP

Stage III and for I and II with B symptoms stages: 4 cycles ABVD, 4 OPPA or OEPA, 4 COPP

Stages IV: 6-8 cycles of chemotherapy

4-week reassessment (including PET CT)

Radiotherapy

At the moment the recommendation for using radiotherapy is limited. Thus for stages non-bulky IA, IB, and II A with complete remission it is preferred to keep it under observation. If the complete remission is not achieved after the chemotherapy, radiotherapy is indicated on the initially involved sites. It is applied as IFRT (Involved Field Radiotherapy) at doses of 21-25.5 Gy.

Treatment of the refractory disease or of relapses

Refreactory disease: high-dose chemotherapy and stem cell transplant

Early relapse (less than 1 year): high-dose chemotherapy and stem cell transplant

Late relapse: second-line chemotherapy, radiotherapy, Rituximab

Relapse after an autologous bone marrow transplant - new treatments: Brentuximab-vedotin-anti-CD30 conjugated monoclonal antibody (clinical trials for the paediatric population)

Palliative chemotherapy (Navelbin weekly)

Post-therapeutic follow-up

The patient will be monitored every 3 months in the first 2 years; every 6 months in the next 3 years; annually after 5 years.

Follow-up criteria over time:

- Regarding the lymphoma (clinical examination, blood count, ESR, ALP, LDH, CRP, abdominal ultrasound, chest radiograph or chest CT exam)
- A biopsy will be performed on the suspicious lesion
- Regarding the sequelae: - checking of the thyroid function (after radiotherapy), cardiological examination (after anthracyclines, radiotherapy), respiratory function tests (after irradiation, radiotherapy)
- Follow-up on the fertility
- Follow-up for the detection of the appearance of the second malignancy

Recommendations

- The recommended chemotherapy follows the recommendations of the EuroNet-Pediatric Hodgkin's Lymphoma Group, differentiated according to the therapeutic group
- The PET-CT examination is recommended initially, after two cycles of chemotherapy and when evaluating the therapeutic response

Bibliography

1. Monika Metzger, Matthew Krasin, Mellisa Hudson, Mihaela Onciu. Hodgkin lymphoma. In: Pizzo PA, Popelack DG, Principles and practice of pediatric oncology. Philadelphia Lippincott Williams& Wilkins. 2011; 638-62

2. Richard T. Hoppe, Ranjana H. Advani, Weiyun Z. Ai et al. NCCN Hodgkin Lymphoma version 1.2017. Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15(5):608–38

3. Pedro A de Alarcon, Vikramjit S Kanwar. Pediatric Hodgkin Lymphoma, htthttps://emedicine. medscape.com/article Mar 20, 2017

4. D.A. Eichenauer, B.M.P. Aleman, M.Andre´, M.Federico, M. Hutchings, T.Illidge, A.Engert,M. Ladetto. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2018; 29 (Supplement 4): 19–29

5. Debra L. Friedman. Chapter 21: Hodgkin Lymphoma.In: Lanzkowsky Philip, Jeffrey Lipton, Jonathan Fish. Manual of pediatric hematology and oncology, Elsevier, Sixth Edition 2016;429-41

6. EuroNet-Paediatric Hodgkin's Lymphoma Group First international Inter-Group Study for classical Hodgkin's Lymphoma in Children and Adolescents 2006

7. Schulz H, Rehwald U, Morschhauser F, et al.: Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). Blood 2008, 111 (1): 109-11.

8. Cole PD, McCarten KM, Pei Q, et al.: Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. Lancet Oncol 2018,19 (9): 1229-38,.

8.1.7 HISTIOCYTOSIS

Histiocytosis is a rare disease characterized by the accumulation of cells derived from dendritic or macrophage cells. Dendritic cells, monocytes and macrophages are members of the mononuclear phagocytic system and histiocytes are actually a term used to define macrophages present in tissues.

The clinical manifestations of histiocytosis range from mild to disseminated, sometimes life-threatening.

The Histiocyte Society proposed in 2015 the following classification of histiocytoses: (1)

L group Histiocytosis

- Langerhans cell histiocytosis (LCH)
- indeterminate cell histiocytosis (including Erdheim-Chester disease and disseminated juvenile xanthogranuloma)
- mixed type Langerhans histiocytosis / Erdheim-Chester disease

C Group histiocytosis (cutaneous and mucocutaneous):

- non-Langerhans cutaneous histiocytosis
- non-Langerhans cutaneous histiocytosis with a major systemic component

"M" Group of histiocytosis (malignant histiocytosis):

- primary malignant histiocytosis
- secondary malignant histiocytosis

R Group histiocytosis (Rosai-Dorfman disease and non-cutaneous histiocytosis, various non-Langerhans):

- Rosai-Dorfman family disease
- classic Rosai-Dorfman disease (nodal)
- extranodal Rosai-Dorfman disease
- Rosai-Dorfman disease associated with malignancies
- Rosai-Dorfman disease associated with immune diseases
- other non-C, non-L, non-M and non-H histiocytosis

H Group histiocytosis (hemophagocytic lymphohistiocytosis and macrophage activation syndrome):

- Primary hemophagocytic lymphohistiocytosis (diseases with Mendelian transmission that can be determined by hemophagocytic lymphohistiocytosis)
- Secondary hemophagocytic lymphohistiocytosis (apparently non-Mendelian hemophagocytic lymphohistiocytosis)

Langerhans cell histiocytosis (LCH)

Langerhans histiocytosis is a disease characterized by the proliferation and accumulation of abnormal Langerhans cells in the bones, skin, liver, spleen, lung, bone marrow and brain.

Langerhans cells are dendritic cells originating in the bone marrow. Abnormal Langerhans cells, which are labelled CD1a+/- CD207, represent less than 10% of the cellularity present in LCH lesions, the rest of the cells being polymorphic inflammatory cells: lymphocytes, eosinophils, normal histiocytes. In LCH, abnormal Langerhans cells are activated, activation for which advocates the synthesis of various pro-inflammatory cytokines, this being an argument for the inflammatory / immune theory of the disease. For the malignant theory of LCH, the

claims are demonstrated by the clonality of Langerhans cells and various genetic abnormalities, such as the BRAF V600E mutation or the recurrent mutations of MAP2K1 (which encodes MEK1). These findings have led the WHO to currently define LCH as being "neoplastic clonal proliferation of Langerhans cells". (2, 3, 4)

Epidemiology

LCH affects 4-8 children/1 million, an incidence similar to that of Hodgkin's lymphoma. (2)

Classification

LCH is divided, according to new classifications of the Histiocyte Society from 2015, into 4 groups depending on the number of organs/systems that are involved, lung involvement and involvement to at least 1 of the 3 " risk organs" (liver, spleen and bone marrow):

- LCH with single system involvement;
- LCH with lung involvement;
- LCH with multisystemic involvement without affecting " risk organs";
- LCH with multisystem involvement with "risk organs" affected.

The lung involvement is considered an unfavourable prognosis, however according to the new classification, the lung is no longer considered a "risk organ".

"CNS risk" lesions are defined as lesions in the orbit, mastoid, temporal bone, sphenoid bone, ethmoidal bone, jaw, sinuses, anterior/middle cranial fossa with extension to the intracranial soft tissue that causes a high risk of diabetes diabetes insipidus. (1, 4)

The presence of lesions in certain sites determines their classification as "special sites" due to the local, functional complications that they can cause. (4, 6, 7)

The clinical picture of LCH is extremely heterogeneous, ranging from self-limiting forms of the disease to disseminated forms with fulminant evolution.

The signs and symptoms that need to be looked for in particular, both by the anamnesis and by the objective examination, are: (2, 5)

- fever;
- skin rash, often in the form of seborrhoeic-like dermatitis in young children, on the scalp, retroauricular, lower chest and abdomen, flanks;
- edema;
- lymphadenopathy, hepatomegaly, splenomegaly;
- otorrhea;
- bone pain, frequently in the long bones;
- changes in the gums, dentition;
- clinical signs of anaemia, thrombocytopenia;
- diarrhoea, but intestinal involvement is rare;
- polydipsia, polyuria caused by diabetes insipidus that is common in LCH, either part of multisystem involvement or single system bone disease (in case of damage to craniofacial bones);
- dyspnoea, tachypnea, traction, lung involvement is more common in smokers;
- loss of appetite, weight loss / unsatisfactory weight gain, failure to thrive;
- neurological and behavioural changes (2, 5)

Recommended paraclinical examinations and radiological evaluations:

- complete blood count;
- ferritin;
- inflammatory samples: ESR, fibrinogen, PCR;

- complete coagulogram: PT, IP, INR, aPTT;
- liver function: ASAT, ALAT, γGT, FA, bilirubin, total proteins, albumin;
- renal function: urea, creatinine;
- urinary density (ideally in the morning on waking after water deprivation at night);
- chest radiograph; bone skeleton radiographs. The bone scintigraphy is optional and should only be performed as an additional examination of bone skeleton radiographs; (7) abdominal ultrasound. CT of lungs and furhter CNS studies should be performed on clinical indications.

PET-CT: it is indicated for pre- and post-therapeutic evaluation, pre- and post-autologous stem cell transplantation evaluation, recurrence suspicion.

Recommended additional paraclinical, imaging and specialist clinical examinations for various organ involvements:

- bicytopenia, pancytopenia, single unexplained cytopenia, multisystem involvement: osteomedullary aspirate / osteomedullary biopsy
- liver involvement: abdominal ultrasound, liver biopsy is indicated only if the result changes the treatment (e.g. differential diagnosis between active LCH and sclerosing cholangitis)
- lung involvement: chest CT, respiratory function tests (if the patient's age allows this examination), if considered absolutely necessary for diagnosis: bronchoalveolar lavage (LCH diagnosis: > 5% CD1a+ cells in non-smokers), lung biopsy if lavage was inconclusive
- suspicion of involvement of the craniofacial bones, including the jaw and mandible: cranial MRI with contrast substance, which will include the brain, the hypothalamic-pituitary axis and the craniofacial bones; (7)
- suspicion of endocrine abnormalities: endocrine tests (including water deprivation test, dynamic pituitary function test and thyroid tests), cranial MRI
- suspected ear/mastoid involvement: ENT consultation with audiogram, cranial MRI
- neurological abnormalities: specialized neurological consultation, cranial MRI
- gum involvement, dental abnormalities: dental consultation, panoramic dental radiographs and mandibular and maxillary CT
- unexplained chronic diarrhoea, failure to thrive, malabsorption: upper digestive endoscopy with mucosal biopsy

The criteria for the diagnosis of organ involvement and their definition as "risk organs" or "risk sites" are presented in Table 1. (5, 6, 7)

Table 1. Criteria required for the diagnosis of organ involvement in LCH

Involvement	Criteria	RS	RO
Bone	Bone involvement: any radiologically documented, histologically confirmed lesion It can be: unifocal (1 bone) or multifocal (> 1 bone)		
	Craniofacial bones: lesions of the orbital, temporal, mastoid, sphenoidal, zygomatic or ethmoidal bones; jaws or paranasal sinuses, cranial fossa; with extension into the intracranial soft tissue	X	
	Vertebral involvement without extension in the soft tissue (e.g. vertebra plana)		
	Vertebral involvement with extension in the soft tissue or odontoid lesions	X	

	Scintigraphic or hypersignal abnormality on MRI, uncorrelated symptoms or with a radiological change is not considered bone involvement!		
Hematological	Mild (both changes must be present): Hemoglobin between 7-10 g/dl and thrombocytopenia 20,000-100,000/mm^3		X
	Severe (both changes must be present): Hemoglobin <7 g/dl and Thrombocytopenia <20,000/mm^3		
Splenic	Splenomegaly at >3 cm below the costal margin confirmed by ultrasound		X
Hepatic	Hepatomegaly at >3 cm below the costal margin confirmed by ultrasound, or Hepatic impairment: hyperbilirubinemia > 3 x VN, hypoalbuminemia (<3 g/dl), γGT > 2 x VN, ASAT-ALAT > 3 x VN, ascites, edema, or Intrahepatic nodular masses		X
Pulmonary	Typical lesions (nodules or cysts) on CT Any atypical mass requires exploration by bronchoalveolar lavage to perform a histopathological/cytological diagnosis		
Mucosal	Lesions of the oral / gingival, genital, anal mucosa		
Eye	Involvement of the orbit with proptosis or exophthalmos	X	
Ear	Ear involvement with otitis externa, otitis media or otorrhea	X	
Pituitary gland	Any pituitary hormone deficiency or Tumour of the hypothalamic-pituitary axis		
CNS	Tumour: any expansive intracranial lesion that predominantly affects the brain or meninges	X	
	Neurodegeneration on MRI: MRI images compatible with neurodegenerative disease, e.g. signal with abnormal intensity in the teeth or cerebellum or brain atrophy that is NOT explained by cortisone therapy	X	
	Clinical neurodegeneration: the presence of suggestive symptoms (cerebellar syndrome / learning difficulties) compatible with MRI lesions	X	

RS – risk site; RO – risk organ

The diagnosis certainty of LCH is established by highlighting the CD1a+/- CD207 antigen (Langerin) on the surface of the cells in the lesions (immunophenotyping or immunohistochemistry). CD207 expression on the cell surface is a confirmation of the presence of intracytoplasmic Birbeck granules which makes their demonstration no longer necessary (7).

Treatment

It is recommended to use the LCH-III protocol, a protocol of the Histiocyte Society. (7)

• Local therapy

- Single bone lesion: observation of possible spontaneous retraction, curettage of the lesion if the lesion is small (<2 cm), local injection with steroids. Bone lesions at risk of CNS are treated according to the LCH-III protocol

- Skin lesions: local corticosteroids

- Lung: stop smoking; isolated lung involvement does not require systemic therapy; pneumatoceles (possible complication) is treated by drainage and pleurodesis (5, 6)

• Systemic therapy is recommended for patients with LCH with multiple system involvement, single system involvement with the presence of "risk sites", single system involvement with "multifocal bone lesions" and those with single system involvement with "CNS risk".

o LCH with multiple system involvement:

- all patients: a 6-week block with VBL and PRD
- patients with an initial involvement of "risk organs" or those without an initial involvement of "risk organs" but who do not improve: a second 6-week block of VBL and PRD is recommended
- all patients with multiple system involvement: continuation of the maintenance therapy (continuous 6MP and pulses of VBL and PRD every 3 weeks) for a period of 12 months.
- patients with "risk organs" involvement who do not improve after 12 weeks of initial therapy and those who develop "risk organ" involvement under treatment are recommended to undergo rescue therapy with 2-chlorodeoxyadenosine (2-CdA, Cladribine) and ARA-C
- patients without " risk organs" involvement who do not respond to the first 2 blocks of therapy are recommended to undergo second-line therapy (monotherapy with Cladribine or combination of VCR, PRD, ARA-C)

o LCH with single system involvement with the presence of " risk sites", with "multifocal bone lesions", with "CNS risk": block 1 +/- block 2 of VBL and PRD followed by 12 months of pulse therapy of VBL and PRD at 3 weeks (without 6MP). (7)

Radiation therapy is no longer part of LCH treatment due to long-term sequelae. (5, 6, 7)

The evaluation of the response to treatment is done by following:

- clinical status;
- complete blood count;
- liver and spleen size (clinical and ultrasound);
- liver function tests;
- radiographs and chest CT (for those with lung involvement);
- radiographs of the skeletal bones (only of the bones with initial lesions);
- cerebral MRI in patients with "CNS risk";
- cpinal MRI of those with vertebral lesions;
- PET-CT (if considered necessary); (7)

Prognosis

In the case of patients with single system involvement and those with multisystem involvement without "risk organs" the survival is 100%. However, there is a risk of reactivation of lesions or long-term sequelae, especially orthopedic sequelae and diabetes insipidus. Recent studies show that there is a possibility for LCH secondary neurodegenerative lesions that do not respond well to treatment. (5, 6, 7)

Hemophagocytic lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis is a rare, potentially fatal clinical syndrome caused by a hyperinflammatory status and progressive organ damage due to an excessive but inefficient immune response. The two main types of HLH are: primary and secondary or reactive HLH. (1, 8)

The pathophysiological mechanism of HLH, based mainly on that of primary HLH, is based on the disorder of the cytotoxic mechanisms of cytotoxic T lymphocytes and natural killer cells, namely the impossibility of inserting perforin into the membrane of antigen presenting cells (macrophages and histiocytes) and granule release, leading to the impossibility of apoptosis of the antigen presenting cells. Due to this persistent antigenic stimulation of

cytotoxic and natural killer T cells by antigen presenting cells, an abundant release of cytokines occurs. This "cytokine storm" creates a systemic inflammation that can cause tissue destruction, organ failure and death. Activated macrophages will cause hemophagocytosis, a pathological feature of HLH but its demonstration is not essential for diagnosis. (1, 8, 9, 10)

Primary HLH is associated with various Medelian-transmitted immune diseases. In primary HLH, 4 genes were identified, the most common being PRF1 and UNC13D that determine FHL2 and FHL3. Primary HLH may be associated with hereditary immunodeficiencies: Chédiak-Higashi syndrome, Griscelli type 2 syndrome, and X-linked lymphoproliferative disorder type 1 and 2. Clinical manifestations usually occur in the first year of life, but cases have also been reported in which symptoms installed later on. Even in cases of primary HLH, the clinical manifestations can be triggered by infection, which makes the differential between the primary and secondary forms difficult to diagnose. (9, 10, 11)

Secondary / reactive HLH is classified as HLH associated with infections, of which EBV infection is the most commonly involved, HLH associated with malignancies and HLH associated with autoimmune diseases (the term "macrophage activation syndrome" being used in association with rheumatic diseases). Secondary HLH has also been reported in patients with post-transplant immunosuppressive therapy, possibly in the context of opportunistic germ infections which these patients are prone to. (1, 8, 9, 10, 11)

The clinical manifestations are those of a sudden onset of a systemic inflammatory syndrome (SIRS): (10, 11, 12)

- fever, altered general condition;
- hepatosplenomegaly;
- jaundice;
- generalized lymphadenopathy;
- cytopenias;
- skin rash (frequently of the measles-like type);
- neurological manifestations: seizures, encephalopathy, ataxia, cranial nerve palsy, irritability;

Paraclinical examinations: (10, 11, 12)

- blood count revealing cytopenias on at least 2 lines;
- hypofibrinogenemia
- highly elevated ferritin levels; (values > 10,000 ng/dl have a 90% sensitivity and a 96% specificity for HLH);
- hypertriglyceridemia;
- altered liver tests: increased transaminases, hyperbilirubinemia, increased LDH;
- CSF: hypercellularity and hyperproteinemia;

Histopathological examinations: (10)

- diffuse and significant accumulation of mature lymphocytes and macrophages which occasionally show hemophagocytosis in the bone marrow, lymph nodes, liver, skin, lung, meninges, CSF and rarely in the subcutaneous tissue;
- in the bone marrow, the hematophagocytosis of mature and immature hematopoietic elements is characteristic, along with myeloid and erythroid hypoplasia and megakaryocytic hyperplasia;

For HLH diagnosis criteria, see table 2. (10, 11, 12)

Particular care is needed to make the differential diagnosis between HLH and other diseases that can be confused with due to clinical or paraclinical similarities: SIRS due to other causes, especially severe sepsis (in which the phenomenon of hemophagocytosis can occur),

neonatal hemochromatosis and metabolic disorders in infants with organomegaly or hypertriglyceridemia, malignant lymphomas. (8, 10, 11)

Treatment

It is recommended to use the HLH-2004 protocol, a protocol of the Histiocyte Society. The protocol is intended for patients with primary or secondary HLH, regardless of the confirmed presence of infections. (11, 12)

The initial protocol consists of 8 weeks of treatment with Dexa, Cyclosporine and VP16. If after 2 weeks of treatment there are progressive neurological symptoms or changes in the CSF examination, the administration of MTX and PRD it is recommended (4 weekly courses).

In the case of patients with secondary HLH who responded to the initial protocol, it is recommended to stop the therapy and monitor them closely for possible recurrences.

In patients with secondary HLH who do not enter remission after the initial protocol, it is recommended to undergo treatment with the follow-up protocol consisting of the same combination of drugs administered for up to 30 weeks.

For patients with primary HLH, the treatment with the follow-up protocol is recommended after the initial protocol until hematopoietic stem cell transplantation is performed, which is the only curative therapeutic method.

In patients with HLH secondary to EBV infection who do not respond to the HLH-2004 protocol, the treatment with Rituximab is recommended. (8, 9)

In patients with primary or secondary HLH who do not respond to treatment, while waiting for hematopoietic stem cell transplantation, it is recommended to follow the rescue therapy with e.g ATG, Alemtuzumab orEmapalumab. (8, 9)

Table 2. HLH diagnosis criteria (according to the HLH Guide - 2004)

The diagnosis of HLH can be established if criterion 1 or 2 is met

1. Positive molecular diagnosis for HLH
2. The presence of 5 out of the 8 positive diagnostic criteria for HLH:

Initial diagnosis criteria (to be evaluated in all patients)

- fever
- splenomegaly
- cytopenias, affecting at least 2 out of the 3 lines: - hemoglobin < 9 g/dl
  - platelets <100.00 / mm^3
  - neutrophils <1,000 / mm^3
- hypertriglyceridemia and/or hypofibrinogenemia: - triglycerides after 12 h fasting <265 mg/dl
  - fibrinogen <150 mg / dl
- haemophagocytosis in the bone marrow, spleen or lymph nodes; absence of malignancy

New diagnosis criteria

- low or no activity of natural killer cells
- ferritin ≥ 500 ng/dl
- soluble CD25 (soluble IL-2 receptor) ≥ 2.400 U/ml

Prognosis

Prior to the introduction of the HLH, HLH-94 and then HLH-2004 protocols, the prognosis for the patients was severe, especially for those with the primary form of the disease which was fatal. The results of the HLH-94 protocol reveal 5-year survival of over 50%, the

results of the HLH-2004 protocol have not yet been published. The introduction of hematopoietic stem cell transplantation as therapy in patients with primary or secondary forms of HLH who do not respond to other therapies has increased the survival of these patients to over 50%. (10, 11)

Recommendations

- The classification of the histiocytosis was established by the Histiocyte Society in 2015
- Langerhans histiocytosis is treated according to the LCH-III protocol, a protocol of the Histiocyte Society
- The treatment of primary or secondary hemophagocytic lymphohistiocytosis is done according to the protocol HLH-2004, protocol of the Histiocyte Society
- The prognosis of hemophagocytic lymphohistiocytosis improved after the use of HLH protocols and hematopoietic stem cell transplantation

Bibliography

1. Emile JF et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood.* 2016;127(22):2672-2681
2. Thacker NH, Abla O. Pediatric Langerhans Cell Histiocytosis: State of the Science and Future Directions. *Clin Adv Hematol Oncol.* 2019;17(2):122-131
3. Allen CE, Ladisch S and McClain KL. How I treat Langerhans cell histiocytosis. *Blood*. 2015;126(1):26-35
4. Euro Histio Net Work Group for LCH Guidelines. Langerhans cell histiocytosis (LCH) - Guidelines for diagnosis, clinical work-up and treatment during childhood: 1-18. webgate.ec.europa.eu
5. Donadieu J, Chalard F and Jeziorski E. Medical management of langerhans cell histiocytosis from diagnosis to treatment. *Expert Opin. Pharmacother.* 2012;13(9):1309-1322
6. Haupt R et al. Langerhans Cell Histiocytosis (LCH): Guidelines for Diagnosis, Clinical Work-Up and Treatment for Patients Till the Age of 18 Years. *Pediatr Blood Cancer.* 2013;60:175–184
7. Langerhans Cell Histiocytosis. Histiocyte Society Evaluation and Treatment Guidelines. April 2009. www2.hematologie-amc.nl>hematologie
8. Imashuku S. Hemophagocytic lymphohistiocytosis: Recent progress in the pathogenesis, diagnosis and treatment. *World J Hematol.* 2014;3(3):71-84
9. Morimoto A. Hemophagocytic lymphohistiocytosis: Pathogenesis, diagnosis, and management. *Pediatrics International*. 2016;58:817–825
10. Sieni E et al. Familial hemophagocytic lymphohistiocytosis: when rare diseases shed light on immune system functioning. *Front. Immunol*. 2014; https://doi.org/10.3389/fimmu.2014.00167
11. Rosado FGN, Kimm AS. Hemophagocytic Lymphohistiocytosis. An Update on Diagnosis and Pathogenesis. *Am J Clin Pathol.* 2013;139:713-727
12. Henter Ji et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48:124–131

8.2 PRIMARY TUMOURS OF THE CENTRAL NERVOUS SYSTEM

8.2.1 EPENDYMOMA

Epidemiology

Ependymomas are brain tumours that develop from the ependymal cells lining the cerebral ventricles or the central canal of the spinal cord. (1) Ependymomas are the third commonest paediatric central nervous system (CNS) tumour, accounting for 6-12% of brain tumours in children. (2)

Approximately 90% of all ependymomas are in the intracerebral site (supratentorial and infratentorial). They are more common in children than in adults. About two-thirds of them grow in the posterior cerebral fossa, this representing the fourth tumour in regard to frequency in this site, after medulloblastoma, cerebellar astrocytoma and brainstem glioma. Spinal ependymomas are more common in adults.

The highest incidence is up to the age of 7, and the boys/girls ratio is 1.3/2. (1)

According to the National Register of Childhood Cancers in Romania, the paediatric oncology section reports an average of 7 new ependymoma cases per year. (Class ICCC3 III a).

Symptomatology

The clinical picture varies according to the age of the onset and to the primary site of the tumour. The most common site is the fourth ventricle and the symptoms are represented by: nausea, vomiting (especially in the morning), headache, lethargy, cerebellar syndrome, cranial nerve palsy (VI-X). Other manifestations at the onset can be: macrocrania, seizures, focal neurological deficits or behavioural changes, occurring usually in older children.

Spinal tumors present with the following symptoms due to the spinal cord compression syndrome: neuropathic pain, paresthesia, hemiplegia, spastic tetraparesis, urinary/fecal incontinence. (3, 4) The onset may be uncharacteristic, represented only by persistent low back pain in a child with no history of trauma. When the patient presents with motor neurological deficiencies, the situation becomes a neuro-oncological emergency. In the absence of an urgent intervention (48-72 hours) to remove the spinal compression due to the tumour, the neurological deficits may be irreversible. For newly developed neurological symptoms, the child should be referred urgently to a paediatric neurology consultation.

Diagnosis, staging

The specific aspect of MRI is represented by low signal intensity on T1, heterogeneous hypersignal intensity on T2 and gadolinophilic uptake. In the posterior cerebral fossa, the ependymoma may present an extension through the foramen of Luschka, through the cerebellopontine angle and/or through the foramen of Magendie. (5)

CSF cytological examination: if there is no contraindication to perform the lumbar puncture CSF is preferably drawn before surgery. In case of contraindications CSF can be drawn at 10-14 days postoperatively. (6)

The definitive diagnosis is established by the histopathological examination of the excised or biopsied tumour.

The oldest staging was proposed by Chang et al. in 1969 (originally designed for medulloblastoma). The criteria taking into account were the following: the size of the tumour at the time of the surgery and the degree of macroscopic invasion of neighbouring structures (strictly surgical classification). (see Table 1)

Table 1 Surgical staging according to CHANG, 1969

T1	Tumour less than 3 cm in diameter, limited to the classical sites (fourth ventricle, vermis, cerebellar hemispheres)
T2	Tumour over 3 cm in diameter, invading a neighbouring structure or partially occupying the fourth ventricle
T3a	Tumour that invades 2 neighbouring structures or that completely occupies the fourth ventricle, with extension at the level of the foramen of Magendie or the foramen of Luschka, with marked internal hydrocephalus
T3b	Tumour with a starting point in the roof of the fourth ventricle or in the brainstem and occupying the fourth ventricle
T4	Tumour that extends past the aqueduct, invading the third ventricle or midbrain or extending to the cervical spinal cord
There is no N stage	
M0	No metastases
M1	Neoplastic cells detected in the CSF
M2	Macroscopic metastases in the cerebellum and/or in the subarachnoid space and/or in the supratentorial ventricular system
M3	Macroscopic metastases in the spinal subarachnoid space
M4	Metastases outside the CNS

Currently, it is recommended to use the M staging system to assess the extent of the disease depending on the presence of the metastases, assessed by craniospinal imaging evaluation and cytological analysis of CSF. (3, 7) (see Table 2)

Table 2 Staging according to the M staging system

Localized disease	M0 - without other tumour formations visible at imaging scans (craniospinal MRI), outside the primary site; without atypical cells in the CSF
Metastatic disease (brain metastases, spinal metastases, tumour cells detected by the cytological examination of the CSF)	M1 - atypical cells / tumour cells in CSF
	M2 - imagistically visible brain metastases
	M3 - spinal metastases or in the cervicomedullary junction
	M4 - metastases outside the CNS

Adapted according to Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines (7)

Histopathological forms. Classification

The WHO classification of the central nervous system tumours (2016) classifies ependymomas in 3 grades, depending on the histological aggression: (8)

Grade I: mixopapillary ependymoma (9394/1), subependymoma (9383/1)

Grade II: classic ependymoma (clear cell, papillary, tanycytic), RELA fusion-positive ependymoma (9393/3)

Grade III: anaplastic ependymoma (9392/3)

The new WHO 2016 classification introduces molecular parameters, in addition to the histopathological ones that were already used, so that, especially for supratentorial ependymomas, the testing for the RELA-fusion protein is additionally recommended. (8)

In order to improve the correct assessment of the prognosis and the optimal choice of a more or less aggressive treatment, efforts are made to differentiate between grades II and III of ependymomas. (8) ICD- 0-10 coding: C71.0 - C71.9, C72.0, C72.1.

Treatment

Prognostic factors that influence the therapeutic decision:

- Currently, the most important prognostic factor for deciding how to treat is the grade of extension of the tumour resection (total ablation vs. partial ablation or biopsy). (9)

- The young age at onset (less than 3 years of age) has a negative impact on the prognosis, due to its frequent site in the posterior fossa with invasion of the brainstem) which makes the total ablation per primam impossible. More so, the use of radiotherapy at these ages is limited. (1)

Surgery

The treatment of choice is surgery performed by a specialized team of neurosurgeons. Whenever possible, total ablation of the tumour mass will be performed. If this is not feasible, the biopsy (stereotactic or open) or the subtotal resection of the tumour is recommended. (9)

Cerebellar mutism syndrome is a common complication of the surgery on the posterior fossa, especially when there is a brainstem invasion. It can occur with a latency of 1-7 days and can last up to 1 year. (3)

Spinal tumours are approached by classical laminectomy, and the success rate depends very much on the intramedullary extension. (3)

The therapeutic recommendations for newly diagnosed children with WHO grade II and III ependymomas are shown in Table 3, adapted according to the EANO Guide for the diagnosis and treatment of ependymal tumours, 2018.

Table 3 Therapeutic recommendations - Grade II and III ependymomas, WHO classification

Recommendations	Grade	Level of recommendation
The total resection is the treatment of choice, when it can be obtained. It is extremely important both for the subsequent prognosis and for the reliable histopathological diagnosis	II	B
Postoperative MRI to confirm the grade of resection	n.a.	Good practice point
A second-look intervention * is recommended, if the residue of the tumor can be subjected to total ablation	II	B
Because there is a risk of CSF dissemination, any newly diagnosed child should be evaluated in regard to the grade of the disease with the help of a craniospinal MRI and a cytological examination of the CSF (not earlier than 2-3 weeks postoperatively).	n.a.	Good practice point
Children> 18 months - postoperative radiotherapy, with doses up to 59.4 Gy	II	B

Children of 12-18 months or over 18 months with impaired neurological status - postoperative radiotherapy, with doses of 54 Gy	II	B
The chemotherapy is recommended as the only oncological treatment in children under 12 months and as an optional treatment for those under 18 months (in which RT cannot be performed yet)	III	C
Craniospinal irradiation in patients with positive CSF or spinal involvement, with boost on focused lesions (age-appropriate doses)	IV	Good practice point

Table 3, adapted according to the EANO Guide for the diagnosis and treatment of ependymal tumours, 2018

** second-look intervention = Surgery performed after primary treatment to determine if there is any remaining tumour tissue.*

Cytostatic treatment

The systemic cytostatic treatment is recommended for young patients as well as for those with postoperative residual tumour. Adjuvant chemotherapy protocols have been designed to delay the radiotherapy. (8) The optimal time to initiate adjuvant chemotherapy is 4 weeks postoperatively, if the patient's clinical condition allows it. (10)

Therapeutic protocols for children under 1 year of age are still being developed and designed. The purpose of these cytostatic treatments is to postpone radiotherapy until after the age of 12/18 months, as well as to make the tumor operable, in case of a second-look intervention. Long-term survival depends on the possibility of total tumour resection. (10)

Radiotherapy

The standard therapy for ependymoma in children is localized radiotherapy. The usual practice recommends radiotherapy starting with the age of 3, although the latest studies have shown good tolerance even at younger ages. Thus, the German protocol HIT 2000 proposes the initiation of the radiotherapy from the age of 18 months, while the protocols SIOP-EP II and EANO, indicate the age of 12 months. (9, 11)

The optimal interval for initiating radiotherapy after surgery should be less than 6 weeks. The standard dose is 59.4 Gy for conventional localized RT and 54 Gy for children younger than 4 years of age. (9)

Recommended radiotherapy techniques: 3D conformal radiotherapy / IMRT. Proton therapy should be considered as an alternative to photon radiotherapy in attempt to limit neurocognitive side effects and the effects on the auditory nerve structures. (6,11)

The role of chemotherapy after radiotherapy is not well defined, being studied in unfinished trials (COG and SIOP Ependymoma II, to be published). (9)

Multimodal treatment strategies

Non-surgical treatment recommendations for Grade II and III ependymomas are shown in Table 4. Proton therapy should be considered in all localized ependymomas whenever possible.

Table 4 Non-surgical treatment recommendations for grade II and III Ependymomas, WHO classification

	PCT protocol	PCT indication	RT indication	Total dose, Gy	Gy Dose / fraction	RT technique
Localized tumour, age> 18 months	VEC ±DDP	Post RT maintenance	Post-operatively	59.4	1.8	conformational 3D/IMRT
Localized tumour, age> 18 months + tumour residue	VEC ±DDP ±MTX HD	Post-operatively	Post-operatively and post RT	59.4 + 8 boost in the residue of the tumour	4	conformational 3D/IMRT
Localized tumour, 12-18 months	Baby UK	Post RT maintenance	Post-operatively (indication still debatable)	54	1.6-1.8	-
Localized tumour, age <12 months	Baby UK	Post-operatively	No RT indication	-	-	-
Metastatic disease	VEC ±DDP	Before RT	Post-operatively/ post PCT	24 or 36 (depending on age) + boost up to 59	1.8	-
Site recurrence	-	Clinical trials	Post-operatively	59	1.8 or hypo-fractionated (5-8)	conformational 3D/IMRT/RT stereotactic hypo-fractionated

Adapted from the recommendations of the EANO Guide for the diagnosis and treatment of ependymal tumours, 2018 (6)

The AEIOP II protocol (2002-2004), paediatric intracranial ependymomas in children over 3 years of age, recommends surgery as the first therapeutic choice, followed by radiotherapy or chemotherapy (VEC cycles: VCR, VP16, CTX), depending on the tumour residue, age and histopathology (WHO staging grade II and III). (10) (see Table 5)

Table 5 Treatment recommendations according to the AEIOP II protocol

WHO grade II ependymoma, without tumour residue, age > 3 years	Total tumour ablation	Focal RT, conformational 3D technique, TD: 59.4Gy *
Grade III ependymoma, without tumour residue, age > 3 years	Total tumour ablation	Focal RT, 3D conformational technique, TD: 59.4Gy *, followed by 4 VEC cycles
Ependymoma grade II or III, with visible tumour imaging residue, age > 3 years	Partial ablation / biopsy	Post-surgical chemotherapy (4 VEC cycles), followed by second-look intervention (when possible) and RT 59.4Gy * + 8Gy boost

Ependymoma grade II, without tumour residue, age < 3 years	Total ablation	6 VEC cycles and strict imaging tracking

Table 5, adapted according to the recommendations of the AIEOP II guide, 2016
***** for children aged between 12 and 18 months, TD for RT is 54Gy

Recent studies show that localized radiotherapy is well tolerated at younger ages, so the HIT-MED 2017 protocol recommends radiotherapy from the age of 18 months, while the EANO guide indicates the start of radiotherapy at the age of 12 months. (9) See Table 6

Table 6 Recommendations for oncological treatment according to the HIT - MED 2017 protocol:

Age	Metastases	Tumour residue	Recommended protocol
< 18 months	M0	R0	5 SKK *****cycles, followed by localized RT (54Gy) Or SIOP EP II - the study has not yet been published
>18 months < 21 years	M0	R0	Conventional localized RT 59.4 Gy (Conventional localized RT 59.4 Gy for children <4 years)
<21 years	M0	R > 0.5 cm^2	2 modified SKK cycles, followed by 2nd surgery and localized RT
<21 years	M1	Any	Individualized regimen

Adapted according to the HIT-MED 2017 protocol
*****SKK: cycles containing: VCR, CTX, MTX, Carbo, VP16; without intrathecal MTX

The HIT 2000 protocol proposes the following therapeutic regimen for the cases with tumour residue:

- Surgery per primam, followed by 2 modified SKK cycles (without MTX)
- In patients who are more than 18 months old, the radiotherapy will be initiated (more than 4 years– 68 Gy at the level of the tumour bed and 72 Gy at the level of the tumour residue; younger than 4 years – 54 Gy at the level of the tumour bed + weekly VCR)
- In patients younger than 18 months, the chemotherapy is continued with 3 complete SKK cycles, until reaching the optimal age for initiating radiotherapy
- Surgical reintervention should be considered whenever possible, in patients with tumour residue. Studies have shown that post-surgical chemotherapy alone, without further reintervention, does not bring benefits in terms of survival rate. (9)

The published clinical studies to date show similar data for the HIT 2000 and AEIOP II protocols on clinical and demographic parameters (long-term survival, residual disease, EFS).

Although the regimens in the two protocols are discreetly different, the stratification by risk groups is similar, using the same risk factors (age, grade of the primary resection, WHO histopathological classification). To date, there are no comparative studies between the two protocols to prove their advantages or disadvantages. (12)

The leptomeningeal metastases or the metastatic cells found in the CSF examination should be checked repeatedly before initiating intensive cancer treatment. In these cases, it is recommended to contact the study groups in the work centres, for individualized treatment. (9)

The effectiveness of maintenance chemotherapy, after radiotherapy is debatable in the case of ependymomas without visible tumour residue imaging. (6)

Patients with disseminated disease are treated with surgery of the primary tumor, as complete as possible, followed by craniospinal irradiation and tumor bed boost

Proton therapy must be considered whenever possible in order to reduce the incidence of side effects.

Treatment of relapses

In case of relapses, the following aspects are discussed: surgical reintervention, reconsideration of radiotherapy when it was not performed at the beginning (age of the child under 18 months / 3 years) or supplementation of irradiation doses, resumption of chemotherapy or inclusion of the patient in a clinical trial the prognosis being extremely reserved. (9).

Second-line chemotherapy follows the HIT REZ-2005 protocol for patients with medulloblastoma, PNET, ependymoma, local recurrence, or metatases. The protocol was described in the chapter on Medulloblastoma (Chapter 8.2.4). There is the therapeutic variant E-HIT-REZ-2005 for ependymomas with stages M0-M4 and the age group 3 months - 30 years, as specified in the protocol HIT-REZ 2005.

In patients with multiple recurrences, who are no longer eligible for local treatment (surgery, radiotherapy) and who have good performance status, various regimens of cytostatic chemotherapy may be administered, including high-dose chemotherapy and autologous stem cell transplantation, but with unsatisfactory results. (6) Metronomic, antiangiogenic therapies have managed to temporarily stabilize the disease in some cases (5). The MEMMAT protocol is now just recently open for inclusion for patients with relapsed ependymoma (Antiangiogenic Therapy for Children With Recurrent Medulloblastoma, Ependymoma and ATRT: MEMMAT. ClinicalTrials.gov Identifier NCT01356290).

Treatment of spinal ependymoma

Spinal ependymomas have a lower frequency in children compared to adults. Maximal safe surgical resection is recommended whenever possible. Postoperative radiotherapy is indicated for anaplastic tumors and tumors grade I or II with incomplete resection (TD= 45-54 GY). Tumors grade I or II can be observed if completely resected (6)

The treatment of local recurrence consists on maximal safe surgical resection and radiotherapy if no prior RT. Reirradiation can be considered after surgery for patients with prior radiotherapy (6)

Post-therapeutic follow-up

Imaging monitoring by brain/craniospinal MRI is recommended every 3 months in the first 2 years after the completion of the oncological treatment, then every 4 months in the 3rd and 4th year, and then every 6 months in the long term, due to the increased rate of late recurrences. (10)

The monitoring of the side effects of the oncological treatment (radiotherapy/chemotherapy) is done in a multidisciplinary team consisting of: paediatric oncologist, paediatric neurologist, child psychologist/psychiatrist, endocrinologist, ENT specialist (audiologic evaluation), ophthalmologist, medical recovery doctor and physical therapist. (13) (see Table 7)

Table 7 Long-term monitoring regimen

Late side effects	Recommended period	The doctor performing the monitoring	Recommended test
Neurological disorders (paresthesia, dysesthesias, gait disorders, paresis, structural epilepsy, peripheral neuropathies, aphasia, hypotonia)	Evaluation at the onset, then monthly, at 2 months, at 3 months, at 6 months and annually	Neurologist, medical recovery doctor / physical therapist	Complete neurological examination, EEG, EMG
Cognitive-behavioural disorders (speech, writing, reading, attention, memory, post-surgical/post-RT neuropsychiatric disorders), IQ deficiency	Evaluation at onset, then post-RT and every 3 months	Paediatric neuropsychiatrist, psychologist, social worker	Psychotherapy, speech therapy, integration in special recovery communities
Vision disorders, cataracts	Evaluation every 6 months, then annually	Ophthalmologist, optometrist	Visual acuity testing, eye fundus examination (annual)
Hearing disorders (hearing loss, deafness, tinnitus, otosclerosis)	Evaluation every 6 months, then annually	ENT specialist	Audiogram, otoscopic examination
Endocrinological disorders (adrenal post-corticosteroid failure, ovarian dysfunction, infertility, STH deficiency, early puberty, hypo/hyperthyroidism)	Post-RT evaluation, then every 3 months, then every 6 months, annually	Endocrinologist	Hormonal dosages, pelvic/testicular/thyroid ultrasound
Post-RT / post-PCT dental problems	Evaluation every 6 months	Dentist	Dental examination and specific treatment
Glomerulopathy, post-PCT tubulopathies (cyclophosphamide)	Evaluation at the onset, then monthly, at 2 months, at 3 months, at 6 months and annually	Paediatric oncologist / nephrologist	Renal function monitoring
Hepatic cytolysis, cholestasis syndrome (especially post-MTX)	Evaluation at the onset, then monthly, at 2 months, at 3 months, at 6 months and annually	Paediatric oncologist	Liver function monitoring

Bone density reduction (prolonged post-corticosteroid therapy)	Annual evaluation	Paediatric oncologist	Bone density assessment, DXA examination
Avascular necrosis (prolonged post-corticosteroid therapy)	Annual evaluation	Paediatric oncologist	Musculoskeletal clinical examination
Post-RT complications (permanent alopecia, local fibrosis, hyper/hypopigmentation)	Annual evaluation	Oncologist, psychologist	Local clinical examination, psychotherapy
Post-RT craniofacial asymmetries/defects	Annual evaluation	Oncologist, psychologist, psychiatrist	Clinical examination, psychotherapy
Post-RT chronic sinusitis	Annual evaluation	ENT specialist	ENT examination, sinus CT scan
Second malignancy (post-PCT or irradiation field) Haematological malignancies (after VP16) Skin neoplasm Bone neoplasm Neoplasm of the oral cavity The second brain neoplasm	Annual evaluation up to 10 years after the completion of cancer treatment	Paediatric oncologist	- blood count, peripheral blood smear, cytological examination of the bone marrow - if we have clinical suspicion -dermatological examination - neurological examination

Monitoring regimen adapted according to Children's Oncology Group, Long-Term Follow-Up Guidelines, version 5.0 - October 2018 (13)

Recommendations

- WHO 2016 histopathological classification must be applied
- Clinical staging: M staging system **(Chang staging system)**
- Staging according to "Toronto Childhood Cancer Stage Guidelines" for cancer registry
- The radicality of the surgery is the most important prognostic factor
- The sequentiality of radiotherapy-chemotherapy differs depending on the protocol
- Proton radiotherapy should be considered in an attempt to limit neurocognitive side effects and the effects on the auditory nerve structure.
- Side effects are significant and they require a multidisciplinary approach

Bibliography

1. Pizzo, Philip A., and David G. Poplack. Principles and practice of pediatric oncology. Lippincott Williams & Wilkins, 2015, Cap. 25, pag 739-741

2. Khatua S, Ramaswamy V, Bouffet E. Current therapy and the evolving molecular landscape of paediatric ependymoma. Eur J Cancer 2017; 70:34–41.

3. Jeffrey N Bruce, MD, Ependymoma,Febr 2018, https://emedicine.medscape.com/article/277621

4. https://www.cancer.gov/rare-brain-spine-tumor/tumors/ependymoma

5. Stevens, Michael CG, Hubert N. Caron, and Andrea Biondi, eds. Cancer in children: clinical management. Oxford University Press, 2012. ed a 6a, pag 261-262

6. Rudà, Roberta, et al. "EANO guidelines for the diagnosis and treatment of ependymal tumors." Neuro-oncology 20.4 (2018): 445-456.

7. Gupta, Sumit, et al. "Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines." The Lancet Oncology 17.4 (2016): e163-e172.

8. Louis, David N., et al. "The 2016 World Health Organization classification of tumors of the central nervous system: a summary." Acta neuropathologica 131.6 (2016): 803-820.

9. Stefan Rutkowski, Katja von Hoff et al. HIT-MED Guidance for Patients with newly diagnosed Medulloblastoma, Ependymoma, CNS Embryonal Tumour* and Pineoblastoma, 2017. cap. 2.2 Ependymoma

10. Massimino, Maura, et al. "Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma." Neuro-oncology 18.10 (2016): 1451-1460.

11. https://clinicaltrials.gov/ct2/show/NCT02265770

12. Jünger, Stephanie T., et al. "Improved risk-stratification for posterior fossa ependymoma of childhood considering clinical, histological and genetic features–a retrospective analysis of the HIT ependymoma trial cohort." Acta neuropathologica communications 7.1 (2019): 181.

13. http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf

8.2.2 HIGH GRADE GLIOMA (HGG)

The high grade gliomas (HGG) are tumours originating in the glial cells (astrocytes, oligodendrocytes) of the central nervous system, classified as grade III or IV tumour types by the WHO.

The new WHO 2016 classification takes into account both phenotypic and genetic factors for an accurate prognosis and for the therapeutic approach of gliomas. (1)

High grade gliomas according to the new WHO 2016 classification:

- Anaplastic astrocytoma, IDH - mutant (grade III)
- Glioblastoma, IDH - wildtype (grade IV)
- Glioblastoma, IDH - mutant (grade IV)
- Diffuse midline glioma, H3 K27M - mutant (grade IV)
- Anaplastic oligodendroglioma, IDH - mutant and 1p/19 q - codeleted (grade III)
- Anaplastic pleomorphic xanthoastrocytoma (grade III)
- Anaplastic ganglioglioma (grade III)

Epidemiology

High-grade gliomas are some of the most common histopathological forms of CNS tumours in adults. In children, they represent 8% -12% of CNS tumours. They are very aggressive tumours, very few patients achieving significant long-term survival, despite the current multiple therapies. (2) New biological, molecular and genetic data show that paediatric high-grade gliomas are different from those in adults.

In terms of site, although they can be anywhere in the CNS, the most common site is in the supratentorial region. Approximately 35% - 50% are located in the cerebral hemispheres, lower percentages are found in the thalamus, hypothalamus, basal ganglia and the third ventricle. (2) The primary spinal tumours are much rarer, with an incidence of about 3% in children. (3) A peak incidence for the supratentorial site was found in adolescents (15-19 years), while the infratentorial tumours are more common at an early age.

Categories of patients at risk of developing HGG:

- Previous exposure to radiation therapy (increased risk of second malignancy)
- Constitutional Mismatch Repair Deficiency (CMMRD)
- Patients with germline mutations
- Neurofibromatosis 1 (4)
- Li-Fraumeni Syndrome

Symptomatology

Unlike low grade gliomas (LGG), these tumours have a much shorter "onset to diagnosis"- period due to rapid cell proliferation. Patients can present with two types of symptoms:

Tumour-induced symptoms, depending on the site:

- Tumours of the cerebral hemispheres: seizures (less common in HGG, as opposed to LGG), motor deficits
- Cerebellar tumours: gait and balance disorders
- Hypothalamic tumours: diencephalic syndrome (failure to thrive, emaciation despite adequate nutritional intake, euphoric and hyperactive child, macrocephaly, visual impairment)

- In infants and young children, the symptoms are nonspecific: growth retardation, lethargy, vomiting, macrocephaly.

Symptoms of increased intracranial pressure (ICP): headache, morning sickness, diplopia (caused by the abducens nerve palsy)

Diagnostic evaluation

- Neurological examination
- Ophthalmological examination: eye fundus examination can diagnose the ICP in early stages
- Native brain CT scan - sufficient to assess ICP
- Brain MRI with contrast both at diagnosis as well as after surgery. For a proper MRI evaluation, the sequences T1 (hypointense lesions), T2 (hyperintense lesions), FLAIR (evidence of edema), and DWI are required. There are no distinctive features of MRI for HGG. In most cases, they are imprecisely delimited tumours, with mass effect on the surrounding structures and with nodular contrast enhancing. Most often, they are locally invasive tumours without secondary leptomeningeal metastasis. (5)

Examinations for the disease extension assessment:

- Spinal MRI with contrast agents - for diagnostic assessment, then periodic evaluation only in patients who have spinal metastases at onset (rarely) or in case of specific symptoms.
- Cytological examination of the cerebrospinal fluid (CSF) - obtained by lumbar puncture

After performing the disease extension evaluation, Chang staging is used, described in the chapter on ependymomas (Chapter 8.2.1).

Evaluation during treatment

- Periodic neurological consultation (for disease progression)
- Brain MRI with contrast agents every 3 months
- Spinal MRI and lumbar puncture are repeated only if they were positive at diagnosis or in case of specific symptoms.

Histopathological forms:

Microscopic characteristics: hypercellularity, nuclear atypia, elevated mitotic index, with or without microvascular proliferation.

For a complete evaluation of these categories of tumours, it is necessary to evaluate the IDH status (mutations in IDH genes 1 and 2), its prognostic influence is currently documented in adults. From this point of view, the vast majority of anaplastic astrocytomas fall into the IDH - mutant variant. For patients whose IDH status cannot be assessed, the diagnosis will have the NOS specification.

Glioblastomas are divided according to the WHO 2016 classification into the following variants:

- Glioblastomas, IDH - mutant (90%)
- Glioblastomas, IDH - wildtype (characteristic for young patients, may be secondary in patients previously diagnosed with diffuse LGG)
- Glioblastomas, NOS (in which the IDH status cannot be assessed)
- Epithelioid glioblastomas (this diagnosis refers to the old forms of giant cell glioblastoma and gliosarcoma), characteristic subtype: IDH-wildtype. This is characteristic for young children/adults, and it is represented by tumours located in the cerebral hemispheres or diencephalic structures, with associated BRAF gene mutation
- Glioblastomas with primitive neuronal component (PNET-like); they associate a MYC amplification; characteristically, they show leptomeningeal dissemination

- Small cell / granular cell glioblastomas (show EGFR amplification)

- Diffuse midline glioma H3 K27M - mutant (in the previous classifications it was found under the name of Diffuse intrinsic pontine gliomas (DIPG)

- Pleomorphic xanthoastrocytoma. Patients with anaplastic (grade III) have a shorter survival prognosis than patients diagnosed with pleomorphic xanthoastrocytoma (grade II).

Prognosis

Despite numerous therapeutic attempts, the prognosis for these tumours remains very poor, with 5-year survival between 15 and 35%. (2)

The most important prognostic factor, regardless of the site of the tumour, is the degree of tumour resection.

In terms of molecular characteristics: the IDH mutation associates a better prognosis, while the K27M mutation associates an unfavourable prognosis. (6)

Treatment

The therapeutic decision regarding the diagnosed cases should be made by the multidisciplinary tumour board (neurosurgeon, oncologist, radiotherapist, medical imaging specialist). The treatment is multimodal, with surgery, followed by adjuvant therapy: radiotherapy and chemotherapy.

• Surgical treatment

Surgery is the first therapeutic act. Often, due to the rapid tumour growth, there is an obstructive ICP. This is neurosurgical emergency; in these situations the first approach is aimed at restoring CSF circulation by inserting a drainage system (external ventricular drainage, ventriculoperitoneal drainage) or by performing a ventriculostomy.

Complete surgical excision is associated with a better prognosis. However, even in the case of complete macroscopic excision, most of the time, there is still some residual microscopic tissue left. (7)

Depending on the degree of the tumour resection, there is a neurosurgical staging (Table 1), a postoperative imaging staging (Table 2) and staging that combines surgical and imaging data (Table3).

Table 1 The neurosurgical staging

S1	Complete excision, absence of remaining identifiable tumour tissue at the level of the operating bed
S2	Tumour residue smaller than 1.5 cm^2; possible residual infiltration at the level of the adjacent structures of the tumour bed
S3	Tumour residue larger than 1.5 c cm^2
S4	Biopsy, large remaining tumour volume

Table 2 Staging according to the postoperative imaging evaluation:

R1	Absence of visible tumour residue
R2	Linear contrast enhancement around the postoperative cavity
R3	Residual tumour volume, with measurable nodular lesion
R4	Slightly altered tumour volume

Table 3 Evaluation of the tumour resection by combining neurosurgical and imaging staging

The quality of the excision	Postoperative imaging depending on the quality of the excision
TOTAL	R1 S1
SUBTOTAL	R1/R2 S2
PARTIAL	R3 S2/S3
BIOPSY	R4 S4

- Cytostatic treatment

A. HIT-GBM-D Protocol:

- Induction treatment (concomitantly with radiotherapy), consisting of the sequence of the following series:

- PEV (DDP + VP16 + VCR);

- PEIV (DDP + VP16 + VCR + IFO)

- Maintenance treatment: 8 series VCR, CCNU, PRD (Starting 4 weeks after RT completion)

B. Temozolomide: TEM administered concomitantly with radiotherapy (75 mg/m^2 daily) and after its completion (200 mg/m^2, 5 days), with serial MRI evaluation

- Radiation therapy

The radiation therapy is an important component of the adjuvant therapy for HGG.

The techniques that are used: conventional 3D radiation therapy, IMRT (intensity modulated radiation therapy)

Irradiation field: tumour bed + edges 1-2 cm

Irradiation doses: 54 Gy with dose supplementation up to 60 Gy on the remaining tumour tissue (1.8 Gy/fraction) (7)

Treatment of the recurrence and of the progressive disease

- Surgery whenever the complete/partial excision of the recurrence is possible

- Chemotherapy - Resumption of initial chemotherapy or other combinations of second line and third line treatment

- Another therapeutic option is the combination of Irinotecan + Bevacizumab (off-label medication in Romania for this paediatric pathology). Studies have not shown an increase in the overall survival, but the stabilization of the disease during treatment is mentioned. (8)

- Targeted biological therapy (in clinical trials: www.clinicaltrials.eu)

- Radiotherapy - for patients who have not had radiotherapy in the initial therapeutic protocol (usually due to the young age). Also, reirradiation has shown increased survival compared to standard treatment in these patients. (9)

Patients who have already undergone radiotherapy may benefit from stereotactic radiosurgery if the volume of the tumour to be irradiated is very small.

Evolution and treatment characteristics in the diffuse midline gliomas

This category of tumors has a severe prognosis: the survival is generally less than 1 year (2-year survival <20%). Extensive clinical trials have for many years been conducted to try to increase survival in this patient group.

Although the imaging evaluation is most often sufficient to establish the diagnosis, biopsy is recommended in order to evaluate the molecular characteristics of the tumour.

Radiotherapy is the essential therapeutic approach in the treatment of these tumours - a temporary improvement of the symptoms and imaging regression is observed in most patients, but the duration of these effects is limited (a matter of months). Conventional 3D or IMRT radiotherapy is used, at the level of the tumour bed, with total doses between 54 and 60 Gy.

Chemotherapy has not been shown to be effective in these patients.

Post-therapeutic monitoring

- Serial imaging evaluation (MRI) every 3 months
- Periodic neurological evaluation
- Monitoring the side effects of the disease and of the oncological treatment

Recommendations

• WHO classification 2016, complete diagnosis now incorporates molecular biology parameters for several diagnoses.

• Radiotherapy and chemotherapy increase survival

• The most important prognostic factor is the extent of tumour removal

• NMYC amplification and EGFR amplification are associated with an unfavourable prognosis

• Diffuse midline H3 K27M glioma including the well-known diffuse pontine glioma (DIPG) have very poor prognosis

Bibliography

1. Louis D, Perry A and all, The 2016 World Health Organisation Classification of Tumors of the Central Nervous System: a summary, Acta Neuropathol 2016, 10: 1-18

2. Fangusaro J and all, Pediatric high grade glioma: a review and update on tumor clinical characteristics and biology, Frontiers in Oncology, 2012, 2: 105

3. Wolff B, Ng A and all, Pediatric high grade glioma of the spinal cord: results of the HIT-GBM database, Journal of Neuro-Oncology, 2012, 107: 139-146

4. Rosenfeld A, Listernick R, Neurofibromatosis type 1 and high- grade tumors of the central nervous system, Childs Nerv Syst, 2010, 26: 663 – 667

5. Panigrahy A, Bluml S and all, Neuroimaging of Pediatric Brain Tumors: From Basic to Advanced MRI, Journal of Child Neurology, 2009, 24 (11): 1343-65

www.cancer.gov:child-astrocytoma-treatment

6. Vanan M, Eisenstat D, Management of high-grade gliomas in the pediatric patient: past, present and future, Neuro-Oncology Practice, 2014, 4: 145-157

7. Constine L, Tarbell N, Halperin E, Chapter 3: Malignant Gliomas, - Pediatric Radiation Oncology, 40 – 41

8. Gururangan S et al, Lack of efficacy of bevacizumab and irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a PBTC study, *J Clin Oncol,* 2010, 3069 – 3075

9. Lu VM, Welby JP, Mahajan A, Laack NN, Daniels DJ. Reirradiation for diffuse intrinsic pontine glioma: a systematic review and meta-analysis. Childs Nerv Syst 2019;35(5):739–46.

8.2.3 LOW GRADE GLIOMA

Low grade gliomas (LGG) are tumours originating in the glial cells (astrocytes, oligodendrocytes) of the central nervous system, classified as grade I or II tumor types by the WHO.

Epidemiology

Low grade gliomas (LGG) are the most common tumours of the central nervous system in children (approximately 40%). (1) These tumours have various histopathological aspects, being classified in the WHO international staging with grade I or II. The most common location of LGG is in the posterior fossa (15-25%), followed by the cerebral hemispheres (10-15%) and the optic pathways (6%). (2) The average age at diagnosis varies between 6 and 11 years, with a discreet predominance of males (male/female sex ratio 1.1 - 1.2/1). (3)

Certain categories of patients have an increased risk of developing low grade gliomas.

There is a common association between low-grade gliomas and *type 1 neurofibromatosis*. Twenty percent of all patients with neurofibromatosis develop astrocytomas, usually pilocytic astrocytoma, located mainly in the optic pathways. These patients can be diagnosed with several types of brain tumours (synchronous or metachronous), more commonly with brainstem tumours. Gliomas associated with neurofibromatosis have a slower evolution than sporadic ones (4). Other hereditary neuro-oculo-cutaneous syndromes (phakomatoses) are also associate a certain risk for developing of brain tumors. Out if this category, patients with *tuberous sclerosis* have a predisposition for low grade gliomas, especially subependymal giant cells astrocytomas

Symptomatology

These tumors have an insidious onset, most likely over months. Patients can present with two types of symptoms:

- Tumour-induced symptoms, depending on the site:
  - Tumours of the optic pathways: impaired vision (from altered visual field to blindness), nystagmus
  - Tumours in the cerebral hemispheres: seizures, motor deficits
  - Cerebellar tumours: gait and balance disorders
  - Hypothalamic tumours: diencephalic syndrome (failure to thrive, emaciation despite adequate nutritional intake, euphoric and hyperactive child, macrocephaly, visual impairment)
- Symptoms of increased intracranial pressure (ICP): headache, morning sickness, diplopia

Diagnosis

- Neurological examination
- Ophthalmological examination: assessment of visual field and visual acuity, eye fundus examination
- Endocrinological tests (especially for –hypothalamic/chiasmatic tumours)
- Brain MRI with contrast both at diagnosis as well as after surgery. T1, T2, FLAIR, DWI sequences are required for proper MRI evaluation.

- Neurosurgical evaluation for diagnostic purposes (exception: optical and hypothalamic/chiasmatic pathways tumours in which the surgical approach involves increased morbidity)

- Investigations for the evaluation of spinal cord metastases:

- Spinal MRI with contrast agents; spinal metastases are diagnosed in 10% of children with LGG. (5)

- Lumbar puncture: CSF cytology

The staging is done according to the Chang classification (See chapter 8.2.2 High grade gliomas)

Evaluation during treatment

- Weight monitoring (especially in patients with diencephalic syndrome)

- Neurological examination (for disease progression and post-chemotherapy toxicity)

- Ophthalmologic examination every 3 months for patients with optical pathways tumours

- Brain MRI with contrast every 3 months

- Spinal MRI and lumbar puncture are repeated only if they were positive at diagnosis

- Audiogram every 6 months (to assess Carboplatin-induced toxicity)

Histopathological forms

The histopathological entities included in the category of low-grade gliomas have been redefined in the new WHO 2016 classification. (see Table 1)

Table 1 LGG treated according to the LGG 2004 protocol are those classified as WHO 2007

Low grade gliomas according to the LGG protocol (WHO 2007 classification):	Low grade gliomas according to the new WHO 2016 classification:
Pilocytic astrocytoma grade I Subependymal giant cell astrocytoma grade I Diffuse astrocytoma (fibrillar, gemistocytic, protoplasmic) grade II Pilomixoid astrocytoma grade II Oligoastrocytoma grade II Oligodendroglioma grade II Pleomorphic xanthoastrocytoma grade II Ganglioglioma grade I or II Gangliocytoma grade I Desmoplastic infantile ganglioglioma Grade I Dysembryoplastic epithelial tumor	Pilocytic astrocytoma Grade I Subependymal giant cell astrocytoma grade I Diffuse astrocytoma grade II (IDH-mutant) Oligodendroglioma (IDH - mutant, 1p/19q-codeleted) Grade II Pleomorphic xanthoastrocytoma grade II - !Caution: anaplastic pleomorphic xanthoastrocytoma is grade III Angiocentric glioma Grade I Chordoid glioma of the third ventricle Gangliocytoma grade I Ganglioglioma grade I or II Ganglioglioma and desmoplastic infantile astrocytoma grade I

The definition for pilomixoid astrocytoma is unclear in the WHO 2016 classification, and further studies are needed to assign it either to grade I or II. (6)

Special mention: exophytic brainstem gliomas may be included in the LGG, but intrinsic diffuse brainstem gliomas which are much more aggressive do not belong to this low grade category.

Genetics

The genetic factors associated with LGG, used in the WHO 2016 classification are: IDH mutation (mutant or wildtype tumour) for diffuse astrocytoma; 1p/19q-codeleted for the diagnosis of oligodendroglioma. (6) Alterations of the BRAF gene were also observed. (7)

Gliomatosis cerebri (*cerebral gliomatosis*) has been removed from the WHO 2016 classification. It is not considered to be an independent histopathological entity, but it rather represents a growth pattern for several types of gliomas.

Prognosis

The prognosis is generally favourable, with 10-year survival ranging from 85 to 96%. Despite the very good survival rate, patients with this diagnosis frequently have neurological and endocrine sequelae following the disease and treatment. (8)

Prognostic factors:

- quality of surgical resection
- association with neurofibromatosis

Treatment

The therapeutic decision regarding the diagnosed cases must be made by the tumour board (neurosurgeon, paediatric oncologist, radiotherapist, medical imaging specialist).

The principles of multimodal treatment in LGG are presented in Figure 1.

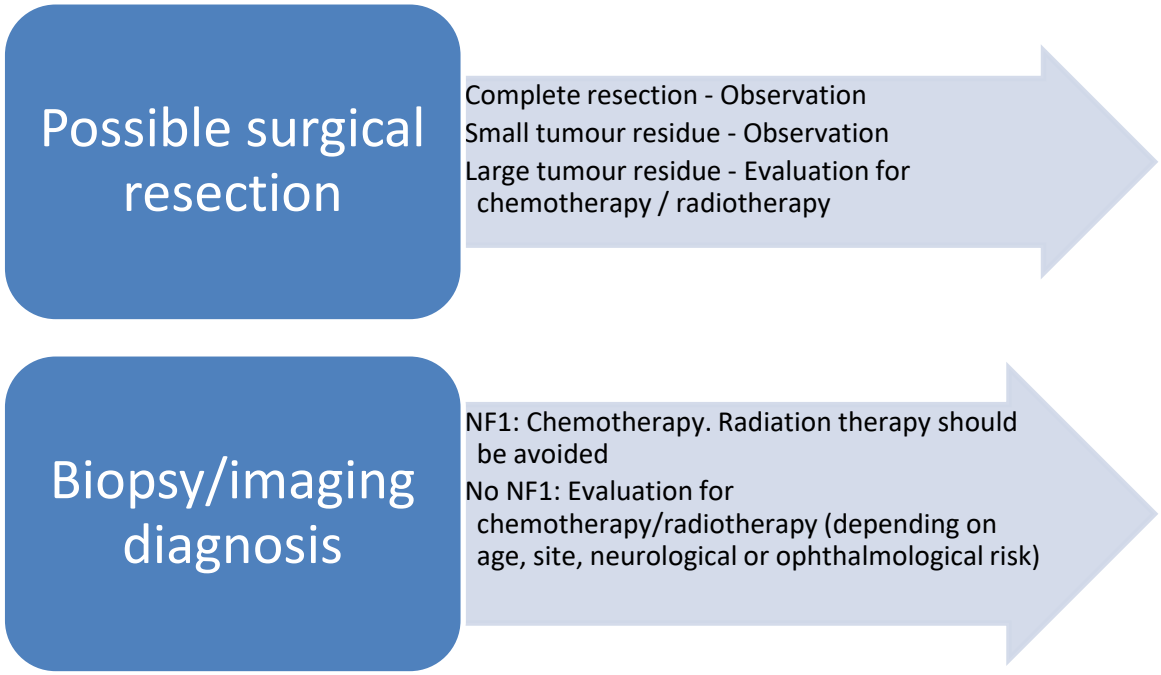


Figure 1: The principles of multimodal treatment in LGG

- Surgery: Surgery is the first therapeutic act.

Depending on the degree of tumour resection, LGG are classified by neurosurgical staging, postoperative imaging staging and staging combining surgical and imaging data are performed (See chapter 8.2.2 High-grade gliomas).

Due to the risk of severe and permanent neurological sequelae, in patients with optic pathway gliomas, including hypothalamic-chiasmatic ones, biopsy/surgery may be left out. In these cases the diagnosis is established only by imaging evaluation (MRI). (5, 8)

For completely resected tumours, the event-free survival (EFS) is greater than 90%. For the tumours in which total resection is not possible, the local control can be obtained by combining chemotherapy and/or radiotherapy. Sometimes only clinical and imaging observation is preferable.

The overall 5 years survival rate is greater than 80%. (5)

Particularities of the surgical intervention depending on the site of the tumour:

- Tumours of the cerebral hemispheres or cerebellum: possible complete resection; in patients for whom complete resection cannot be performed, observation is initially sufficient for the majority of cases, without other associated oncological treatment. Seizures that are present at the beginning usually disappear after surgery.
- Hypothalamic-chiasmatic tumours: difficult to approach surgically, with increased risk of comorbidities (hypothalamic damage, endocrine, neurological, visual deficits). They have a particular imaging aspect that can support the diagnosis, without the need for a biopsy. Usually surgery is limited to biopsy.
- Brainstem tumours: only the exophytic part can be resected; often there is an infiltrative tumour residue left in the brainstem.

- Non-surgical oncological treatment. (Table 2)

Special remarks regarding the criteria set out in the table:

- Progression by increase in tumour volume: in case of tumours with solid component + cystic component, the growth of the cystic component is not sufficient for initiating oncological treatment.
- Decrease of the visual function: The decrease of the visual function (marked by decreased visual acuity or visual field) is an argument for initiating cancer treatment, regardless of the imaging evaluation (even if we have dimensional stability of the tumour)
- Neurofibromatosis 1 + metachronous tumours: in patients with NF1 several CNS tumours can be shown at diagnosis (especially in patients with optic nerve glioma). ! Pay attention to the differential diagnosis with metastatic disease. ! It is recommended to evaluate the indication for oncological treatment for each site.

Table 2 Conditions for initiating non-surgical oncological treatment (SIOP-LGG 2004 protocol):

Indications for initiating non-surgical oncological treatment after initial partial resection (S2 / S3)	Indications for initiating non-surgical oncological treatment at diagnosis, after biopsy / initial imaging diagnosis	Indications for initiating non-surgical oncological treatment after the observation period, if surgery is not possible
a. Severe pre-existing ophthalmological impairment: - risk of vision loss in both eyes; - visual impairment; - nystagmus - especially in children <2 years with visual impairment) b. Clinical criteria: - diencephalic syndrome -symptomatic metastases	a. Severe pre-existing ophthalmological impairment: - risk of vision loss in both eyes; - visual impairment; - nystagmus - especially in children <2 years with visual impairment) b. Severe neurological impairment: - diencephalic syndrome - focal neurological deficits caused by tumor growth	a. Progressive neurological symptomatology: - The occurrence of new neurological symptoms; - Increase of the severity of pre-existing neurological symptoms; - Diencephalic syndrome - Symptomatic metastatic disease b. Progressive visual impairment: - Decreased vision / decreased visual field

NB: The presence of a postoperative tumour residue shown by imaging is not an indication for non-surgical oncological treatment	- Increased intracranial pressure symptoms (obstruction caused by the tumour) - seizures caused by tumour growth - symptomatic metastases NB: The presence of a postoperative tumour residue shown by imaging is not an indication for non-surgical oncological treatment	- Any reduction in vision in the unaffected eye, if the contralateral eye has lost its sight c. Imaging progression: - Tumour growth / increase in optic nerve calibre - Impairment of new brain structures, unaffected at previous imaging test - Dimensional progression of metastases

Figure 2: The algorithm of the principles of non-surgical treatment in LGG

SURGERY
→ INCOMPLETE RESECTION → ONCOLOGICAL TREATMENT DECISION → <8years CT; >8years + RT if necessary (worsening of symptoms, progression)
→ASYMPTOMATIC→OBSERVATION (no progression)
→COMPLETE RESECTION→OBSERVATION

• Cytostatic treatment

Recommended in the above mentioned situations (partial resection/unresectable tumours):

1)LGG 2004 protocol (VCR/Carbo series):

- Induction treatment (24 weeks): VCR and Carbo administration every 3 weeks
- Maintenance treatment (52 weeks): administration of VCR and Carbo, every 6 weeks. In case of Carbo allergy (frequency <20%) it is replaced with CTX/DDP in alternate series.

2) Weekly vinblastin for 52 weeks

• Radiation therapy

Radiation therapy, when compared to chemotherapy, has a greater chance of event free survival but has a risk of more severe late side effects. (9)

Long-term side effects of radiation therapy can be: cognitive impairment, cerebral vasculopathy, endocrine dysfunction, hearing impairment, secondary malignancies. The side effects associated with radiation therapy are more significant in young children and in patients with neurofibromatosis.

Recommended radiotherapy technique: conventional 3D radiation therapy, IMRT

Irradiation field: tumour volume + edges 0.5 - 1 cm

Recommended doses (SIOP-LGG 2004):

In case of brain tumors the total dose will be 54 Gy with fractions of 1.8 Gy/administration, 5 days/week. In case of spinal tumors, the total dose will be limited to 50.4 Gy. For children all under 5 years of age, the total dose will be limited to 45 Gy (1.8 Gy/fraction). The irradiation field is represented by the tumor volume + 0.5 cm edges.

For cases with leptomeningeal dissemination (rare), cranio-spinal irradiation is recommended. (10) The stereotactic radiosurgery can also be used, especially for small tumours in patients with neurofibromatosis, where there is a risk of other brain tumours secondary to standard radiotherapy. (11)

Regarding the use of other radiotherapy techniques (IMRT) or proton radiotherapy, there are no standardized recommendations, but some studies have shown that neurological toxicity is lower in the long term. (12)

Treatment of relapses/ progressive disease

The imaging definition of the disease progression is made by RECIST criteria: an increase by 25% of the tumour measured by summing the product of the 2 largest dimensions of the target lesions.

Another situation in which we talk about recurrence/progression is when we have neurological or visual impairment combined with growth of the tumour (Caution! Symptoms may be secondary to cancer treatment: peritumoral inflammation/tumour necrosis. Sometimes biopsy may be required for differential diagnosis)

Treatment of relapse or progressive disease:

- Surgery is the treatment of choice
- If radiotherapy has not been used previously, it will be considered a non-surgical treatment of choice
- If there is no indication for radiotherapy, chemotherapy will be recommended.

Second line cytostatic treatment:

- Resumption of the SIOP LGG protocol (VCR/Carbo)
- Monotherapy with VBL weekly for 52-70 weeks (13)
- Temozolomide: 10-12 cycles (14)
- Bevacizumab / IRI (Bevacizumab is an off-label medication for this paediatric pathology in Romania): Studies show that this treatment regimen is a back-up oncological treatment for tumours in which multiple therapeutic options have been tried. Stabilization of the disease can be achieved most of the time only during treatment. (15, 16)
- Clinical trials: www.clinicaltrialsregister.eu

Treatment characteristics for patients with LGG and neurofibromatosis

The particularity of treatment for this group of patients is represented by the avoidance of the irradiation as much as possible.

Therapeutic recommendations:

- For patients with small tumours and neurofibromatosis, periodic imaging examination (MRI) is recommended (short periods – every 3 months)
- As a non-surgical therapy, standard VCR/Carbo chemotherapy is recommended - SIOP LGG 2004 recommendation. In case of progression, it is recommended to continue chemotherapy with other therapeutic combinations of cytostatic agents (see above).
- Radiotherapy is indicated in patients with neurofibromatosis 1, in the following situations:
  - optic nerve gliomas with exclusive intraorbital site
  - patients with disease progression after the second and third line chemotherapy (SIOP LGG 2004)

Post-therapeutic monitoring

- Imaging evaluation every 3 months for the first 2 years, then every 6 months up to 5 years, then annual follow-up for up to 10 years (for incompletely resected tumours)
- Ophthalmologic evaluation associated with imaging evaluation for tumours that affect vision
- Assessment of long-term adverse effects, disease and cancer treatment:

a. Neurological sequelae: ataxia, seizures

b. Cognitive sequelae: memory impairment, concentration, information processing and reaction speed

c. Endocrinological impairment: hypothyroidism, central diabetes insipidus, growth hormone deficiency, pubertal impairment (early, delayed), infertility, adrenocortical insufficiency

d. Visual impairment

e. Hearing impairment

f. Risk of secondary malignancy (especially in patients with NF1)

Recommendations

- Surgery is the treatment of choice
- Observation, with neurological, ophthalmological, endocrinological and long-term serial imaging evaluations is recommended in cases with:

- Complete resection

- Partial resection without neurological/ophthalmological/endocrinological criteria of severity

- Non-surgical treatment (chemotherapy and/or radiotherapy) is established according to well-defined criteria (see table above)
- In cases where chemotherapy or radiotherapy must be chosen, the age and the (non) association with neurofibromatosis will be taken into account.

Bibliography

1. Rickert CH, Paulus W; Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification; Childs Nerv Syst 2001; 17: 503 – 511

2. Pollack IF; The role of surgery in pediatric gliomas; J Neurooncol 1999; 42: 271- 288

3. Kaatsch P., Rickert C. and all; Population – based epidemiologic data on brain tumors in German children; ACS Journals, 2001

4. Guillamo LS, Creange A and all; Prognostic factors of CNS tumors in Neurofibromatosis 1: a retrospective study on 103 patients; Brain 2003; 126: 152-160

5. Hessissen L, Parkes J and all, SIOP PODC Adapted treatment guidelines for low grade gliomas in low and middle income settings; Pediatric Blood and Cancer 2017; 64: 1- 15

6. Louis D, Perry A and all, The 2016 World Health Organisation Classification of Tumors of the Central Nervous System: a summary, Acta Neuropathol 2016, 10: 1-18

7. Zhang J, Wu G and all, Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas, Nat genet 2013, 45: 602-612

8. Protocol LGG 2004 – variantă din 2010

9. Muller K, Gnekow A and all, Radiotherapy in pediatirc pillocytic astrocytomas. A subgroup analysis within the prospective multcenter study HIT-LGG 1996 by GPOH, Strahlenther Oncol 2013, 189: 647 – 655

10. Capitol 3: Supratentorial Brain Tumors din Pediatric Radiation Oncology 6th Edition Constine, Tarbell Halperin, pag 27-34

11. Mazloom A, Hodges JC and all, Outome of patients with pylocitic astrocytoma and leptomeningeal dissemination, Int J Radiat Oncol Biol Phys, 2012, 84: 350 – 354

12. Greenberger BA, Pulsifer MB and all, Clinical outcomes and late endocrine, neurocognitive and visual profiles of proton radiation for pediatric low-grade gliomas, Int J Radiat Oncol Biol Phys 2014, 89: 1060-1068

13. Lassaletta A, Scheinemann K and all, Phase II Weekly Vinblastine for Chemotherapy- Naive Children with Progressive Low-Grade Glioma: A Canadian Pediatirc Brain Tumor Consortium Study, Journal of Clinical Oncology 2016, 29: 3537 – 3543

14. Gururangan S, Fisher MJ and all, Temozolomide in children with progressive low-grade glioma, Neuro Oncol 2007, 9: 161-168

15. Gururangan S, Fangusaro J and all, Eficacy of Bevacizumab plus Irinotecan in children with recurrent LGG – a Pediatric Brain Tumor Consortium study, Neuro-Oncology, 2013, 16: 310 – 317

16. Zhukova N, Rajagopal R amd all, Use of Bevacizumab as a single agent or in adjunct with traditional chemotherapy regimens in children with unresectable or progressive LGG. Cancer Medicine, 2018, 1-22

8.2.4 MEDULLOBLASTOMA

Medulloblastoma is the most common malignant brain tumour of the posterior fossa in children. By definition, it is a primitive cerebellar tumour, of neuroectodermal origin, derived, presumably, either from undifferentiated progenitor medulloblasts located in the cerebellar external granular layer, or from the deep subventricular median zone, from the posterior medullary velum. It is a tumour that metastasize trough cerebrospinal fluid (CSF). About 30% of patients have spinal or endocranial metastases at diagnosis. (1) Metastases outside the central nervous system are uncommon.

Epidemiology

Medulloblastomas represent approximately 20% of CNS tumours in children, aged between 0 and 14 years, having two peaks of incidence, between 3-4 years and between 8-10 years. Boys are three times more affected than girls. (1, 2)

Etiology

The etiology is unknown in most patients. There is no clear link between the exposure to environmental factors and the occurrence of the medulloblastoma. The exposure to ionizing radiation is associated with an increased risk of developing all types of brain tumours, including medulloblastoma. Some studies have identified a link to pesticide exposure.

Genetic predisposition

There are some associations with the Gorlin syndrome (mutation in the PCTH1 gene on chromosome 9 and in the SUFU gene), with the familial adenomatous polyposis (APC gene, on chromosome 5), with Li-Fraumeni syndrome (TP53 gene on chromosome 17p). (3)

Symptomatology

The clinical aspect is a combination of signs and symptoms, evolving over weeks/months, caused by the tumour itself and/or by the increased intracranial pressure.

- Signs of increased intracranial pressure (ICP)

The obstruction of the cerebrospinal fluid (CSF) circulation in the third or fourth ventricle caused by the tumour, with secondary hydrocephalus, causes headache and vomiting in 80% of patients. The headache, initially nonspecific, evolves over time into to the typical morning headache without nausea and initially relieved by vomiting. The papillary edema is present in 75% of patients. The clinical resonance of ICP can be objectified during the clinical examination by identifying the Cushing triad - hypertension, bradycardia, respiratory rhythm disorders. In infants, the increased intracranial pressure leads to increased cranial perimeter and lethargy. The typical sun-setting sign appearance occurs in 10% of cases at this age.

- Signs caused by the tumour

The ataxia is predominantly truncal, determined by the frequently median position of the tumours, associating a wide-base gait and difficulties in walking on tiptoes and heels. In patients with a paramedial development of the tumours, the dysmetria occurs in the "index finger to nose" and "heel-knee" tests and intentional tremor. Cranial nerve palsy may occur, the most frequently affected being the sixth cranial nerve (in 90% of cases), with the occurrence of strabismus, diplopia. Other signs: laterocollis, signs of meningeal irritation, weight loss.

Diagnostic evaluation

- Neurological examination
- Ophthalmological examination –eye fundus examination
- MRI imaging with contrast agents or CT scan if emergency imaging or not available MRI

The brain MRI highlights the expansive process in the cerebellum, isointense or hypointense on T1 sequences, hyperintense on T2, with inhomogeneous gadolinium uptake, signs of haemorrhage and necrosis, of cystic areas. (4, 5) The compression of the fourth ventricle causes imaging signs of hydrocephalus and cerebral edema. The presence of nodules or linear contrast uptake in the ventricles or on the surfaces of the cerebral or cerebellar hemispheres is evidence of leptomeningeal tumour involvement. For the evaluation of the spinal metastases MRI examination is indicated. When present, the imaging aspect is nodular or more frequently linear. The MRI examination of the spinal cord should be performed prior to surgery. If it is not performed preoperatively, it is recommended to be performed 14 days postoperatively.

The CT scan of the native brain may reveal a hyperdense mass in the posterior cerebral fossa, with increased uptake after the administration of the contrast agent.

- The cytological examination of the CSF, preoperatively or 14 days postoperatively. About a third of all cases metastasize into the CNS through the CSF pathway. The lumbar puncture may be contraindicated preoperatively due to the increased risk of herniation. The leptomeningeal dissemination can remain undiagnosed in 14% -18% of cases if only one of the evaluation methods is used (either CSF cytology or MRI examination). It is recommended to use both methods for the assessment of the leptomeningeal involvement. (6) Preoperatively, there may be false positive results (circulating cells from the primary tumour). The predictive value of CSF is higher if the puncture is performed at least two weeks postoperatively.
- Bone marrow aspirate, for the evaluation of marrow metastases, if suspected
- The definitive diagnosis is established by the histopathological examination, postoperatively.

Staging and risk classification

The preoperative parameters of the tumour within the Chang staging system were replaced by the degree of the resection, more precisely by the postoperative residual disease.

The M Stages remain an important and significant clinical prognostic parameter and they were described in the Ependymomas chapter (Chapter 8.2.1).

Risk groups:

- Standard risk → age> 3 years, <1.5 cm^2 residual tumour, stage M0
- Increased risk → age <3 years,> 1.5 cm^2 residual tumour, stages M1-M4

Histopathological classification

The various histopathological aspects, recently combined with the genetic profile, provide indications on the prognosis and therefore also on survival. (see Table 1)

Table 1 WHO classification of medulloblastoma (7)

GENETIC PROFILE	HISTOLOGY	PROGNOSIS
Medulloblastoma, WNT-activated	Classic	Low risk, classical morphology is found in most WNT-activated tumours
Medulloblastoma, WNT-activated	Large cell / anaplastic (very rare)	Tumours with unclear clinicopathological significance
Medulloblastoma, SHH-activated and TP53-mutant	Classic	Unusually high risk
Medulloblastoma, SHH-activated and TP53-mutant	Large cell / anaplastic	High risk; common in children aged 7-17 years
Medulloblastoma, SHH-activated and TP53-mutant	Desmoplastic / nodular (very rare)	Tumours with unclear clinicopathological significance
Medulloblastoma, SHH-activated and TP53-wildtype	Classic	Standard risk
Medulloblastoma, SHH-activated and TP53-wildtype	Large cell / anaplastic	Tumours with unclear clinicopathological significance
Meduloblastom, SHH-activated and TP53-wildtype	Desmoplastic / nodular	Low risk in infants; common in infants and adults
Medulloblastoma, SHH-activated and TP53-wildtype	Extensive nodularity	Low risk, in children
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard risk
Medulloblastoma, non-WNT/non-SHH, group 3	Large cell / anaplastic	High risk
Medulloblastoma, non-WNT/non-SHH, group 4	Classic (for most tumours in group 4)	Standard risk
Medulloblastoma, non-WNT/non-SHH, group 4	Large cell / anaplastic (rare)	Tumours with unclear clinicopathological significance

Treatment

The multimodal treatment of medulloblastoma basically associates a maximum neurosurgical resection, craniospinal radiotherapy and chemotherapy.

Surgical treatment

- The surgery aims to establish the definitive diagnosis, to restore the normal flow of the CSF and the excision/cytoreduction of the tumour. Sometimes it is necessary to initially perform an urgent derivation of CSF, either temporary (external ventricular drainage) or permanent (ventriculocisternostomy). The tendency is to give up the ventriculoperitoneal shunting, given the risk of possible intra-abdominal dissemination through it. In some cases, a second surgery is performed for tumour excision within 1-2 weeks after the restoration of the CSF flow and for the neurological stabilization of the patient.

Medulloblastoma is staged according to the degree of tumour resection and postoperative imaging similar to other brain tumours (see the chapter on high-grade gliomas, Chapter 8.2.2.)

- Radiotherapy (RT)

Maximal safe resection is followed by craniospinal irradiation and adjuvant chemotherapy:

- Low- dose craniospinal irradiation with 23,4 Gy in 17 fractions with boost to tumor bed to 54,0 Gy for patients with standard risk

- High-dose craniospinal irradiation with 36,0 Gy in 20 fractions and boost to tumor bed to 54,0 Gy for high risk. Boost to other sites of gross disease is also indicated.

For children < 3 -4years of age and children with M2-M4 disease, maximal safe resection is followed by intensive chemotherapy. The goal is to omit or delay radiotherapy as long as possible in order to decrease long-term toxicity for the youngest children and to start immediately with induction chemotherapy after surgery and thereafter continue to radiotherapy and maintanance chemotherapy for high risk groups

Using new technologies (IMRT, proton therapy) we can better protect normal tissues and organs at risk.

Some protocols have included weekly Vincristine during radiotherapy (COG). (8, 9)

The combination of chemotherapy and radiotherapy has been proven to be more effective than radiotherapy alone in managing the disease at all stages, but the optimal combination has not yet been established. In the present PNET5 protocol there is a randomisation in the standard risk group to receive Carboplatin or not.

- Chemotherapy

The inclusion of patients into risk groups and treatment groups is made taking into account the following:

- The risk of recurrence, which is related to the spread of pre- and post-surgical disease

- The risk of treatment toxicity - children < 3-4 years of age being at the highest risk of developing post-RT neurocognitive disorders

According to the HIT 2000 protocol (11), the stratification of patients leads to the following categories:

- CHILDREN UNDER 4 YEARS OLD, WITHOUT METASTASIS (M0) →HIT 2000-BIS4

The postoperative chemotherapy involves the administration of 3 cycles of HIT-SKK 2000, consecutively every 3 weeks, each cycle being composed of the sequence IIS, IIIS, IIIS, IVS at 2 weeks:

IIS →VCR + CTX; IIIS →VCR + HDMTX, IVS → Carbo + VP16

The patients will receive intraventricular MTX (Ommaya reservoir)

The patients with a residual tumor at the evaluation after 3 cycles and who are 18 months old, will undergo a local conformal RT, DT 54 Gy, and then continue chemotherapy with 4 cycles VCR + DDP + CCNU.

The patients in complete remission after 3 cycles of HIT-SKK 2000 will continue chemotherapy with 2 more such cycles every 3 weeks, but without IIIS and without intraventricular MTX.

- CHILDREN OVER 4 YEARS OLD, WITHOUT METASTASES (M0) → HIT 2000- AB4

Postoperatively at 2 weeks or at 4 weeks the latest, conventional radiotherapy is initiated, during which weekly VCR is administered.

The treatment continues post-radiotherapy with 8 cycles of chemotherapy, administered every 6 weeks, VCR + DDP + CCNU.

- CHILDREN UNDER 4 YEARS OLD, WITH METASTASES (M1) → MET- HIT 2000- BIS4

A modified induction chemotherapy will be applied to this category of patients, consisting of three cycles of treatment, consecutively every 4 weeks, in the following combination:

Day 1 → DDP + VCR + intraventricular MTX
Day 2 → VP16 + CTX + intraventricular MTX
Day 3 → VP16 + CTX + intraventricular MTX
Day 4 → HDMTX
Day 8, 15 → VCR

If complete or partial remission is achieved (according to RECIST criteria), chemotherapy is continued with two cycles of high-dose treatment and stem cell support. Treatment can be stopped if complete remission is achieved and maintained. If there is a tumour residue after HD-PCT, the patient is referred to conventional radiotherapy (24 Gy craniospinal, 54.6 Gy in the posterior fossa and 49.2 Gy in the remaining metastases).

If after the first three cycles, a stable disease or a progression is found by imaging examination, the conventional radiotherapy will be applied (24 Gy craniospinal, 54.6 Gy at the level of the posterior fossa and 49.2 Gy at the level of the remaining metastases). After radiotherapy, the patient will undergo maintenance chemotherapy, 6 cycles of VCR, CCNU, DDP, every 6 weeks.

- CHILDREN OVER 4 YEARS OLD, WITH METASTASES (M1) → MET- HIT 2000- AB4

The postoperative chemotherapy involves the administration of 2 HIT-SKK 2000 cycles, described above, after which surgery is attempted, then conventional radiotherapy (35.2 Gy craniospinal, 55 Gy in the posterior fossa, 49.6 Gy in the remaining metastases).

Treatment of the progressive disease and relapses

Approximately 20-30% of patients relapse in the first 3 years after the diagnosis, either by local recurrence, or by leptomeningeal metastases, or by local recurrence and metastasis. Surgical excision reintervention of the relapsed tumor can be tried. The postoperative chemotherapy is resumed with second and third line cytostatic combinations. For infants and young children who have been treated exclusively with chemotherapy at diagnosis, RT appears to increase the survival without signs of disease.

- For the patients in M0 category <4 years old, who have completed the treatment and relapse, the therapeutic approach is differentiated as follows: For the patients in M0 category <4 years old, who have completed the treatment and undergo a relapse of the disease, the therapeutic approach is differentiated as follows:

- Local tumour progression, age > 3 years → RT + maintenance chemotherapy (VCR, Cisplatin, CCNU)
- Local tumour progression, age <3 years → Chemotherapy Protocol SKK-REZ 2000
- Progression by metastases → Chemotherapy Protocol MET-HIT 2000-BIS

- In cases of early local recurrence, age < 4 years → Chemotherapy Protocol SKK-REZ 2000

Stem cell apheresis is performed, followed by two cycles of treatment combining Carbo and VP16. In case of complete or partial remission (according to RECIST criteria), the chemotherapy is continued with a third cycle. If complete remission is maintained the patient will receive high-dose chemotherapy and stem cell support, followed by conventional radiotherapy in the posterior fossa.

If after three cycles of treatment a resumption of tumor evolution is noticed conventional craniospinal radiotherapy is immediately performed (with 24 GY spinal and 56 Gy

at the level of the posterior fossa), followed by the maintenance chemotherapy with VCR, CCNU and DDP.

If after the first two cycles of treatment, a stable disease or progression is found during the imaging examination, conventional craniospinal radiotherapy is likewise performed (with 24 GY spinal and 56 Gy in the posterior fossa), followed by maintenance chemotherapy with VCR, CCNU and DDP.

High-dose chemotherapy and stem cell support has been shown to increase the disease-free survival by 20% in patients who have not had RT. (12)

The second-line chemotherapy follows the HIT REZ 2005 protocol for patients with medulloblastoma, PNET, ependymoma, with local recurrence, or metastases. (13) Concise description of the protocol:

Two cycles of Carbo and VP16 are used. If the imaging examination does not detect progression of the disease (according to RECIST criteria), 2 more such cycles are performed, with stem cell harvesting between cycle 3 and 4. If complete remission is obtained after 4 cycles, the patient will undergo high doses chemotherapy and stem cell support. If only stable disease or partial remission is obtained, the patient will continue with maintenance therapy. If the disease is progressing, either after two or after four cycles of treatment, another therapeutic regimen will be used.

The evaluation after 2 cycles may find complete remission, partial remission or stable disease, situations in which the treatment continues with another 2 cycles; after cycle 3, stem cells are harvested. The complete remission after 4 cycles leads to high-dose chemotherapy and stem cell support. If after 4 cycles the disease is stationary or in partial remission, the treatment continues with temozolomide maintenance therapy.

TEMIRI PROTOCOL (14) – it proposes the administration at every three weeks of:

IRI p.o. 10mg/m2/day on days 1-5, days 8-12

TEM p.o. 10 - 125 mg/m2 /day, days 1-5

The combination of Bevacizumab + IRI + / _ TEM appears to have an objective response (15), keeping in mind that Bevacizumab is an off-label medication. (15)

Antiangiogenic metronomic therapy can stabilize metastatic disease - MEMMAT clinical trial (16)

- Bevacizumab every 2 weeks
- Celecoxib: 100 mg x2/day,

> 20 kg: the dose can be increased to 200 mg p.o. x2/day depending on tolerance

> 35 kg: the dose can be increased to 300 mg x2/day depending on tolerance

> 50 kg: the dose can start with 200 mg p.o.x2/day and increase up to 400 mg p.o.

- Fenofibrate: 90 mg/m^2/day, (max 200 mg/day, taken with food, single dose)
- Thalidomid 3 mg/**kg** x 1 at night
- CTX: 2.5 mg/kg/day, 21 days, alternatively with VP16 50 mg/m^2/day, 21 days.
- Etoposide intrathecaly (Ommaya) for 5 consecutive days every 4 weeks and cytarabin intrathecaly (Ommaya) twice per week for two consecutive weeks ever 4 week.

Clinical trials: www.clinicaltrialsregister.eu

Late secondary complications

After surgery the posterior fossa syndrome (cerebellar mutism) can occur, which can last for weeks/months. For the late side effects monitoring table, see chapter 8.2.1.

Post-therapeutic monitoring

The imaging monitoring by brain/craniospinal MRI is recommended every 3 months in the first 2 years after the completion of the oncological treatment, then every 4 months in the 3rd and 4th year, and then every 6 months.

The monitoring of the side effects of the oncological treatment (radiotherapy/ chemotherapy) is done by a multidisciplinary team consisting of: pediatric oncologist, pediatric neurologist, child psychologist/psychiatrist, endocrinologist, ENT specialist (audiological evaluation), ophthalmologist, doctor in medical recovery and physical therapist. (See chapter 8.2.1 Ependymoma). (15)

Recommendations

- Medulloblastoma is a tumour of embryonic origin located in the posterior cerebral fossa
- The correlation between age, molecular and histologic subtypes is an important prognostic factor.
- Staging, risk stratification and age < 3 -4 years are important in treatment decision.
- Treatment is multimodal: surgery, craniospinal irradiation (with concommitant chemotherapy in some protocols) and adjuvant chemotherapy.
- Total dose prescribed for craniospinal irradiation depend on risk stratification.
- The chemotherapy according to the updated HIT 2000 protocol is recommended
- There are variants of second line chemotherapy and treatment options for relapsed disease.

Bibliography

1. Robinson GW, Orr BA, Wu G, Gururangan S, Lin T, Qaddoumi I, et al. Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032. J Clin Oncol. 2015;33(24):2646-54

2. Packer RJ, Rorke- Adams LB, Lau CC, et al. Capitol 26B: Tumori embrionare si de regiune pineala. In: Principles and Practice of Pediatric Oncology, 6th ed, Pizzo P, Poplack D (Eds), Lippincott Williams & Wilkins, St. Louis 2011. p.772.

3. https://www.uptodate.com/contents/histopathology-genetics-and-molecular-subgroups-of-medulloblastoma?sectionName=GENETIC%20PREDISPOSITION&search=clinical%20presentation,%20diagnosis%20and%20risk%20stratification%20of%20medulloblastoma&topicRef=5219&anchor=H4&source=see_link#H4

4. Wolpert SM, Barnes PD. MRI in Pediatric Neuroradiology, Mosby, St. Louis 1992.

5. Poretti, A., Meoded, A. and Huisman, T., 2011. Neuroimaging of pediatric posterior fossa tumors including review of the literature. *Journal of Magnetic Resonance Imaging*, 35(1), pp.32-47.

6. Fouladi, M., Gajjar, A., Boyett, J., Walter, A., Thompson, S., Merchant, T., Jenkins, J., Langston, J., Liu, A., Kun, L. and Heideman, R., 1999. Comparison of CSF Cytology and Spinal Magnetic Resonance Imaging in the Detection of Leptomeningeal Disease in Pediatric Medulloblastoma or Primitive Neuroectodermal Tumor. *Journal of Clinical Oncology*, 17(10), pp.3234-3237.

7. Louis, D., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W., Ohgaki, H., Wiestler, O., Kleihues, P. and Ellison, D., 2016. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica*, 131(6), pp.803-820.

8. Fukunaga-Johnson, N., Lee, J., Robertson, P., Sandler, H., McNeil, E. and Goldwein, J., 1997. 20 Patterns of failure following treatment for medulloblastoma: Is it necessary to treat the entire posterior fossa?. *International Journal of Radiation Oncology*Biology*Physics*, 39(2), p.144.

9. Capitol 4: Tumors of the Posterior Fossa and the Spinal Canal din Pediatric Radiation Oncology 6th Edition Constine, Tarbell Halperin, pag 57-34

10. Wolden, S., Dunkel, I., Souweidane, M., Happersett, L., Khakoo, Y., Schupak, K., Lyden, D. and Leibel, S., 2003. Patterns of Failure Using a Conformal Radiation Therapy Tumor Bed Boost for Medulloblastoma. *Journal of Clinical Oncology*, 21(16), pp.3079-3083.

11. HIT 2000 - Multicenter therapy optimising trial for the treatment of children and adolescents with medulloblastoma, intracranial primitive neuroectodermal tumours of the central nervous system (CNS-PNET), and ependymoma

12. Graham, M., Herndon, J., Casey, J., Chaffee, S., Ciocci, G., Krischer, J., Kurtzberg, J., Laughlin, M., Longee, D., Olson, J., Paleologus, N., Pennington, C. and Friedman, H., 1997. High-dose chemotherapy with autologous stem-cell rescue in patients with recurrent and high-risk pediatric brain tumors. *Journal of Clinical Oncology*, 15(5), pp.1814-1823.

13. HIT-REZ 2005-Therapy-Optimization Trial and Phase II Study for the Treatment of Relapsed or Refractory Primitive Neuroectodermal Brain Tumors and Ependymomas in Children and Adolescents

14. Grill, J., Geoerger, B., Gesner, L., Perek, D., Leblond, P., Canete, A., Aerts, I., Madero, L., de Toledo Codina, J., Verlooy, J., Estlin, E., Cisar, L., Breazna, A., Dorman, A., Bailey, S., Nicolin, G., Grundy, R. and Hargrave, D., 2013. Phase II study of irinotecan in combination with temozolomide (TEMIRI) in children with recurrent or refractory medulloblastoma: a joint ITCC and SIOPE brain tumor study. *Neuro-Oncology*, 15(9), pp.1236-1243.

15. Aguilera, D., Mazewski, C., Fangusaro, J., MacDonald, T., McNall-Knapp, R., Hayes, L., Kim, S. and Castellino, R., 2013. Response to bevacizumab, irinotecan, and temozolomide in children with relapsed medulloblastoma: a multi-institutional experience. *Child's Nervous System*, 29(4), pp.589-596.

16. Metronomic and Targeted Anti-angiogenesis Therapy for Children With Recurrent/Progressive Medulloblastoma (MEMMAT)

8.2.5 EMBRYONAL BRAIN TUMOURS

The embryonal tumours represent a new category of brain tumours in the WHO 2016 classification. This category emerged following the 2016 reassessment of the WHO classification of brain tumours, which uses molecular parameters associated with histological ones.

The new WHO 2016 classification of brain tumors lists the following entities as embryonal brain tumors: medulloblastoma, atypical rhabdoid/theratoid tumors(AT/RT), pinealoblastoma, embryonal tumor with multiple rosettes (ETMR)/*C19MC*-altered, medulloepitheliomas, CNS neuroblastoma, CNS ganglioneuroblastoma, CNS embryonal tumour non otherwise specified(NOS), CNS embryonal tumour with rhabdoid features.

The embryonal tumour with multilayered rosettes (ETMR) is characterized by the presence of the C19MC gene mutation on chromosome 19. The tumours previously called embryonal tumour with abundant neuropil and true rosettes, ependymoblastoma, medulloepithelioma, are now included in this category. In cases where the genetic determination is not possible, the term "embryonal tumour with multilayered rosettes, *not otherwise specified (NOS)*" is used.

At the same time, the old term of primitive neuroectodermal tumour was abandoned. (1)

In the current classification, in situations where molecular diagnosis is not possible, the primitive neuroectodermal tumours of the CNS are included in the category "CNS embryonal tumours, NOS".

They are aggressive tumours, poorly differentiated, with a high proliferation rate, included in the WHO grade IV. (2)

Epidemiology

The incidence is about 2-3% of all paediatric brain tumours. (3)

About 25% of cases are diagnosed in the first two years of life and 80% of cases by the age of 10. (3) The distribution by sex is equal.

Symptomatology

The most common symptoms at onset are related to the intracranial hypertension: vomiting and headache. Infants show increased skull circumference, lethargy, and irritability. The time from onset to diagnosis is shorter than in medulloblastomas, about a month. The most common site being the cerebral hemispheres, with a predilection for the frontal and temporal lobes, the seizures and the motor deficits are part of the symptomatology in one third of the cases.

Diagnostic evaluation

- Neurological examination
- Ophthalmological examination with eye fundus
- craniospinal MRI imaging with contrast agents; CT scan if MRI not available (4)

The CT scan of the native brain can reveal a well-circumscribed mass, in a cerebral hemisphere, with calcifications (50% of cases), hemorrhagic areas (20% of cases) and cystic areas, with inhomogeneous uptake after administration of the contrast agents.

The brain MRI examination provides additional details about the tumour process, the hyperintense areas in the T1 sequences identifying haemorrhage. The peritumoral edema is absent in most cases.

The spinal MRI examination reveals leptomeningeal metastases, which are present from the beginning in 10-15% of cases. (5)

- The lumbar puncture for CSF cytological examination is contraindicated before surgery.
- The definitive diagnosis is established by histopathological, immunohistochemical and molecular examination. Macroscopically, they are soft tissue masses with a cystic appearance and hemorrhagic areas. Microscopically, proliferation of small tumour cells with hyperchromatic nuclei is observed. Homer Wright rosettes and perivascular pseudorosettes are present, as well as necrosis areas.

Staging and risk stratification

The same staging systems are used as for ependymomas (see chapter 8.2.1).

The degree of tumour spread at diagnosis is a predictive factor for survival. Metastatic stages have a poor prognosis.

Systemic staging (chest, abdomen, pelvis CT scan, bone scintigraphy) is not routinely used.

Treatment

All embryonal tumours other than medulloblastomas receive the same treatment. The medulloblastoma is discussed in a different chapter. (see chapter 8.2.4) They are highly aggressive tumours with pour survival rates, ranging from 5-30% 5 year event free survival rates. The multimodal treatment combines surgery, craniospinal radiotherapy and chemotherapy. The neurosurgical treatment aims to establish a definitive diagnosis, to restore the normal CSF flow and excision/cytoreduction of the tumour. Depending on the degree of the tumour resection, neurosurgical staging, postoperative imaging staging and staging combining surgical and imaging data are performed (See Chapter 8.2.2).

Being well-vascularized large tumours that invade the functional cortex, the gross total resection (GTR) is difficult to achieve. The degree of resection was a variable predictive factor for survival. (6, 7) In about 50% of cases an S2 resection can be performed. (6)

The radiation therapy has a very important role in the control of the disease, being the standard treatment in children older than 3-4 years. Radiotherapy immediately follows surgery.

The craniospinal irradiation is indicated, with supplementation of targeted irradiation at the level of the primary tumour area. The determination of the irradiated tumour volumes should take into account the preoperative tumour volume, with a correction for tissue changes that occur postoperatively and an extension of about 1 cm to the healthy tissue (sometimes more in the case of infiltrative tumours). (8) It is necessary to fixate the patients in order to ensure the daily reiteration of the established irradiation parameters. The use of IMRT is beneficial by limiting the doses in the peritumoral brain tissue. (8)

The usual dose is 36 Gy for the entire craniospinal axis, with an additional dose up to 54 Gy on the primary tumour area. For patients under 4 years of age, irradiation is not indicated, as the risk of severe long-term side effects is very high.

Cytostatic treatment

The adjuvant chemotherapy regimens are those used in patients with medulloblastoma.

The pre-irradiation chemotherapy appears to increase the risk of early progression. (9)

According to the HIT 2000 protocol, the stratification of patients by therapeutic groups leads to the following treatment groups: (10)

- CHILDREN UNDER 4 YEARS OLD, WITH OR WITHOUT METASTASES (M0, M1) → P- HIT 2000- BIS4

Two cycles of treatment combining Carbo and VP16 will be administered. After two cycles, a second surgery is performed, if necessary and possible. The chemotherapy is continued with the third cycle of Carbo + VP16, followed by a tandem of high-dose chemotherapy and stem cell support (2 procedures, at different intervals, depending on the child's hematological and biological tolerance). If the evaluation after the second procedure shows complete remission, the treatment is stopped. If the complete remission has not been achieved, the treatment will be completed with radiation therapy.

- CHILDREN OVER 4 YEARS OLD WITHOUT METASTASES (M0) (11)

The radiation therapy is initiated (dose of 36 Gy craniospinal, with additional dose at the level of the tumour bed). After radiotherapy maintenance chemotherapy is administrated→ 8 cycles of chemotherapy, administered every 6 weeks, with VCR + Cisplatin + CCNU:

- CHILDREN OVER 4 YEARS OLD, WITH METASTASIS (M1-4) (11)

The postoperative chemotherapy involves the administration of 2 cycles of HIT-SKK 2000, consecutively every 3 weeks, each cycle being composed of the sequence IIS, IIIS, IIIS, IVS at 2 weeks:

IIS → VCR + CTX; IIIS → VCR + MTX; IVS → Carbo + VP16

The patients will receive intraventricular MTX (Ommaya reservoir). Radiation therapy at a dose of 40 Gy craniospinal and supplementation of irradiation at the level of the tumour bed follow thereafter. After the completion of the radiotherapy, the maintenance therapy is initiated.

The high-dose chemotherapy and the stem cell support can improve survival despite the treatment toxicity. (12, 13)

Treatment of progressive disease and relapses

Although the therapeutic approach is aggressive, the recurrences are frequent and they occur early.

The surgical reintervention for excision or cytoreduction of the tumour is recommended, whenever possible. Radiotherapy is recommended for children older than 3 years who have undergone only chemotherapy.

The second line chemotherapy follows the HIT REZ protocol, for patients with medulloblastoma, PNET, ependymoma, with local recurrence or metastases. (14). The protocol was described in the chapter on Medulloblastoma (Chapter 8.2.4).

The TEMIRI protocol is indicated.

The antiangiogenic metronomic therapy can stabilize the metastatic disease - MEMMAT clinical trial (16)

Clinical trials: www.clinicaltrialsregister.eu

The high-dose chemotherapy and the stem cell support has been shown to increase disease-free survival by 20% in patients previously treated without radiotherapy. (9)

The prognosis of this type of tumour is poor. The 3 years overall survival is about 50%. (3, 9) The survival in infants varies between 20% and 40%.

Post-therapeutic monitoring

The immediate complications following the treatment must be monitored. The late complications cannot be estimated, given the short-term survival in a rare disease. The

monitoring of the late side effects in the case of long-term survivors will be performed according to the recommendations for medulloblastoma and ependymoma (see chapters 8.2.4 and 8.2.2).

The clinical, biological, neurological and imaging evaluation by craniospinal MRI are done every 3 months in the first 2 years after the completion of the oncological treatment, then every 4 months in the 3rd and 4th year, then every 6 months up to 5 years, and then annual follow-ups.

Recommendations

- They are aggressive tumours, grade IV WHO, which occur more frequently in young children
- The therapy consists of surgical resection, chemotherapy and craniospinal irradiation
- The high-dose chemotherapy with stem cell support is recommended as first line treatment for children under 4 years to avoid craniospinal radiation
- The prognosis is poor and it depends on the stage of the disease and the degree of resectability

Bibliography

1. Louis D, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee W et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathologica. 2016;131(6):803-20.
2. Sin-Chan P, Li B, Ho B, Fonseca A, Huang A. Molecular Classification and Management of Rare Pediatric Embryonal Brain Tumors. Current Oncology Reports. 2018;20(9).
3. Pizzo, P., Poplack, D., Packer, R., Rorke- Adams, L. and Lau, C., 2011. *Principles And Practice Of Pediatric Oncology*. 6th ed. St. Louis: Williams & Wilkins, pp.772-790.
4. Depper MH, Hart BL. Pediatric Brain Tumors. In: Neuroimaging, Orrison WW (Ed), WB Saunders, Philadelphia 2000. 1625-31.
5. Wolpert SM, Barnes PD. MRI in Pediatric Neuroradiology, Mosby, St. Louis 1992.
6. Albright AL, Wisoff JH, Zeltzer P, et al. Prognostic factors in children with supratentorial (nonpineal) primitive neuroectodermal tumors. A neurosurgical perspective from the Children's Cancer Group, Pediatr Neurosurg. 1995; 22(1):1.
7. Tomita T, McLone DG, Yasue M, Cerebral primitive neuroectodermal tumors in childhood. J Neurooncol. 1988; 6(3):233.
8. Capitol 3: Supratentorial BrainTumors in Pediatric Radiation Oncology 6th Edition Constine, Tarbell Halperin, pag 41-42
9. Timmermann B, Kortmann RD, Kühl J, et al., Role of radiotherapy in the treatment of supratentorial primitive neuroectodermal tumors in childhood: results of the prospective German brain tumor trials HIT 88/89 and 91, J Clin Oncol. 2002;20(3):842.
10. HIT 2000 - Multicenter therapy optimising trial for the treatment of children and adolescents with medulloblastoma, intracranial primitive neuroectodermal tumours of the central nervous system (CNS-PNET), and ependymoma
11. HIT-MED Guidance for Patients with Medulloblastoma Ependymoma CNS-PNET and Pineoblastoma Version 3.0
12. Graham ML, Herndon JE 2nd, Casey JR, et al. High-dose chemotherapy with autologous stem-cell rescue in patients with recurrent and high-risk pediatric brain tumors. J Clin Oncol 1997; 15:1814
13. Pérez-Martínez A, Lassaletta A, González-Vicent M, et al., High-dose chemotherapy with autologous stem cell rescue for children with high risk and recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors, J Neurooncol. 2005;71(1):33.
14. HIT-REZ 2005-Therapy-Optimization Trial and Phase II Study for the Treatment of Relapsed or Refractory Primitive Neuroectodermal Brain Tumors and Ependymomas in Children and Adolescents

15. Grill J[1], Geoerger B, Gesner L, Phase II study of irinotecan in combination with temozolomide (TEMIRI) in children with recurrent or refractory medulloblastoma: a joint ITCC and SIOPE brain tumor study. Neuro Oncol. 2013 Sep;15(9):1236-43

16. Metronomic and Targeted Anti-angiogenesis Therapy for Children With Recurrent/ Progressive Medulloblastoma (MEMMAT)

8.2.6 GERM CELL BRAIN TUMOURS

The intracranial germ cell tumours (GCTs) develop mainly in the midline (in the pineal gland and suprasellar region), with an increased frequency in the second decade of life, mainly between 10 and 14 years, more commonly in males. Due to a mesoderm migration error in the third week of gestation, the extragonadal site of this type of tumour appears. (1, 2)

Depending on the histopathological type, they are divided into 2 subclasses: pure germinomas and non-germinoma GCTs (see Table 1).

Epidemiology

Intracranial GCTs account for approximately 2%-4% of primary brain tumours in children in Europe and the USA, with a much higher incidence in Japan and Taiwan (up to 11-15%). (3) This site represents approximately 30% of all germ cell tumours. Down syndrome and Klinefelter syndrome predispose to this type of brain tumours (1). Most intracranial GCTs are germinomas (up to 65% of all cases). In Romania, during 2010 - 2018, 25 cases of intracranial GCTs were reported in the National Register of Childhood Cancer in Romania (on average, 3 new cases/year).

In Europe, the 5-year survival for localized tumours varies between 82% and 90%, lower for non-germinoma GCTs. (2) Survival in metastatic tumours reaches up to about 75%. (3)

Symptomatology

The symptomatology is variable and depends on tumor localization, the diagnosis being sometimes difficult (symptoms may appear months/years before the diagnosis - diabetes insipidus, mental retardation or learning disorders).

The GCTs located in the pineal region can cause intracranial hypertension (IH) - headache, nausea, vomiting. The neurological signs determined by the site of the tumour can be: diplopia, balance disorders, axial hypotonia, Parinaud syndrome (inability for vertical gaze, predominantly superior, to which convergent nystagmus can be added, eyelid retraction). (1, 2, 4)

The GCTs located in the suprasellar region may cause symptoms secondary to hormonal deficiencies (growth hormones, sex hormones, antidiuretic hormone): diabetes insipidus occurs in 70% -90% of cases, sexual development disorders, growth disorders. Another category of clinical signs is the visual impairment: decreased visual acuity, bitemporal hemianopsia. In approximately 35% of cases the onset symptoms may be present up to 12 months before the diagnosis. (1, 2, 4) Teratomas (+/- immature elements) occur predominantly in very young children. They are usually congenital and cause symptoms of increased intracranial pressure (ICP), macrocephaly. (4)

In 5-10% of cases, the tumour may be bifocal or multifocal.

Diagnosis

The mandatory evaluations for diagnosis and the assessments of the extent of the disease are:

- Craniospinal MRI examination/brain CT scan with contrast agents to establish the degree of the disease extension; it should be noted that the imaging aspect is not characteristic for germinoma or non-germinoma GCTs. Craniospinal MRI examination is mandatory before biopsy.

- Cytological examination and determination of tumour markers (AFP, **β**-HCG) in cerebrospinal fluid (CSF); if the lumbar puncture cannot be performed before the biopsy (hydrocephalus), it will be postponed until day 10 postoperatively

- Determination of serum tumour markers (AFP, **β**-HCG); there is a recommendation for concomitant determination of serum markers in CSF

- Tumour biopsy if serum and CSF markers are negative.

- Chest-abdominal-pelvic CT examination, testicular ultrasound to exclude tumours with concomitant germ cells, with another site.

Mandatory assessments at the start of the treatment (5):

- Complete clinical examination, including neurological examination
- Quality of life assessment, neuro-cognitive assessment (if possible) and social inquiry
- Blood count with total leukocyte count
- Renal function (urea, creatinine, uric acid, ionogram, urine osmolarity, phosphates and urinary creatinine)
- Liver function (ALT, AST, GGT, FAL, serum albumin level), coagulogram
- Viral serology examinations (usually hepatitis B, hepatitis C, HIV)
- Endocrinological, ophthalmological and ENT evaluation
- Serum and CSF tumour markers (if more than 2 weeks have passed between the diagnosis and the initiation of the treatment)
- Pregnancy test (for adolescent girls at the age of procreation)
- It is possible to discuss the preservation of sperm for boys and the preservation of fertility for girls

Evaluations during treatment, before each series of chemotherapy (5):

- Complete clinical examination, including neurological evaluation
- Complete blood count and leukocyte count
- Renal, hepatic function, ionogram
- +/- audiogram
- Tumour markers - if they had high values
- Imaging evaluations (MRI, CT) at the clinical suspicion of the resumption of evolution

End-of-treatment evaluations (5):

- Craniospinal MRI with contrast agents
- Serum and CSF tumour markers (if positive for diagnosis)
- CSF cytology
- Ophthalmologic evaluation, endocrinological evaluation, evaluation of renal function and audiogram, evaluation of the cognitive function

Diagnosis certainty

In case of increased CSF values of tumour markers (AFP and/or **β**-HCG), the tumour biopsy can be omitted, the diagnosis being that of non-germinoma GCT. (1)

The tumour biopsy is mandatory for patients with pineal region tumour with specific tumour markers in serum and/or negative CSF, to establish a definitive diagnosis and for the differential diagnosis from other midline tumours (pinealoma, pineocytoma, low grade gliomas, embryonal brain tumours). (1, 4)

Histopathological diagnosis, classifications

From a histopathological point of view, intracranial GCT can be classified into 2 groups: pure germinomas and non-germinoma GCTs with 6 histological subgroups. The location codes are C7000-C729, C751-753. The ICCC3 (International Cancer of Childhood Cancer- the third edition) classification falls into category Xa 1-6.

- Pure germinoma
- Non-germinoma
-embryonal carcinoma
-Yolk sac tumor (endodermal sinus tumour)
-choriocarcinoma
-mature teratoma
-immature teratoma
- teratoma with malignant transformation
-mixed germ cell tumour

Classifications:

Classification according to tumour localization:

The most common location is in the pineal region (50-60%) followed by the suprasellar region (30-35%); in 5-10% of cases, the GCTs are bifocal or multifocal (usually the germinomas and they occur frequently in boys). Exceptionally, they can also affect the basal ganglia or thalamic nuclei.

Classification according to tumour markers (Table 1):

- Non-secreting GCTs (pure germinomas) occur most frequently in adolescents and young adults; there is a syncytiotrophoblastic subtype that secretes a small amount of β-HCG.

- Secreting GCTs are characterized by elevated serum and/or CSF values of AFP > 25 ng/ml and/or β-HCG> 50 IU/l. The determination of serum and CSF tumour markers is essential for proper staging. In addition to the diagnostic and staging role, they are a way to monitor the response to treatment. Other tumour markers are being studied in order to monitor the response to treatment: placental alkaline phosphatase and the soluble isoform of c-kit. (1)

Table 1. WHO classification of intracranial GCTs according to tumour markers

Tumour type	Tumour marker			
	β-HCG	AFP	PLAP	c-kit
Pure germinoma	±	-	±	+
Germinoma with syncytiotrophoblastic predominance	+	-	±	+
Yolk sac tumour	-	+++	±	-
Choriocarcinoma	+++	_	±	-
Embryonal carcinoma	+	+	+	-
Mixed germ cell tumour	+/-	+/-	±	±
Mature teratoma	-	-	-	-
Immature teratoma	+/-	+/-	-	±

AFP with much higher values occurs in Yolk sac tumors, β-HCG in choriocarcinoma (values> 1000 IU) and both markers appear with high values in embryonal carcinoma.

Prognostic factors

The prognostic factors in intracranial GCTs are: histopathological type, disease stage, AFP value and response to cytostatic treatment. (see Table 2)

Table 2. Prognostic groups for intracranial GCTs (2)

Good prognosis	Pure germinoma
	Mature teratoma
Intermediate prognosis	Germinoma with a syncytiotrophoblastic component
	Immature teratoma
	Mixed GCTs in which the elements of germinoma or teratoma are predominant
	Teratoma with malignant transformation
Unfavourable prognosis	Choriocarcinoma
	Embryonal carcinoma
	Yolk sac tumour
	Mixed GCTs where elements of carcinoma, choriocarcinoma or Yolk sac tumour are predominant

Treatment (5, 6)

The therapeutic approach is decided based on:

- histopathological type: germinoma or non-germinoma GCTs
- degree of disease spread: localized disease or metastatic disease (presence of atypical cells in CSF establishes the diagnosis of metastatic disease, regardless of the absence/presence of secondary determinations visible at the imaging examination. (5)

Currently, in Romania, the treatment of intracranial GCT is done according to the SIOP CNS GCT II protocol and it is carried out by a multidisciplinary team (neurosurgeon, paediatric oncologist, radiotherapist, neurologist, endocrinologist). The SIOP CNS GCT II protocol is closed for inclusion but is recommended as best available treatment until new protocol is launched.

- The role of surgery in the treatment of intracranial GCT is:
  - certifying the diagnosis (stereotactic/open biopsy)
  - CSF drainage in the case of symptomatic hydrocephalus secondary to tumour obstruction (ventricular-peritoneal drainage, ventriculocisternostomy or other temporary or permanent drainage)
  - therapeutic - when tumour excision is possible

- The role of chemotherapy in the treatment of intracranial GCTs

GCTs are chemosensitive tumours regardless of site, including those located intracranially. The role of chemotherapy is to reduce the both doses of radiotherapy and the late side effects related to irradiation.

Localized germinomas can be treated by:

- radiotherapy exclusively, or
- neoadjuvant chemotherapy + radiotherapy

Four cycles of chemotherapy are administered every 21 days. The chemotherapy series consists of Carbo + VP16 alternatively with IFO + VP16.

Metastatic germinomas will be treated by systemic chemotherapy and craniospinal radiotherapy.

Non-germinoma secreting GCTs and germinomas with histological component of Yolk sac tumour, choriocarcinoma or embryonal carcinoma will be treated with neoadjuvant chemotherapy + radiotherapy. Neoadjuvant chemotherapy consists of 4 cycles: PEI protocol: DDP + VP16 + IFO, at 21 days.

- The role of radiotherapy in the treatment of intracranial GCTs (5, 7)

Germinomas are radiosensitive, the survival rate for germinomas treated only with radiotherapy can reach up to 90%. The purpose of introducing neoadjuvant chemotherapy was to reduce the field and doses of radiotherapy, and the late side effects of the cranial irradiation, respectively. The recommended techniques are conformal radiotherapy and IMRT.

- For localized germinomas with complete remission after 4 series of chemotherapy, total ventricular irradiation will be administered, up to a total dose of 24 Gy.
- For localized germinomas with partial remission or stationary disease after neoadjuvant chemotherapy, total ventricular irradiation with additional dose on the tumour bed will be administered up to a total dose of 40 Gy.
- For metastatic germinomas, craniospinal radiotherapy will be administered up to a total dose of 40 Gy.

Unlike germinomas that are highly radiosensitive, for non-germinoma GCTs the combination of neoadjuvant chemotherapy in multimodal treatment is mandatory.

- For localized non-germinoma GCTs, focal radiotherapy will be administered (up to a total dose of 54 Gy).
- For metastatic non-germinoma GCTs, craniospinal radiotherapy will be administered. If there are spinal metastases highlighted macroscopically on more than ⅔ of the spine, the maximum dose of spinal radiotherapy will be 45 Gy.

In an attempt to limit the long-term side effects of radiotherapy, proton radiotherapy is being evaluated.

The evaluation of the response to treatment is done by imaging evaluation (craniospinal MRI with contrast agents) and determination of tumour markers if they had high values at diagnosis.

The response to treatment parameters:

- complete remission: normal craniospinal MRI and tumour markers within the age limits
- partial remission: dimensional decrease of +/- metastatic tumour lesions on MRI by more than 50% + normalized tumour markers or pituitary stalk thickening/more intense contrast in the pituitary gland or tumour markers above the normal value for that age and normal craniospinal MRI
- stationary disease: decrease by less than 50% of the tumour shown by MRI
- progressive disease: dimensional increase of more than 25% on MRI in any size of the tumour or the occurrence of new lesions or growing tumour markers (except for the first week after chemotherapy)

Treatment of relapses

There is no standardized treatment for recurrences in intracranial GCTs. The risk of recurrence is higher for secreting tumours. In case of recurrence, survival is higher for germinomas. Standard chemotherapy (if not originally used) or its resumption, supplementation of radiotherapy or high-dose chemotherapy and stem cell support may be used in the case of non-germinoma GCTs. (7, 8, 9, 10)

Post-therapeutic monitoring

The monitoring will be done for at least 5 years after the end of treatment, the follow-up protocol being dependent on the histopathological type.

- Germinoma (negative markers): craniospinal MRI with contrast agents at the end of the treatment, then every 3 months in the first year, every 6 months in the second year and annually thereafter. If the spinal MRI is normal at the end of the treatment, it will be repeated alongside the first two brain MRI examinations, or whenever needed.

- Secreting GCTs (positive markers): the imaging evaluation is the same as for germinomas. As for tumour markers, they will be tested monthly in the first year, every 2 months in the second year, every 3 months in the third year, then annually.

In the first year, a complete clinical and neurological examination will be performed with haematological, renal and hepatic function, ophthalmological and endocrinological evaluations every 3 months, every 6 months in the second year, subsequently annually or whenever there is a suspicion of resumption of development/relapse.

Recommendations

- Intracranial GCTs is classified histopathologically into pure germinomas and non-germinoma GCT, according to the ICCC3 Classification
- The treatment of intracranial GCT is performed according to the SIOP CNS GCT II protocol, differentiated according to histopathological type, secreting status and disease spread
- Mixed tumours are treated according to the protocol for the most aggressive component

Bibliography:

1. Michael C. G. Stevens , Hubert N. Caron, Andrea Biondi, *Cancer in Children: Clinical Management 6th Edition* – Oxford University Press, 2012, cap 20, pag 263-265

2. Platforma cancer.gov - https://www.cancer.gov/types/brain/hp/child-cns-germ-cell-treatment-pdq

3. Calaminus G,Frappaz D,Kortmann RD,Krefeld B,Saran F,Pietsch T,Vasiljevic A,Garre ML,Ricardi U,Mann JR,Göbel U,Alapetite C,Murray MJ,Nicholson JC - Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial - Neuro Oncol. 2017; 19(12):1661-1672

4. Philip A. Pizzo, David G. Poplack - *Principles and Practice of Pediatric Oncology Seventh Edition* – Wolters Kluver, 2016, cap 26B, pag 691-695

5. SIOP CNS GCT II - treatment protocol available on https://www.skion.nl/workspace/uploads/2_siop_cns_gct_ii_final_version_2_15062011_unterschrift_hoppenheit.pdf

6. Murray M., Bartels U., Nishikawa R., Fangusaro J., Matsutani M., & Nicholson J. C. - Consensus on the management of intracranial germ-cell tumours. The Lancet Oncology 2015, Sep; 16 (9) e470-e477

7. Louis S. Constine MD, Nancy J. Tarbell MD, Edward C. Halperin MD - *Pediatric Radiation Oncology 6th Edition* - Wolters Kluver, 2016, cap 3, pag 44-51

8. Murray MJ,Bailey S,Heinemann K,Mann J,Göbel UK,Saran F,Hale JP,Calaminus G,Nicholson JC - Treatment and outcomes of UK and German patients with relapsed intracranial germ cell tumors following uniform first-line therapy Int J Cancer. 2017 Aug 1;141(3):621-635

9. Hu YW,Huang PI,Wong TT,Ho DM,Chang KP,Guo WY,Chang FC,Shiau CY,Liang ML,Lee YY,Chen HH,Yen SH,Chen YW - Salvage treatment for recurrent intracranial germinoma after reduced-volume radiotherapy: a single-institution experience and review of the literature Int J Radiat Oncol Biol Phys. 2012 Nov 1;84(3):639-47

10. Modak S,Gardner S,Dunkel IJ,Balmaceda C,Rosenblum MK,Miller DC,Halpern S,Finlay JL. - Thiotepa-based high-dose chemotherapy with autologous stem-cell rescue in patients with recurrent or progressive CNS germ cell tumors J Clin Oncol. 2004 May 15;22(10):1934-43

8.2.7 PRIMARY BRAIN LYMPHOMA

Epidemiology

Primary lymphoma of the central nervous system (CNS) is a rare form of non-Hodgkin's lymphoma that occurs only in the CNS (brain parenchyma, spinal cord, cranial nerves, eyes and meninges), with no signs of systemic involvement (2); occurs very rarely in children (USA - 1% of all primary cerebral lymphomas occur in patients <19 years); congenital or acquired immune deficiencies increase the risk of developing primary cerebral lymphoma. (1) Due to the rarity of the disease, there are no prospective trials in the paediatric population and no verified treatment protocols. In the specialized literature, there are only case presentations and analyzes on small series of patients that include about 100 patients in the last 20 years. (2)

The disease can be localized to the brain (more commonly) or the meninges. Multiple lesions may be present at diagnosis. The deep brain structures (basal ganglia, cerebellum, brainstem) are frequently involved. Isolated meningeal involvement is rare. (1)

Symptomatology

The most common signs are intracranial hypertension (headache, nausea / vomiting) followed by cerebellar signs (ataxia, dysarthria, dysmetria), seizures, hemiparesis. In some cases, vision problems, photophobia, nystagmus, diplopia and proptosis may occur. Rare symptoms: multiple involvement of the cranial nerves, Parinaud syndrome (in the pineal location), endocrine dysfunction. In the vast majority of cases, lymphadenopathy and type B signs are missing. (1)

Diagnosis

Imaging diagnosis: the recommended investigation is the MRI examination with contrast media (solitary or multiple lesions, isointense or hypointense in T2. (2)

A positive definitive diagnosis is established by biopsy of the tumour (stereotactic or surgical resection) and/or by cytological and immunophenotypic examination of the CSF. (1)

Histopathological types: non-Hodgkin's lymphoma (diffuse large B-cell lymphoma DLBCL in 30% -70% of cases), anaplastic large cell lymphoma (ALCL), lymphoblastic lymphoma, Burkitt's lymphoma. Confirmation by immunophenotyping is required. The WHO 2016 classification of brain tumours is used (see Table 1)

Table 1. Classification of primary cerebral lymphomas

Lymphoma type	Lymphoma subtype	Morphology code ICD-O
B-cell lymphoma	Diffuse large B-cell lymphoma DLBCL of the CNS CNS lymphomas associated with immunodeficiencies: Diffuse large B cell lymphoma secondary to AIDS Epstein-Barr virus (EBV) positive diffuse large B-cell lymphoma (DLBCL), FAI Lymphomatoid granulomatosis Intravascular large B-cell lymphoma Low-grade CNS B lymphomas	9680/3 9766/1 9712/3

T-cell and NK/T-cell lymphoma	ALK positive anaplastic large cell lymphoma (ALCL) ALK negative anaplastic large cell lymphoma (ALCL) MALT lymphoma of the dura	9714/3 9702/3 9699/3

Treatment

• The role of surgery: in most cases surgery is limited to biopsy for diagnosis purposes or surgery for debulking in cases with imminent hernias. The attempts to completely remove the tumour often present an increased risk of neurological complications with no benefit for survival. (2)

• Chemotherapy: Studies show that long-term survival can be achieved in patients treated only with chemotherapy (protocols that include HDMTX), without brain radiotherapy. (1)

Systemic chemotherapy. Cytostatic agents that cross the blood-brain barrier are administered. Drugs with low CNS penetration should be avoided, even if they are included in the systemic lymphoma treatment protocols (e.g. anthracyclines, cyclophosphamide). Combinations of cytostatic agents containing (HD-MTX) 3-8g/m2, HD-AraC (3g/ m2) and triple intrathecal therapy are recommended. (2)

It is reasonable to administer induction chemotherapy with Methotrexate 5-8g/m2 followed by consolidation with HD- AraC and HD-MTX 3g/m2 or high-dose chemotherapy and stem cell support. There is insufficient evidence to support a specific chemotherapy protocol for children. Favourable results were obtained with the FAB/LMB96 and BFM protocols, as well as with mono chemotherapy with HD-MTX and/or HD-AraC. Cranial radiotherapy is also recommended in anaplastic lymphomas. (2. 3)

Intrathecal chemotherapy (MTX, AraC, Hydrocortisone). The role of intrathecal treatment in children with parenchymal primary cerebral lymphoma and negative CSF cytology, types of disease that represent 84% of all primary cerebral lymphomas in children, has not been established. There are no comparative studies between groups of children treated with HDMTX chemotherapy with or without intrathecal chemotherapy. Studies in adults with primary CNS lymphoma do not show benefits of combining intrathecal chemotherapy with systemic chemotherapy containing HDMTX. (2)

High-dose chemotherapy and autologous stem cell transplantation may be used in children with recurrences of primary CNS lymphoma. There are ongoing studies on the role of high-dose chemotherapy and autologous stem cell transplantation as a consolidation treatment for patients newly diagnosed with primary CNS lymphoma. (2)

• The role of whole-brain radiotherapy. Studies in adult patients suggest that whole-brain radiotherapy combined with chemotherapy can improve disease-free survival, but not overall survival compared to chemotherapy as a single treatment. There are no randomized studies in children. In anaplastic lymphomas, chemotherapy and cranial radiotherapy are recommended. (2. 3)

Given the potentially severe neurotoxicity of the brain radiotherapy in children, it should be reserved only for cases refractory to cytostatic therapy or recurrence. (2)

• Immunotherapy - Rituximab was given to a small number of children with CD20(+) primary cerebral lymphoma, which did not allow to draw a conclusion on the effectiveness of this therapy. (2) Therapy with-rituximab should be taken into consideration taking into account

its benefits in treating pediatric patients with systemic non Hodgkin's lymphoma and its successful use in adult patients with brain lymphomas. (2)

- Corticosteroids (Dexamethasone 4-16mg/day) are often used before chemotherapy in order to

Reduce the cerebral edema. Cortisone therapy should be avoided until the sampling for histopathological diagnosis is done. (2)

The prognosis depends on the intensity and type of treatment. Diagnosis performance status was reported as a prognostic factor. (1) There is little information on the prognosis of primary CNS lymphoma in children; the evolution in the published series is similar to that of systemic non-Hodgkin's lymphoma with CNS involvement with an overall survival of 62% - 83% in 3 years. (2) The evolution is better in children than in adults. (1)

Survivors may experience long-term side effects: learning disorders, chronic headache, depression, aggression, seizures, hearing loss.

Recommendations

- Surgery is limited to biopsy for diagnosis purposes. Tumour resection is recommended only in particular cases (grade 2C).
- Systemic chemotherapy with cytostatic agents combinations that include HDMTX with or without HDAraC (grade 2C) is recommended.
- There are no data on the use of intrathecal chemotherapy in children with primary CNS lymphoma (grade 2C).
- Rituximab administration should be considered (grade 2C).

Bibliography

1. Abla O, Weizman S, Blay J et al. Primary CNS Lymphoma in Children and Adolescents: A Descriptive Analysis from the International Primary CNS Lymphoma Collaborative Group (IPCG).Clin Cancer Res; 17(2) January 15, 2011, on-line at: https://www.researchgate.net/publication/49745209

2. Roth L, Abla O, Batchelor. Management of primary central nervous system lymphoma in children. Hematology Am Soc Hematol Educ Program (2016) 2016 (1): 386–389. https://doi.org/10.1182/asheducation-2016.1.386

3. Thorer H, Zimmermann M et al. Primary central nervous system lymphoma in children and adolescents: low relapse rate after treatment according to Non-Hodgkin-Lymphoma Berlin-Frankfurt-Münster protocols for systemic lymphoma.Haematologica. 2014 Nov; 99(11): e238–e241. doi: 10.3324/haematol.2014.109553PMCID: PMC4222469. PMID: 25107886

8.2.8 CRANIOPHARYNGIOMA

Craniopharyngioma is considered to be a primary brain tumour with low-grade malignancy, although it has a benign histological structure with well-differentiated cells. Crainopharyngeoma are classified as WHO grade 1.

It is considered to be congenital, originating in the remnants of the Rathke's pouch and it is located in the suprasellar region with extension in the sellar region. (1) Craniopharyngioma is very adherent to the adjacent structures and it has a digitiform invasion mode affecting the optic chiasm, the hypothalamus and even the Willis polygon. (2) In some cases, it may extend to the third ventricle.

Survival at 5 and 10 years, respectively, is over 90%. (1)

Epidemiology

The incidence of craniopharyngioma is between 1.5 and 9% among all primary brain tumours in children, with a higher frequency in Japan and some areas of Africa. There is no gender predominance. There are 2 peaks of incidence: between 5 and 14 years (adamantinomatous form) and between 50 and 75 years (papillary form). (3, 4) The adamantinomatous form is 3-9 times more common than the papillary form. Craniopharyngioma does not occur in infants.

In the National Register of Childhood Cancer in Romania, during the period 2010 - 2018, there were 2 cases of craniopharyngioma reported (both being the adamantinomatous subtype).

Symptomatology

Due to the slow growth of this tumour, the symptoms are scarce; the onset of the disease may precede the moment when the diagnosis is established by about 1 year. Usually, the endocrine deficits are present in about 90% of cases and consist of: growth disorders, delayed puberty, diabetes insipidus, hypothalamic central obesity and visual impairment. The visual impairment is variable, it occurs in 50-90% of patients, affecting the visual field (most commonly homonymous hemianopsia and bitemporal hemianopsia) and the visual acuity. Papilledema is less common due to the slow tumour growth. (1, 4)

The extension of the tumour at the level of the third ventricle can cause obstructive intracranial high pressure, with headache, nausea and vomiting. Sometimes the tumour can spread to the posterior fossa causing ataxia, diplopia and hearing impairment. (1)

Positive diagnosis

Imaging and laboratory tests:

- Brain CT scan (which frequently shows calcification masses s in the suprasellar region, suggestive of the adamantinomatous subtype)
- Cerebral MRI with contrast agents: it establishes more precisely the relationship with the hypothalamus and the vascular system, essential elements for the surgical treatment of craniopharyngioma. (1, 3, 4). The MRI of the spine is not mandatory for assessing the extent of the disease. (1)
- Serum messurements of tumour markers β-HCG and AFP, to exclude secreting intracranial germ cell tumors. (5)

The diagnosis is established by histopathological examination. It is also useful in the differential diagnosis with other diseases of the suprasellar region: Rathke's pouch cyst, pituitary macroadenoma, optic nerve glioma, intracranial germ cell tumours, brain metastases, sarcoidosis, histiocytosis. (3)

Preoperative endocrine evaluation is very important for highlighting and treating possible deficits that may affect the perioperative and postoperative evolution. The following will be evaluated: the pituitary function with determination of cortisol, ACTH, FT4, TSH, IGF1, FSH, LH, testosterone / estradiol in serum, as well as serum ionogram and urinary osmolality. These parameters will be monitored periodically postoperatively and remotely for the treatment of possible complications (panhypopituitarism, disorders of the hypothalamus function). (1, 3, 4)

The ophthalmological evaluation will be done pre-operatively, during the treatment and after its completion. (1, 3, 4) Visual evoked potentials may be done in infants and young children. (5)

Histopathological types

There are 2 histopathological subtypes of craniopharyngioma: adamantinomatous and papillary. It has been shown that the adamantinomatous type in childhood, has mutation in the beta-catenin gene that is important for the wnt-signal pathway. The mutation leads to an overactivation of beta-catenin and then also wnt. This also activates other signal pathways «downstream» and contributes to tumor development.

Classification, prognostic factors

The adamantinomatous subtype is more common in children and adolescents; it has a higher degree of local invasiveness than the papillary subtype and a higher risk of recurrence. The papillary subtype occurs mainly in adults and it frequently has a mutation in the BRAF V600 E gene. (2)

The prognosis depends on the degree of local invasiveness in adjacent structures (hypothalamus, optic chiasm), the type of resection (endocrine complications in case of impaired hypothalamus function by extensive resection). Late mortality is more often caused by endocrinological complications and not by the progression of the tumour. (3)

Treatment

The treatment for craniopharyngiomas is multimodal. There is no consensus on the best treatment strategy for this type of tumour. Several factors must be considered: tumour site and size, local extension and short and long term side effects (diabetes insipidus, hypothalamic central obesity,).

For the patients undergoing only surgery (complete / partial resection,) the risk of recurrence is between 30% and 70% in the first 3 years of follow-up. (6, 7)

The most common therapeutic approach, considered to have fewer long-term side effects and a survival rate of up to 85% -90%, is the partial resection associated with external radiotherapy. (1, 2, 3, 4, 8)

Surgical treatment

The purposes of the surgery are: performing the diagnosis, treatment of high intracranial pressure and the therapeutic purpose. The tumour is resected as much as possible with as few side effects as possible. Partial or total tumour biopsy / resection is recommended. In case of hydrocephalus, the drainage is indicated. Accessibility for the intention of complete resection is different depending on the site of the tumour:

- 70-90% of the craniopharyngiomas in children affect the retrochiasmatic area with extension in the hypothalamus and the third ventricle which makes them less accessible for complete resection.
- 10-30% of the tumors are located on the prechiasmatic level between the optic nerves and they are more accessible to surgery. (2)

Radiotherapy

The combination of radiotherapy with surgical treatment has significantly increased the survival rate for craniopharyngiomas with partially operated. The recommended techniques are 3D conformal radiation therapy, stereotactic radiotherapy or IMRT, with a total dose of 50-54 Gy with 1.8 Gy/fraction. (2)

In the first year after the completion of the radiotherapy, an increase in the size of the cystic component of the craniopharyngioma can be observed, which is not considered a tumour progression. (2)

The proton radiotherapy is being evaluated for the treatment of craniopharyngioma, currently this technique is not available in Romania. (9.10)

Chemotherapy

There is currently no indication for chemotherapy for craniopharyngiomas. There are undergoing studies regarding the intracystic administration of Bleomycin or interferon alfa. (1, 2, 4)

Treatment of relapses (11)

The craniopharyngioma has a higher risk of recurrence in the first 3 years after the completion of the treatment. In case of recurrence, surgical reintervention, radiotherapy or gamma Knife radiosurgery are recommended.

In the case of surgery for recurrence, post-operative complications are more frequent (due to changes in the local structure after the radiotherapy). This will be followed by localized radiotherapy, 3-12 weeks after surgery, in doses and types of radiotherapy that will be assessed according to the first irradiation plan, if it was part of the initial treatment. The neurocognitive deficit is more severe after the treatment for relapses.

If radiotherapy is the only choice, it will be administered as soon as possible.

Post-therapeutic monitoring

Late side effects of the disease and treatments in craniopharyngioma are varied and include several areas of organic functionality (2):

- Late endocrine side effects: panhypopituitarism, disorders of the hypothalamus function - central obesity, thermoregulation disorders, circadian rhythm disorders, diabetes insipidus.
- Neurological side effects: neurocognitive disorders, circadian rhythm disorders, behavioural disorders
- Visual side effects - worsening of visual disturbances
- Vascular side effects: temporal cavernoma, aneurysm, cerebrovascular ischemia
- Risk of a second malignancy: meningioma, glial tumours

The monitoring period should be at least 5 years, depending on the degree of the initial resection and of the rest of the tumour. Long-term monitoring:

- Cranio-cerebral MRI with contrast agents every 3 months in the first year, every 6 months in the second and third year, yearly up to 5 years

- Endocrinology evaluation: every 6 months in the first 2 years or more frequently when needed, especially if replacement treatment is needed. Growth hormone replacement therapy, initiated 1 year after the diagnosis in cases without progression, has been shown to significantly increase the quality of life for patients diagnosed with craniopharyngioma without increasing the risk of recurrence. (12, 13) Endocrinological monitoring is necessary throughout life.

- Ophthalmologic evaluation annually or more often if the symptoms worsen (3, 4)

Recommendations

- It is a primary brain tumour with low-grade malignancy, slow growth and it is often diagnosed when the tumour volume is high
- The treatment of choice is multimodal and most often starts with surgery.
- Radiation therapy is indicated in case of incomplete resection or recurrence
- Endocrine, neurological, visual side effects are significant

Bibliography:

1. https://www.cancer.gov/types/brain/hp/child-cranio-treatment-pdq
2. Louis S. Constine MD, Nancy J. Tarbell MD, Edward C. Halperin MD - *Pediatric Radiation Oncology 6th Edition,* Wolters Kluver, 2016, cap 3, pag 42-44
3. https://www.uptodate.com/contents/craniopharyngioma?search=craniopharyngioma&source=search_result&selectedTitle=1~49&usage_type=default&display_rank=1
4. Philip A. Pizzo, David G. Poplack - *Principles and Practice of Pediatric Oncology Seventh Edition.* Wolters Kluver, 2016, Cap. 26A, pag 657-659
5. https://adc.bmj.com/content/archdischild/103/Suppl_1/A145.1.full.pdf - Arch Dis Child 2018; 103(Suppl 1):A1–A212, 2018
6. Cabezudo JM,Vaquero J,Areitio E,Martinez R,de Sola RG,Bravo G - Craniopharyngiomas: a critical approach to treatment, J Neurosurg. 1981 Sep;55(3):371-5.
7. Hetelekidis S,Barnes PD,Tao ML,Fischer EG,Schneider L,Scott RM,Tarbell NJ - 20-year experience in childhood craniopharyngioma Int J Radiat Oncol Biol Phys. 1993 Sep 30;27(2):189-95
8. Müller HL - Risk-adapted treatment and follow-up management in childhood-onset craniopharyngioma Pituitary. 2017 Apr;20(2):267-281
9. Mojca Jensterle,Soncka Jazbinsek,Roman Bosnjak,Mara Popovic,Lorna Zadravec Zaletel,Tina Vipotnik Vesnaver,Barbara Faganel Kotnik, andAsst. Prof., Primoz Kotnik, M.D., Ph.D - Advances in the Management of Craniopharyngioma in Children and Adults - Radiol Oncol. 2019 Dec; 53(4): 388–396.Published online 2019 Oct 25
10. Marcus HJ,Rasul FT,Hussein Z,Baldeweg SE,Spoudeas HA,Hayward R,Jeelani NUO,Thompson D,Grieve JP,Dorward NL,Aquilina K - Craniopharyngioma in children: trends from a third consecutive single-center cohort study - J Neurosurg Pediatr. 2019 Dec 20:1-9
11. Boekhoff S,Bogusz A,Sterkenburg AS,Eveslage M,Müller HL -Long-term Effects of Growth Hormone Replacement Therapy in Childhood-onset Craniopharyngioma: Results of the German Craniopharyngioma Registry (HIT-Endo) - Eur J Endocrinol. 2018 Oct 12;179(5):331-341.
12. Alotaibi NM,Noormohamed N,Cote DJ,Alharthi S,Doucette J,Zaidi HA,Mekary RA,Smith TR - Physiologic Growth Hormone-Replacement Therapy and Craniopharyngioma Recurrence in Pediatric Patients: A Meta-Analysis - World Neurosurg. 2018 Jan;109:487-496.e1.

8.2.9 BENIGN TUMOURS OF THE CENTRAL NERVOUS SYSTEM

The benign tumours of the central nervous system (CNS) are a group of tumours with different origins and benign behaviour. The WHO 2016 classification of CNS tumours groups benign tumours along with malignant tumours according to their site and histopathology. (Annex 1) (1, 2)

Certain benign tumours appear in well-defined genetic syndromes (von Hippel-Lindau, Li-Fraumeni, Aicardi neurofibromatosis, tuberous sclerosis). (3)

The symptomatology is determined by the site and the growth rate of the tumour: seizures, neurological deficits, paresis of cranial nerves, headache, clinical signs of intracranial hypertension. Although imaging investigations (CT, MRI) may suggest the benign nature of the tumour, the histopathological examination is the one that establishes the definitive diagnosis.

The treatment of choice is surgery; in certain types of tumours, drug treatment may be recommended; while radiotherapy has a minor role in treating these tumours. The main benign tumours from the following groups are described below: choroid plexus tumours, neuronal and mixed neuronal-glial tumours, tumours of the cranial and paraspinal nerves, meningiomas, mesenchymal non-meningothelial tumours, melanocytic tumours, germ cell tumours, pituitary tumours, cystic lesions.

Choroid plexus papilloma (4, 5)

Choroid plexus papillomas are benign tumours of the choroid plexus (tumors originating in the ventricular ependyma, which produce cerebrospinal fluid). They are located more frequently in the lateral ventricles, but rarer sites have also been described: third ventricle, Turkish saddle, intraparenchymal, ponto-cerebellar angle; they represent 2-4% of intracranial tumours in children of any age, being more common in young children (12-13% of intracranial tumours in children <1 year); boys are affected more frequently (boys/girls = 2.8/1). Approximately 85% of cases are diagnosed before the age of 5 years. (6)

The presence of choroid plexus papilloma has been associated with von Hippel-Lindau, Li-Fraumeni, Aicardi syndromes.

The symptoms are caused by the production of excess cerebrospinal fluid which can cause hydrocephalus (occurs in 80% of cases). Large tumors can lead to a mass effect, with symptoms depending on the site of the tumour. Described symptoms: headache, nausea and vomiting, dizziness, ocular paresis (by affecting the third and sixth cranial nerves), papillary edema, visual disturbances, possible blindness. Infants, especially those with a tumour located in the third ventricle, may or may not have hydrocephalus or macrocephaly associated with clinical signs of intracranial hypertension. Fourth nerve paresis, seizures may occur rarely.

Examinations

- The transfontanelle ultrasound may reveal the presence of the tumour in infants.
- MRI examination
- Brain CT scan (if MRI not available): homogeneous intraventricular tumour, slightly hyperdense, with cystic areas, with punctate calcifications
- Angiography may show enlargement of the choroidal arteries (6)

The differential diagnosis is made with choroid plexus hyperplasia, atypical papilloma, choroid plexus carcinoma, papillary ependymoma, medullary epithelium, germ cell tumour.

Treatment

Complete resection of the tumour leads to healing; monitoring of hydrocephalus and intracranial pressure is recommended both before and after surgery. The role of endoscopic surgery in the treatment of benign choroid plexus tumors is discussed.

Partially resected choroid plexus papillomas may become malignant, therefore complete resection is recommended. (5)

Neuronal and mixed neuronal-glial tumours (7)

Neuronal and mixed neuronal-glial tumours are characterized by varying degrees of neuronal and glial differentiation; the majority are circumscribed tumours, with a favourable evolution. They have the behaviour of grade I tumours according to the WHO classification. The treatment is often only surgical.

• Gangliocytoma is the most common tumour in the group of neuronal and mixed neuronal-glial tumours; it can occur anywhere in the central nervous system, but most tumours are located supratentorially in the temporal lobe. It occurs mainly in children and young adults. It is most often manifested by seizures, which can long precede the diagnosis of the disease. Imaging investigations: at the MRI examination, the tumors are hyperintense on T2; in 50% of cases they are cystic and about 1/3 of them have calcifications. The treatment of choice is complete surgical resection. The prognosis is good even in case of partial resection.

• Dysembryoplastic neuroepithelial tumours are slow-growing supratentorial tumours detected in children and young adults with a long history of refractory focal epilepsy. Rarely, tumours are located in the septum pellucidum, in which case they cause hydrocephalus and intracranial hypertension. In 30% of cases the BRAF V600E mutation is present. Imaging investigations: the MRI examination reveals tumors located in the cerebral cortex, sometimes with extension in the white matter, hypointense on T1 and hyperintense on T2; 50% of cases capture the contrast agents, rather on certain areas and multifocal than diffuse. Treatment: surgical resection is indicated in patients with refractory epilepsy; if epileptic seizures are controlled by medication, monitoring is recommended. The seizures disappear after surgery, but may reoccur later. Risk factors for recurrent seizures are age> 10 years and history of seizures> 2 years before surgery. Recurrences and malignant transformation have rarely been reported.

• Dysplastic cerebellar gangliocytoma (Lhermitte Duclos disease) is an extremely rare disease characterized by loss of normal architecture of the cerebellar cortex and focal thickened cerebellar gyri. Histopathologically, there is a reduction in the cerebellar white matter and the presence of abnormal hypertrophic ganglion cells; the lesions appear in the cerebellar hemispheres and rarely spread to the vermis. Developmental abnormalities (macrocephaly, mental retardation) are often associated. The disease can be familial or sporadic; the association with the germline mutation of the PTEN gene and with Cowden syndrome has been described. The disease usually occurs in young and middle-aged adults, although cases have also been reported in 3-year-old children. The cerebellar symptoms may be present a few years before the diagnosis; the obstructive hydrocephalus is common. Imaging investigations: the MRI examination highlights the thickening of the cerebellar gyri with the distortion of the architecture and sometimes the presence of cysts; the tumour mass is circumscribed and well individualized compared to the typical surrounding tissue, the lesion does not capture the contrast agents, it is hypointense on T1, it has a laminar pattern with high and low signal alternation on T2; it occasionally captures the contrast agents. The treatment consists of surgical resection. Recurrences after complete resection have been described. The inhibition of the PI3K/PTEN/AKT pathway with Rapamycin appears to be effective in some cases. (8)

Tumours of the cranial and paraspinal nerves

About 65% of intradural nerve sheath tumours are schwannomas, most of the others are neurofibromas; they can occur isolated (especially in adults), or in some syndromes: neurofibromatosis type 1, neurofibromatosis type 2 (90% of cases have spinal tumours, usually multiple, schwannomas or meningiomas), schwannomatosis. (9)

• Schwannomas (cellular, plexiform, melanotic) - occur by proliferation of the Schwann cells in the nerve sheath. Spinal schwannomas occur in 75% of patients with schwannomatosis; about 2% of spinal schwannomas occur in patients with type 2 neurofibromatosis. They appear as circumscribed tumours, attached to the nerve. (9) They are common in adults (10).

• Neurofibromas (atypical, plexiform) - occur by mixed proliferation of the Schwann cells, perineural cells and fibroblast cells in the nerve sheath. Plexiform neurofibromas occur in 30-50% of patients with type 1 neurofibromatosis. (9) Schwannomas and neurofibromas are slow-growing tumours, often becoming symptomatic when they reach a large volume. The clinical signs are given by the involvement of the nerve involved. (9)

Imaging investigations: MRI shows round or oval tumours with moderate signal on T1 and heterogeneous signal on T2, which evenly captures the contrast agents. Soft tissue ultrasound may be useful in the diagnosis of schwannomas.

The definitive diagnosis is established by biopsy.

Treatment:

- Small, asymptomatic, incidentally detected tumours will be monitored by imaging examinations (MRI every 3-6 months). (9)

- Large or symptomatic tumours: complete/partial surgical resection is recommended, with an acceptable preservation of the nerve function; endonasal endoscopic approach is possible in trigeminal schwannomas. (10) Fractional radiotherapy or stereotactic radiosurgery are therapeutic options in case of partial resection or in cases where surgery cannot be performed. (9)

The treatment decision is often complex and difficult for schwannomas/neurofibromas that appear in syndromes (multiple tumours, with multiple sites, central or peripheral tumours); it is recommended to avoid radiotherapy due to the increased risk of malignancy due to the underlying disease. (9)

Both schwannomas and neurofibromas can become malignant and follow up is needed. (10)

Meningiomas

Meningiomas represent about 1/3 of the primary tumours of the CNS in adults; most are intracranial, 10% are spinal. In children, meningiomas occur rarely, except in cases associated with hereditary syndromes (neurofibromatosis type 2) or with a history of radiotherapy. Approximately 80-85% of meningiomas are grade I according to the WHO classification. (11)

Risk factors associated with meningiomas:

• Exposure to ionizing radiation

In patients who have undergone radiotherapy for CNS tumours and for tumours in the head and neck region, prophylactic craniospinal irradiation for leukemias, meningiomas usually appear with a latency > 20 years. The risk is higher for patients treated at a younger age (<5 years), female, high dose of irradiation.

Exposure may be incidental: frequent dental x-rays, brain CT scans.

• Genetic predisposition

Type 2 neurofibromatosis - about 50% of patients with NF2 have meningiomas, usually multiple, mostly located intracranially; meningiomas appear at a younger age and are more commonly atypical or anaplastic compared to sporadic meningiomas.

Schwannomatosis - meningiomas are part of the schwannomatosis phenotype in some patients

Multiple endocrine neoplasia type 1 (MEN 1)

- Hormonal factors - meningiomas occur more frequently in postpubertal girls/women
- Obesity - due to endogenous hormonal factors

According to the WHO classification, meningiomas are divided into 3 groups: grade I (benign), grade II (atypical meningiomas, with clear cells and cordoids) and grade III (malignant).

Meningiomas are slow-growing tumours that remain asymptomatic for a long time.

The symptoms depend on the localization. When they grow and become symptomatic, they can cause seizures (30% of intracranial meningiomas), location-specific neurological deficits (visual and hearing disorders, altered mental status, motor deficits of the limbs), obstructive hydrocephalus.

Imaging investigations: (12)

- MRI: typical meningiomas appear as extra axial tumour masses, located at the level of the dura, isointense or hypointense compared to the gray matter on T1 and isointense or hyperintense on T2, they show uniform uptake of the contrast agents.

- CT: typical meningiomas appear as extra axial tumour masses that move the normal brain, with regular contour, adjacent to the dural structures, sometimes multilobed, with calcifications; they have an isodense structure compared to the brain tissue, they capture the contrast agents evenly.

Treatment of grade I meningiomas: (11)

Principle: complete resection with as little neurological deficit as possible.

For young patients, surgical resection, surgical resection + radiotherapy or only radiotherapy are recommended. Surgical resection includes resection of the attached dura and modified bone; after surgery 7-25% of grade I meningiomas reoccur. Preoperative embolization may be helpful.

Adjuvant radiotherapy (50-54 Gy in daily fractions of 1.8-2 Gy) after incomplete resection may improve the local control (indicated only in selected cases due to side effects).

Radiation therapy is also recommended in unresectable tumours.

Monitoring (12)

- Asymptomatic or minimally symptomatic patients who do not have surgery will be monitored by imaging examination (preferably MRI) every 3-6 months for a year, then annually for 3-5 years, then every 2-3 years, as long as there are no signs of progression.

- Patients who have undergone surgery +/- radiotherapy will be monitored depending on the degree of the resection, tumour site and histopathological subtype; in general, imaging examination will be repeated postoperatively annually for 3-5 years and then every 2-3 years as long as there are no signs of progression.

Mesenchymal, non-meningothelial tumours

Mesenchymal non-meningothelial tumours originating in the central nervous system are a group of benign and malignant tumours that occur more frequently in the meninges than in the brain parenchyma. They represent <1% of all intracranial neoplasms.

• Solitary fibrous tumours/grade 1 hemangiopericytoma are considered variants of the same entity characterized by the presence of the NAB2-STAT fusion protein; they represent <1% of primary CNS tumours. They usually occur in adults, 70% are supratentorial, 15% are located in the posterior fossa and 15% at the spinal level. They are slow-growing tumours that become

symptomatic by compression of adjacent structures or by intracranial hypertension. The treatment is surgical; recurrences can be treated surgically, with radiotherapy or with stereotactic radiosurgery. (12)

• Lipomas represent 0.4% of intracranial tumours; about half being located in the interhemispheric fissure and in the pericallosal region; they can also occur along the spinal cord, and can be intra-axial or extra-axial. Midline lipomas can be associated with brain malformations: agenesis of the surrounding tissue, frontal bone defects, facial dysplasia, absent/tortuous or aneurysm blood vessels, abnormal nerve branches, absence or duplication of cranial nerves. Lumbosacral lipomas may be associated with the ponytail syndrome. The diagnosis is established by imaging examinations (CT or MRI). Lipomas are often asymptomatic.

Surgical resection is not routinely recommended, but should be considered in patients with treatment-refractory epilepsy.

• Hibernomas - are rare tumours originating in brown adipose tissue; most of them are in the
intradural extramedullary, rarely intracranial site. They are treated surgically.

• Angiolipomas are benign mesenchymal tumours that contain mature adipocytes and abnormal vascular elements. They can be encapsulated (non-infiltrative) or non-encapsulated (infiltrative). Most of them occur in the spinal canal, epidural, especially in the chest. Clinically it causes local pain and symptoms of progressive spinal cord compression. Intracranial angiolipomas can bleed, causing subarachnoid hemorrhage.

Primary melanocytic tumours

The meningeal melanocytosis is a benign form of the primary melanocytic tumour of the central nervous system that occurs through the proliferation of melanocytes in the subarachnoid space. It can occur at any age, from the newborn to the second decade of life. It may be associated with cutaneous melanocytic lesions in neurocutaneous melanosis (rare disease characteristically associated with giant congenital nevi. Approximately 25% of patients with meningeal melanocytosis have significant skin lesions, approximately 10-15% of children with giant congenital nevi develop asymptomatic melanocytosis; the prognosis is dismal in both diseases, even when the histopathological examination does not show malignancy. The prognosis is often dismal due to progressive meningeal thickening and the risk of malignancy. (13)

The symptoms are represented by: hydrocephalus, seizures or focal neurological deficits caused by the leptomeningeal disease.

Treatment: not well established; complete resection cannot be performed due to its diffuse nature; the role of chemotherapy and radiotherapy in this benign but often fatal disease is unclear; symptomatic treatment, often palliative, is applied in all cases. (14) Case reports of targeted treatment have shown interesting and promising results. (15).

Mature teratoma (16)

Teratomas (2-4% of all brain tumours in children) are non-germinomatous germ cells tumours formed from a combination of tissues from the three germ layers - ectoderm, endoderm and mesoderm; in mature teratomas all cellular components are well differentiated. The prognosis of mature teratomas is very good; the 10-year survival is > 90%. Mature teratomas can turn malignant.

Site: usually the sellar and suprasellar region.

Symptomatology:

Sellar tumours cause clinical signs secondary to obstructive hydrocephalus (headache, nausea, visual disturbances). Suprasellar tumours cause endocrine disorders by affecting the

hypothalamic-pituitary axis (early puberty, hypopituitarism, growth hormone deficiency) and visual field deficits (bilateral temporal hemianopsia).

Imaging investigations: CT- intracranial expansive tumor with cystic component, calcifications and lipid content. MRI - hypointense or isointense formation on T1 and hyperintense on T2 with inhomogeneous uptake of the contrast agents.

Treatment: Surgical – the complete resection can ensure healing.

Intracranial cystic lesions (7)

Non-cancerous cystic lesions can cause neurological symptoms and can simulate the presence of a brain tumour. Epidermoid, dermoid, arachnoid, colloid cysts are described. For the first two categories, the malignant transformation into squamous cell carcinomas is possible. External radiotherapy is indicated in epidermal cysts with rapid progressive growth as well as in those with multiple recurrences.

Pituitary adenomas (17)

Along with craniopharyngiomas, pituitary adenomas are the most common tumours of the pituitary region in children and adolescents; they represent <3% of supratentorial tumours and > 90% of the intrasellar tumours in children; the most common ones are prolactinomas, followed by corticotropinomas and somatotropinomas; non-secreting adenomas as well as those secreting TSH and gonadotropin, respectively, are very rare (3-6% of all pituitary tumours). ACTH-secreting adenomas occur early, usually prepubertally, while GH-secreting adenomas are very rare before puberty.

The symptoms are determined by secondary endocrine dysfunction (e.g. growth deficit, primary amenorrhea) more frequently than by mass effect.

Imaging: MRI is the investigation of choice for highlighting the tumour of the pituitary region

Treatment of pituitary adenomas (see Table 1)

Table 1. Treatment of pituitary adenomas

Pituitary adenoma type	Treatment		
	Surgery	Pharmaceutical	Other
Prolactinoma	if there are complications[1]	dopaminergic agonists (Bromocriptine)	
Pituitary adenoma	transsphenoidal adenomectomy (of choice)		
GH-secreting adenomas	transsphenoidal adenomectomy (of choice)	somatostatin analogues (Octreotide)	Radiotherapy (rarely)
TSH-secreting adenomas		somatostatin, lanreotide	
Clinically non-functioning adenomas	transsphenoidal adenomectomy (of choice)	dopamine agonists (Cabergoline)	Radiotherapy (in subtotal resections)

[1]decreased visual acuity, hydrocephalus

Recommendations

- Benign tumours of the CNS are of great diversity and are classified according to site and histopathology
- The treatment of choice is surgery
- Malignant degeneration is possible for some of the entities
- Although they have benign histology, they are often disabling and can lead to death

Bibliography

1. WHO Classification of Tumours of the Central Nervous System, 4th ed, Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (Eds), IARC, Lyon 2016.
2. Louis D, Schiff D, Batchelor T. Classification and pathologic diagnosis of gliomas. https://www.uptodate.com/contents/classification-and-pathologic-diagnosis-of-gliomas?topicRef=6251&source=see_link
3. Lau C, Wan-Yee T. Epidemiology of central nervous system tumors in children. https://www.uptodate.com/contents/epidemiology-of-central-nervous-system-tumors-in-children
4. Palmer L. Choroid Plexus Papilloma. https://emedicine.medscape.com/article/250795-overview
5. Chow E, Reardon DA, Shah AB. Pediatric choroid plexus neoplasms. *Int J Radiat Oncol Biol Phys*. 1999 May 1. 44(2):249-54. [Medline].
6. Kornienko VN, Pronin IN. Diagnostic Neuroradiology. Springer Verlag. (2009) ISBN:3540756523. Read it at Google Books - Find it at Amazon
7. Chheda M, Wen P. Uncommon brain tumors. https://www.uptodate.com/contents/uncommon-braintumors?sectionName=Pilocytic%20astrocytoma&topicRef=6251&anchor=H3168817707&source=see_link#H3168817707
8. Zak M, Ledbetter M, Maertens P. Infantile Lhermitte-Duclos Disease Treated Successfully With Rapamycin. J Child Neurol 2017; 32:322.
9. Laufer I, Bilsky M. Intradural nerve sheath tumors.https://www.uptodate.com/contents/intradural-nerve-sheath-tumors
10. Dickey I. Neurilemmoma (Schwannoma). https://emedicine.medscape.com/article/1256405-overview
11. Park J. Epidemiology, pathology, clinical features, and diagnosis of meningioma. https://www.uptodate.com/contents/epidemiology-pathology-clinical-features-and-diagnosis-of meningioma?topicRef=6251&source=see_link
12. Park J, Shih H. Management of known or presumed benign (WHO grade I) meningioma. https://www.uptodate.com/contents/management-of-known-or-presumed-benign-who-grade-i-meningioma
13. Miro J, Fargas R et al. Meningeal melanocytosis: A possibly useful treatment for a rare primary brain neoplasm. Available from: https://www.researchgate.net/publication/49769247_Meningeal_melanocytosis_A_possibly_useful_treatment_for_a_rare_primary_brain_neoplasm [accessed Feb 18 2020]
14. Aslan S, Gocmen R et al. Two cases of primary leptomeningeal melanomatosis mimicking subacute meningitis. The Neuroradiology Journal 2018, Vol. 31(1) 42–46. DOI: 10.1177/1971400917708581 journals.sagepub.com/home/neu
15. Veronica A Kinsler et al MEK inhibition appears to improve symptom control in primary NRAS-driven CNS melanoma in children. Br J Cancer. 2017 Apr 11; 116(8): 990–993
16. Abdelmuhdi A, Almazan A, Dissi N. Intracranial Teratoma: Imaging, Intraoperative, and Pathologic Features: AIRP Best Cases in Radiologic-Pathologic Correlation. RadioGraphics 2017; 37:1506–1511 https://doi.org/10.1148/rg.2017160202
17. Calao AM. Pituitary adenomas in childhood. [Updated 2017 Dec 26]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279057

8.2.10 METASTASES OF THE CENTRAL NERVOUS SYSTEM

Paediatric cancers as malignant haematological diseases, solid brain tumours and solid extracerebral tumours, can spread into the central nervous system and lead to cerebral or leptomeningeal metastases. The central nervous system (CNS) is labelled as a pharmacological sanctuary. The CNS metastases benefit from therapeutic strategies effective at this level.

Brain metastases

Brain metastases are less common in children with solid tumours than in adults. However, improving survival in paediatric cancers increases the interval when the child is at risk of developing brain metastases.

Compared to other organs that can be the site of metastases of solid tumours (lymph nodes, lungs, bone, liver), brain metastases have a much lower incidence.

Paediatric solid extracerebral tumours that most commonly cause brain metastases are: Ewing's sarcoma, rhabdomyosarcoma, osteosarcoma, germinal tumours, malignant melanoma, neuroblastoma. The average interval from diagnosis to metastasis is 15 months. (1) They can be single or multiple, they can be diagnosed in the context of generalized metastasis or, less often, the brain can be the only site of the metastases. Sometime brain metastasis is detected at necropsy.

Some patients may experience asymptomatic brain metastases from the onset and they are undiagnosed because brain imaging is indicated only in symptomatic patients.

Brain metastases are located in the cerebral hemispheres (80%), cerebellum (15%), posterior fossa (5%). (2).

The symptoms consist of signs of increased intracranial pressure (IIP), progressive neurological dysfunction, cognitive dysfunction, seizures. The occurrence of any of these signs requires cerebral imaging investigation by MRI.

The depletive and symptomatic treatment (anticonvulsant, analgesic, anxiolytic) must be administered as soon as possible. The specific treatment consists of surgery for solitary or small numbers of metastases. An intensive chemotherapy protocol is discussed in the case of highly chemosensitive tumours (germ cell tumours).

Radiation therapy is of less importance in the treatment of brain metastases in children than in adults. It is indicated in order to relieve the symptoms: pain, intracranial hypertension phenomena, and neurologic impairments. The radiated volume is the entire skull. As for paediatric patients there are few retrospective studies and there are no prospective studies on the total dose, fractioning and toxicity, the doses and fractionating used in adults are indicated for children: 16 Gy in 4 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 25 Gy in 10 fractions. Radiation therapy is indicated depending on the general condition of the patient, the extent of the disease, the intensity of the symptoms, and the life expectancy.

Brain metastases have a poor prognosis. Without treatment, death occurs on average at 0.9 months, and with treatment the average survival is 6-9 months. (1, 3)

Leptomeningeal metastases (4)

In childhood cancers, leptomeningeal spreading of the disease is more common compared to parenchymal metastases.

The symptoms of leptomeningeal spreading may be faded initialy, this is why brain and spinal cord contrast enhanced MRI, as well as CSF cytology are performed routinely.

If present, the common symptoms are signs of IIP, signs of cranial nerve involvement, weakness, pain, ataxia, paraparesis, confusion, memory loss, seizures, mental disorders up to dementia.

Radiologic investigations and cerebrospinal fluid (CSF) analysis diagnose the leptomeningeal metastases.

The standard chemotherapy for malignant haematological diseases (leukaemia, lymphomas), provides the prophylaxis of the central nervous system involvement, using high-dose chemotherapy, and intrathecal chemotherapy (MTX, ARA-C).

The brain tumours at risk for leptomeningeal metastases are the high grade tumours: medulloblastoma, atypical teratoid / rhabdoid tumour, high-grade glioma and ependymoma, germ cell tumours. The leptomeningeal involvement may be present at diagnosis, may occur during local recurrence, or as a single metastasis. A risk factor seems to be the young age. (5)

Medulloblastoma is a tumour predisposed to developing meningeal metastases. This is shown at the onset of the disease in 27-43% of infants and young children, compared to 20-25% in children over 3 years of age. Leptomeningeal metastases are relatively common in germinal brain tumours (10%), they occur less frequently in patients with ependymomas and very rarely in low-grade malignancies and choroid plexus carcinoma.

Leptomeningeal metastases can also be found in the case of solid extracerebral tumours and they are always a serious event with a severe prognosis.

Rhabdomyosarcomas and primitive neuroectodermal tumours have an increased risk of meningeal dissemination in the case of parameningeal sites, a situation in which the CSF cellularity is analysed. In the case of retinoblastoma, the malignant cells spread directly from the retina, along the optic nerve, to the optic chiasm and leptomeninges; another possibility is the dissemination through the central vessels of the retina to the subarachnoid space.

In other cancers such as Ewing's sarcoma, neuroblastoma and malignant melanoma, the leptomeningeal metastases occur only in stage IV of the disease or in the case of generalized dissemination.

Emergency therapy addresses the improvement of neurological symptoms by administering depletive medication. The patient will also benefit from palliative therapy (analgesic, anticonvulsant, anxiolytic).

The specific treatment of the leptomeningeal metastases consists of general chemotherapy, with protocols adapted to the underlying disease, including cytostatics able to cross the blood-brain barrier and chemotherapy administered in the CSF (intrathecal by lumbar punction or through the Ommaya reservoir). (5)

The radiotherapy can be administered as craniospinal radiation with a total dose between 30-36 Gy by 2-1.8 Gy per fraction with boost on certain sites of the cranio spinal axis depending on clinical data, or as localized radiation on certain segments of the spinal axis (20 Gy in 5 fractions, 8 Gy in a single fraction, 30 Gy in 10 fractions). If the patient is included in a clinical trial or he/she is treated according to a specific protocol, the specified indications will be followed (5).

Since the onset of the leptomeningeal metastases, the prognosis for the disease is severe, the median survival reported by the authors is 6 months (4-118 months), better in malignant haematological diseases compared to solid tumours. (6)

Recommendations

- Brain metastases are less common in children with solid tumours than in adults
- The treatment of the parenchymal metastases in children is done similarly to adult therapy (surgery, chemotherapy, radiation therapy)
- The leptomeningeal metastases are more common compared to the parenchymal metastases
- The prophylaxis of leptomeningeal involvement is standard therapy in malignant haematological diseases and in some brain tumours

Bibliography

1. Bouffet E, Doumi N, Thiesse P, Mottolese C, Jouvet A, Lacroze M, Carri C, Frappaz D, Brunat-Mentigny M.Brain metastases in children with solid tumors. Cancer. Jan 1997, 15;79(2):403-10.

2. Patrick Y Wen, Jay S. Loeffler, Management of Brain Metastases, Oncology,1999, vol 13, Issue 7.

3. Dima Suki, Rami Khoury Abdulla, Minming Ding, SoumenKhatua, Raymond Sawaya, Brain metastases in patients diagnosed with a solid primary cancer during childhood: experience from a single referral cancer center, Journal of Clinical, , 2014, vol 14, Issue 4: 329-437.

4. Kaplan J, DeSouza T, Farkash A. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas, and leukemias. J Neurooncol. 1990, 9:225-229.

5. Rao DA, Figueiredo MLS, Yegya-Raman N et al, Clinical Practice and outcomes of palliative radiation therapy in pediatric oncology patients: An international comparison of experiences from two distinct countries and health care systems; Radiotherapy and Oncology.2019. 140, 1-5.

6. Chamberlain MC, A review of leptomeningeal metastasies in pediatrics, Journal of Childhood Neurology. 1995, 10 (3), 191-199, (Pub Med).

8.3 SOFT TISSUE SARCOMAS

Epidemiology

Soft tissue sarcomas are tumours of mesenchymal origin, with different histology, clinical course, and variable prognosis. Soft tissue sarcomas represent 6-8% of all pediatric cancers and they are conventionally divided in: rhabdomyosarcoma (RMS) which account for 50-60% of cases and non-rhabdomyosarcomatous soft tissue sarcomas (NRSTS), a heterogeneous group of tumours comprising more than 30 different subgroups. (1, 2)

Rhabdomyosarcoma is the third most common extracranial solid tumour in children, after neuroblastoma and nephroblastoma. In 2/3 of the cases, rhabdomyosarcoma occurs before the age of 6, but a second peak of incidence occurs in adolescents.

The aetiology is unknown. Although the vast majority of soft tissue sarcomas occur sporadically, genetic factors may play an important role, since there is an association between soft tissue sarcomas and Li-Fraumeni syndrome, congenital abnormalities (affecting the genitourinary system and the central nervous system) or other genetic disorders (neurofibromatosis type 1, Beckwith-Wiedermann syndrome). Some non-rhabdomyosarcomatous soft tissue sarcomas (particulary malignant fibrous histiocytoma) can develop within a previously irradiated site.

Clinical presentation

Clinical presentation is influenced by site of the primary tumour:

- Head and neck area:
- orbit: proptosis
- middle ear: pain, sinusitis, chronic otitis media
- nasopharynx: nasal obstruction, epistaxis
- Genitourinary tract: problems of urination, hematuria, vaginal bleeding, scrotal tumour mass (paratesticular)
- Extremities and trunk: can present initially as an asymptomatic solid mass but then become symptomatic because of invasion of adjacent anatomical structures
- Local extension to the skull base causes meningeal symptoms, cranial nerve palsies or visual loss
- Asthenia and weight loss can be found in the advanced stages of the disease. (3)

Diagnostic and staging investigations

The diagnosis and staging of the disease should be performed in accordance with the current therapeutic protocols and they must include adequate imaging of the primary site and regional lymph nodes as well as an accurate assessment of sites of potential metastatic spread.

- Complete physical examination
- Laboratory investigations: full blood count, creatinine, glomerular filtration rate (GFR)/creatinine clearance either by estimation or direct measurement, sodium, potassium, calcium, magnesium, phosphate, alkaline phosphatase, liver transaminase, bilirubin, LDH, urinanalysis, blood groups and Rhhematological and biochemical tests

- Imaging examinations:
- magnetic resonance imaging (MRI) or computed tomography (CT) of the primary site
- chest X-Ray and chest CT scan for evaluation of lung metastases
- ultrasound or MRI of the abdomen to identify lymph node or liver metastases
- skeletal scintigraphy for evaluation of bone metastases
- positron emission tomography (PET-CT) is recommended for staging at diagnosis in all patients with rhabdomyosarcomas, except for those in subgroup A (4)
- bone marrow aspirate

Tumours dimensions should be recorded in three diameters, so that the therapeutic response can be correctly evaluated later on by assessing tumour volume. MRI examination is preferred in genitourinary tumours, head and neck tumours with possible skull base invasion and paraspinal tumours.

- Other examinations:
- ophthalmological examination
- echocardiogram (prior to chemotherapy courses containing anthracyclines)
- pediatric audiometry (prior to course containing Carboplatin)
- electroencephalogram
- cerebral spinal fluid examination for cytospin and cell count is required only for parameningeal tumours

Histopathological diagnosis and classification

The diagnosis is established based on the histopathological examination. Biopsy should be the initial surgical procedure in all patients, except when primary excision of the tumour with adequate tumour-free margins is possible.

Core needle biopsy is performed under imaging guidance (ultrasound or CT-guided). When not enough material can be obtained through this method, incisional (open) biopsy is recommended. The biopsy track and the scar must be included en bloc in the subsequent definitive surgical procedure. In case of sarcoma of the extremities, the incision should be made longitudinally. Endoscopic biopsies are appropriate for bladder, prostate and vaginal tumours.

The histopathological diagnosis of soft tissue sarcomas in children is done according to the World Health Organization (WHO) classification (5).

The histological subtypes of rhabdomyosarcoma are:

- Embryonal rhabdomyosarcoma with two variants:
- the botryoid subtype
- the spindle cell variant
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma

The histological classification of non-rhabdomyosarcoma soft tissue sarcomas is based on the cell of origin. The most important histological subtypes occurring in children are: fibrosarcoma, synovial sarcoma and peripheral nerve sheath tumour.

The translocation t(2; 13) occurs in 70-80% of cases of alveolar rhabdomyosarcoma. Many of the non-rhabdomyosarcoma soft tissue sarcomas have chromosomal abnormalities.

Staging

Clinical staging has an important role in predicting the clinical outcome and determining the most effective treatment. The staging system from the American Joint Committee on Cancer (AJCC) that is used for adults has not been validated in pediatric studies. There are two staging systems used in children:

TNM Staging System (6)

IRS Post-Surgical Staging System (Intergroup Rhabdomyosarcoma Study) (7)

Intergroup Rhabdomyosarcoma Study Staging System (IRS)

Group I: Localized tumour completely resected with histologically negative margins

Group II: Grossly resected tumour with microscopic residual disease and/or regional lymph node spread

Group III: Macroscopic residual disease after incomplete resection or initial biopsy

Group IV: Metastatic disease

Prognostic factors

- Histology:
- favourable - all embryonal rhabdomyosarcomas
- unfavourable - alveolar rhabdomyosarcoma
- Tumour site:
- favourable - orbit, genitourinary (paratesticular, vagina, uterus), head and neck non parameningeal
- unfavourable - all other sites: parameningeal, extremities, bladder, prostate
- Lymph node involvement (N):
- favourable - no clinical or pathological node involvement (N0)
- unfavourable - clinical or pathological nodal involvement (N1)
- Initial surgery:
- favourable – complete (IRS Group I)
- unfavourable – incomplete (IRS Group II or III)
- The presence of distant metastases
- Tumour size and patient age
- favourable - tumour size ≤ 5 cm and age <10 years
- unfavourable - tumour size > 5 cm and age ≥ 10 years

The 5-year overall survival rate is over 70% for patients with localized RMS. Patients with metastatic disease at diagnosis have the worst prognostic with an overall survival rate between 20-30%. Relapses usually occur within 3 years from diagnosis and the overall survival rate at 5 years is below 30%. (3)

Treatment

The treatment of soft tissue sarcomas in children is multimodal and consists of chemotherapy, surgery and/or radiotherapy. Rhabdomyosarcomas are treated according to EpSSG RMS 2005 protocol and high-grade malignant non-rhabdomyosarcoma soft tissue sarcomas are treated according to EpSSG NRSTS 2005 protocol. (8, 9)

- Surgery

Local control is essential to cure children with localized rhabdomyosarcomas and it can be achieved by surgery and/or radiotherapy (or alternatively brachytherapy). Surgery is recommended at diagnosis only if the tumour can be resected with histologically negative

margins, without functional impairment or mutilating surgery. If this is not possible, a biopsy of the tumour will be performed for diagnostic purposes. The type of treatment chosen depends on the tumour site, the size of the primary tumour, the patient's age and the response to chemotherapy. The evaluation of regional lymph nodes is important, but radical lymph node dissection is contraindicated. (8)

In the case of non-rhabdomyosarcoma soft tissue sarcomas, the surgical principles are identical to those used for the treatment of rhabdomyosarcomas. (9)

- Chemotherapy

According to EpSSG RMS 2005 protocol (updated in March 2019), chemotherapy in patients with rhabdomyosarcomas is different depending on the risk group (Table 1):

- low risk group: VA chemotherapy (VCR and ACT-D)
- standard risk group: IVA chemotherapy (IFO, VCR, ACT-D) + VA
- high risk group: IVA chemotherapy
- very high risk group: IVADo chemotherapy (IFO, VCR, ACT-D, Doxo) + IVA, followed by 6 months of maintenance treatment with Vinorelbine and Cyclophosphamide
- metastatic disease: IVADo + IVA chemotherapy, followed by 12 months of maintenance treatment with Vinorelbine and Cyclophosphamide (9)

Non-rhabdomyosarcoma soft tissue sarcomas are in most cases less sensitive to chemotherapy than rhabdomyosarcomas.

The EpSSG NRSTS 2005 protocol divides non-rhabdomyosarcoma tumours into three groups:

- synovial sarcoma – appears to be more sensitive to chemotherapy than many other soft tissue sarcomas. If complete surgical resection is not possible, chemotherapy with IFO and Doxo is recommended in order to reduce the tumour size before the surgical treatment
- adult type soft tissue sarcomas (angiosarcoma, leiomyosarcoma, liposarcoma, alveolar soft part sarcoma, dermatofibrosarcoma protuberans, clear cell sarcoma) - IFO-Doxo chemotherapy
- other histotypes:
  - infantile fibrosarcoma - VA, IVA, IFO-Doxo chemotherapy depending on the response
  - desmoplastic small round cell tumour - IVADo chemotherapy
  - peripheral primitive neuroectodermal tumour (pPNET) or extraosseous Ewing sarcoma - in the past it was treated as rhabdomyosarcomas, but now the recommended protocols for Ewing sarcoma are used
  - desmoid tumours (aggressive fibromatosis) – in case of tumour progression or incomplete resection, chemotherapy with low-dose methotrexate and vinblastine should be the first option
  - Patients with metastatic non-rhabdomyosarcoma soft tissue sarcomas should receive IVADo chemotherapy.

Extra-cranial malignant rhabdoid tumours are rare but very aggressive tumours with an increased mortality rate. The EpSSG NRSTS 2005 protocol recommends aggressive chemotherapy with VCR/Doxo/CTX alternatively with CTX/CARBO/VP16. (9)

Table 1. Treatment guide in rhabdomyosarcomas

Risk group	Sub-group	Histology	IRS stage	Site	Node stage	Size and age	Chemotherapy	Local treatment
Low	A	favourable	I	Any	No	favourable	VA (8 cycles)	surgery
Standard	B	favourable	I	Any	No	unfavourable	IVA (4 cycles) + VA (5 cycles)	surgery
	C	favourable	II, III	favourable	No	any	IVA (4 cycles) + VA (5 cycles)	surgery + radiotherapy
High	D	favourable	II, III	unfavourable	No	favourable	IVA (9 cycles) + maintenance	radiotherapy
	E	favourable	II, III	unfavourable	No	unfavourable	IVA (9 cycles) + maintenance	radiotherapy
	F	favourable	II, III	Any	N1	any	IVA (9 cycles) + maintenance	radiotherapy
	G	unfavourable	I, II, III	Any	No	any	IVA (9 cycles) + maintenance	radiotherapy
Very high	H	unfavourable	I, II, III	Any	N1	any	IVADo (4 cycles) +IVA (5 cycles) + maintenance	radiotherapy
	Meta-static	All	IV	Any	Any	any	IVADo (4 cycles) +IVA (5 cycles) + maintenance	radiotherapy

Other accepted protocols:
CWS 2009, SIOP-MMT

In the 2009 CWS protocol, the treatment of patients with rhabdomyosarcomas is differentiated depending on the risk group. The risk groups are similar to those in the EpSSG RMS 2005 protocol, except for the very high risk group (H), which includes only IRS II and IRS III groups.

- low risk group (subgroup A): surgery, 8 cycles of VA chemotherapy
- standard risk group (subgroup B): surgery, chemotherapy: 4 cycles of IVA + 5 cycles of VA
- standard risk group (subgroup C): surgery, chemotherapy: 9 cycles of IVA (subgroup C1: tumour ≤5 cm; age <10 years, complete secondary surgical resection) or 5 cycles of IVA + 4 cycles of VA (subgroup C2 which includes the rest of the patients). Radiatiotherapy is recommended in patients in subgroup C2.
- standard risk group (subgroup D): surgery, chemotherapy: 9 cycles of IVA, radiotherapy
- high risk group (subgroups E, F, G): debulking surgery is not recommended. Surgery should be conservative, avoiding mutilating interventions or those with functional impairment. In case of IRS III group patients, surgery should be considered after neoadjuvant chemotherapy. Chemotherapy consists of 9 cycles of IVA. Radiotherapy is recommended for all patients.
- very high risk group (subgroup H): The surgical and radiotherapy principles are similar to those of the patients in the high risk group. Chemotherapy consists of 4 cycles of IVAd and 5 cycles of IVA.
- synovial sarcoma, peripheral primitive neuroectodermal tumor (pPNET) or extraosseous Ewing sarcoma: surgery, chemotherapy 4 cycles of IVAd and 5 cycles of IVA, radiotherapy for patients in IRS II and III groups

- in patients with non-rhabdomyosarcoma soft tissue sarcomas in the low risk group, only surgical treatment is recommended. Patients in the standard risk group require radiotherapy and for those in the high risk group, chemotherapy is associated (4 cycles of IVAd and 5 cycles of IVA).

- metastatic disease: CEVAIE chemotherapy: 3 cycles of IVA + 3 CEV cycles (Carbo, Epi, VCR) + 3 IVE cycles (IFO, VCR, VP16)

- Radiotherapy

In patients with rhabdomyosarcomas, the indications for radiotherapy, the total dose administered, the time of administration are decided according to stage, group (radicality of surgery) and risk stratification (low risk, high risk and intermediate risk).

Radiotherapy may be exclusive local treatment (in combination with chemotherapy) in sites where surgery is not possible (e.g. various locations in the head and neck).

- Group I Embryonal - Radiotherapy is not indicated
- Group I Alveolar - DT = 36 Gy; 1.8 Gy/fr, on the tumour volume prior to chemotherapy
- Group II N0 (residual microscopic disease after surgery) - TD = 36 Gy; 1.8 Gy/fr, on the tumour volume prior to chemotherapy
- Group II N1 (positive lymph nodes excised) - TD = 41.4 Gy; 1.8 Gy/fr, on the tumour volume prior to chemotherapy and the lymph node region
- Group III non-orbital - TD = 50.4 Gy; 1.8 Gy/fr
- Group III orbital - TD = 45 Gy; 1.8 Gy/fr, if there is a complete remission after induction chemotherapy and TD = 50.4 Gy; 1.8 Gy/fr if there is not a complete remission
- Patients with stage IV disease, metastatic disease, may be irradiated on the primary tumour and/or on metastases

In the case of soft tissue sarcomas other than rhabdomyosarcomas (non-RMS), radiotherapy may be performed before (tumour size, site, extension) or after surgery.

The size of the tumour (smaller or larger than 5 cm), degree of differentiation (low or high), the margin status of resection (negative, positive or close margins) are important factors in the therapeutic decision.

- Preoperative radiotherapy DT = 45-50.4 Gy; 1.8 Gy/fr
- Postoperative radiotherapy DT = 55.8 Gy; 1.8 Gy/fr

Treatment of relapse and refractory disease

- surgery
- radiotherapy
- second line chemotherapy

For rhabdomyosarcomas:

- Topo-Carbo regimen (Topo, Carbo, CTX, VP16)
- Doxo-Carbo regimen (Doxo, Carbo, CTX)
- VIT protocol (VCR, IRI, TEM)
- Crizotinib, Afatinib

- There is a new international treatment protocol from EpSSG, «FaR-RMS: An overarching study for children and adults with frelapsed RhabdoMyoSarcoma» where there is a randomisation between different treatment arms:

1. cyclophosphamide/topotecan
2. irinotecan/temozolomide
3. gemcitabin/docetaxel
4. High-dose ifosfamide

For non-rhabdomyosarcoma tumours:

- Vin/CTX
- High dose IFO (synovial sarcoma)
- GEM/Doce (leiomyosarcoma)
- Paclitaxel (angiosarcoma)
- Trabectidine (liposarcoma)
- Imatinib (dermatofibrosarcoma protuberans)
- Sorafenib (vascular sarcomas and leiomyosarcoma)
- Temozolomide/Topo

Post-therapeutic follow-up

The final evaluation is performed one month after the end of the treatment and it includes clinical examination, biological examinations and imaging examinations depending on the site of the primary tumour.

After the completion of the treatment, all patients should be monitored for possible tumour relapse and for monitoring the side effects of the treatment. The periodic evaluation includes clinical examination, ultrasound ± CT scan or MRI examination of the primary tumour site, chest X-ray ± chest CT scan.

Patients are followed-up:

- every 3 months in the first year
- every 4 months in the 2nd and 3rd year
- every 6 months in the 4th and 5th year
- annually until the 10th year after the diagnosis

During the periodic examinations, information will be obtained with respect to short and long term toxicities of the treatment, thus the height and weight, the blood pressure, the Tanner puberty stages, the cardiac function, the renal function, the hearing function, the school performance, the possible behavioural disorders. The details of the post-therapeutic follow-up are described in the therapeutic protocols.

Recommendations

- The diagnosis and the staging of soft tissue sarcomas in children should be performed in accordance with the current therapeutic protocols
- The treatment of the soft tissue sarcomas in children is multimodal and it consists of chemotherapy, surgery and/or radiation therapy
- In patients with rhabdomyosarcomas, the therapeutic indications are decided based on histology, stage, tumour site, type of surgery and risk groups stratification
- If the tumour cannot be completely resected, with histologically proven negative margins, only a biopsy will be performed for diagnostic purposes to avoid mutilating surgery.
- Rhabdomyosarcomas are treated according to the EpSSG RMS 2005 protocol and high-grade malignant non-rhabdomyosarcoma soft tissue sarcomas are treated according to the EpSSG NRSTS 2005 protocol

Bibliography

1. Weiss SW, Goldblum JR: General considerations. In: Weiss SW, Goldblum JR: Enzinger and Weiss's Soft Tissue Tumors. 5th ed. St. Louis, Mo: Mosby, 2008, pp 1-14

2. Spunt SL, Million L, Coffin C: The nonrhabdomyosarcoma soft tissue sarcoma. In: Pizzo PA, Poplack DG, eds.: Principles and Practice of Pediatric Oncology. 7th ed. Philadelphia, Pa: Lippincott Williams and Wilkins, 2015, pp 827-54

3. Bisogno G, Ferrari. Soft tissue sarcoma. I: Stevens MCG, Caron HN, Biondi A, red. Cancer in children: clinical management. 6th edition, Oxford: Oxford University Press; 2011, pp 274–292

4. Norman G, Fayter D, Lewis-Light K, Chisholm J, McHugh K, Levine D, Jenney M, Mandeville H, Gatz S, Phillips B. An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: systematic review. BMJ Open. 2015, Jan 8; 5(1)

5. Fletcher CDM, Bridge JA, Hogendoorn P, et al., eds.: WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon, France: IARC Press, 2013

6. Harmer MH: TNM Classification of pediatric tumors. Geneva, Switzerland, UICC International Union Against Cancer, 1982, pp 23-28

7. Maurer HM, Beltangady M, Gehan EA, et al: The Intergroup Rhabdomyosarcoma Study-I: a final report. Cancer, 1988, 61:209-220

8. RMS 2005: a protocol for non metastatic rhabdomyosarcoma. Version 1.3 International : European paediatric soft tissue sarcoma study group; 2012. https://www.skion.nl/workspace/uploads/Protocol-EpSSG-RMS-2005-1-3-May-2012_1.pdf

9. NRSTS 2005: a protocol for localized non rhabdomyosarcoma soft tissue sarcomas. Version 1.1. European paediatric soft tissue sarcoma study group; 2009. https://www.skion.nl/workspace/uploads/EpSSG-NRSTS-version-1-1.pdf

8.4 BONE TUMOURS

8.4.1 OSTEOSARCOMA

Epidemiology

Osteosarcoma is the most common primary malignant bone tumour in children and adolescents and it represents 3% of all cancers in children, the highest incidence is between 13 and 16 years of age. Osteosarcomas are more common in boys than girls (1.4:1) and in patients of African descent compared to Caucasians. The most common site is the metaphysis of long bones: distal femur, proximal tibia and humerus.

The aetiology of osteosarcoma is unknown, but a history of radiotherapy, treatment with alkylating agents, combination of anthracyclines and radiotherapy are factors that increase the risk of developing this tumour. A history of irradiation appears to be implicated in approximately 3% of cases, the interval between irradiation and onset of osteosarcoma as a second malignancy is approximately 12-16 years, but this interval appears to be shorter in patients irradiated for the treatment of a childhood cancer.

Some bone lesions predispose to osteosarcomatous transformation: Paget's disease of the bone (considered to be a premalignant lesion), solitary or multiple osteochondroma, solitary enchondroma or enchondromatosis (Ollier's disease), hereditary multiple exostoses, fibrous dysplasia, chronic osteomyelitis, areas of metal implants for benign diseases.

A series of germline mutations encountered in conditions such as: hereditary retinoblastoma, Li-Fraumeni syndrome, Bloom syndrome, Werner syndrome, and Rothmund-Thomson syndrome predispose to osteosarcoma. (1)

Symptomatology

The most important symptom that should raise the suspicion of a bone tumour is bone pain, initially intermittent, later persistent, nocturnal and in the absence of mobilization. This symptom alone is sufficient to indicate a radiological investigation (initially a two-plane X-Ray), if the X-Rays do not elucidate the source of pain, investigations should be followed-up with a CT scan. Subsequently, local swelling occurs, sometimes with severe functional impairment (about 10% of osteosarcomas debut with a pathological bone fracture), oedema of the surrounding soft tissues, regional or distant lymphadenopathy. Advanced disease is associated with systemic symptoms such as fever and weight loss.

Local clinical examination shows a palpable tumour mass and must be followed by a complete physical examination (including performance status, height, and weight) that can identify symptoms of metastatic disease: pleural effusion or respiratory failure, bone pain, intracranial hypertension. (2)

Staging work-up

If there is a high suspicion of a bone tumour clinically and radiologically, the paediatrician or the family doctor who raised the suspicion of the diagnosis should contact a centre specialized in the treatment of sarcomas (specialized paediatric oncology or

orthopaedics departments) and refer the patient for further investigations, or to carry out these investigations under the coordination of the expert centre. (3)

Recommended laboratory examinations: initial blood count with differential white count; blood type and Rh. Blood chemistry: creatinine, urea, sodium, potassium, calcium, magnesium, phosphorus, alkaline phosphatase, albumin, liver transaminases, bilirubin, LDH, C-reactive protein; coagulation; urine test; renal function tests (with direct or estimated creatinine clearance). LDH and alkaline phosphatise levels at diagnosis have prognostic value. (4)

Cardiac examination with measurement of left ventricular ejection fraction and audiogram should be performed at diagnosis.

Recommended imaging studies:

- **for the evaluation of the primary lesion** in order to plan the biopsy and subsequent surgery, bone X-Ray completed at least with a CT scan of the concerned bone region; MRI examination is important because it brings information related to bone marrow infiltration, soft tissue involvement, vascular and nervous system invasion.

- **for the identification of distant metastases** one of the following investigational methods will be chosen, depending on patient status and on-site availability of the investigation: chest radiograph, chest CT, bone scintigraphy, PET-CT examination or "whole-body" MRI. For a correct staging, biopsies can also be performed on suspicious metastatic lesions.

Sperm preservation is recommended for boys. Girls can discuss options for fertility preservation with a specialist.

Histopathological diagnosis, classification

The biopsy of the primary tumour is performed after preliminary examinations, of which imaging is essential. This will be performed in specialized centres, either by the operating team that will perform the final resection of the tumour by open biopsy, or by an interventional radiologist specializing in sarcomas who can perform imaging guided core needle biopsy (ultrasound, CT).

The conditions that the biopsy technique must meet are the following:

- The biopsy must collect a viable, representative tumour fragment - the viable areas of the tumour are located closer to its periphery, the central area being frequently necrotic.

- A sample of extra-osseous soft tissues is almost always sufficient, which allows a faster examination.

- It is recommended to avoid a bone biopsy that causes the opening of the medullary canal, due to the risk of fracture and haematoma which could lead to dissemination of malignant cells. The viable areas are best seen on a CT scan or an MRI with contrast agents.

- The place of the skin incision must be chosen in such a way as to cause contamination of a single compartment to be excised at the moment of the tumour resection. It is recommended to avoid contamination of nerve bundles and joints.

- The biopsy area must be included in the region that is going to be excised; in case of performing the biopsy in the interventional radiology department, the path of the biopsy should be marked either by a small incision in the skin or by a tattoo.

- The drainage will be conducted only through the wound.

- The area chosen for the biopsy must be located distally, so as not to hinder the amputation.

All biopsies suspected of bone sarcomas should be reviewed by an expert pathologist and discussed in the multidisciplinary team. The sample must be accompanied by relevant clinical data: age of the patient, site of the tumour, type of biopsy, imaging description of the primary tumour, heredo-collateral history of the patient, if relevant.

Histological variants:

- High grade:

- conventional osteosarcoma: high histological degree of malignancy

- telangiectatic osteosarcoma unfavourable prognosis, early metastasis

- small cell osteosarcoma (difficult to differentiate from Ewing's sarcoma): severe prognosis, responds to radiation therapy

- malignant fibrous histiocytoma: more common around the age of 60

- multifocal osteosarcoma multiple synchronous bone lesions, each having, from a radiological point of view, the characteristics of a primary tumour; the evolution is severe and rapid with metastases to the lungs and soft tissues. This osteosarcoma could be associated with germline p53 gene mutation).

- extraosseous osteosarcoma (occurs in adults in the soft tissues of the lower limbs (post-radiotherapy)

- Intermediate grade:

periosteal osteosarcoma (on the bone surface, without invasion of the medullary canal); located at the level of the proximal metaphysis of the tibia, it has a more severe prognosis than parosteal osteosarcoma

- Low grade:

- parosteal osteosarcoma (juxtacortical): located in the distal femur; low degree of malignancy; characteristic radiological aspect (involvement of the cortex, without invasion of the medullary canal); better prognosis.

Staging and / or classification into risk groups, prognostic factors

Staging is done according to the TNM system for bone sarcomas, version 8 in 2017 established by the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC). This version contains separate classifications for the primary tumour (T) depending on site limbs, trunk, skull, facial bones and separately for the spine and pelvic bones. (5)

Unfavourable prognostic factors: metastatic disease at onset, axiall tumour, bulky tumour (over 5 cm), pathological bone fracture, telangiectatic osteosarcoma, osteosarcoma developed on Paget's disease of the bone, poor response to neo-adjuvant chemotherapy under 10 years of age and over 20 years of age. (4)

Treatment

Most osteosarcomas are high grade and they require multimodal treatment according to the EURAMOS1 protocol. Low-grade osteosarcomas can be treated with surgery alone and do not require chemotherapy, the resection should be carefully examined, and if it contains high-grade areas, chemotherapy must be done after surgery.

The treatment plan for osteosarcomas that are metastatic at diagnosis has the same principles as that for localized disease.

Treatment algorithm is: neo-adjuvant chemotherapy - surgery - adjuvant chemotherapy.

The pathological response to neo-adjuvant chemotherapy has prognostic value: tumour necrosis more than 90% good prognosis.

Surgical treatment

The surgery must be performed approximately at week 11 from the start of the chemotherapy. The discussion about surgery must be done with the orthopaedic surgeon from the beginning, when the paediatric oncology leads the treatment plan, especially in cases

where it is not technically possible to perform the biopsy in the same centre where the surgery will be performed.

The surgical techniques currently used in the treatment of osteosarcomas are conservative surgery and amputation. The decision to opt for conservative surgery must be considered but when the tumour does not seem to respond adequately to chemotherapy as shown by clinical and imaging examinations, amputation should be performed if there is the slightest doubt that the conservative surgery does not guarantee negative margins.

The conservative surgery can be performed-in the following circumstances:

- absence of major neuro-vascular invasion
- resection in healthy tissue (bone and muscle) in all directions
- block removal of previous biopsy sites as well as potentially contaminated tissues
- bone resection is done at a distance of 3-4 cm from the area considered to be invaded at the CT scan/MRI examination

The contraindications for conservative surgeries are: major neuro-vascular invasion, pathological fracture (relative contraindication), biopsies performed in improperly placed areas, infection of the primary tumour (septic condition), skeletal immaturity (estimated discrepancy should not exceed 6-8 cm), extensive muscle invasion (not enough muscle left for reconstruction).

The amputation is the surgical treatment that is chosen when conservative surgery is not a prudent gesture, since the limit of oncological safety cannot be obtained, or if, for technical reasons, conservative surgery is not feasible.

Metastases benefit from surgical treatment. If the patient is treated with curative intent, then all the metastases that are detected at onset must be completely resected. Surgery for metastases should be performed between week 11 and 20. For lung metastases, thoracotomy with manual exploration of both lungs is recommended. The thoracoscopy is discouraged. The first cycle of chemotherapy after thoracotomy should not be with HDMTX, because post-thoracotomy collections may form that will lead to delayed elimination of methotrexate. When the patient's stuatus does not allow for thoracotomy, techniques such as stereotactic radiotherapy, cryotherapy, radiofrequency ablation can be used.

Chemotherapy

The most active agents in osteosarcoma are Doxorubicin, Cisplatin, High Dose Methotrexate (MAP). The treatment is performed according to the EURAMOS protocol, the standard arm. There are no trials that prove the role of neo-adjuvant chemotherapy in increasing overall survival, but it offers the following benefits: symptom control, rapid treatment of micrometastatic disease, it facilitates resection, it provides time procure the endoprosthesis and it provides prognostic information. (7)

Postoperatively, the same chemotherapy is recommended regardless of the histopathological response. The entire treatment lasts between 7 to 9 months.

The addition of interferon treatment for patients with a good histological response and the addition of ifosfamide and etoposide brings no additional benefits. Also high-dose chemotherapy followed by hematopoietic stem cell rescue treatment has not been proven to be beneficial in the treatment of metastatic osteosarcoma. (8)

It is possible to opt for 2 cycles of Ifosfamide + Etoposide instead of MAP before surgery (according to a protocol of POG) for patients with metastases at diagnosis, with high tumour burden and for those with bone metastases, with a higher rate of objective responses, but with excess toxicity. (9)

Radiotherapy

Osteosarcoma are generally considered resistant to radiotherapy except for some histological variants that are more radiosensitive.

Radiation therapy is recommended in the following situations:

- inoperable patients (due to associated diseases, topography and/or extension of the tumour, performance status)
- when surgery cannot provide safety margins: close or positive margins
- if complete surgery is not possible
- at relapse
- for palliative purposes

The total dose administered after surgery for the so-called curative purpose is between 60-70 Gy (at least 66 Gy) with 2Gy/fraction.

Total lung irradiation for prophylactic purposes is not recommended.

The chemotherapy should not be stopped during radiotherapy.

Treatment of refractory disease and relapses

Using current treatment protocols, approximately two-thirds of children, adolescents, and adults under the age of 40 with nonmetastatic extremity osteosarcomas will be long-term survivors . The survival of patients with malignant bone sarcomas has improved due to the use of effective chemotherapy. Long-term survival after local tumor control without chemotherapy was only 16 percent, the addition of systemic chemotherapy with three or more drugs provided a five-year overall survival rate of 70 percent.

For patients who present with or develop overt metastatic disease long-term survival can be expected in less than 20 percent of all; but up to 35 to 40 percent of those with limited pulmonary metastases may be cured with multimodality therapy.

- surgical (metastasectomy, lymph node dissection, tumour resections/excisions)
- second-line chemotherapy (depending on the initial treatment regimen): IFO and VP16, Carbo and VP16, GEM and DOCE, Carbo and IRI
- radiotherapy

Post-therapeutic monitoring

The evaluation of the therapeutic response is made one month after the end of the adjuvant chemotherapy or 2 months after radiotherapy.

Examinations:

- clinical examination
- biological examinations (LDH, C-reactive protein, ESR)
- imaging studies (X-Ray/ CT scan/ bone MRI, ultrasound) for the primary tumour, depending on the site and type of surgery, +/- bone prosthesis
- chest CT scan
- bone scintigraphy
- examinations for other types of metastases
- audiogram

Post-therapeutic follow-up should be performed

- every 3 months in the first 2 years (bone scintigraphy every 6 months)
- every 4 months in the third year
- every 6 months between 4 and 5 years
- annually after 5 years

Recommendations

- Osteosarcoma should be treated by a multidisciplinary team in specialized centres.
- The biopsy must be done only after performing the clinical examination, biological and imaging studies, preferably by the same team that will perform the final surgery, or by an interventional radiologist specializing in sarcomas who can perform imaging guided core needle biopsy.
- The treatment of osteosarcoma is done according to the EURAMOS1 protocol.
- In order to obtain optimal results, the sequence of neo-adjuvant chemotherapy, surgery, adjuvant chemotherapy must be observed.
- It is recommended that high-dose methotrexate be administered only in centres where methotrexate levels continuously can be monitored and its toxicity can be monitored and treated.

Bibliography

1. Fuchs B, Pritchard DJ. Etiology of osteosarcoma. Clinical Orthop Rel Res.2002;3 97:40–52.
2. Grimer RJ, Briggs TW. Earlierdiagnosis of bone and soft-tissue tumours. J Bone Joint Surg Br 2010; 92: 1489–1492.
3. Blay JY, Soibinet P, Penel N et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol 2017; 28:2852–2859.
4. The ESMO/European Sarcoma Network Working Group, Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology, Volume 25, Issue suppl_3, September 2014, Pages iii113–iii123, https://doi.org/10.1093/annonc/mdu256
5. Kneisl JS, Rosenberg AE, Anderson PM, et al.. Bone. In: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.471.
6. Aitken JF, Youlden DR, Moore AS, Baade PD, Ward LJ, Thursfield VJ, Valery PC, Green AC, Gupta S, Frazier AL. Childhood cancer staging for population registries according to the Toronto Childhood Cancer Stage Guidelines. Cancer Council Queenslandand Cancer Australia: Brisbane, Australia; 2017. Available at https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf
7. Gerrand, C., Athanasou, N., Brennan, B. et al. UK guidelines for the management of bone sarcomas. Clin SarcomaRes 6, 7 (2016). https://doi.org/10.1186/s13569-016-0047-1
8. National Cancer Institute Clinical Trials. Phase III randomized study of neoadjuvant induction therapy comprising doxorubicin, cisplatin, and high-dose methotrexate (MAP) followed by surgery and adjuvant maintenance therapy comprising map alone versus map and peg-interferon alfa-2b or MAP combined with ifosfamide and etoposide in patients with resectable high-grade osteosarcoma; available at: https://clinicaltrials.gov/ct2/show/NCT00134030?term=AOST+0331&rank=1,
9. Goorin AM, Harris MB, Bernstein M, Ferguson W, Devidas M, Siegal GP, Gebhardt MC, Schwartz CL, Link M, Grier HE Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncologygroup trial. J Clin Oncol. 2002;20(2):426.

8.4.2 EWING SARCOMA OF BONE

Epidemiology

Ewing sarcoma is a tumour that occurs in the bone from neural crest undifferentiated cells, being the second most common bone tumour in children.

It affects children, adolescents and young adults, the peak incidence being around puberty (average age 14-15 years). It predominates in males (ratio 1.5/1).

It is a very aggressive disease, with great sensitivity to oncological treatment (chemo-therapy, radiotherapy), so it is essential that the treatment be performed in multidisciplinary specialized centres.

In 50% of cases the primary tumour is located in the limbs, especially the lower limbs (diaphysis) and in 20% of the cases in the pelvis; it can also affect other bones.

To date, no genetic or environmental risk factors that can predispose to Ewing sarcomas have been clearly identified.

In 85-90% of cases of Ewing sarcoma, a recurrent translocation t(11; 22) (q24; q12) fuses the 5'end of the EWSR1 gene on chromosome 22 with the 3' end of the FLI1 gene on chromosome 11. This fusion can be detected using in situ fluorescent hybridization (FISH). Other cytogenetic abnormalities that may be encountered are: t(21; 22); t (7; 22). (1)

Symptomatology

At physical examination, the patient usually presents with localized pain and swelling that has been lasting for several weeks or months, often associated with functional impairment. When systemic signs and symptoms appear it indicates advanced disease (fever: 20%, weight loss). Some patients may show signs of bone marrow invasion from the first visit to the doctor.

In developing countries, 20% of Ewing sarcoma cases are metastatic at diagnosis. The most common metastatic sites are lungs and bone marrow. Lymph nodes, liver, or brain metastases occur less frequently. (2)

Investigations

Initial **staging and during treatment work-up** and examinations during treatment

- complete physical examination (+ performance status, weight, height)
- blood count with differential white count, ESR
- blood chemistry: creatinine, urea, sodium, potassium, calcium, magnesium, phosphorus, transaminases, alkaline phosphatase, LDH, C-reactive protein and creatinine clearance measured or estimated
- imaging examinations:
- bone X-Ray in two planes
- CT scan and/or MRI examination of the bone region concerned
- bone scintigraphy
- chest X-Ray/CT thorax
- abdominal, pelvic and thoracic MRI or ultrasound
- Optional PET-CT scan can be performed. In the case of a localized disease with negative PET-CT, there is very little chance that the bone marrow biopsy will indicate metastases. (3)

- bone marrow biopsy and bone marrow aspirate from at least one region distant from the primary tumour or metastases

- cardiac examination with echocardiography to evaluate the ejection fraction of the left ventricle

- Sperm preservation is recommended in boys, and girls may discuss fertility preservation options with a fertility specialist. These measures should not delay the start of the treatment due to the particularly aggressive nature of the disease. Please note that in some centres these measures are not available.

Histopathological diagnosis, classification

The biopsy is the only examination able to establish a definitive diagnosis. It is performed from an area that will be excised at the moment of the final surgery. The surgeon who will operate on the primary tumour should be consulted before performing the biopsy, it should be carefully planned so as to bring enough tissue to establish the diagnosis, but without compromising the final surgical intervention, especially if a conservative operation is considered. The biopsy should be performed after the imaging examination of the primary tumour, visualized in the multidisciplinary team by the surgeon, radiologist, radiotherapist, paediatric oncologist and pathologist.

The amount of tissue obtained by biopsy must be sufficient for the pathologist to be able to make the correct diagnosis and to make the differential diagnosis with other small round blue cell tumours.

If technically possible, core needle biopsy will be performed using CT or ultrasound guidance. If the sample is inconclusive, an open biopsy will be necessary. Given that Ewing sarcomas sometimes present Celsian signs or fever due to metastatic disease, a sample should be sent to microbiology to rule out a rapid diagnosis of osteomyelitis.

Ewing sarcoma is a high-grade tumour with small round blue cells, PAS and MIC2 (CD99) positive. It can express neural markers.

Histological sub-classification:

- Classic Ewing sarcoma
- Extraskeletal Ewing Sarcoma (soft tissues)
- Askin tumour (chest wall)
- Primitive neuroectodermal tumour (PNET) located in the bone, soft tissues, brain

Staging, prognostic factors

The staging is done according to TNM. (4)

According to "Childhood cancer staging for population registries according to the Toronto Childhood Cancer Stage Guidelines", only two stages are used for Ewing sarcoma: localized Ewing sarcoma and metastatic Ewing sarcoma. (5)

Unfavourable prognostic factors:

- metastatic disease at onset, bone metastases have a more severe prognosis than lung metastases
- bulky tumour
- elevated LDH
- primary site other than extremities
- patient older than 15 years
- unsatisfactory histopathological response after neo-adjuvant chemotherapy
- genomic analysis of the EWSR1 gene which reveals variations in the number of copies
- STAG2, TP53 and CDKN2A mutations (6)

Treatment

The treatment is multimodal, according to the results of the EURO EWING 99 trial or according to the EURO EWING 2012 protocol, the standard arm. (6) Initially, 6 cycles chemotherapy are given followed by surgery/local treatment, then followed by adjuvant chemotherapy; total duration of treatment is about 1 year. (7, 8)

- **Surgical treatment**

Surgery in Ewing sarcoma aims to resect all the structures that were initially affected by the tumour, before the chemotherapy treatment. If the multidisciplinary tumour board considers that the surgery cannot provide safety margins or that there is a poor response to neo-adjuvant chemotherapy, preoperative radiotherapy may be chosen.

Conservative operations:

Conditions:

- lack of major neuro-vascular invasion
- resection in healthy tissue of bone and muscles in all directions
- block removal of previous biopsy sites as well as potentially contaminated tissues
- resection of the bone at a distance of 3-4 cm from the area shown by the CT and MRI examinations to be invaded
- the possibility of adequate motor reconstruction, achieved by the transfer of regional muscles, adequate coverage with soft tissues

Contraindications to conservative operations:

- major neuro-vascular invasion
- biopsies performed in improperly placed sites
- infection (of primary tumour, septic condition)
- skeletal immaturity: the estimated discrepancy must not exceed 6-8 cm, a size over which expandable prostheses are not effective;
- muscle invasion should not be too extensive (there should be enough muscle left for reconstruction).

Amputation is the surgical treatment of choice when conservative surgery is not prudent or not feasible due to technical reasons.

- **Radiotherapy**

Radiotherapy is an important treatment alongside surgery to ensure local control. The indications for radiotherapy are:

- Postoperative, for residual disease after surgery or microscopically positive resection margins
- Pre-operative to reduce the risk of local recurrences (soft tissue seeding during surgery)
- Radiation therapy for curative purposes, in combination with chemotherapy, if surgery is not possible due to the site of the tumour.
- Total lung irradiation for patients with lung metastases, especially those with a good response after chemotherapy.
- Irradiation of the homolateral hemithorax for tumours located in the chest wall, with pleural infiltration or intraoperative pleural contamination.
- Chemotherapy is often given concomitantly with radiotherapy, but combinations of anthracyclines, actinomycin should be avoided; they increase toxicity.

The recommended total dose for macroscopic disease is 55.8 Gy with 1.8 GY/fraction and 50.4 Gy for microscopic disease. For paravertebral tumours, near the heart, the dose may be

limited to 45-50.4 Gy. Total pulmonary irradiation or of a hemithorax is done with TD = 15 Gy with 1.5 Gy/fraction in 10 fractions.

- **Chemotherapy**

Chemotherapeutic agents with activity in Ewing sarcoma are doxorubicin, ifosfamide, cyclophosphamide, vincristine, actinomycin and etoposide.

The treatment in the Ewing sarcoma of the bone is currently in accordance with the results of the European protocols Euro Ewing 99 and 2012.

Euro Ewing 99 protocol:

Induction chemotherapy: VIDE (Vincristine, Ifosfamide, Doxorubicin, Etoposide) x 6 courses (18 weeks)

Consolidation chemotherapy is stratified based on risk factors:

- Localized standard risk (SR): 8 VAC (Vincristine, Actinomycin, Cyclophosphamide)
- Localized High risk (HR), 1VAI + Bu/Mel (Busulfan Melphalan) when feasible or 8VAI
- Lung metastatic disease: 8 VAI + Whole Lung Irradiation (WLI)
- Multimetastatic Ewing: BuMel

The high-dose chemotherapy followed by rescue treatment with autologous stem cell transplantation has not been shown to be beneficial in the treatment of metastatic disease.

Euro Ewing 2012 protocol

Induction/consolidation chemotherapy: VDC/IE x 9 courses + IE/VC x 5 courses (18 + 10 weeks) became the standard over VIDE induction chemotherapy + VAI/VAC consolidation chemotherapy

- Localized standard risk (SR): VDC/IE x 9 courses + IE/VC x 5 courses
- Localized High risk (HR) BU/mel recommended when feasible, but rarely used
- Lung metastatic disease: VDC/IE x 9 courses + IE/VC x 5 courses + WLI
- Multimetastatic Ewing: VDC/IE x 9 courses + IE/VC x 5 courses

Treatment of refractory disease or relapses

- surgical (metastasectomy, lymph node dissection, tumour resections-excisions)
- second-line chemotherapy (depending on the initial treatment regimen): Cyclophosphamide/Topotecan, Irinotecan/temozolomide +/- Vincristine, HD-Ifosfamide, Docetaxel + Gemcitabine. According to the partial results of the rEECur trial, the combination of Docetaxel and Gemcitabine proved to be inferior to the others and the arm was closed. (9)

Post-therapeutic follow-up

The evaluation of the therapeutic response is made one month after the end of the multimodal treatment by:

- physical examination
- blood count and blood chemistry (LDH, C-reactive protein, ESR, hepatic and renal function)
- imaging examinations (X-Ray, CT scan, bone MRI, ultrasound) - for the primary tumour, depending on the site and type of surgery, +/- bone prosthesis
- Chest CT scan
- Bone scintigraphy
- Examinations for other types of metastases
- PET-CT

Post-therapeutic follow-up

- every 3 months in the first two years

- every 4 months in the third year
- every 6 months in the fourth and the fifth years
- annually after the fifth year

Examinations during monitoring:
- general clinical examination
- pulmonary X-Ray and/or chest CT scan
- bone X-Ray and/or CT scan and/or ultrasound of the primary site
- blood count, ESR, blood chemistry (LDH, C-reactive protein, assessment of possible liver or kidney damage)
- bone scintigraphy (every 6-12 months)
- examinations for identifying late side effects of the treatment (cardiac) and for the possibility of a second neoplasm.

Recommendations
- The diagnostic biopsy should be taken in or in collaboration with centres with special competence on sarcoma.
- The biopsy must bring enough material for the pathologist to make a definite diagnosis , with differential diagnosis from other small round blue cell tumours.
- The treatment is done according to the EURO EWING 99 protocol or EURO EWING 2012 protocol, the standard arm.

Bibliography

1. The ESMO/European Sarcoma Network Working Group, Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology, Volume 25, Issue suppl_3, September 2014, Pages iii113–iii123, https://doi.org/10.1093/annonc/mdu256

2. Zucman J, Delattre O, Desmaze C, Plougastel B, Jou bert I, Melot T, Peter M, De Jong P, Rouleau G, Aurias A Cloning and characterization of theEwing sarcoma and peripheral neuroepithelioma t(11;22) translocation breakpoints. GenesChromosomes Cancer. 1992;5(4):271.

3. Newman EN, Jones RL, Hawkins DS. An evaluation of [F-18]-fluorodeoxy-D-glucose positron emission tomography, bone scan, and bone marrow aspiration/biopsy as staging investigations in Ewing sarcoma. PediatrBlood Cancer 2013; 60: 1113–1117.

4. Kneisl JS, Rosenberg AE, Anderson PM, et al.. Bone. În: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.471.

5. Aitken JF, Youlden DR, Moore AS, Baade PD, Ward LJ, Thursfield VJ, Valery PC, Green AC, Gupta S, Frazier AL. Childhood cancer staging for population registries according to the Toronto Childhood Cancer Stage Guidelines. Cancer Council Queenslandand Cancer Australia: Brisbane, Australia; 2017. Available at https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf

6. The Protocol EURO-EWING 99 available at https://www.skion.nl/voor-professionals/behandelrichtlijnen/protocollen/124/euro-ewing-99/?pid=al-p

7. Gerrand, C., Athanasou, N., Brennan, B. et al. UK guidelines for the management of bone sarcomas. Clin Sarcoma Res 6, 7 (2016). https://doi.org/10.1186/s13569-016-0047-1

8. The Protocol EURO-EWING 2012 available at https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/trials/EE2012/index.aspx

9. Martin G. McCabe, Veronica Moroz, Maria Khan, UtaDirksen, Abigail Evans, Nicola Fenwick, Nathalie Gaspar, JukkaKanerva, Thomas Kühne, Alessandra Longhi, Roberto Luksch, Cristina Mata, Marianne Phillips, KirstenSundbyHall, Claudia Maria Valverde Morales, Andrew J. Westwood, Mark

Winstanley, Jeremy Whelan, KeithWheatley, and Euro Ewing Consortium Results of thefirst interim assessment of rEECur, an international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma. Journal of ClinicalOncology 2019 37:15_suppl, 11007-11007

8.4.3 BENIGN BONE TUMORS OF ONCOLOGICAL IMPORTANCE

Osteochondroma (Exostosis) is a benign tumour that appears frequently in the adolescent population, representing 35% of all benign tumours. It may occur in any bone, it is mostly asymptomatic, but it may rarely induce pain and irritation to the surrounding tissue. The lesion originates in the cartilage. The lesion may increase in size as the child grows but it stops when the skeleton reaches maturity. Radiographic features - the osteochondroma appears as a spur that arises from the surface of the bone.

Hereditary multiple exostoses (hereditary multiple osteochondromas) is characterized by the presence of two or more exostoses in the appedincular or axial skeleton. Most cases are caused by germline mutation in the EXT1 or EXT2 tumour suppressor genes that are inherited in an autosomal dominant manner, however, spontaneous mutations may occur. The prevalence of hereditary multiple exostoses in the population is about 1 in 50.000. This disease has an increased risk of inducing joint deformities, movement limitation and of malignant degeneration.

Prognosis: exostoses grow during childhood and stop when the growth cartilages close, remaining unchanged throughout life. There is a moderate risk of recurrence if they are incompletely excised before the cartilage closes. The positive prognostic factors, meaning mild symptoms, are represented by the female sex, the involvement of less than 5 sites and the EXT2 mutation. None of these factors are predictive of malignant transformation. The lesions in the proximal femur can cause hip osteoarthritis. There is a low risk of malignant transformation into chondrosarcoma, this transformation occurs in adults and most commonly in those with multiple hereditary exostoses (5% of cases). The malignant transformation can be heralded by a change in size of an exostosis after maturation of the skeleton or by the onset of new symptoms. Osteochondromas of the spine, scapula, pelvis and proximal femur are more commonly subject to malignant transformation.

Treatment: Most osteochondromas can be monitored without treatment. Patients should be examined clinically every year and X-Rays may be taken. Indications for excision include: local symptoms (pain, deformity of the region) or suspicion of malignant transformation (cartilage cap thicker than 2cm in adults), increase in size of the lesion after reaching skeletal maturity, growth disorders, new symptoms,lesions of the spine, scapula, pelvis or of the proximal femur. (1)

Enchondroma is a benign cartilaginous tumour that develops in the medullary cavity of the long bones. It accounts for about 3% of benign bone tumours in children. On X-Ray it appears as a radio-transparent lesion associated with cortical thickening and it is usually discovered accidentally or following a pathological bone fracture. Enchondromatosis has as subtype the Ollier's disease defined as multiple enchondromas with unilateral site. Another subtype of enchondromatosis is the Maffucci syndrome characterized by multiple enchondromas associated with vascular malformations. Most cases of enchondromatosis are sporadic and are associated with somatic mutations in the isocitrate dehydrogenase 1 and 2 genes (IDH1 and IDH2).

Prognosis: solitary enchondromas are usually self-limiting. Recurrences after curettage are rare. Enchondromas of the long bones and pelvis can become malignant, this transformation usually occurring on the mature skeleton and it is associated with presence of pain. The malignant transformation of solitary enchondromas is very rare, less than 1%. The risk of malignant transformation is increased by up to almost 50% in patients with enchondromatosis.

Enchondromatosis is associated with extraosseous non-sarcomatous cancers, including brain tumours.

Treatment: It depends on the presence of symptoms and size. Those that are asymptomatic, small and do not have a risk of pathological fracture can be monitored. The risk of fracture increases when the lesions are in a weight bearing bone, have a diameter greater than 25 mm and involve more than 50% of the diameter of the bone cortex. The follow-up frequency depends on the size, site and number of lesions. Symptomatic enchondromas are treated with curettage and bone graft. When symptoms occur in the absence of fracture, low-grade chondrosarcoma should be ruled out. The fractures must heal before curettage. (2)

Giant-cell tumour of bone accounts for approximately 3 to 5 percent of all primary bone tumors and 15 to 20 percent of all benign bone tumors, it is a benign tumour that may be locally aggressive. It presents as a lytic lesion in the metaphyseal epiphyseal region of long bones in young adults.

Prognosis: The clinical behaviour of these tumours is unpredictable, although considered as benign lesions they have a tendency to local recurrence after simple curettage and they may even metastasize. Lung metastases do not have the same poor prognosis as metastases that occur in other neoplasms. The giant cell tumour can undergo malignant transformation in rare cases. There are no clinical, histological or radiological parameters that predict the degree of aggression of this tumour. (3)

Treatment: surgery represented by curettage of the lesion followed by filling the cavity with cement is the treatment of choice for primary or recurrent intra-bone lesions. In case of tumours with extraosseous extension, pathological fractures or tumour involvement of bones such as fibula and distal ulna, en block excision with or without reconstruction is recommended, if it does not affect the functionality. There are studies recommending the use of neo-adjuvant treatment with Denosumab in patients in whom resection is associated with significant morbidity or loss of function. Denosumab, radiotherapy or arterial embolization may be used in patients with unresectable local recurrence. Resection of metastases rather than monitoring is recommended) in patients with potentially resectable lung metastases. Denosumab, is recommended in patients with unresectable metastases.

Post-treatment follow-up: is done with X-rays or low-dose CT, every 3 months in the first year, every 3 to 6 months in the second and third years and then every 4-6 months for up to 5 years. Then X-Rays will be performed until the end of life because there is an increased risk of late loco-regional recurrence and metastases. (4)

Recommendations:

- Bone tumours in children should be treated and monitored in specialized centres by multidisciplinary teams consisting of paediatric orthopaedic surgeon, paediatric oncologist, radiologist and pathologist with experience in this field.
- Small fibromas, fibrous cortical defects, and asymptomatic osteochondromas that are detected incidentally may not require referral.
- Patients and their families should be informed of the risk of malignant transformation of certain lesions, sometimes later on after diagnosis and the need for compliance with a long-term follow-up program.
- Both patient and physician must be aware of changes that may indicate malignant transformation in order to avoid making the diagnosis in advanced stages.

References

1. Yildiz C, Erler K, Atesalp AS, Basbozkurt M. Benign bone tumors in children. Curr Opin Pediatr 2003; 15:58.

2. Verdegaal SH, Bovée JV, Pansuriya TC, et al. Incidence, predictive factors, and prognosis of chondrosarcoma in patients with Ollier disease and Maffucci syndrome: an international multicenter study of 161 patients. Oncologist 2011; 16:1771.

3. Puri A, Agarwal MG, Shah M, et al. Giant cell tumor of bone in children and adolescents. J Pediatr Orthop 2007; 27:635

4. Müller DA, Beltrami G, Scoccianti G, et al. Risks and benefits of combining denosumab and surgery in giant cell tumor of bone-a case series. World J Surg Oncol 2016; 14:281.

8.5 KIDNEY TUMOURS

Epidemiology

Renal tumours account for about 5% of all malign tumours in children. The most common histology (approximately 95%) is nephroblastoma (Wilms' tumour). Nephroblastoma is a malignant tumour that originates in the renal embryonic cells. Wilms' tumour most commonly affects children between 1 and 5 years of age, rarely children over 8 years of age. The average age at diagnosis for patients with unilateral disease is 43 months for girls and 37 months for boys. Bilateral disease is diagnosed at a younger age (average age 31 months for girls and 24 months for boys).

In rare cases nephroblastoma can be also found in adults. Renal cell carcinoma (RCC) is the most common kidney cancer in adolescents. (1)

Certain congenital syndromes/abnormalities are frequently associated with Wilms' tumour: WAGR syndrome (characterized by Wilms' tumour, aniridia, genitourinary abnormalities, mental retardation), Denys-Drash syndrome; Beckwith-Wiedemann syndrome (BWS); Dicer1-syndrome; isolated hemihypertrophy; isolated urogenital abnormalities (hypospadias, cryptorchidism, congenital uterine abnormalities, renal ectopias); aniridia and Perlman syndrome. Children known to have these syndromes/developmental abnormalities should receive regular evaluations for early diagnosis of nephroblastoma. (2, 3)

Symptomatology

In about 50% of cases, children have no symptoms and tumours are discovered incidentally by investigations carried out for other conditions or during scheduled paediatric consultations. In some cases, the parents notice an increased size of the abdomen. 30-40% of patients have abdominal pain, increase in size of the abdomen or hematuria (12-25%), altered general condition (5%). Moreover, patients may have high blood pressure (25%), thrombocytosis, fever or scrotal oedema. (4)

Diagnosis

Complete clinical examination with increased attention upon palpation of the abdomen. A firm palpation of the tumour formation, which can be painful, should be avoided. Vigorous palpation can cause rupture of the renal capsule and the disease to spread. (4, 5)

Laboratory examinations:

- Full blood cell count
- Urine analysis (leukocyturia, hematuria, proteinuria, urinary VMA for differential diagnosis with neuroblastoma
- renal function (urea, creatinine, uric acid)
- liver function
- coagulation test
- ESR, C-reactive protein, LDH
- serum electrolytes, increased calcium in patients with rhabdoid tumour of the kidney
- cardiac examination (treatment with anthracyclines, irradiation)
- Blood type, Rh

There are no specific tumour markers associated with nephroblastoma.

Imaging studies establish the presence of a renal tumor, evaluate the contralateral kidney, the presence or absence of lombo-aortic lymphadenopathies and detect tumor infiltration of the renal vein, determining their proximal extension.

- Abdominal ultrasound: simple, fast, non-invasive method. It is generally the first imaging study performed when suspecting a Wilms' tumour. It is useful in differentiating between cyst and kidney tumour, assessing small contralateral tumours, identification of thrombi in the inferior vena cava and liver and abdominal metastases. The tumour should be measured in three dimensions whenever possible. Measurements should be performed before starting neoadjuvant therapy and before the surgery is performed.
- Contrast-enhanced abdominal CT scan is not mandatory, but it is highly recommended. Increased attention to the contralateral kidney. CT scan should be replaced by MRI when possible.
- AP and lateral chest X-Ray are recommended in all patients. Chest CT scan is recommended in all patients. Chest X-Ray is mandatory even if chest CT scan is performed.
- Bone scintigraphy is performed postoperatively in patients with clear cell renal sarcomas, as well as in all patients, regardless of the histological type of the renal tumour, who have liver or lung metastases, or who have symptoms suggestive of bone metastases.
- Brain CT scans will be performed on patients with renal tumours with unfavourable histology (clear cell sarcomas, rhabdoid tumours).
- Selective renal arteriography or angio-MRI is performed preoperatively in cases of bilateral Wilms' tumour or in patients with renal malformations or whenever the surgeon considers such information necessary preoperatively.

The biopsy is not mandatory before starting neoadjuvant chemotherapy. Treatment can be initiated based on clinical and imaging features compatible with the diagnosis of nephroblastoma. If a biopsy is considered necessary, the risk of bleeding and tumour rupture should be considered. The biopsy is performed under general anaesthesia by an experienced interventional imaging physician. Tru-cut needle biopsy is recommended. Wedge biopsy causes tumour over-staging!

Definitive **diagnosis** is established by the histopathological evaluation of the specimen obtained after surgery or biopsy.

Macroscopy: frequently tumour > 5cm (1/3 of cases > 10cm), solitary, located at the level of the poles, smooth or bumpy surface, delimited by a friable pseudocapsule, well vascularized;

Microscopy: frequently the tumour has a three-phase pattern: undifferentiated blastemal cells and cells differentiated in different degrees and proportions: epithelial and mesenchymal elements;

Histology represents the most important prognostic factor; it is unfavourable or favourable depending on the presence or absence of *anaplasia* (focal or diffuse).

Pathological risk group after neoadjuvant chemotherapy: (6)

LOW RISK:

- Mesoblastic nephroma (common in the first year of life; 2 subtypes: classic and cellular; no prognostic or therapeutic impact)
- Cystic partially differentiated nephroblastoma
- Complete necrotic nephroblastoma (excellent prognosis: 100% survival regardless of stage)

INTERMEDIATE RISK

- Epithelial type nephroblastoma (post-chemotherapy regressive changes account for less than 66% of tumour mass, the epithelial type is predominant)
- Stromal type nephroblastoma (post-chemotherapy regressive changes account for less than 66% of tumour mass, the stromal type is predominant)
- Mixed-type nephroblastoma (post-chemotherapy regressive changes account for less than 66% of tumour mass, no predominant type)
- Regressive type nephroblastoma (post-chemotherapy regressive changes account for over 66% of the tumour mass)
- Nephroblastoma with focal anaplasia

HIGH-RISK:

- Blastemal type nephroblastoma
- Nephroblastoma with diffuse anaplasia
- Clear cell sarcoma of the kidney
- Rhabdoid tumour of the kidney

Pathological risk group for primary operated tumors

LOW RISK:

- Mesoblastic nephroma
- Cystic partially differentiated nephroblastoma

INTERMEDIATE RISK:

- All variants of non-anaplastic nephroblastoma
- Nephroblastoma with focal anaplasia

HIGH RISK:

- Nephroblastoma with diffuse anaplasia
- Clear cell sarcoma of the kidney
- Rhabdoid tumour of the kidney

Staging

In Europe, the most commonly used staging system is SIOP staging, which is based on surgical assessment after administration of the neoadjuvant chemotherapy. (7)

-**Stage I** - Tumour completely resected and limited to the kidney, or if it exceeds the contour of the kidney, the tumour is surrounded by a fibrous pseudocapsule. The tumour may infiltrate the renal capsule or pseudocapsule, but does not reach the outer surface and is completely resected (negative resection margins). The tumour can plunge into the pelvic system and ureter, but does not infiltrate their walls. The vessels of the renal sinus are not involved. Intrarenal vessels involvement may be present. Macroscopically, there is no residual tumour outside the resection margins, and the resection margins are tumour-free. Fine needle aspiration or tru-cut biopsy does not upstage the tumour. The presence of necrotic tumour induced by chemotherapy in the renal sinus and/or perirenal fat is not a reason for upstaging, if the resection has been complete and the resection margins are tumour-free.

-Stage II - Tumour extension outside the kidney or the tumour penetrates through the renal capsule and/or pseudocapsule and invades perirenal fat, but is completely resected (clear resection margins). The tumour infiltrates the renal sinus and/ or invades the blood or lymph vessels outside the renal parenchyma, but is completely resected. The tumour can infiltrate adjacent organs and vena cava, but is completely resected.

-Stage III - Incomplete tumour resection with microscopic or macroscopic residual tumour. This includes: invasion of the regional lymph nodes, tumour invasion in the peritoneal surface, peritoneal carcinomatosis, preoperative or intraoperative tumour rupture,

intravascular tumour thrombus at the resection margins, surgical biopsy before chemotherapy or surgery.

-Stage IV - Haematogenous metastases (lung, liver, bone, brain) or lymph node metastasis outside the abdominal-pelvic region.

-Stage V - Bilateral renal tumour. Staging of each tumour will be performed, according to the above mentioned criteria, based on the tumour extension before the histological examination.

Treatment is performed according to the SIOP recommendations, Umbrella SIOP 2016 Protocol. (8)

In children < 6 months and > 16 years of age, primary surgery is recommended with the consent of the tumour board.

Localized disease

Preoperative treatment: VCR 1.5mg/ m^2 (max 2mg) weekly for 4 weeks + ACT-D 45 micrograms/ kg (max 2 mg) on weeks 1 and 3.

Surgery should be performed in week 5-6.

Postoperative treatment

Criteria for assessing the risk group:

- tumour volume (increased risk over 500 ml) evaluated before surgery by imaging studies
- histological type
- stage of the disease

Table 1. Overview of the postoperative treatment for localized disease

		Tumour volume after preoperative chemotherapy	Stage I	Stage II	Stage III
Low risk (CN only)		All	no treatment	long AV	long AV
Intermediate risk		<500ml	Short AV	long AV	long AV + RT
Intermediate risk (except for blastemal and epithelial type which are treated with short AV in stage I and long AV in stage II regardless of tumour volume)		> 500ml	Short AV	AVD	AVD + RT
High risk	Blastemal type	All	AVD	HR-1	HR-1 + RT
	Diffuse anaplasia	All	AVD	HR-1 + RT	HR-1 + RT

CN - completely necrotic, A - ACT-D-D, V-VCV, D-Doxo, HR - High risk, RT - radiation therapy

-Stage I low risk: no treatment. If the histopathological result is not available in due course, a dose of postoperative VCR may be administered until the histopathological result is obtained.

-Stage I intermediate risk: short AV chemotherapy

According to the GPOH guide (German Society of Paediatric Oncology and Haematology), in case of focal anaplasia, mixed and regressive type with tumour volume > 500ml, adjuvant chemotherapy will be administered according to the high risk (AVD) regimen.

-Stage I high risk: AVD chemotherapy

This treatment is also administered to patients with stage II and III with focal anaplasia, mixed or regressive type and tumour volume > 500 ml after preoperative chemotherapy.

Total duration of the adjuvant chemotherapy is 27 weeks.

-Stage II and III low and intermediate risk: long AV chemotherapy

This treatment is administered to patients with stage II and III. In case of focal anaplasia, mixed and regressive type with tumour volume > 500ml, Doxo is associated according to the regimen for high risk stage I (AVD).

Total duration of the adjuvant chemotherapy is 27 weeks.

-Stage II and III high risk: adjuvant chemotherapy: Carbo and VP16 alternatively with CTX and Doxo.

6 cycles of each chemotherapy regimen will be performed.

Postoperative chemotherapy is started when the patient's condition allows it. Chemotherapy should be started, if possible, no later than 21 days after the last dose of preoperative chemotherapy.

If possible, it is preferable that radiotherapy is performed concomitant with chemotherapy.

Metastatic disease (stage IV)

Biopsy of suspicious lesions outside the lungs should be considered when feasible. All lesions should be re-evaluated before surgery. In case of an incomplete response, it should be tested if the surgical resection is feasible and safe, without long-term morbidity.

If there is a discrepancy between the histology group of the primary renal tumour and the resected metastases, the postoperative treatment will be performed according to the highest risk of histology.

- Preoperative chemotherapy

Preoperative treatment is performed according to the size of lung nodules. At the end of preoperative chemotherapy, lung nodules are re-evaluated by chest CT scan in order to assess the response to treatment and establish the subsequent therapeutic conduct.

- 1-2 mm lung nodules: are not classified as metastases and will be treated with 4 weeks preoperative AV, as in localized tumours.

- Lung nodules 3-5 mm: Preoperative AVD chemotherapy. In case of persisting lung nodules after preoperative chemotherapy, resection of lung nodules is recommended - if possible. If complete resection is not possible, then resection of representative nodules is recommended in order to direct postoperative treatment.

If presence of viable tissue or malignant necrotic tissue is ruled out by histology, the patients will be treated according to the localized tumour guidelines. However, if histology shows viable tumour tissue, malignant necrotic tissue or if biopsy is not feasible, postoperative treatment is performed according to the recommendations for stage IV.

If a complete response has been obtained in lung nodules, chemotherapy with low cumulative dose of doxorubicin (AVD150) may be performed in patients with low and intermediate histology.

- Lung nodules over 5 mm are considered lung metastases: preoperative AVD chemotherapy.

- Patients with non-pulmonary metastases are treated in the neoadjuvant setting with the AVD regimen and reassessed prior to surgery. In case of incomplete response, surgical resection should be taken into consideration if feasible, safe and without long-term morbidity.

• Postoperative chemotherapy:

For patients with lung nodules < 3mm, treatment is performed according to the result of preoperative CT scan:

- No nodules detectable at the CT scan: postoperative treatment administered according to local stage and histology according to the guidelines for localized disease. Chest CT scan is recommended every 8-12 weeks for at least 2 years after the diagnosis.

- Persistent lung nodules. If feasible, resection of at least one representative nodule is recommended.

a) If histology excludes viable tissue or necrotic tumour, the treatment is continued according to the guidelines for localized tumours according to stage and histology.

b) If biopsy shows viable tissue or necrotic tumour then the AVD 250 regimen (i.e. 150mg / m^2 cumulative dose of Doxo) is administered with reassessment at week 10. If the nodules persist at that time, the whole lung irradiation is recommended.

c) In case of diffuse anaplasia, if metastases are histologically verified, whole lung irradiation is recommended.

d) If the biopsy is not feasible, treatment is continued as for localized disease, according to histology, with a minimum administered long AV, regardless of stage.

- In case of increasing size of nodules, if feasible, resection for at least one representative nodule should be performed.

a) If histology excludes viable tissue or necrotic tumour, treatment is continued as for localized tumours according to stage and histology at least with long AV regimen.

b) If biopsy shows viable tissue or necrotic tumour then the AVD 250 regimen (i.e 150mg / m^2 cumulative dose of Doxo) is administered with reassessment at week 10. If the nodules persist at that time, whole lung irradiation is recommended.

c) In case of diffuse anaplasia, if metastases are histologically verified, whole lung irradiation is recommended.

d) If biopsy is not feasible, treatment is continued as for localized disease according to histology, with a minimum of long AV administered, regardless of stage.

For patients with lung nodules exceeding 3mm

There are 4 post-operative scenarios:

A. Absent or completely resected metastases / nodules and low or intermediate risk histology

A1. lung nodules between 3 and 5 mm at diagnosis and low or intermediate histology

A2. Lung nodules > 5mm at diagnosis and low or intermediate risk histology

A3. Complete resection of non-malignant tissue

B. Metastases / nodules > 3mm at diagnosis incompletely resected or multiple inoperable nodules and low-risk histology of primary tumour

C. Metastases / nodules > 3mm at diagnosis incompletely resected or multiple inoperable nodules and intermediate risk histology of primary tumour

D. Patients with high risk histology of the primary tumour (including those with a complete response after preoperative chemotherapy and surgery) or with progressive histologically proven metastatic disease during preoperative chemotherapy (except predominantly stromal histology).

Group A1: Local stage I / II / III with low or intermediate risk histology. Complete response of 3-5mm lung nodules obtained by chemotherapy or completely resected by the surgeon.

- Recommended treatment: AVD 150

- If complete response has been obtained by surgery and a viable tumour has been identified radiotherapy is recommended.

- Patients with local stage III intermediate risk receive abdominal radiotherapy.

Group A2: Local stage I / II / III with low or intermediate risk histology. Complete response of lung nodules > 5mm obtained by chemotherapy or completely resected by surgeon.

- Recommended treatment: AVD 250

- If complete response has been obtained by surgery and a viable tumour has been identified radiotherapy is recommended.

- Patients with local stage III intermediate risk receive abdominal irradiation.

Group A3: Local Stage I/II/III, low or intermediate risk histology with complete surgical clearance of other non-malignant histology. Recommended treatment: According to local stage for localized disease.

Group B: Local stage I / II / III with low risk histology with residual nodules after chemotherapy or surgery.

- Resection of at least one representative nodule is recommended. Postoperative treatment is based on histology

a) Without proven metastases (viable tissue or malignant necrotic tissue has been ruled out) treatment according to local stage of the disease can be considered.

b) If there is no viable tissue, but necrotic nodules are present in a representative number of metastases: postoperative AVD 150 regimen for 27 weeks with a cumulative dose of Doxo of 150mg/m^2 . CT reassessment at week 10. Pulmonary radiotherapy is not required.

c) Viable tumour in resected lung nodules: AVD 250 regimen and pulmonary radiotherapy. If histology is not low risk, the change to the CDCV regimen can be considered.

d) Representative lung nodules cannot be resected: postoperative AVD 250 regimen for 27 weeks with a cumulative dose of Doxo of 250 mg/ m^2. CT reassessment at 10 weeks. Lung nodules still visible - consider resection of a lung nodule. Consider lung irradiation (lung nodules may not be low risk).

Group C: Local stage I/ II/ III intermediate risk histology with residual nodules after chemotherapy or surgery.

Resection of at least one nodule is recommended.

a) Without proven metastases (viable tissue or malignant necrotic tissue has been ruled out) treatment according to local stage of the disease can be considered (provided that several nodules have been resected, and those not resected are not suspected of metastases); postoperative AVD 250 regimen can be considered.

b) If there is no viable tissue, but necrotic nodules are present in a representative number of metastases: postoperative AVD 250 regimen for 27 weeks with a cumulative dose of Doxo of 250mg/ m^2 . CT scan assessment at 10 weeks. If nodules are still visible: reconsider complete resection or lung irradiation. In case of persistent lung nodules at week 10, pulmonary radiotherapy is indicated.

c) Viable tumour in resected lung nodules: CDCV regimen for 34 weeks with postoperative reassessment at week 10. Pulmonary radiotherapy is indicated even if a complete response is obtained at week 10.

d) Representative lung nodules cannot be resected: postoperative CDCV regimen for 34 weeks. CT reassessment at 10 weeks. Pulmonary nodules still visible - pulmonary radiotherapy is recommended.

Group D: Local stage I / II / III with high risk histology regardless of the metastatic status and patients with progressive disease and intermediate risk histology (except for predominant stromal type) with histologically demonstrated metastases with residual nodules after chemotherapy or surgery.

- Group with particularly poor prognosis. The current SIOP RTSG recommendation is for dose-intensive chemotherapy regimens, associated with pulmonary and abdominal radiotherapy and high-dose chemotherapy. The efficacy of this treatment has not been proven in prospective clinical trials and it is based best available evidence.

- Centres that cannot adhere to high-dose consolidation chemotherapy may use the dose intensive VI / CCE / VDCy regimen without applying high-dose chemotherapy.

- Centres that cannot adhere to the VI/ CCE / VDCy dose-intensive regimen can perform the 4- drug regimen used in the SIOP 2001 protocol.

Bilateral disease (stage V)

Synchronous bilateral nephroblastomas account for approximately 5% of cases. The greatest challenge in the treatment of such patients is to achieve high rates of curability while preserving as much functional renal tissue as possible, in order to maintain sufficient renal function for normal growth and development. The strategy used in the last decades to achieve these goals is represented by: preoperative chemotherapy to reduce tumour volume, conservative renal surgery whenever possible and adjuvant chemotherapy adjusted according to the highest histological grade and the highest local stage.

Standard preoperative chemotherapy with VCR and Actinomycin-D is recommended. Assessment of treatment response is performed at week 4 and every 4 weeks thereafter. Treatment should be continued as long as the tumour shows signs of regression and until conservative surgery can be performed. The GPOH group reported an increased risk of progressive disease if the chemotherapy is prolonged for more than 3 months. Therefore these cases should be discussed within multidisciplinary tumor board, and if possible in multinational network.

Postoperative chemotherapy is adapted according to local stage and the highest histological grade.

General recommendations for surgical treatment

Wide surgical approach with an incision above the navel and laparotomy access is recommended. Minimal invasive surgery is not recommended. The abdominal cavity should be inspected and palpated carefully to avoid dissemination. If possible, the artery should be clamped first. The adrenal gland is removed along with the kidney if the tumour is not far from it. Lymph node biopsy is important, but radical lymph node dissection is not recommended. Mutilating and heroic surgery is not recommended because most tumours are sensitive to both chemotherapy and radiotherapy. Preoperative chemotherapy reduces the risk of capsule rupture, but makes assessment of tumour margins more difficult due to necrosis and inflammation. Imaging studies performed before treatment should be evaluated. Thrombus in the renal vein or vena cava should be removed by venotomy. Cardio-pulmonary bypass may be required for thrombus extending to the atrium. Partial nephrectomy is not recommended for unilateral tumours. (7, 8, 9)

In case of bilateral tumours, surgical treatment must be individualized. Treatment goal is partial bilateral nephrectomy with preservation of as much functional renal tissue as possible. The least affected kidney should be operated first. Complete nephrectomy on one side and partial contralateral nephrectomy is a good option, as long as enough functional renal tissue

can be preserved. The enucleation of small tumours may be an optimal approach, especially in the case of multiple, small tumours in a kidney. (7, 8, 9)

Liver metastases may be excised during surgery for the primary tumour. In case of multiple liver metastases, a biopsy should be performed. (7, 8, 9)

General recommendations for radiotherapy

Radiotherapy is applied in the form of abdominal flank irradiation (Flank RT - flank radiotherapy), whole abdomen irradiation (WAI) and whole lung irradiation (WLI).

- Patients with favourable histology

- Irradiation of an abdominal flank (hemi-abdomen) TD = 10.8 Gy in 6 fractions. If the residual disease is greater than 3 cm, a boost is delivered with another 10.8 Gy in 6 fractions.

- Whole abdomen Irradiation with TD = 10.5 Gy in 7 fractions.

- Whole lung irradiation with TD = 12 Gy in 8 fractions. There are dose variations depending on the patient's age.

- Patients with unfavourable histology (diffuse anaplasia, rhabdoid tumour) hemi-abdominal irradiation is done with higher doses, up to TD = 19.8 Gy in 11 fractions.

- Metastatic disease

  - Bone metastases can be irradiated with 25.2 Gy in 14 fractions or 30.6 Gy in 17 fractions in patients over 16 years of age.
  - Brain metastases: TD = 21.6 Gy in 12 fractions on the entire skull, 30.6 Gy in 17 fractions in patients over 16 years of age
  - Liver metastases TD = 19.8 Gy - 21.6 Gy

Treatment of relapse

Most relapses are diagnosed in the first 2 years after diagnosis. Pulmonary and pleural recurrences account for 50-60% of total recurrences, abdominal recurrences for 30%, other sites (central nervous system, bone) represent 10-15% of cases.

Currently, 3 risk categories for recurrent nephroblastoma are proposed depending on known risk factors:

- Standard risk: relapse after initial treatment with Vincristin and Actinomycin D only (usually correspond to Stage I and II low- or intermediate-risk histology)

- High risk: relapse after chemotherapy based on three or more agents.

- Very high risk: relapse in patients with diffuse anaplastic or post-chemotherapy blastemal-type Wilms tumour, treated initially with 4 or more than 4 agents.

A general principle in treatment of relapses is the use of agents that were not used in the initial treatment. Several studies have proved the efficacy of CTX, IFO, VP16, Carbo, Topo, alone or combined. HD-CT followed by stem cell transplantation has also been shown to be effective in clinical trials. (7, 8, 10, 11, 12)

Recommendations for the treatment of relapses

First treatment is represented by second line chemotherapy.

Except for unique, late lung metastases (over 2 years) and life-threatening central nervous system metastases, surgical approach should be performed after second-line chemotherapy when all remaining lesions can be completely excised. The goal of surgery is: "negative resection margins."

Surgery is not recommended for metastases that have progressed under chemotherapy. In their case, changing the line of chemotherapy or radiation therapy is recommended.

Surgical resection of lung or liver metastases is reserved for patients with a small number of resectable nodules after chemotherapy, not progressive after chemotherapy.

In case of recurrence in the irradiation field, all necessary efforts must be made for a complete resection.

However, there is currently no common protocol/ guide for treatment of relapses. The indication for radiation therapy will be discussed within the tumour board.

Post-therapeutic follow-up

Treatment response is evaluated one month after the end of chemotherapy and 2 months after the end of radiotherapy. The follow-up visit consists of: physical examination, laboratory examinations (blood, urine), imaging studies for local response and distant metastasis assessment.

The next evaluations are performed every 3 months for 2 years, every 6 months for the next 3 years, annually further on.

Patients have an increased risk of high blood pressure, kidney failure and late cardiotoxicity throughout their life. Late post-radiotherapy side effects (depending on age, irradiated volume, total dose) may be scoliosis, lordosis, muscular hypoplasia, pneumonitis (4% for WLI) pulmonary fibrosis, increased cardiac morbidity, second malignancy (1% -2% in 15 years).

Recommendations

- Children diagnosed with hereditary genetic syndromes associated with an increased frequency of Wilms' tumour should undergo regular assessment for early diagnosis of nephroblastoma
- European main strategy for nephroblastoma treatment is delayed surgery after neoadjuvant chemotherapy for tumor reduction and consolidation.
- A preliminary nephroblastoma diagnose for starting up neoadjuvant chemotherapy can be made from work up with imaging without biopsy.
- The definitive diagnosis is given by histopathological confirmation following surgical excision. Biopsy can give a preliminary diagnosis. Tru-cut biopsy is recommended. Wedge biopsy causes tumour over-staging! Biopsy is not mandatory before neoadjuvant chemotherapy.
- SIOP staging is the most commonly used in Europe. It is based on surgical assessment after administration of neoadjuvant chemotherapy.
- Treatment according to the SIOP recommendations – the Umbrella SIOP 2016 Protocol is recommended
- Assessment of the therapeutic response is performed one month after the end of chemotherapy and 2 months after the end of radiation therapy. Subsequently, patients are regularly monitored at predetermined intervals throughout their life.

Bibliography

1. Breslow N, Olshan A, Beckwith JB, Green DM, Epidemiology of Wilms tumor, Med Pediatr Oncol. 1993;21(3):172-81.

2. Scott RH, Stiller CA, Walker L, Rahman N, Syndromes and constitutional chromosomal abnormalities associated with Wilms tumor., J Med Genet. 2006;43(9):705. Epub 2006 May 11

3. Wiedemann HR, Tumours and hemihypertrophy associated with Wiedemann-Beckwith syndrome, Eur J Pediat, 1983, 141: 128

4. Fernandez C, Geller JI, Ehrlich PF, et al. Renal tumors. In: Principles and Practice of Pediatric Oncology, 6th ed, Pizzo P, Poplack D (Eds), Lippincott Williams & Wilkins, St. Louis 2011. p.861.

5. Servaes S, Khanna G, Naranjo A, et al. Comparison of diagnostic performance of CT and MRI for abdominal staging of pediatric renal tumors: a report from the Children's Oncology Group, PediatrRadiol. 2015 Feb;45(2):166-72.

6. Vujanic GM, Sandstedt B, Harms D et al., Revised International Society of Paediatric Oncology (SIOP)Working Classification of Renal Tumors of Childhood. Med Pediatr Oncol, 2002. 38: p. 79-82

7. Protocol SIOP Wilms Tumour 2001

8. Protocol Umbrella SIOP-RTSG 2016

9. Fuchs J, Kienecker K, Furtwangler R, Warmann SW, Burger D, Thurhoff JW, et al. Surgical aspects in the treatment of patients with unilateral Wilms tumor: a report from the SIOP 93-01/German Society of Pediatric Oncology and Hematology. Annals of surgery. 2009;249(4):666-71.

10. Metzger ML, Stewart CF, Freeman III BB, et al. Topotecan is active against Wilms' tumor: results of amulti-institutional phase II study. J Clin Oncol, 2007. 21:3130-3136

11. Pein F, Michon J, Valteau-Couanet D, et al. High-dose melphalan, etoposide, and carboplatin followed by autologous stem-cell rescue in pediatric high-risk recurrent Wilms' tumor: a FrenchSociety of Pediatric Oncology study. J Clin Oncol, 1998. 16:3295-3301

12. Pinkerton CR, Groot-Loonen JJ, Morris-Jones PH, Pritchard J: Response rates in relapsed Wilms'tumor. A need for new effective agents. Cancer, 1991. 67:567-71

8.6 NEUROBLASTOMA

Epidemiology

Neuroblastoma is the most common extracranial solid malignant tumour in infants. Neuroblastoma originates in the neuronal (neuroblastic) embryonic cells that migrate during development along the nervous system and they relocate in the sympathetic ganglia, in the medulla of the adrenal glands, etc.

Neuroblastoma occurs most commonly in infants and young children but is occasionally seen also in adolescents. Its frequency is reported to be of around 9.5 cases per million children and it represents about 7% of all the malignancies in children. Boys are more frequently affected than girls (ratio = 1.2: 1). In Romania, 6% of all cases of cancer in children are represented by neuroblastoma. (1)

The 5-year survival of neuroblastoma patients increased steadily from 24% during 1960-1963 to 55% during 1985-1994. Prognosis of neuroblastoma now varies from almost 100% with localized disease and good prognostic markers to around 50% in children above 1 yr with metastatic disease. Children >18 months at diagnosis carry the worst prognosis.

The survival rate is influenced by several factors:

- age when diagnosed (EFS-5 years is 83% for those under 1 year old, 55% for children between 1 and 5 years old and 40% for children over 5 years old)
- extension of the disease (very frequently the disease presents with distant metastases when diagnosed)
- histological type and unfavourable molecular markers, which negatively influence the survival rate in these patients, (EFS - 3 years is below 20% if conventional chemotherapy, surgical and radiotherapy treatment are used). (2)

Taking all these facts into consideration, the treatment of the neuroblastoma varies from the simple observation in the cases with the most favourable factors, to the multimodal treatment (chemotherapy, surgery, radiotherapy, high-dose chemotherapy with autologous stem cell support, immunotherapy) in the cases with unfavourable prognosis factors.

Clinical symptoms and signs

The clinical manifestations of neuroblastoma vary depending on the site and extent of the disease and they are most commonly represented by abdominal pain, vomiting, weight loss, fatigue, irritability, loss of appetite leading to anorexia, bone pain (sometimes bone fractures in neuroblastoma with metastases), perspiration, increased abdominal circumference, untreatable diarrhoea by means of secretion of intestinal vasoactive peptides (considered as paraneoplastic manifestation, it is more common in differentiated forms with favourable prognosis), hypertension (caused by compression of the renal artery), Horner syndrome (in the thoracic and cervical neuroblastoma), fever, periorbital ecchymoses (in the disease with periorbital metastases), neurological manifestations in paravertebral neuroblastoma (paresis, plegia, sphincter disorders), respiratory manifestations in thoracic involvement (cough, dyspnoea), manifestations due to infiltration of the hematopoietic marrow (cytopenia). Although it is a rare symptom of neuroblastoma, some patients report suffering from "the dancing eye syndrome". The medical term is opsoclonus-myoclonus-ataxia.

Life-threatening symptoms that require chemotherapy are:

- spinal cord compression
- systemic involvement
- severe pain requiring opioid treatment
- over 10% weight loss, vomiting that requires intravenous hydro-electrolyte rebalancing and/or nasogastric tube insertion,
- respiratory failure in the absence of infection (tachypnea, need of oxygen therapy and/or assisted ventilation),
- hypertension, compression of the inferior vena cava and/or edema of the lower limbs,
- renal failure with increased creatinine values by 2-fold the normal value, oliguria, hydroureter / hydronephrosis
- signs of disseminated intravascular coagulation or bone marrow invasion
- bladder or intestinal dysfunction as a result of the compression caused by the tumour mass.
- the presence of a large tumour with a major risk of rupture, symptoms of systemic involvement.

Paraclinical investigations:

- Common investigations:

- complete blood count,
- blood electrolytes (sodium, potassium, calcium, chlorine, magnesium),
- liver function tests (TGP, TGO, GGT, alkaline phosphatase, direct and indirect bilirubin),
- renal function tests (creatinine, urea, uric acid, creatinine clearance),
- coagulation (APTT, INR, prothrombin time, fibrinogen, D-dimers, AT III)
- ABO blood group and Rh group
- serology hepatitis B virus, hepatitis C virus, HIV, CMV
- urine tests and urinalysis

- Tumour markers:

-LDH - with abnormal values depending on age:

- Ferritin with values higher than the maximum limit for that age.
- Neuron-specific enolase (NSE) with values higher than the maximum age limit (attention should be paid to this sample as false positive values can be given by hemolysis of the sample and its degradation at room temperature)
- Catecholamine metabolites: vanillylmandelic acid (VMA) and homovanillic acid (HVA): in urine in limits higher than normal for that age.

- Imaging examinations:

- Ultrasound of the involved region (abdomen, pelvis, cervical, cutaneous, transfontanelle in infants, etc.)
- Chest X-ray in thoracic neuroblastoma
- Echocardiography with ventricular ejection fraction (VEF) to assess the cardiac status
- Bone X-ray in case of bone metastases
- MRI of the region where the primary tumour develops is mandatory
- MRI of the spine at diagnosis in paravetrebral tumours in order to confirm / exclude intraforaminal or intraspinal extension.
- MRI of the skull is recommended in all patients to highlight/exclude intracranial or orbital involvement.
- ^{123}I- MIBG scintigraphy is positive in 85% of neuroblastoma cases. This type of uptake is specific for neuroblastoma, ganglioneuroma and pheochromocytoma. It is currently not available in Romania.

- PET-CT to highlight the primary tumour. PET-CT is not recommended if ^{123}I- MIBG is positive. If MIBG scan is not available PET-CT is a good alternative.

- Bone scintigraphy with technetium-99 to highlight/exclude bone metastases, given that normal bone X-ray cannot rule out incipient bone metastases.

- **Bone marrow examination.** The bone marrow involvement in neuroblastoma is focal. For this reason, it is mandatory to perform a bone marrow aspiration from 2 different sites. If the aspiration puncture is not conclusive, 2 bone marrow biopsy samples will be collected from 2 different sites.

- **Cytogenetic and molecular abnormalities** with an impact on the prognosis:

- The MYCN gene amplification, present in 25% of cases, tends to be present in cases with advanced disease or with rapid progression and is considered a negative prognostic factor, especially in young children

- The deletion on the short arm of chromosome 1 (1p36) is the most common chromosomal change in neuroblastoma and is a negative prognostic factor

- Chromosome 11 abnormalities in the q arm (frequent 11q23 deletions) are an independent unfavourable prognostic factor, especially in older children.

- DNA index is another factor that correlates with the response to treatment in infants: thus hyperploidy (DNA index> 1) is associated with a favourable response to cyclophosphamide and doxorubicin, and the DNA index = 1 imposes more aggressive chemotherapeutic regimens. In the cases of children over 1 year of age, the DNA index has no prognostic impact.

The diagnosis is established by histopathological and immunohistochemical confirmation after performing tumour biopsy or by highlighting the neuroblastoma cells at the cytological examination of the marrow smear in the bone marrow metastases**.**

The **Shimada histopathological classification** of neuroblastoma has been included in the INPC classification (International Neuroblastoma Pathology Classification). It is based on the following characteristics: degree of neuroblast differentiation, stroma-rich/reduced stroma, MKI index (mitosis-karyorrhexis index), nodular pattern and age. Using these criteria, patients are classified into groups with favourable histology and groups with unfavourable histology, as follows:

- Groups with favourable histology:

- patients of any age, with stroma-rich and no nodular pattern tumours

- patients under 18 months, with reduced stroma tumour, with MKI index less than 200/5000 and differentiated or undifferentiated neuroblasts

- patients under 60 months, with reduced stroma tumour, with MKI index less than 100/5000 and well-differentiated tumour cells.

- Groups with unfavourable histology:

- patients of any age with rich stroma and nodular pattern

- patients of any age, with reduced stroma tumour, with MKI index greater than 200/5000 and differentiated or undifferentiated neuroblasts

- patients over 18 months, with reduced stroma tumour, with MKI index between 100/5000 and 200/5000 and differentiated neuroblasts

- patients over 60 months, with reduced stroma tumour, with MKI index less than 100/5000 and well-differentiated tumour cells.

Staging and therapeutic response

The staging of neuroblastoma has undergone a continuous transformation the last decades. It was initially based on degree of surgical resection as in **The International Neuroblastoma Staging System (INSS**) (Table 1). Since many new risk factors were recognised, the **International Neuroblastoma Risk Group Staging System (**INGRSS) has been developed as a pre-treatment classification based on all known risk criteria, and this is now the preferred staging system in new protocols.

INSS was applied even before the 1990s, to which, in addition to the clinical and imaging evaluation criteria, was added the surgical criteria, with or without the involvement of vital anatomical structures (thus making the difference between the surgical approaches). (3, 4)
(see Table 1)

Table 1:

I N S S	International Neuroblastoma Staging System
Stage 1	Localized tumour with complete gross excision, with or without microscopic residual disease. in the ipsilateral lymph nodes microscopically negative for tumor
Stage 2A	Tumour with incomplete gross excision; with ipsilateral nonadherent lymph nodes negative for tumour microscopically.
Stage 2B	Localized tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative for tumor.
Stage 3	Unresectable unilateral tumour, infiltrating across the midline*****, with or without regional lymph node involvement; or localized unilateral tumour with contralateral lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, (skin,) liver and/or other organs (except as defined for stage 4S).
Stage 4S	Localized primary tumour, as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow******, Limited to infants < 1 year of age

Multifocal primary tumors should be staged according to the greatest extent of disease and be followed by a subscript "M" (i.e.Stage 3_M)

*****The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.

******Marrow involvement in Stage 4S should be minimal (i.e.<10% nucleated cells in bone marrow biopsy). More extensive marrow involvement should be considered Stage 4.The MIBG scan should be negative in marrow for Stage 4S.

Image-defined risk factors (IDRFs). The absence of these local risk factors makes the complete resection possible and it is considered a positive predicting factor. Taking these aspects into account, the **International Neuroblastoma Risk Group Staging System (INRGSS)** (Table 2) has divided neuroblastoma patients into the following stages, as follows:

Table 2:

Stage L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
Stage L2	Locoregional tumor with presence of one or more image-defined risk factors
Stage M	Distant metastatic disease (except stage MS)
Stage MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver and/or bone marrow (Bone marrow involvement should be limited to <10% og total nucleated cells on smears or biopsy)(5, 6)

The choice of neuroblastoma therapy depends on the staging and takes into account the prognostic factors (age, staging, whether there is MYCN gene amplification or not, the presence of chromosomal changes, life-threatening symptoms) and it may include:

- chemotherapy that includes combinations with DDP, CTX, Carbo, VCR, DOXO, TOPO, IRI
- surgical treatment, which is essential in establishing the diagnosis by biopsy; depending on the operative risk, radical intervention is indicated during the second phase, after an induction chemotherapy
- consolidation with high–dose chemotherapy and stem cell transplantation, for high risk forms (HR) and with 13 cis retinoic acid
- MIBG locoregional radiotherapy
- treatment with specific anti-GD2 antibodies, which is not yet accessible in our country.

Very low risk neuroblastoma (Very low risk NB)

- stage L1/L2 with ganglioneuroma maturing or gangljoneuroblastoma intermixed histology
- stage L1 with non-amplified MYCN
- stage MS in children younger than 18 months of age with no 11q aberration

Low risk neuroblastoma (low risk NB)

Staging criteria: -Stage 1, 0-21 years, no MYCN amplification
-Stage 2, 0-21 years, no 1p aberration, no MYCN amplification
-Stage 3, 0-2 years, no 1p aberration, no MYCN amplification
-Stage 4s, 0-1 year, no MYCN amplification

Stage 1 patients with hyperdiploidy, but without N-myc amplification, can be treated by surgical resection alone. (7, 8) In the perinatal type, most cases can evolve favourably without therapy and the anaesthetic risk on the one hand and the surgical risk on the other hand must be taken into account, therefore the therapeutic strategy is observation. Studies have shown that 80% of patients who were only observed had a 100% OS. (9)

In the resectable locoregional disease, according to the European working group LNESG1, NB without MYCN amplification has a 99% survival after the complete resection. In patients in Stage 2A - 2B INSS with incomplete resection, with or without involvement of the regional lymph nodes, surgery alone ensures a 5-year EFS survival of 88% in the COG study and 83% in LNESG 1 study. In stage L2 INRGSS, with unfavourable histology, the EFS and OS were 61% and 76%, respectively (10).

Intermediate risk neuroblastoma (IR NB)

Staging criteria: -stage 2/3, 0-21 years, 1p or 11q deletion in tumour tissue, no MYCN amplification
-stage 3,> 2-21 years, no MYCN amplification
-stage 4, <1 year, no MYCN amplification

Patients in stage II, or III without N-myc amplification, can be treated with either surgery alone or biopsy followed by chemotherapy and subsequent intervention. Most cases with unresectable L2 type or in Stage 3 INSS with favourable or unfavourable histology are treated with chemotherapy which includes: CTX, DOXO, DDP, VP16, local radiotherapy, followed by surgery. The number of cycles varies from 4 to 8 cycles. A higher relapse rate was observed in patients with chromosomal aberrations.

High risk neuroblastoma (HR NB)

Staging criteria: -Stage 4> 1 year -21 years
-regardless of the stage, aged 0-21 years, with the presence of MYCN amplification

Patients in the L2 INRGSS or Stage 3 INSS stages who underwent biopsy at the time of diagnosis with MYCN amplification, regardless of age, have an unfavourable prognosis and should be considered being HR.

The infant with metastatic disease with MYCN amplification is stratified into the HR therapeutic group. If there is no MYCN amplification, the therapy is less aggressive and the EFS was 93% in this category, while in those with MYCN amplification, EFS is 10%. (3)

Neuroblastoma in MS stage

Both prospective and retrospective studies have shown excellent survival in this stage. EFS with MYCN amplification was 82% and OS 91% and OBSERVATION is recommended in infants <3 months.

Chemotherapy is recommended for the intermediate risk group and radiotherapy is reserved for life-threatening types and symptoms. The infant with MYCN amplification is treated according to the SIOPEN 99.4 protocol, with multimodal therapy and the biopsy is performed at the beginning.

NB CLASSIFICATION - Classification in risk groups and therapeutic strategy according to the INRG Consensus (3) and according to the SIOPEN working group (European Low and Intermediate Risk Neuroblastoma Protocol: A SIOPEN Study Version 4.2; 2nd January 2013) (see Table 3)

Table 3 Classification in risk groups and therapeutic strategy according to the INRG Consensus (3, 6)

INRG Stage	Age	Histology	Differentiation grades	MYCN	Life threatening symptoms	11q aberration	Ploidy	Stage Gr. LINES	Risk group
Adrenal mass n.n.	< 90 days								VLR
L1	Any age			No					LNESG2
L1/L2		GNB –mature / immature							VLR
L1		Any except GNB –mature /immature		No					VLR
L1 INSS st1	Any			Yes				9	IR
L1				Yes					HR
L2	≤ 18 months	Any except GNB –mature /immature		No	No No	No Yes		1 3	LR
L2	≤ 18 months			No	Yes	No Yes		2 3	LR
L2	Any			Yes					HR
L2	≥ 18 months	GNB nodular Neuroblastoma	differentiated	No		No			LR
L2	≥ 12 months		differentiated	No		Yes		7	IR
L2	≥ 18 months		Weak / undifferentiated	No				9	IR
L2	any			Yes					HR
M	≤ 18 months			No			Hyperploidy		LR

M	≤ 12 months			No			Diploidy	10	IR
M	12 - 18 months			No			Diploidy		IR
M	≤18 months			Yes					HR
	≥ 18 months			No					HR
Ms	≤12 months			No	No No	No Yes		4 6	LR
Ms	≥12 months			Yes	Yes	Yes			HR
L1 INSS st 2, L2 MMs	any			Yes					HR

Chemotherapy treatment

Chemotherapy is an important treatment modality for patients with neuroblastoma who have an intermediate or high-risk disease and it is also used in low-risk patients with the involvement of vital organs.

LR: SIOPEN LINES protocol (6)

IR: SIOPEN LINES protocol (6)

HR: HR –NRL-1 SIOPEN protocol (11, 12)

MS: SIOPEN LINES / HR-1 NBL -1 SIOPEN protocol according to MYCN amplification

Treatment of low risk group (LR) NB

In table 4 and 5 there are the therapeutic recommendations according to the European Low and Intermediate Risk Neuroblastoma Protocol: A SIOPEN Study Version 4.2; 2nd January 2013.

Table 4. Treatment of LR NB (6)

GR observational	OBSERVATION - at 8 weeks	REVALUATION - evidence of regression, evaluation at 12 weeks- at 1 year	Progression LTS- /	Surgical resection Only if IDRF- one year after diagnosis
Gr 1 L2, MYCN- ≤18l, NCA, - LTS-	CHEMOTHERAPY **2x CO▪**	Evaluation **2xVP/Carbo**	IDRF – Surgical resection	Revaluation IDRF+- **2xCO** – Observation IDRF- Resection
Gr 2 L2, MYCN – ≤18 l, NCA LTS+	CHEMOTHERAPY **2xVP/Carbo**	Evaluation IDRF + LTS+ **2xCADO** IDRF- Resection	IDRF- LTS- Resection	IDRF+ Observation
Gr 3 L2,MYCN- ≤18l,SCA LTS +/_	CHEMOTHERAPY LTS- **2xVP/Carbo** LTS+ **2xVP/Carbo**	Evaluation LTS+ + **2xCADO** LTS- **2xVP/Carbo**	Evaluation **2xVP/Carbo** Revaluation SD IF IDRF – Resection IDRF – Resection	Surgical resection
Gr 4 Ms, MYCN- ≤12 l, NCA LTS-	OBSERVATION	REVALUATION Every 8 weeks	Highlighting the regression - evaluation at 12 weeks- 1 year	Progression- Treatment Resection for primary tumour is NOT indicated
Gr 5 Ms, MYCN – ≤12 l, NCA LTS+	CHEMOTHERAPY **2xVP/Carbo**	LTS- Observation	Evaluation LTS+ **2XCADO** **Observation**	Surgery is NOT indicated
Gr 6 Ms MYCN- ≤12l,SCA	CHEMOTHERAPY LTS- **4xVP/Carbo**- LTS+ **4xVP/Carbo**	Evaluation	Evaluation LTS **-2xVP/Carbo** LTS+ **2XCADO**	Surgical resection indicated in IDRF-

Treatment in the intermediate risk group

Table 5 Treatment of IR NB (6)

Gr 7 L2 , ≥ 18 l Differentiated NB Nodular ganglione uroblastoma	**CHEMOTHERAPY** **2XVP/Carbo**	Evaluation Good response- **2x VP/Carbo**	NO response- **2xCADO**	Surgical resection IDRF-
Gr 8 L2 , ≥ 18 l Poorly differentiated NB Undifferentiated	**CHEMOTHERAPY** **2XVP/Carbo** **2xCADO**	Evaluation **IDRF+ - VP /Carbo /** **-Surgery+2xCADO**	Evaluation IDRF –**Surgery-** **VP/Carbo+** **CADO+2xCADO**	Local radiotherapy 6 cycles 13 cis-RA
Gr 9 INSG L1 MYCN+	**CHEMOTHERAPY** **2XVP/Carbo** **2xCADO**	**CHEMOTHERAPY** **2xVP/Carbo+** **2xCADO**	**Radiotherapy-**	6 cycles - 13 cis - RA

Gr 10 St M ≤12 l	**CHEMOTHERAPY** **2VP/Carbo**	Evaluation Response + **2VP/Carbo** Response - **2xCADO**	Metast - CR- Metast + **2xCADO**	Surgical resection Metast-

(European Low and Intermediate Risk Neuroblastoma Protocol: A SIOPEN Study Version 4.2; 2nd January 2013)

▪CO: CTX 150mg/m^2 (day 1-5) +VCR 1.5 mg/m^2 (day 1) - to be repeated at day 14

▪▪VP Carbo: Carbo 200mg/m^2 (day 1-3) + VP 16 150mg/m^2 (day 1-3) - to be repeated at day 21

▪▪▪ CADO: CTX 300 mg/m^2 (day 1-5) + Doxo 30 mg/m^2 (day 4-5) + VCR 1.5mg/m^2 (day 1 and 5) - to be repeated at day 21

High risk neuroblastoma (see table 6)

Prior to the multimodal therapy, the survival in HR NB was 15%.

The treatment regimen accepted in HR NB comprises 3 phases: induction, consolidation and maintenance in order to control the minimal residual disease (MRD).

• *Induction therapy*: Its purpose is to reduce the primary tumour and the distant metastases.

Neuroblastoma is a chemosensitive tumour when it has MYCN amplification. Retrospective studies have shown that regimens containing platinum salts provide a better survival.

The HR group will be treated with chemotherapy (CTX, DDP, DOXO, VP16, VCR), second-look surgery, RT on the residual disease sites. The effectiveness of the induction regimen should be monitored at the end of it and after surgery, ideally by MIBG scintigraphy. The better therapeutic response at the end of the induction, the longer long-term survival. In COG studies, the TOPO and CTX induction regimens were introduced and their effect on the stem cell harvesting potential and survival was monitored.

• *Consolidation therapy*: Its purpose is to eliminate the residual tumour clone. Myeloablative chemotherapy and/or total body irradiation (TBI) are applied, followed by autologous peripheral blood stem cell transplantation (PBSCT). High-dose therapy (megatherapy) results in better outcomes than maintenance therapy in high-risk neuroblastomas. In Europe, the experience with busulfan + melphalan myeloablative regimens has shown a higher cure rate compared to other regimens. (3) The timing of stem cell harvesting continued to be a controversy - the recommendation is to repeat the harvest to have enough cells for supportive treatment in case of tandem transplantation. (12)

• *MRD-guided post-consolidation therapy*: The goal of the therapy is to eradicate residual tumour cells using active agents against chemoresistant cells in MRD. Retinoids are a class of components that can induce , cell differentiation, and decrease cell proliferation in NB, proven in vivo. The recommendation to administer 6 cycles of 13 c RA after transplantation demonstrated a significant increase in survival.

• *Immunotherapy* with anti-GD2 antibodies is an alternative that has proven to be effective. The human-mouse chimeric monoclonal antibody Ch 14.18 in combination with IL 2 was used by the German group and the toxicity, although high, was controllable, but the survival was better compared to those who received maintenance with 13 c RA, at 2 years EFS was 66% compared to 46%. (3, 19) This study has demonstrated the need to include immunotherapy in the HR protocol.

• *Targeted radioimmune therapy with 131I-MIBG, biological therapies with retinoic acid or anti-GD2 monoclonal antibodies* have shown, in some pilot studies, response rates between 10 and 57% in minimal residual disease. These types of therapy are not yet accessible in Romania.

Recently, it has been estimated that the group of children with metastatic neuroblastoma <1 year of age, whose tumours regress spontaneously, does not require treatment, but only close supervision (stage IVS, MS). Allogeneic bone marrow transplantation was recently abandoned after studies conducted by the European Bone Marrow Transplant Registry (EBMTR) showed a better therapeutic outcome after autologous transplantation, with lower side effects and graft-versus-host disease effects being practically null.

Table 6 High risk group (HR) treatment

HR criteria	**Induction**	**Evaluation**		**Consolidation**	**Post Consolidation**	**Immunotherapy**
V < 21 years	**R COJEC+**		Response – **2TVD**	**BuMel MAT +**		
St INSS 2, 3, 4, 4 s	Stem cell harvesting	Radiotherapy		**Stem cell transplantation**		
St 4 INSS without amplification > 12 months			Response + ↓		**6 cycles 13 cis RA**	
			Surgical resection			

Rapid COJEC Protocol (11, 12)

R COJEC	Doses/kgc	Doses /m²	Day											
Block			A	B	C	B	A	B	C	B				
Day			0	10	20	30	40	50	60	70	80	90	100	110
Carbo	25mg/kgc	750mg/m²	↓				↓							
VP16	5.8mg/kgc	175mg/m²	↓↓		↓↓		↓↓		↓↓					
VCR	0.05mg/kgc	1.5mg/m²	◆	◆	◆	◆	◆	◆	◆	◆				
DDP	2.6mg/kgc	80mg/m²		↘		↘		↘		↘				
CTX	35/kgc	1050/m²			↓↓				↓↓					
Aphaeresis											H	H	H	
Surgery												S		
Staging														MAT

Therapeutic alternatives

• *Treatment in NB, in the risk group requiring observation (OG) according to the German protocol (NB 2004)*

If there is no progression and no symptoms, the observation is made over a period of 12 months, or until the end of the second year in infants. If there are remission criteria, it remains

to be observed, and if not, surgery is indicated. If the disease progresses or life-threatening symptoms occur, an N4 block (DOXO, VCR, CTX) is indicated; if the disease regresses afterwards, the chemotherapy is no longer recommended. If there is a progression of the disease, it is recommended to repeat a maximum of 4 x N4. If, however, the progression of the disease continues, it is indicated to switch to medium risk (MR) treatment in children <1 year, and to reassess those > 1 year in the high risk group (HR).

• *Treatment in MR NB (NB 2004)*

After the biopsy or the tumour resection, 6 cycles are administered alternating N5 (DDP, VP16, Vindesin) and N6 (VCR, DTIC, IFO, DOXO) at an interval of 21 days, followed by surgical phase. External beam radiation therapy is recommended on the residual tumour, followed by maintenance therapy with 4xN7 (low dose oral CTX) and enhancement with 9 x 13-cis-retinoic acid (one cycle for 14 days) for 12 months. Infants <6 months of age at the time of diagnosis will begin with N4.

• *Treatment in HR NB*

After biopsy, 6 cycles of chemotherapy alternating N5 and N6 are recommended, followed by MIBG evaluation, transplantation, irradiation and consolidation with 9x 13 cis RA.

In cases of HR, despite all combinations of chemotherapy, there is a high risk of relapse and the immunotherapy with Ac - GD2 which shows promising results is recommended in the international community. Stem cell transplantation can be applied in several centres in our country in cases of HR.

• *Treatment in Perinatal Neuroblastoma*

Perinatal neuroblastoma can be detected by ultrasonography during pregnancy, and depending on the size and site and evolution, only the observation is indicated.

The goals of therapy

The goal of the surgical treatment in neuroblastoma is total resection, without mutilation or severe operative risk. The radical approach can be performed during phase two, after chemotherapy in cases of HR. In cases with favourable biological markers, tumour remnants are also accepted.

Preoperative chemotherapy is often indicated for its effect on metastases and the primary tumour. If risk factors are present, preoperative chemotherapy should be given. In the case of metastatic disease, the preoperative chemotherapy will also be administered even if the primary tumour is free of risk factors, unless the radical removal of the primary tumour is the best alternative for the histopathological diagnosis.

The preoperative chemotherapy makes the tumours smaller, more fibrous, less vascularised, and generally easier to manage. This reduces the risk of intraoperative dissemination. It is also acceptable to divide the tumour during surgery and remove it in pieces, as tumours often surround vessels that need to be preserved. Tumours can adhere strongly to the vessel wall, but infiltration into the vessel wall is very rare. The most common approach is open surgery, but for some localized tumours, laparoscopy or thoracoscopy may be appropriate. Although many neuroblastomas are very sensitive to chemotherapy, the primary tumour will not completely disappear, except some cases in infants.

Treatment of refractory disease and relapses

Patients with primary refractory disease

Approximately 10-20% of patients with HR neuroblastoma have a refractory disease, failing to obtain an adequate response to be able to obtain enhancement with myeloablative therapy. In case of an inadequate response to HR-NBL1 SIOPEN induction chemotherapy (rapid COJEC or modified N7), it is recommended to administer 2 TVD cycles.

If there is a partial response, it is recommended to administer 2 - 4 additional cycles of TVD, provided that they have not been treated with anthracyclines (for example, as part of modified N7) and subsequently to apply myeloablative therapy with autologous hematopoietic stem cell (HSC) support.

Patients who obtain a partial response to re-induction chemotherapy may then benefit from enhancement with pharmaceutical radionuclides therapy and/or myeloablative chemotherapy with autologous HSC support. After the myeloablative chemotherapy, these patients are candidates for clinical trials with systemic immunotherapy (anti-GD2 +/- IL2).

Patients with refractory types of the disease are also candidates for the BEACON protocol. (13)

Patients with recurrence of the disease

Data from the literature state that 60% of children diagnosed with HR neuroblastoma will have a recurrence of the disease. (14) The general principles of treatment in case of recurrence are:

- second biopsy of tumours at the time of recurrence. The neuroblastoma can acquire ALK or TP53 mutations on recurrence, the genomic profile being able to change substantially;
- since ALK aberrations are present in approximately 10% of all cases of neuroblastoma at onset and in a higher percentage in patients with recurrence, their mandatory testing is required. It is recommended to enrol these patients in phase 1 and 2 clinical trials;
- after recurrence of HR neuroblastoma, the survival may be prolonged, but usually not in the long term.

The therapy will consider the benefit of therapy in relation to toxicity:

- patients at the first recurrence of the disease will be treated with an induction regimen based on chemotherapy, followed by consolidation with pharmaceutical radionuclides radiotherapy. Subsequently, cis-RA treatment and/or immunotherapy may be considered for patients who have not previously received this treatment;
- patients with recurrence, who obtained an adequate response to re-induction therapy, who have not benefited from myeloablative chemotherapy, may benefit from this type of treatment, before immunotherapy;
- children with a second recurrence may be enrolled in clinical trials

For second line chemotherapy for relapsed HR neuroblastoma, one of the following chemotherapy regimens is recommended: TEM, IRI, TEM/IRI, Topo/TEM, Topo/VCR/Doxo, Topo/CTX, Topo/VP16, CTX/Topo/ VCR, Topo, Topo/CTX/VP16, TEM/IRI + Temsirolimus or + Dinituximab. (15, 16, 17) SIOPEN reports, after administration of TVD, CR and PR in 64% of cases and 47% CR and PR in GPOH with second line Topo/VP16 regimen. Administration of TEM alone or in combination with IRI or Topo revealed good results with respect to SD in all studies.

The recommendation of the re-induction regimen is made individually, depending on the previous therapies, on the toxicity of the medication and on the desire of the patient and the family. It is recommended to evaluate the outcome of the disease after 2 cycles. If CR, PR, SD are found, another 4-6 cycles can be administered up to a maximum of 12. The consolidation of the response obtained with radiotherapy with pharmaceutical radionuclides (^{131}I-mIBG or ^{177}Lu-DOTATATE) is usually indicated after the 6th re-induction cycle. Patients who have not received myeloablative chemotherapy have this indication before starting maintenance treatment. Patients showing a therapeutic response or presenting SD have an indication for systemic anti-GD2 +/- IL2 immunotherapy if they have not previously received this treatment.

In case of recurrence/subsequent progression, a treatment option is enrolment in clinical trials, administration of oral VP16 or symptomatic (palliative) treatment.

Patients with recurrences of the central nervous system (CNS)

The estimated risk of CNS recurrence following treatment for stage 4 neuroblastoma (all ages) is approximately 8% at 3 years. Half of these patients have an isolated recurrence of the CNS.

Despite the unfavourable prognosis, it has been shown that intensive targeted therapy, including surgical excision of isolated recurrences, craniospinal radiotherapy and consolidation chemotherapy can achieve some control of CNS recurrences. A proposed therapeutic strategy is presented below:

- Neurosurgical resection of the CNS disease
- Craniospinal radiotherapy (21Gy in 1.5Gy fractions)
- TEM ± IRI
- Patients with very good CR/PR who have not had myeloablative chemotherapy may benefit from this type of treatment (busulfan/melphalan), followed by systemic anti-GD2 immunotherapy (for patients who have not previously had this treatment), plus oral cis-retinoic acid.

Memorial Sloan Kettering Cancer Center reported preliminary results using intrathecal radioimmunotherapy after CNS recurrence. Other molecularly targeted radiotherapy approaches (^{177}Lu-DOTATATE or ^{131}I-mIBG) should not be considered in uncontrolled CNS determinations.

NEW ACCEPTED OR UNDER STUDY TREATMENTS (18)

The survival of children with HR neuroblastoma or disease recurrence is still extremely low. Therefore, these children continue to need new treatment strategies based on a better understanding of tumour biology. Numerous phase I and II clinical trials combining the action of systemic chemotherapy with radiotherapy and/or targeted molecular therapy, cellular immunotherapy or monoclonal antibodies are ongoing. (https://www.researchgate.net/figure/Current-open-clinical-trials-for-refractory-and-relapsed-neuroblastoma_tbl1_328644649).

The immunotherapy with GD-2 antibody (with or without cytokines) shows promising results (HR-NBL1-SIOPEN). The results of the combination of the anti-VEGF-Bevacizumab monoclonal antibody with chemotherapy are analyzed in the BEACON study. The results of studies on the action of ALK inhibitors in cases of ALK amplification or mutation, as well as those related to haploidentical stem cell transplantation with donor lymphocyte infusion (DLI), are expected to be published. Studies using: Regorafenib, Volasertib, Lenvatinib, Abraxane, Pembrolizumab, Trametinib, Afatinib are also ongoing. The LuDO Lutetium -177 DOTATATE study aims to establish the toxicity and antitumor activity profile of ^{177}Lu-DOTATATE in children with relapsed or refractory neuroblastoma.

Post-therapeutic follow-up (19, 20)

The evaluation of the therapeutic response is made 1 month after the end of the treatment by:

- clinical examination
- biological examinations, tumour markers: LDH, ferritin, neuron-specific enolase (NSE), urinary and blood catecholamines (vanillylmandelic acid and homovanillic acid)
- MRI of the region affected by the disease
- I-MIBG or In-Octreotide for I-MIBG-negative and In-Octreotide-positive types of neuroblastoma
- marrow biopsy puncture if there were positive results at the last evaluation

Post-therapeutic follow-up and examinations during monitoring:

- general clinical examination - every 6 weeks in the first year
- every 3 months in the first 2 years - 5 years

- every 6 months after the fifth year
- urinary catecholamines - every 3 months in the first year
- every 3 months in the first 2 years - 5 years
- every 6 months after the fifth year
- MRI/ ultrasound examination / CT/ chest radiograph (location dependent)
- every 3 months in the first year
- every 6 months in the first 2 years - 5 years
- every 6 months after the fifth year

In patients with tumour residue - general clinical examination, urinary catecholamines, ultrasound examination / chest radiograph (location dependent)

- every 6 weeks in the first year
- every 3 months in the first 2 years - 5 years
- every 6 months after the fifth year
- LDH and NSE - every 3 months in the first year
- every 6 months in the first 2 - 5 years
- MRI - every 3 months in the first year
- every 6 months in the first 2 - 5 years
- Bone scintigraphy - every 6 months until normalization
- Spinal cord biopsy puncture - every 6 months until normalization
- ECG and cardiac ultrasound - annually for the first 5 years and then every 2 years
- audiogram - annually for the first 5 years and then every 2 years, at least for 10 yrs
- urea, creatinine - every 3 months in the first year
- every 6 months in the first 2 years - 5 years
- annually after the fifth year
- TSH, FT3, FT4 - every 6 months in the first 5 years
- annually after the fifth year
- waist and weight percentages - every 6 months in the first 5 years
- annually after the fifth year
- evaluation of the puberty - every 6 months in the first 5 years
- annually after the fifth year

Post-therapeutic follow-up of patients with MR and HR neuroblastoma is performed for a period of at least 8-10 years.

Recommendations

- Neuroblastoma affects infants and young children more often
- Prognostic factors are age at diagnosis, disease extent, histological type and molecular markers
- Chemotherapy includes combinations with DDP, CTX, Carbo, VCR, DOXO, TOPO, IRI
- Therapeutic approaches are: surgical treatment, chemotherapy, treatment with high-dose chemotherapy and autologous stem cell transplantation for high-risk types (HR) and 13 cis retinoic acid, MIBG locoregional radiotherapy, treatment with specific anti-GD2 antibodies
- Treatment is differentiated according to the risk group
- The prognosis is good for the low risk group
- For the high-risk group, the therapeutic progress in recent years has improved the prognosis, however, the therapeutic results are still modest

Bibliography

1. http://www.srohp.ro/wp-content/uploads/2019/04/Raport_RNCCR_-1-feb-2019.pdf
2. Haupt R., Garaventa A., Gambini C. et al. Improved Survival of Children With Neuroblastoma Between 1979 and 2005: A Report of the Italian Neuroblastoma Registry. J. Clin Oncol.2010 Mar 29. 28:2331-2338
3. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology Seventh Edition. Brodeur GM, Hogarty MD, Bagatell R, et al. Neuroblastoma 2016:772-795
4. Brodeur GM, Seeger RC, Barrett A, et al. International Criteria for diagnosis, staging and response for treatment in patients with neuroblastoma . J Clin Oncol 1988;6 1874-1891, and Brodeour GM, Pritchard J, Berthold F, et al. Revisions in the international criteria for neuroblastoma diagnosis staging and response to treatamnet J Clin Oncol 1993; 11: 1466-1477
5. Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG)Staging System: an INRG Task Force Report. J Clin Oncol 2008;27: 298-303
6. European Low and Intermediate Risk Neuroblastoma Protocol: A SIOPEN Study Version 4.2; 2nd January 2013 pg 111
7. Cecchetto G, Mosseri V, De Bernardi B, Helardot P, Monclair T, Costa E, et al. Surgical risk factors in primary surgery for localized neuroblastoma: the LNESG1 study of the European International Society of Pediatric Oncology Neuroblastoma Group. J Clin Oncol. 2005 Nov 20;23(33):8483-9.
8. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. J Clin Oncol. 2009 Jan 10;27(2):298-303.
9. De Bernardi B, Mosseri V, Rubie H, Castel V, Foot A, Ladenstein R, et al. Treatment of localised resectable neuroblastoma. Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group. British journal of cancer. 2008 Oct 7;99(7):1027-33.
10. Bagatell R, Beck-Popovic M, London WB, Zhang Y, Pearson AD, Matthay KK, et al. Significance of MYCN amplification in international neuroblastoma staging system stage 1 and 2 neuroblastoma: a report from the International Neuroblastoma Risk Group database. J Clin Oncol. 2009 Jan 20;27(3):365-70.
11. Canete A, Gerrard M, Rubie H, Castel V, Di Cataldo A, Munzer C, et al. Poor survival for infants with MYCN-amplified metastatic neuroblastoma despite intensified treatment: the International Society of Paediatric Oncology European Neuroblastoma Experience. J Clin Oncol. 2009 Mar 1;27(7):1014-9. [
12. European HRNBL1.7/ Protocol: A SIOPEN Study valid per 04.04.2014
13. DA Morgenstern, G Barone, L Moreno, J Anderson, P Brock, M Elliott, M Gaze, J Gray, G Makin, R Squire, D Tweddle, R Ramanujachar, K Wheeler and ADJ Pearson - Options for the treatment of Patients with Relapsed/Progressive High-Risk Neuroblastoma – CCLG –NSIG – March 2015
14. Garaventa A, Parodi S, De Bernardi B, Dau D, Manzitti C, Conte M, et al. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer. 2009 Nov 1; 45(16):2835–42.
15. Fiona Herd, Nermine O. Basta , Richard J.Q. McNally, Deborah A. Tweddle - A systematic review of re-induction chemotherapy for children with relapsed high-risk neuroblastoma – Review - European Journal of Cancer 111 (2019) 50e58
16. Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Yaniv I, Laureys G, Brock P, Michon JM, Owens C, Trahair T, Chan GCF, Ruud E, Schroeder H, Beck Popovic M, Schreier G, Loibner H, Ambros P, Holmes K, Castellani MR, Gaze MN, Garaventa A, Pearson ADJ, Lode HN - Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. - Lancet Oncol. 2018. 10.1016/S1470-2045(18)30578-3
17. RajenModyMD[a] ArleneNaranjoPhD[b] CollinVan RynMS[b] ProfAlice LYuMD[cd] Wendy BLondonPhD [e]ProfBarry LShulkinMD[f] ProfMarguerite TParisiMD[g] Sabah-E-NoorServaesMD[h] Mitchell BDicciannIPhD[c] ProfPaul MSondelMD[i] Julia GBenderMD[j] ProfJohn MMarisMD[h] ProfJulie RParkMD[gt] DrRochelleBagatellMD[ht]- Irinotecan–temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial – The Lancet Oncology - Volume 18, Issue 7, July 2017, Pages 946-957

18. Peter E. Zage- Novel Therapies for Relapsed and Refractory Neuroblastoma – Review - Children **2018**, 5, 148; doi: 10.3390/children5110148- www.mdpi.com/journal/children

19. NB2004 – High Risk Trial Protocol for the Treatment of Children with High Risk Neuroblastoma – GPOH – Ver.:3

20. DCOG NBL 2009 TREATMENT PROTOCOL for Risk Adapted Treatment of Children with Neuroblastoma Amendment 1, 12 September 2012

8.7 LIVER TUMOURS

The malignant liver tumours are rare tumours in the paediatric pathology (1 -3% of cancers in children). The most common liver cancers in children are those of epithelial origin - 90% (hepatoblastoma/hepatocellular carcinoma), the remaining 10% being tumours of mesenchymal origin (rhabdomyosarcoma, angiosarcoma, rhabdoid tumour). In Romania, the malignant liver tumours account for 1% of registered childhood tumours.

HEPATOBLASTOMA

Epidemiology

Hepatoblastoma - is an embryonal tumour of the liver and it is generally specific to young children (over 80% of cases occurring at less than 3 years of age, with an average age of 16 months). Congenital or familial types are also described. (1)

The etiology is unknown. It can occur in some genetic syndromes - the Beckwith-Wiedemann syndrome, trisomy 18 or familial adenomatous polyposis. A link between the hepatoblastoma and a very low birth weight was described, the duration of the oxygen therapy required by these newborn children being a factor associated with this risk. The favouring factors were also discussed – the oral contraception, the alcohol consumption during pregnancy, the hormonal treatments for infertility, as well as the occupational exposure of parents to heavy metals or petroleum products. (1.2)

The incidence is estimated at 0.5 - 1.5 new cases/1,000,000 children annually, with predominance in males (sex ratio 1.4-2:1). (3)

Diagnosis

- **Symptomatology**

The asymptomatic abdominal mass is the most common form of presentation in patients with hepatoblastoma (4). In case of large tumours, abdominal pain or digestive discomfort may occur. The general signs are often missing. Rarely, boys show signs of early puberty (due to increased beta HCG secretion). In case of tumour rupture or intratumoural hemorrhage, signs of acute abdomen or shock may be associated.

- **Laboratory work-up:**

- Blood count –may show thrombocytosis (particularly for hepatoblastomas, by intratumoral production of circulating thrombopoietin), mild anaemia
- Coagulogram
- Liver function (normal liver enzymes -50% of cases, increased direct bilirubin in 15% of cases), renal function, electrolytes, lipidogram (cholesterol level may be increased in some forms with severe prognosis)
- Urine test
- Serology of HBV and HCV
- Tumour markers - the determination of alpha fetoprotein (AFP) is essential - very sensitive marker, increased in over 90% of cases in hepatoblastomas and in 50% of cases in

hepatocellular carcinomas (but it is not specific for this type of tumours, since it may have high values in germ cell tumours. (3, 5) The values are very high at birth and gradually decrease in the first months of life until after the age of 1 year when they reach the normal value (≤10ng/ml). This is why the interpretation of the result at young ages requires caution. (see Table 1). β HCG (human chorionic gonadotropin β) may reveal high values, the clinical correspondent being early puberty.

• **Imaging evaluation** – its purpose is to establish the intrahepatic extension, the potential of surgical resectability, as well as the presence of possible metastases

- for intrahepatic evaluation (description of the lesion, relations with the hepatic vessels, inferior vena cava and the portal veins system, as well as with the other neighbouring abdominal organs) – the abdominal ultrasound (first investigation used), abdominal MRI abdominal CT, (angiogram, cholangiogram if necessary)

- for extrahepatic evaluation: chest radiograph in two planes, chest CT scan (about 20% of patients may have lung metastases from onset), cranial CT scan, bone scintigraphy if necessary

Table 1 *Modified according to Wu JT, SUDAR K, Serum AFP levels in normal infants. Pediatr Res 1981.*

AGE	VALUES
Premature	150 000 ng/mL
Newborn	50 000 ng/mL (± 30 000)
1 month	1400 – 10 000 ng/mL
2 months	300 ± 300 ng/mL (maximum 1300 ng/mL)
4 months	74 ± 56 ng/mL (maximum 400 ng/mL)
8 months	8 ± 6 ng/mL (maximum 87 ng/mL)
12 months	< 10 ng/mL

Other useful pre-therapeutic examinations
- cardiac examination (before the treatment with anthracyclines)
- audiogram (in case of treatment with cisplatin, carboplatin)

Histopathological diagnosis, classification

The diagnosis of hepatoblastoma is suggestive in young children (6 months to 3 years), with a large liver tumour and high AFP values.

In any other cases as children of different age and children with low AFP values (<100 ng/ml), tumor biopsy is required (in order to differentiate between other liver tumours, such as hepatocellular carcinoma and mesenchymal hamartoma, or the physiologically increased values in the first months of life). This can be done by puncture or laparoscopy / minilaparotomy.

Hepatoblastomas are tumours consisting of epithelial and mesenchymal components, generally solitary and located more frequently in the right hepatic lobe. They are classified into (2):

Epithelial tumours (55%)
- fetal type (30%, with the best prognosis),
- mixed fetal / embryonal type (20%),
- macrotrabecular type (3%)
- small cell undifferentiated type (2%, most reserved prognosis)

Mixed epithelial-mesenchymal tumours (45%) - with or without teratoid characters

Staging

Two staging systems are currently in use. The pre-surgical staging, PRETEXT (PRE Treatment EXTension), is developed by the European specialists from the International Childhood Liver Study Group, SIOPEL. (see Table 2)

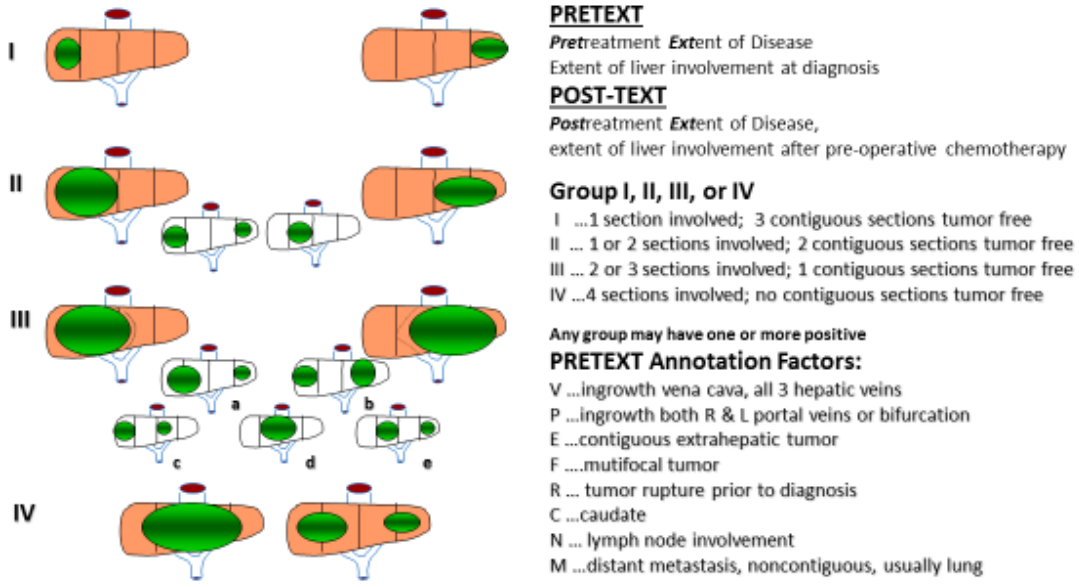
In the PRETEXT staging - based on imaging results, the types of hepatoblastoma are divided according to the sections affected by the tumour (each of the 2 lobes having 2 sections); intra-abdominal involvement (E), vascular - suprahepatic veins/inferior vena cava (V) and in the portal veins system (P) and the presence of distant metastases (M) are also considered. In Europe chemotherapy is chosen as the first-line treatment, followed by surgery.

Table 2

PRETEXT STAGING	DESCRIPTION
I	The tumour involves one section three adjoining sections are free
II	The tumour involves one or two sections; two adjoining sections are free
III	The tumour involves three adjoining liver sections or two non-adjoining liver sections; there are one or two non-adjoining liver sections that are free of tumour
IV	The tumour involves all four sections, there is no liver section free of tumour

PRETEXT Groups (I, II, III, IV) and PRETEXT Annotation Factors (V,P,E,F,R,C,N,M) (6)

I



The post-surgical staging, based on the outcome of the surgery, was developed by American specialists (North American Cooperative Group of Childhood Hepatic Tumours). (see Table 3) In the USA, the approach with surgery at the beginning is preferred, possibly followed by adjuvant chemotherapy.

Table 3

COG STAGING SYSTEM	DESCRIPTION
I	Complete gross resection of the tumour with no microscopic residual disease
II	Incomplete gross resection of the tumour with microscopic residual disease
III	Incomplete gross resection of the tumour/ unresectable tumour with gross residual or with nodal involvement
IV	Metastatic tumour

Classification into risk groups (depending on staging, local extension and AFP level):

- Standard-risk hepatoblastoma: PRETEXT I, II, III staging, without extrahepatic abdominal tumour extension, without distant metastases, without tumour rupture at diagnosis and with high level of AFP (> 100ng/ml)

- High-risk hepatoblastoma: in the presence of one of the following characteristics - PRETEXT IV staging, extrahepatic - vascular or extravascular tumour extension, distant metastases, tumour rupture at diagnosis, low level of alpha-fetoprotein (<100ng/ml)

-

Prognostic factors:

- Favourable prognostic factors:

- the most important factor is represented by the degree of resectability, the surgery with complete tumour resection being the best premise for healing;

- pure embryonal type of hepatoblastoma (which does not require postoperative chemotherapy)

- Unfavourable prognostic factors

- the presence of metastases at diagnosis

- normal or low AFP values (generally <100ng/ml),

- undifferentiated histological type, with small cells

Treatment

The treatment of hepatoblastoma is multimodal and consists of chemotherapy and surgery. As a result of the progress in the recent decades (in the field of chemotherapy, development of surgical techniques, transplantation), the 5-year survival has increased nowadays. from 20% (when only the surgical treatment was used) to 70-80%. (7)

- Surgical treatment

A complete tumour resection is essential for the cure of children with hepatoblastoma. At diagnosis, however, almost half of the children present with inoperable tumours or lung metastases. (8)

As mentioned above, there are 2 different therapeutic approaches depending on the moment of the surgery. The North Americans (the COG group) opt for surgical resection from the beginning (if possible). The Europeans (SIOPEL group) start the treatment with neo-adjuvant chemotherapy: The results are similar in studies.

The use of neo-adjuvant chemotherapy favours surgery (in most cases by shrinking and better delimitating the tumour and by reducing the risk of intraoperative bleeding) and it can destroy existing lung metastases.

The tumour resection is performed following the extension in one or both liver lobes, with the involvement of one or more sections (sometimes until lobectomy) in order to excise the tumour tissue as completely as possible. (3)

In case of diffuse or inoperable tumours (multifocal PRETEXT IV stage, regardless of the result of chemotherapy, or solitary PRETEXT IV stage, in which the stage is maintained after chemotherapy), liver transplantation may be performed after chemotherapy.

• Chemotherapy - is administered according to staging/risk groups, the most active cytostatic agent being Cisplatin. Doxo, Carbo, 5FU, VCR are also used. Limiting the side effects of these therapies is a continuing concern in trying to find the most effective and least harmful therapeutic regimen. The postoperative chemotherapy is administered at least 4 weeks after surgery to allow the liver regeneration.

SIOPEL recommendations - from 2014 (7, 8, 9,10)

- Standard-risk hepatoblastoma - according to SIOPEL 3 protocol - CDDP monotherapy (4 preoperative cycles, followed by 2 postoperative cycles);

o DDP 80mg/m2/24 hours, preoperatively: day 1, 15, 29, 44 and postoperatively days 1, 15

- High-risk hepatoblastoma - according to SIOPEL 3 protocol, SUPERPLADO regimen, alternating DDP cycles with Carbo/Doxo cycles

DDP 80mg/m2/24 hours - preoperatively: day 1, 29, 57, 85 and postoperatively days 1, 29

Carbo/Doxo (Carbo 500mg/m^2/1h, Doxo 60mg/m^2/48 hours) preoperatively: day 15, 43, 71 and postoperatively day 15

- very high risk group (lung metastases, low levels of AFP) - treatment according to SIOPEL 4: weekly alternative cycles with DDP/Carbo/Doxo

Preoperatively (block A1, A2, A3) –DDP 80 mg/m^2/24 hours on day 1, DDP 70 mg/m^2/24 hours on days 8, 15, 29, 36, 43, 57/64, Doxo 30 mg/m^2/24 hours in days 8, 9, 36, 37, 57, 58

Postoperatively (block C) –Carbo AUC 6.6 mg/ml/min on days 1, 22, 43 + Doxo 20 mg/m^2/day on days 12, 22, 23, 43, 44

In incompletely resectable tumors, after preoperative chemotherapy, block B is administered, followed by surgical treatment and block C. Sometimes the resection of lung metastases or the liver transplantation is required.

Block B -Carbo AUC 10.6 mg/ml/min on days 1, 22 + Doxo 20 mg/ m^2/day on days 1, 2, 3, 22, 23, 24

• Other accepted therapies

PLADO cycle (DDP 80mg/m^2/24 hours day 1, Doxo 60mg/m^2/48 hours on days 2, 3) - SIOPEL 3, standard-risk hepatoblastoma

C5V cycle (DDP 90 mg/m^2 in 6 hours on day 1, VCR 1.5 mg/m^2 + 5FU 600 mg/m^2 on day 2) - standard COG treatment

• Radiotherapy has a minor role in the treatment of hepatoblastoma (effective dose exceeding liver tolerance) and is very rarely used. Doses of 12-20 Gy are used, but only in the case of inoperable tumors or microscopic residues. It may be indicated in the treatment of chemoresistant lung metastases.

• There is a new protocol for pediatric liver tumors – the **PHITT protocol** - Paediatric Hepatic International Tumour Trial -launced in 2018 a collaborative trial involving three major clinical groups running paediatric liver tumour trials; the International Society of Paediatric Oncology Epithelial Liver Tumour Group (SIOPEL), the Liver Tumour Committee of the Children's Oncology Group, USA (COG), the Japanese Children's Cancer Group (JCCG).The

Society for Paediatric Oncology and Haematology, Germany (GPOH) is closely collaborating in the European trial.

The treatment of relapses and refractory disease - the prognosis depends on the recurrence site, the treatment previously administered and the individual features. (7, 11)

- surgical (local or metastatic)
- second line chemotherapy (Carbo/VP16, IRI, Gem, Paclitaxel can be used)
- biological therapy, immunotherapy
- radiotherapy (recurrent lung metastases)

Post-therapeutic follow-up

The final evaluation is performed one month after the end of the treatment and it includes clinical examination, biological examinations (the level of AFP-marker is very useful for monitoring residual or metastatic disease, the persistence/recurrence of its high values after treatment being a marker for metastasis or relapse) and imaging examinations (abdominal, thoracic) (10)

The periodic evaluation after the end of the treatment aims to diagnose possible tumour recurrence and possible side effects of the treatment and it includes clinical examination, biological investigations with the determination of tumour markers, imaging investigations (abdominal ultrasound, chest CT, echocardiography), audiogram.

Patient follow-up is primarily done as below:

- every 2-3 months in the first 2 years
- every 6 months for the next 3 years
- annually thereafter (up to 10 years)

The details of the post-therapeutic follow-up are described in the therapeutic protocols.

HEPATOCARCINOMA / HEPATOCELLULAR CARCINOMA

The hepatocellular carcinoma generally occurs in older children (10-14 years) and it is frequently associated with pre-existing liver hepatopathy (cirrhosis, chronic hepatitis B/C infection, tyrosinemia, galactosemia, biliary atresia, Byler disease or α1 antitrypsin deficiency). It is twice as rare as hepatoblastoma.

The palpable abominable mass is the most common sign of this disease, but, unlike hepatoblastoma, patients with hepatocellular carcinoma associate systemic signs more frequently: fatigue, anorexia, abdominal pain, jaundice. If there is a pre-existing liver condition, signs of the underlying disease will complete the clinical aspects.

Biological and imaging evaluation - similar to that of hepatoblastoma (only 50% of patients have elevated AFP levels, liver tests may be altered due to the pre-existing disease).

The diagnosis is based on biopsy. Histopathological - multicentric tumour, with the possibility of invasion of the hepatic veins and the inferior vena cava. Three types are described: adult hepatocellular carcinoma, paediatric carcinoma and fibrolamellar carcinoma (according to some authors, with a better prognosis, developed in healthy liver tissue, normal AFP level, increased transcobalamin level). (2)

The same PRETEXT staging as for hepatoblastoma is used. It generally metastasizes to the lungs and lymph nodes; brain or bone metastases have also been described.

The treatment is based primarily on the initial surgery, the hepatocellular carcinoma being a less chemosensitive and radiosensitive tumour. More than half of the cases are inoperable at the time of diagnosis.

Chemotherapy is performed with protocols similar to those for hepatoblastoma (SIOPEL 3, and 4). Biological therapy with Sorafenib, a multikinase inhibitor, has significantly improved the survival in adults with hepatocellular carcinoma, but it is being studied in children.

Liver transplantation is indicated for unresectable unifocal or unresectable multifocal tumours (not more than 5 lesions and the largest is <5 cm), in the absence of liver cirrhosis and metastases.

The prognosis is unfavourable, survival without relapse does not exceed 20-30%.

Recommendations

- Hepatoblastoma is an embryonal tumour of the liver occurring at a young age
- Biopsy is not required in young children (6 months to 3 years) with large liver tumours and elevated AFP values.
- Classification in risk groups depends on staging, local extension and AFP level
- The treatment of hepatoblastoma is multimodal and it consists of chemotherapy, surgery,
- The most active cytostatic agent is Cisplatin, alone or in combination with Doxo, Carbo, 5FU, VCR
- The hepatocellular carcinoma occurs mostly in older children and it is often associated with pre-existing liver disease

Bibliography

2. Laithier V., Brugieres L, Gauthier F: Tumeurs malignes primitives du foie de l'enfant. In Kalifa C, Pein F, Oberlin O, Hartmann O, Lemerle J - Cancers de l'enfant, 2008 Flammarion SA, pp321-326

3. Perilongo G, Zsiros J: Childhood liver tumours. In Stevens MCG, Caron HN, Biondi A, red. Cancer in children: clinical management. 6th edition, Oxford: Oxford University Press; 2012, pp 357-364

4. Scurtu C, SfrijanD – Mase abdominale la copil, Editura Universitară Carol Davila, 2017, pp26-35

5. Hepatoblastoma: current understanding, recent advances, and controversies - Piotr Czauderna , Hanna Garnier, F1000Research 2018, 7(F1000 Faculty Rev):53 Last updated: 15 jan 2018

6. Rapkin LB, Olson T.A: Hepatic Tumors. In Lanzkowsky P, Lipton JM,Fish JD - Lanzkowsy'sManual of Pediatric Hematology and Oncology, Sixth Edition Elsevier Inc 2016, pp569-575

7. Derek J. Roebuck, et al: 2005 PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol. 2007 Feb; 37(2): 123–132.

8. Meyers RL, Aronson DC, Von Schweinitz D, Zimmermann A, Malogolowkin MH: Pediatric liver tumors. In: Pizzo PA, Poplack DG, eds.: Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams and Wilkins, 2011, pp 838-853

9. Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: Its evolution and the current status as per the SIOPEL trials. J Indian Assoc Pediatr Surg. 2014;19(4):201–207. doi:10.4103/0971-9261.142001

10. SIOPEL 3 HEPATOBLASTOMA AND HEPATOCELLULAR CARCINOMA

11. SIOPEL 4 Intensified pre-operative chemotherapy and radical surgery for HIGH RISK HEPATOBLASTOMA, final version_July 2004

12. Hiyama E. Pediatric hepatoblastoma: diagnosis and treatment. TranslPediatr 2014;3(4):293-299. doi: 10.3978/j.issn.2224-4336.2014.09.01

8.8 GERM CELL TUMOURS

Epidemiology

Germ cell tumours are a heterogeneous group of tumours, which vary considerably in clinical presentation, site, histology and biology. Germ cell tumours can be diagnosed at any age. In young adults and adolescents, the most common site is the gonads. In children, the most common site is extra-gonadal, on the midline of the body: sacrococcygeal, retroperitoneal or at the level of the anterior mediastinum. (1)

Symptomatology

Germ cell tumours generally present as large painless tumour masses, but can cause symptoms by compression on adjacent structures: superior vena cava syndrome, constipation.

Symptoms according to site:

- Ovarian tumours: abdominal pain of varying intensity, up to acute abdomen, increased volume of the abdomen, menstrual disorders, urinary or intestinal transit disorders
- Testicular tumours: painless enlargement of the scrotum (pathognomonic), acute testicular pain (torsion), acute epididymitis, gynecomastia, low back pain, infertility
- Extragonadal tumors: local pain of variable intensity, up to very intense, signs of intracranial hypertension, respiratory signs (dyspnea, wheezing)

Diagnosis

Risk factors: Cryptorchidism, Klinefelter's syndrome (mediastinal tumours), Turner's syndrome (germinomas, gonadoblastomas)

Laboratory tests

- initial blood count with leukocyte count
- Alkaline phosphatase, C-reactive protein,
- renal function tests (creatinine clearance)
- liver function tests (transaminases, ALP, albumin, gammaGT, LDH)
- urinary catecholamines (differential diagnosis)
- serum tumor markers: serum lactate dehydrogenase (LDH), alpha fetoprotein (AFP), human chorionic gonadotropin (HCG), neuron-specific enolase, CA-125, PLAP
- Karyotype: in case of suspicion for Klinefelter’s syndrome, Turner’s syndrome

Imaging examinations

- mandatory: abdominal ultrasound, chest X-Ray, CT scan of the chest abdomen and pelvis and/or MRI of the chest, abdomen and pelvis, testicular ultrasound.
- For symptomatic cases: CT/MRI of the brain, bone scintigraphy
- Whenever possible: - PET CT
- Sperm preservation

Histological diagnosis

Ovarian tumours: laparotomy followed by surgery or biopsy, or biopsy of metastatic sites

Testicular tumours: inguinal orchiectomy (trans-scrotal procedures are prohibited) or biopsy of metastatic sites

Extragonadal germ cell tumours: surgery or biopsy of the primary tumour, or biopsy of metastatic sites

Histological types:

- Mature teratoma
- Immature teratoma
- Teratoma with malignant transformation (+/- Yolk sac tumour or embryonal carcinoma)
- Seminomatous tumours - Germinomas
- Dysgerminomas (ovaries)
- Seminomas (testis)
- Nonseminomatous tumours - Yolk sac tumour / endodermal sinus
- Choriocarcinoma
- Embryonal carcinoma
- Gonadoblastoma
- Mixed tumours

Tumour markers

Secretion of tumour markers (AFP and/or beta-HCG) is depending on histology. One or both tumour markers are elevated in over 90% of cases with metastatic disease. The level of tumour markers is used for clinical diagnosis and staging of germ cell tumours. Secretion of tumour markers, according to the histological type, is shown in Table 1.

Alpha fetoprotein has a half-life of 5-7 days. Elevated levels can also be found in hepatoblastoma, pancreatic tumours, and non-malignant liver diseases, neural tube defects, ataxia telangiectasia. AFP values are very high in newborn children and they do not decrease to adult values until the age of 1-2 years.

Beta human chorionic gonadotropin (beta HCG): elevated levels in germinomas / dysgerminomas, choriocarcinoma. It has a half-life of 24-36 hours.

Serum lactate dehydrogenase (LDH): nonspecific tumour marker, increased in rapid cell proliferation (1).

Table 1: Secretion of tumour markers by histological type

	Tumour markers	
	AFP	HCG
Seminoma/germinoma	-	+
Embryonal carcinoma	+/-	+/-
Yolk sac tumour	+++	-
Choriocarcinoma	-	+++
Mature/ Immature teratoma	-	-

Staging and/or classification into risk groups, prognostic factors

Ovarian tumours are staged according to the Federation of Gynecology and Obstetrics (FIGO) system for epithelial ovarian tumours (2).

- Stage I: tumour limited to the ovaries

- Stage II: extension to other pelvic tissues
- Stage III: disease spread outside the pelvis or in the retroperitoneal lymph nodes, but does not spread outside the abdomen
- Stage IV: distant metastases or liver invasion.

Testicular tumours are staged according to TNM staging.

Mediastinal tumours

- Stage I: well-circumscribed tumours with or without focal adhesion to the pleura or pericardium, but without microscopic invasion to adjacent organs
- Stage II: Tumour limited to the mediastinum with macroscopic and/or microscopic infiltration to adjacent structures
- Stage III: Metastatic disease
- Stage IIIA: metastases in intrathoracic organs
- Stage IIIB: metastases in extrathoracic organs

Extragonadal tumours are usually staged according to the *Paediatric Oncology Group / Children's Cancer Group Staging* (3):

- Stage I: complete resection for any tumour site; coccygectomy for sacrococcygeal tumours, negative tumour margins, positive or negative tumour markers
- Stage II: microscopic residual tumour; negative lymph nodes, negative or positive tumour markers
- Stage III: residual macroscopic tumour or performing only a biopsy, negative or positive retroperitoneal lymph nodes, negative or positive tumour markers
- Stage IV: distant metastases, including liver

Paediatric staging of germ cell tumours according to Children's Oncology Group

	Testis	Extra-gonadal	Ovary
Stage I	Complete resection with negative lymph nodes	Complete resection with negative margins in any site or coccygectomy for sacrococcygeal teratoma	Disease limited to the ovaries (peritoneal evaluation must be negative), no clinical, histological or imaging evidence of non-ovarian disease
Stage II	Trans-scrotal biopsy, microscopic disease in the scrotum or spermatic cord, increased levels of postoperative tumour markers	Microscopic residual disease and negative lymph nodes	Microscopic residual disease, negative peritoneal evaluation, increased levels of postoperative tumour markers
Stage III	Retroperitoneal lymph nodes involvement, but without visceral invasion or invasion outside the abdomen	Lymph node involvement, macroscopic residual disease or just biopsy	Lymph node invasion, metastatic nodule, macroscopic residual disease or just biopsy, visceral extension (omentum, bladder), positive peritoneal evaluation for malignancy
Stage IV	Distant metastases, including liver metastases	Distant metastases, including liver metastases	Distant metastases, including liver metastases

Classification by risk groups according to the International Collaborative Group for metastatic germ cell tumours

Risk	Nonseminomatous tumours	Seminoma
Standard risk	Primary gonadal or retroperitoneal tumour No extrapulmonary visceral metastases AFP<1000UI/L and HCG < 5000UI/L and LDH<1.5xN	Any primary site No extrapulmonary visceral metastases Normal AFP, any HCG, any LDH
Intermediate risk	Primary gonadal or retroperitoneal tumour No extrapulmonary visceral metastases AFP: 1000-10000 UI/L or HCG: 5000-50000UI/L or LDH:1.5-10xN	Any primary site Extrapulmonary visceral metastases Normal AFP, any HCG, any LDH
High risk	Primary mediastinal tumour or Extrapulmonary visceral metastases or AFP: >10000 UI/L or HCG: >50000UI/L or LDH:>10xN	Does not exist

Treatment

Mature teratomas

Complete surgical resection is sufficient, but follow-up is required (clinical examination, ultrasound and tumour markers), as they can relapse both as mature teratomas and as malignant germ cell tumours. In the case of sacrococcygeal tumours, the recurrence rate is 10-14%, and the most common recurrence is represented by Yolk sac tumours.

Immature teratomas

Surgery is the main treatment and is often sufficient. The significance of elevated AFP values in correlation with immature teratomas is controversial. It is recommended that, immature teratomas with AFP > 1000kU/L at diagnosis be treated as malignant germ cell tumours with chemotherapy in addition to surgery, and immature teratomas with AFP < 1000kU/L be closely monitored by ultrasound every 3 months and determination of AFP every 4 weeks until normalization of the tumour marker is reached. In case of an increase of the tumour marker, a new surgery is recommended, followed by chemotherapy. (4)

Malignant germ cell tumours

If no metastases are seen, surgery is considered the first therapeutic step. Unresectable tumours should be biopsied, if possible. Mutilating surgery should be avoided. Surgery after chemotherapy may be considered, but should be avoided if the associated risks are considered high. Most residual lesions after chemotherapy are necrosis, fibrosis or mature/immature teratomas. These patients should be closely monitored for deciding on a possible resumption of treatment. (4)

Testicular germ cell tumours

- Stage I (localized disease of the testis with negative tumour markers)

Surgery represented by radical inguinal orchiectomy followed by clinical, paraclinical monitoring (tumour markers are of major importance) and careful imaging studies.

Lymphovascular invasion is an unfavourable prognostic factor.

- Stage IS, II-IV (localized disease in the testis with positive tumour markers, loco-regionally advanced and metastatic disease)

Standard treatment is radical inguinal orchiectomy followed by adjuvant chemotherapy: (5) 4 cycles of BEP (Bleo, VP16, DDP) will be the choice for boys > 11 yrs with non-seminomas tumors. This regimen can also be used in other settings.

Protocols in the United Kingdom use Carbo (JEB protocol) instead of DDP. Studies have shown equal efficacy with fewer side effects with regard to renal function and hearing loss. If the patient is in the high-risk group, 6 JEB cycles are recommended. (5) This is used for boys under 11 yrs with non-seminomas tumors and also with seminomas in boys >11 yrs.

Other accepted chemotherapy regimens are represented by: EP (VP16, DDP), PVB (DDP, VBL, Bleo), PEI (DDP, VP16, IFO), VAC (VCR, ACT-D, CTX) as per NCCN guidelines. (6, 7)

Ovarian germ cell tumours

Primary treatment consists of surgery, which consists of excision of the primary tumour/unilateral salpingo-oophorectomy, peritoneal washing cytology, biopsy or peritoneal implants or suspicious lymphadenopathy resection, without the need for other biopsies. Complete surgical staging performed in adult women is not generally recommended in the paediatric population (8, 9).

- Stage I FIGO (with negative resection margins or microscopically positive resection margins) does not require adjuvant treatment. Clinical, paraclinical and imaging monitoring is imperative.

- Stage I FIGO with macroscopic residual disease and stage II-IV FIGO require adjuvant platin based chemotherapy, either BEP protocol (Bleo, VP16, DDP) 3-4 cycles or the protocols in the United Kingdom that use Carbo (JEB protocol) instead of DDP. Studies have shown equal efficacy with fewer side effects in regard to renal function and hearing. If the female patient is in the high risk group, 6 JEB cycles are recommended. (5)

Other accepted chemotherapy regimens are represented by: EP (VP16, DDP), PVB (DDP, VBL, Bleo), PEI (DDP, VP16, IFO), VAC (VCR, ACT-D, CTX). (6, 7)

Extragonadal germ cell tumours

- Stage I does not require postoperative treatment. Rigorous clinical, paraclinical and imaging monitoring is recommended.

- Stages II-IV require adjuvant chemotherapy, either BEP protocol (Bleo, VP16, DDP) 4 cycles (10, 11) or the protocols in the United Kingdom that use Carbo (JEB protocol) instead of DDP and recommend 6 cycles of chemotherapy. Studies have shown equal efficacy with fewer side effects in regard to renal function and hearing. (5)

Other accepted chemotherapy regimens are represented by: PVB (DDP, VBL, Bleo), PEI (DDP, VP16, IFO), VIP (DDP, VP16, IFO). (6, 7)

Radiotherapy is rarely recommended, in recurrences or particular cases, situations in which decision is made in the tumour board. Irradiation may be indicated in clinical trials.

Treatment of refractory disease and relapses

Optimal treatment for refractory or recurrent disease depends on previous treatment, response to treatment, site and timing of recurrence and histological type. Each case must be analyzed and discussed in tumour board.

Chemo-naïve patients can benefit from platinum-based chemotherapy (BEP, EP, VIP).

Retroperitoneal lymphadenectomy for patients with testicular nonseminomatous tumours is a therapeutic option for carefully selected patients.

Second line of chemotherapy may consist of chemotherapy regimens that were not used in the primary treatment setting. Some examples are: VIP (DDP, VP 16, IFO), VeIP (VBL, IFO, DDP), TIP (Paclitaxel, IFO, DDP).

- Early recurrences (<4 weeks) after the end of initial chemotherapy are considered refractory to platinum-based regimens. These patients are candidates for high-dose chemotherapy and stem cell transplantation.

- Late recurrences are rare. The recommended treatment is surgery and systemic chemotherapy.

- Brain metastases may occur in association with other systemic metastases or be solitary metastases. Systemic chemotherapy is generally the preferred therapeutic method. It can be used in combination with radiotherapy and/or surgical resection.

Radiotherapy may be disscused in the tumour board for palliative purposes in certain carefully selected cases. (9, 10, 11)

Post-therapeutic monitoring

Tumour markers are monitored once every 1-3 months in the first two years after the treatment, then once every 6 months for the next 3 years. Starting from 5 years after the end of the oncological treatment, the tumour markers are evaluated annually, at least 10 years after the end of treatment.

Patients are monitored for at least 10 years after the end of treatment. The importance of close monitoring lies in the good results that can be obtained in the treatment of relapses. It is also important to monitor the long-term side effects of cancer treatment.

Imaging evaluation is performed every 3 months in the first 2 years. Most patients can be adequately monitored by abdominal ultrasound and chest X-Ray, but some patients require CT/MRI examination for proper monitoring. CT scan should be avoided whenever possible due to irradiation doses. After the completion of the first 2 years of monitoring, imaging evaluation is performed every 6 months and it normally ends 5 years after the end of cancer treatment.

Children who received high doses of chemotherapy that may affect their hearing, renal function, lungs or heart should have specific investigations (audiogram, ventilatory tests, glomerular filtration rate, cardiac ultrasound) at 1, 5 and 10 years after the end of treatment for diagnosis and treatment of possible side effects. Possible endocrinological disorders are monitored in collaboration with an endocrinologist and/or gynaecologist.

Recommendations:

- Germ cell tumours are a heterogeneous group of tumours, which vary considerably in terms of clinical presentation, site, histology and biology.
- Serum tumour markers (serum lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), human chorionic gonadotrophin (HCG), neuron-specific enolase, CA-125, PLAP) play an important role
- Definitive histological diagnosis is performed according to each case by surgery or biopsy of the primary tumour, or biopsy of metastases in metastatic cases. Trans-scrotal interventions are prohibited.
- Treatment is performed depending on the histological type, stage of the disease, site and age of the patient. The treatment consists of surgery +/- chemotherapy. Chemotherapy may precede surgery in carefully selected cases.
- Most commonly used chemotherapy regimens are: JEB (Carboplatin, Etoposide, Cisplatin) and BEP (Bleomycin, Etoposide, Cisplatin)

Bibliography

1. Manual of Clinical Oncology Seventh Edition. Editor Dennis A Casciato, 2012, Philadelphia, Ed. Lippincott

2. Aitken JF, Youlden DR, Moore AS, Baade PD, Ward LJ, Thursfield VJ, Valery PC, Green AC, Gupta S, Frazier AL. Childhood cancer staging for population registries according to the Toronto Childhood Cancer Stage Guidelines. Cancer Council Queensland and Cancer Australia: Brisbane, Australia; 2017. Available at https://cancerqld.blob.core.windows.net/content/docs/childhood-cancer-staging-for-population-registries.pdf

3. Thomas AO, Murray MJ, Rodrigues-Galindo C, et al, Pediatric and Adolescent Extracranial Germ Cell Tumors: The road to collaboration, J Clin Oncol, 2015, 33:3018-3028

4. Feldman DR, State-of-the-Art Management of Germ Cell Tumors, Am Soc Clin Oncol Educ Book, 2018, 38: 319–323. doi:10.1200/EDBK_201139, available in PMC 2019 July 03

5. Depani S, Stoneham S, Krailo M, et al, Results from the UK Children/s Cancer and Leukaemia Group study of extracranial germ cell tumours in children and adolescents, Eu J Cancer, 2019, 118:49-57

6. Protocol MEKEI (MAKEI?) 05 – Extracranial germ cell tumors including Sex Cord Stromal Tumors available at https://www.skion.nl/workspace/uploads/MAKEI-05_1.pdf

7. NCCN Clinical Practice Guidelines in Oncology, Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, versiunea 3.2019 available at https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

8. NCI, Childhood Ovarian Cancer Treatment (PDQ) – Health Professional version, available at https://www.cancer.gov/types/ovarian/hp/child-ovarian-treatment-pdq

9. NCI, Extragonadal Germ Cell Tumors Treatment (PDQ) – Health Professional Version, available at https://www.cancer.gov/types/extragonadal-germ-cell/hp/extragonadal-treatment-pdq

10.William OH, Overview of treatment of testicular germ cell tumors, UpToDate, 2018, available at https://www.uptodate.com/contents/overview-of-the-treatment-of-testiculargerm-cell-tumors?search=relapsed%20germ%20cell%20tumors&sectionRank=2&usage_type=default&anchor=H30&source=machineLearning&selectedTitle=1~150&display_rank=1#H647555346

11. Kantoff PW, Extragonadal germ cell tumors involving the mediastinum and retroperitoneum, UpToDate, 2019, available at https://www.uptodate.com/contents/extragonadal-germ-cell-tumors-involving-the-mediastinum-and-retroperitoneum?search=extragonadal%20germ%20cell%20tumors&source=search_result&selectedTitle=1~40&usage_type=default&display_rank=1

8.9 RETINOBLASTOMA

Epidemiology

Retinoblastoma (RB) is a malignant tumour originating in retinal cells and occurs in young children (10-15% of childhood cancers before the age of one year, 95% of cases are diagnosed in children <5 years); it can be localized unilaterally (60%), bilaterally (40%, most often simultaneously) or trilaterally (bilateral/ unilateral retinoblastoma associated with pinealoblastoma). (1)

One quarter of all retinoblastoma cases are caused by germline mutations in the RB1 gene (tumour suppressor gene associated with an increased risk of melanomas, sarcomas). (4) The presence of the germline mutation explains the characteristics of the congenital retinoblastoma: early onset, bilateral involvement, increased risk of developing other malignancies later in life (osteosarcomas, soft tissue sarcomas, melanomas, tumours of the epithelial cells in the bladder, lung or breast) compared to the general population or survivors with non-congenital retinoblastoma. (4) Non-congenital retinoblastoma accounts for 75% of retinoblastoma cases and it is determined by the presence of sporadic mutations of both RB1 genes in the somatic cells, causing unilateral damage and the late onset of the disease.

The incidence is 1 per 5000-20000 live births (2) or 11 cases per 1 million children <5 years old, girls and boys being equally affected. The average age at diagnosis is 12 months for bilateral forms and 24 months for unilateral forms.

The prognosis is very good, complete remission is recorded in 98% of early diagnosed cases; in the forms with CNS metastases the survival is <10%. (2)

According to the data provided by the National Register of Childhood Cancers in Romania, retinoblastoma represents 2% of all paediatric cancers with an average of 8 new cases per year. (3)

Pathogenesis and genetics

The retinoblastoma occurs by mutation of both alleles of the RB1 gene - tumour suppressor gene located on chromosome 13 band q14. (4) Depending on the status of RB1, two forms of the disease can be described:

- Hereditary RB (familial, with germline mutation, 40% of cases) is associated with the germline genetic mutation of an allele of the RB1 gene (first change), which in most cases may occur de novo, or may be inherited from parents (10%) (4); RB is caused by a somatic mutation in the second allele. This category includes bilateral, multifocal forms of disease, those with a positive family history of RB and those with a proven germline mutation. Trilateral forms with tumour in the pineal region, account for 5% of the cases. The average age at diagnosis for hereditary RB is 12-15 months.

The genetic testing is performed from circulating leukocyte DNA and tumour DNA, if enucleation has been performed.

The genetic abnormality of the RB1 gene is associated with an increased risk of other extraocular malignancies (osteosarcoma, soft tissue sarcomas, especially leiomyosarcoma, malignant melanoma) whose onset occurs in adolescence or adulthood, after a latency of 10-15 years. (1, 5)

- Non-hereditary RB (non-familial, sporadic or somatic, 60% of cases). Results from the somatic mutation of both alleles of the RB1 gene (occurs in non-reproductive cells); causes unilateral, unifocal forms that tend to appear later than hereditary forms (the average age at diagnosis is about 24 months). (5)

Preventive interventions - genetic counselling (2)

- RB is transmitted in an autosomal dominant pattern.
- In hereditary forms, the risk of transmitting the mutation to offspring is 50%. If the variant of the genetic mutation in a family affected by retinoblastoma is known, prenatal testing can be performed in high-risk pregnancies. (5)
- Genetic testing of the first affected person in each family is recommended and if the genetic mutation is identified, all persons at risk should be tested; children of a parent with bilateral RB (50%), children of a parent with unilateral RB (7.5%), siblings of a child with bilateral RB (2.5%), their offspring (1.3%), siblings of a child with unilateral RB (0.4%) have the highest risk. (6)
- Molecular genetic testing is recommended for parents of children with RB; if one of them is affected, other family members may also be affected. (5)
- Parents, relatives of children with hereditary RB as well as adults who had RB in childhood should be genetically counselled by experienced staff.
- If genetic testing is not available, the following is recommended (2): See Table 1

a. Bilateral RB with a negative family history:

- ophthalmological monitoring of all the patient's siblings until the age of 18 months
- ophthalmological monitoring of all the patient's offspring until the age of 3 years

b. Unilateral RB, with a negative family history:

- ophthalmological monitoring of the patient's siblings until the age of 12 months
- ophthalmological monitoring of the patient's offspring until the age of 18 months.

Genetic testing for the RB1 gene mutation is available in Romania but the cost is not covered by the health insurance system.

Table 1- estimated risk of retinoblastoma in siblings and offspring of a patient with retinoblastoma of unknown RB1 status (5, 6)

Type of index case of disease			Family history	Risk of the index case siblings	Risk of the index case offspring
Bilateral	Unilateral				
	Multifocal	Unifocal			
X			Negative	2% [1]	50%
	X		Negative	1-2% [1]	6-50%
		X	Negative	1%	6%
		X	Positive	Variable [2]	Variable [2]
X			Positive	50%	50%

[1]If there is no unaffected sibling (Musarella & Gallte 1987, Draper et al 1992, Skalet et al 2018)
[2] Penetration varies widely in families with unilateral retinoblastoma

Signs and symptoms

The most common signs and symptoms of RB at onset are:
-Leukocoria: 56–69%
-Strabismus: 20–35%
-Red, painful eyes with glaucoma: 7%
-Decrease in visual acuity 5%
-Orbital cellulitis: 3%

-Unilateral mydriasis: 2%

-Heterochromia Iridis: 1%

-Hyphema: 1%

-Uveitis

An emergency eye consultation is recommended for any child with leukocoria or strabismus with sudden onset. (1, 4, 7) Hyphema, pseudohypopyon, staphyloma, orbital cellulitis are associated with high-risk histopathological features. (8)

Investigations

• Screening

Routine determination of the red retinal reflex is recommended as a screening investigation for the early diagnosis of retinoblastoma, congenital cataracts and corneal opacity. The recommendation was taken over in the latest prevention guidelines addressed to primary health care in Romania (2017), guidelines developed under the coordination of the National Institute of Public Health in Romania. (9)

Leukocoria can be detected early in photos; it is recommended to photograph children on a monthly basis from birth to the age of 6 to follow the red retinal reflex. Technique: shooting should be done in dim light with a digital camera with the *red eye reduction* function turned off. The smartphone app (MDEyeCare app) can identify early leukocoria (50% of group B cases, 83% of group C cases, 100% group D and E cases). (10, 11)

It is recommended that all children with leukocoria observed directly or in photographs as well as children with strabismus associated with pupillary red reflex abnormality be advised urgently (within 72 hours of noticing changes) for fundus examination with the pupil dilated to the maximum. (11)

• Early diagnosis in children with a positive family history of RB

Since November 2015, an evaluation guide is available for children at risk of developing RB. (6) Any child who has a positive family history of RB in one of the parents, sister/ brother or 1st and 2nd degree relatives is considered at risk of developing retinoblastoma.

For this category of children, it is recommended:

- Periodic examination of the ocular fundus with the pupil dilated to the maximum performed by an ophthalmologist experienced in RB (grade D).

- Tracking starts early and is initially done more often, then less often as the child grows up (grade C)

- Screening evaluation begins at birth and continues until the age of 7 for all children; children with RB1 gene mutation shall be monitored after this age as well, every 1-2 years for their entire lives; in 1st degree relatives with unknown RB1 status (including older siblings) a single fundus examination with the pupil dilated to the maximum (grade C) is recommended.

- Genetic testing must be performed in both bilateral and unilateral forms (grade C).

- The risk of developing RB is estimated based on the kinship with the affected person; genetic testing is recommended to optimize monitoring. Children in the high risk group need more frequent evaluation (grade C).

- The examination under general anaesthesia should be performed on any child who does not cooperate enough to allow the evaluation of the entire retina (grade D), in order to be able to observe peripheral tumours, more common in older children (grade B).

The risk of RB to occur depending on kinship and type of retinoblastoma (6)

- High risk (> 7.5%): the children of a parent with bilateral RB (50% risk)

- Intermediate risk (1-7.5%): the children of a parent with unilateral RB (risk 7.5%), siblings of a child with bilateral RB (2.5%), the children of the siblings of a patient with bilateral RB (1.3 %).

- Low risk (<1%): siblings of a child with unilateral RB (0.4%), children of the siblings of a patient with unilateral RB (0.2%), first cousins of a child with bilateral RB (0.05%)

- Risk in the general population = 0.007%

• Diagnostic evaluation of children with leukocoria and suspected RB:

- Ophthalmological examination with the patient awake: visual acuity, visual field, pupillary reflex, eye movements are examined.

- Ophthalmological examination under general anaesthesia: ocular fundus examination with the pupil dilated to the maximum. It is recommended to photograph the ocular fundus.

- Blood tests: blood count with leukocyte formula, ionogram, creatinine, LDH, CRP, liver function tests, serological tests for CMV, EBV and chickenpox.

- Complete general clinical examination

Children with confirmed RB will be referred to a centre specialized in the treatment of RB to carry out the investigations and specialized treatment.

• Investigations required in children with RB - positive diagnosis and evaluation of the extent of the disease

- Eye ultrasound (highlights the presence of a tumour mass with calcifications)

- OCT (optical coherence tomography) under general anaesthesia; may show small tumours that are not visible at the ocular fundus; it is also useful for post-therapeutic monitoring (can highlight small relapses, masked by retinal scars) (1)

- MRI examination of the brain and orbit with contrast agent

- Genetic evaluation + genetic advice

- +/- CT exam for orbits

- Genetic analysis for the mutation of the RB1 gene on the fresh sample obtained after enucleation, before formalin fixation.

- For the detection of metastases, it is recommended: aspiration and bone marrow biopsy, CSF cytology, bone scintigraphy. (1)

- Routine examination of the CSF and bone marrow (from at least two sites, both medullary aspirate and biopsy) is debatable in cases diagnosed early (intraocular forms); such investigations are recommended in all patients with stage ≥ II retinoblastoma (International Retinoblastoma Staging System IRSS) to distinguish locoregional extension forms, still curable, from metastatic forms, usually incurable; it is recommended that both procedures be performed under general anaesthesia. (1)

- Genetic tests to identify the RB1 mutation.

- Tumour biopsy is not recommended due to the risk of secondary dissemination and ocular destruction.

Staging

In the case of bilateral disease, each eye must be staged. (7)

Currently 4 staging systems are used (Tables 2, 3, 4)

1. The International Retinoblastoma Staging System (IRSS) - classifies the disease into intraocular/ extraocular/ metastatic forms

2. The International Intraocular Retinoblastoma Classification (IIRC)

3. The intraocular classification of retinoblastoma (ICRB)

4. The Reese – Ellsworth classification (for intraocular forms)

In Romania, the Toronto system is used to relate to the National Childhood Cancer Registry. (Table 3)

Table 2

The International Retinoblastoma Staging System	
Stage	**Features**
0	The eye can be saved with local treatment or systemic chemotherapy
I	Enucleation without tumour residue (low risk histopathological features)
II	Enucleation without tumour residue (high risk histopathological features; the resection margin of the optic nerve invaded by the tumour, scleral or extrascleral extension)
III	Regional extension
IIIA	Orbital extension - at the level of the optic or extraocular nerve
IIIB	Extension in the regional lymph nodes
IV	Metastatic disease
IVA	Hematogenous metastases
IVB	Extension in the CNS

Table 3

The Toronto staging of the retinoblastoma	
Level 1	**Level 2-** anatomopathological classification
Located (L): Intraocular Regional (R): Orbital extension or in regional lymph nodes Metastatic (M): remote metastases	Stage 0: Tumour limited to the eyeball. Enucleation was not performed pStage I: Enucleation with negative margins (R0) pStage II: Enucleation with microscopic residual disease (R1) pStage III: Involvement of the orbit and/ or metastases in the regional lymph nodes cStage IV: Metastatic disease

Table 4 Retinoblastoma staging systems (2, 12)

International Intraocular Retinoblastoma Classification - (IIRC)		**Intraocular classification of retinoblastoma (ICRB)**	**Reese–Ellsworth Classification**	
Group	**Features**		**Group**	
A	Small tumours (<3 mm) limited to the retina, located at a distance from the optic disc and fovea	Retinoblastoma ≤ 3 mm (size of the base or height)	Group 1	1a: single tumour <4 DD * located at or behind the equator 1b: multiple tumours, all <4 DD located at or behind the equator
B	All tumours limited to the retina that are> 3 mm or located near the optic disc or fovea	Retinoblastoma> 3 mm (size of the base or height) macular (≤ 3 mm from the fovea) juxtapapillar (≤ 1.5 mm disc) associates subretinal fluid (≤ 3 mm from the margins)	Group 2	2a: single tumour with sizes 4-10 DD located at or behind the equator 2b: multiple tumours, with sizes 4-10 DD located at or behind the equator
C	Well-defined tumours with small subretinal seeding or in the vitreous	Retinoblastoma with: Subretinal inoculation ≤ 3 mm from the tumour Vitreous seeding ≤ 3 mm from the tumour Subretinal and vitreous seeding ≤ 3 mm from the tumour	Group 3	3a: tumours located anterior to the equator 3b: single tumour> 10 DD located behind the equator
D	Large or poorly delimited tumours with subretinal seeding or in the vitreous +/- retinal detachment larger than a quarter of the surface	Retinoblastoma with: Subretinal inoculation > 3 mm from the tumour Vitreous seeding > 3 mm from the tumour Subretinal and vitreous seeding > 3 mm from the tumour	Group 4	4a: multiple tumours > 10 DD 4b: any tumour extending to the ora serrata

E	Very large tumours, extending into the anterior chamber, complicated by haemorrhage or glaucoma, or associating other features which make it almost impossible to save the eye	Extensive retinoblastoma occupying > 50% of the globe OR Neovascular glaucoma Opaque media by haemorrhage in the anterior chamber, vitreous or subretinal space Postlaminar invasion of the optic nerve Invasion of the choroid (> 2mm), sclera, orbit, anterior chamber	Group 5	5a: the tumour affects >50% of the retina 5b: tumour with vitreous seeding

***** DD- the diameter of the optical disk

Treatment

It is recommended that the treatment of RB be done in a centralized manner in specialized centres in which at least 5-10 newly diagnosed patients are cared for annually; the treatment must be performed by an experienced multidisciplinary team with an ophthalmologist, paediatric oncologist, pathologist, radiotherapist, anaesthetist, psychologist, social worker. (2, 7)

The goals of treatment are: saving lives, saving the eyes, saving eyesight, improving the quality of life of the child and family, especially in cases of permanent bilateral blindness. (2) The treatment modalities are: enucleation, chemotherapy, radiotherapy and other types of local treatment.

a. Enucleation can provide healing in patients with unilateral retinoblastoma.

The enucleation associated with resection of a part as long as possible of the optic nerve (minimum 10-12 mm) is the first therapeutic step for advanced forms of intraocular RB.

Indications for enucleation: very large tumours at diagnosis in which it is not possible to preserve vision (group D-E), recurrences that cannot be controlled with conservative treatment, metastatic tumours.

The indication of first intention enucleation is questionable in the types of unilateral group C RB; conservative treatment may be attempted.

In forms of RB with orbital extension imagistically confirmed, enucleation is performed after cytoreductive chemotherapy; the risk of metastasis is 10-27 times higher in types with orbital invasion than in the intraocular ones.

Orbital exenteration is usually not recommended but may be required in patients with an unsatisfactory response to chemotherapy. (7)

b. Chemotherapy (table 5)

RB is a tumour with high chemosensitivity; combinations containing Carboplatin with very good intraocular penetration are preferred. Indications for chemotherapy:

- reduction of tumour volume in large tumours before other treatments (7)
- after primary enucleation, in the presence of histopathological risk factors (7)
- high-dose chemotherapy and stem cell support in RB stage IV (healing rate of up to 70% in patients without CNS involvement and up to 30% in case of CNS involvement (7)
- when using Carboplatin the child should be evaluated for hearing-loss(audiometry) after every two cycles as it is very challenging for a child to have reduction both in sight and hearing.

Table 5- Chemotherapy regimens for retinoblastoma (7)

	Regimen[a]	**Indications**
1	Carbo 500-560mg/m2 day 1+ VP16 100-150mg/m2 day 1-2 VCR 1,5mg/m2 day 1	Chemoreduction (level 3iiDi)
2	CTX 40mg/kg day 1+ VCR 1,5mg/m2 day 1 +/- Doxo 30mg/m2 day 1	Palliative therapy (level 4)[b] Adjuvant therapy (if Carbo is not available), level 3iiA)
3	Carbo 500mg/m2 day 1-2+ VP16 100mg/m2 day 1-3	Chemoreduction in advanced cases (level 3iiA) Adjuvant chemotherapy (level 3iiA) Neoadjuvant chemotherapy (level 3iiA) Treatment of metastatic disease (level 3iiA)

4	CTX 65mg/kg day 1+ VCR 1,5mg/m2 day 1 + IDA[c] 10mg/m2 day 1	Adjuvant chemotherapy (level 3iiA) Neoadjuvant chemotherapy (level 3iiA) Treatment of metastatic disease (level 3iiA)
5	IFO 1,8g/m2 day 1-5 + VP16 100mg/m2 day 1-5 +/- Carbo 400mg/m2 day 1-2	Adjuvant chemotherapy (level 3iiA) Neoadjuvant chemotherapy (level 3iiDiv) Palliative therapy of metastatic disease (level 4)
	Intrathecal chemotherapy (ARA-C sau Topo)	Palliative therapy of leptomeningeal metastases (level 4)[b] Possible role in preventing CNS relapse in patients receiving low-dose adjuvant therapy (level 4)

For children under 36 months of age or weighing less than 12 kg, the doses are calculated based on the body weight.

Systemic chemotherapy: the recommended protocol is the most commonly used protocol, i.e. **VCE.**

Local chemotherapy (intraarterial in the ophthalmic artery, intravitreal, subconjunctival/ subtenonian, through the episceral reservoir) - see the local treatment

High-dose chemotherapy and stem cell support (Carbo, VP16, CTX, Thiotepa, Melfalan) - the only curative treatment option for RB with metastases outside the CNS (bone, bone marrow).

c) Radiotherapy

RB is a radiosensitive tumour. (1)

Until recently, external radiotherapy was the classic and effective conservative treatment in RB. Studies have shown that radiotherapy increases 6 times the risk of developing a second cancer, often fatal; it also causes aesthetic changes that can be disturbing; therefore, external radiotherapy should be avoided when possible and has now been replaced by systemic chemotherapy combined with local treatment.

External radiotherapy, indications:

-Recurrent tumour in which we want to preserve the eye, when other treatments have been ineffective or when the tumour has spread in the vitreous humor (13)

-Extraocular extension or tumours that are too large or located too close to the fovea in which preservation of eyesight is not possible (2, 13)

-Important vitreous involvement (1)

-Tumour progression during chemotherapy, if all different chemo options fail (1)

-Neoplastic infiltration of the resection end of the optic nerve (the best method of treatment in this situation is still under discussion) (1)

-Metastatic disease, with palliative purposes (2)

In some radiotherapy centres, external proton radiotherapy is preferred for the irradiation of RB in certain situations. (13)

Plaque brachytherapy - see local treatment

d. Local treatment

Transpupillary thermotherapy (TTT): Principle: heating the tumour to 45-60° C. Indications: small tumours (diameter <3mm), without vitreous or subretinal seeding; also indicated for tumours located near the fovea and the optic nerve disc. It can be administered in combination with primary chemotherapy or for relapses; high temperature > 44°C increases the intratumoural concentration of Carboplatin.

Laser photocoagulation: Different types of laser can be used to destroy the vascularization of the tumour. Indications: small tumours (diameter <4-7mm, height <3mm), located in the back,

distant from the fovea and the optic nerve disc. It can be administered in combination with primary chemotherapy or for relapses.

Cryotherapy: The tumour tissue is frozen at -70°C. Indications: small peripheral tumours (diameter <6mm, height <3mm) located in the front, at a distance from the macula and the optical disc; relapses after radiotherapy.

Local chemotherapy

-Intraarterial chemotherapy. It is administered in the ophthalmic artery Melfalan 5 mg-7.5 mg, Topo 1 mg, Carbo 30 mg-50 mg). It is performed in highly specialized centres; it avoids the side effects of systemic chemotherapy. (7)

-Intravitreal chemotherapy (Melfalan 20 ug-30 ug, Topo) is recommended in vitreous involvement, after systemic chemotherapy. After intravitreal injection there is a risk of extraocular extension through the injection site.

-Subconjunctival/subtenonian chemotherapy (Carbo, Topo) - indicated in group C or D RB with vitreous/ subretinal seeding; is associated with systemic chemotherapy.

Chemotherapy administered by episceral reservoir.

Plaque brachytherapy and radioactive seeding of Ru-106 (ruthenium), I-125 (Iodine) Ir-192 (Iridium) Indications: - Tumours with diameter <16 mm, thickness <8-10 mm (20)

- Tumours located <2 mm from the emergence of the optic nerve or macula
- Tumours without vitreous infiltration or with local infiltration <2 mm
- Tumours resistant to treatment/relapse.

The dose is 40-50 Gy at the apex of the tumour or in the extended volume to cover the vitreous seeds. (13)

Advantages: direct tumour irradiation, minimal irradiation of neighbouring normal tissues (1)

Disadvantages: high dose of irradiation at the level of the sclera, significantly lower dose of irradiation at the level of the previous lesions, difficulty of inserting radioactive plaques (1)

No type of local treatment can currently be administered in Romania.

e. Palliative treatment

Cases of relapse resistant to treatment, as well as those with treatment-resistant metastases are indicated for palliative therapy in order to increase the quality of the child's life. It will ensure the control of symptoms (pain, nausea, vomiting, etc.) and psychological support for the child and family.

Treatment of various types of retinoblastoma

• Treatment of the unilateral RB (18) - The current tendency is to administer treatment for the preservation of the eye and vision in the forms of unilateral intraocular RB group A-C (systemic chemotherapy + local treatment). In large tumours, which cause buphthalmia, preoperative chemotherapy is recommended followed by enucleation and adjuvant chemotherapy. If investigations show extraocular extention of disease the treatment after surgery will be radiotherapy and adjuvant chemotherapy.

• Treatment of bilateral RB

The current trend is to preserve at least the less affected eye with reductional chemotherapy followed by local treatment; careful and sustained post-therapeutic monitoring is required, as late recurrences are possible. (7)

Currently, children with bilateral RB diagnosed in Romania and eligible for local treatment are referred to specialized clinics in Europe according to the European collaboration relations.

• Treatment of intraocular RB (2) See table 6

Table 6 The therapy for Intraocular retinoblastoma

A	Small tumours <3 mm outside the macula	Focal treatment
B	Tumours >3 mm OR Tumours located at the level of the macula OR Tumours with accumulation of subretinal fluid	Focal treatment +/- systemic chemotherapy up to 6 cycles
c	Localized vitreous or sub-retinal seeding (<3 mm from the tumour)	**Unilateral:** enucleation **Bilateral:** attempts are made to save the second eye with systemic chemotherapy 6 cycles +/- focal treatment
D	Diffuse vitreous or subretinal seeding (at > 3 mm from the tumour) In case of enucleation, HISTOPATHOLOGICAL RISK FACTORS are considered	**Unilateral:** enucleation **Bilateral:** attempts are made to save the second eye with systemic chemotherapy +/- focal treatment IF IT CANNOT BE SAVED: enucleation **Post enucleation:** Low histopathological risk – no other therapy required High histopathological risk - chemotherapy 6 cycles
E	Tumour in contact with the crystalline lens Neovascular glaucoma Tumour invasion in the anterior chamber Vitreous haemorrhage Aseptic orbital cellulitis Phthisis bulbi	Enucleation **Post enucleation:** Low histopathological risk – no other therapy required High histopathological risk - chemotherapy 6 cycles

- Treatment of the RB with extraocular extension (2) See table 9

Table 7 Treatment of the retinoblastoma without and with extraocular extension

Stage	Definition	Treatment standard
0	The eye can be saved with focal treatment or systemic chemotherapy	See the protocol for intraocular retinoblastoma
I	Enucleation without tumour residue	See the protocol for intraocular retinoblastoma
II	Enucleation with microscopic tumour residue: Scleral Extrascleral extension Tumour invasion of the optic nerve section	Enucleation with histopathological evaluation of risk factors Cerebral and medullary invasion/metastases are excluded Chemotherapy: 12 series in case of tumour invasion in the optic nerve section or extraocular extension 6-12 series in case of scleral invasion (clinical evaluation and CSF cytology every

		3 cycles) External RT post-chemotherapy
III	Regional extension	If ophthalmitis is combined, corticosteroids are administered for 3 days and, in the event of a favourable outcome, the ocular fundus is re-examined for accurate staging. Brain and spinal cord invasion/ metastases are excluded 6-cycle chemotherapy + enucleation/exenteration + external RT (45 Gy) + 6 cycles of chemotherapy (overall 12 cycles) Clinical re-evaluation and CSF cytology after every 3 cycles
IIIA	Clear orbital extension with optic nerve invasion or extraocular extension	
IIIB	Extension at the level of regional lymph nodes	
IV	Metastatic disease	**Palliative treatment** May include: Etoposide p.o., limited cycles of i.v. chemotherapy, other treatments
VA	Haematogenous metastases	
IVB	Extension in the central nervous system	

- Treatment of other particular forms of RB see Table 8

Table 8 Treatment of other particular forms of retinoblastoma

Form of the retinoblastoma	Treatment
CNS metastases	1. Intensive systemic chemotherapy (platinum salts) + craniospinal RT 25-35Gy and boost in CNS lesion 10Gy 2. Systemic chemotherapy (platinum salts) + high dose chemotherapy and stem cell support +/- RT in the CNS. 3. +/- Intrathecal chemotherapy (no clinical or preclinical evidence to support its efficiency)
Extracranial metastases (bone, medullary, hepatic)	Systemic chemotherapy + high dose chemotherapy and stem cell support + RT
Synchronous trilateral retinoblastoma	1. Systemic chemotherapy + surgery + high dose chemotherapy and stem cell support 2. Systemic chemotherapy + surgery and RT
Intraocular progression/ recurrence *	1. Enucleation 2. RT (external or with plates) 3. Local treatment (cryotherapy or thermotherapy) 4. Salvage chemotherapy (systemic or intraarterial) 5. Intravitreal chemotherapy (especially for treatment-resistant/ recurrent vitreous seeding)
Extraocular progression/ recurrence	1. Systemic chemotherapy + RT (orbital disease) 2. Systemic chemotherapy + high dose chemotherapy and stem cell support+ RT (extraorbital disease)

*In children with hereditary RB who have received local treatment, new intraocular tumours may appear which are not considered recurrences; they may respond well to local treatment, including plaque radiotherapy.

New treatments

At present there are studies for molecular therapy (Nutline 3A - molecular inhibitor of MDM2/ MDMX and the interaction with p53; it can be administered subconjunctivally alone or in combination with Topotecan; HDAC inhibitors - histone deacetylase; N-MYC oncogene inhibitors). (14)

Prognosis

The survival rate in retinoblastoma is 98%; local recurrences occur more frequently in the first 8-12 months after having completed the treatment, but extremely rarely after 3 years from the diagnosis.

Recurrences are more common in children diagnosed at an early age, who have large tumours and increased intraocular pressure at diagnosis. (15) The risk of developing a new retinal tumour is 58% for children diagnosed at <3 months and decreases to 14% in those diagnosed at age >6 months. (16)

In the disseminated types at the CNS level, the prognosis is poor (survival <10%).

Complications

Ocular complications after RB (15):

- At the level of the tumour residue and the scar: vascular abnormalities, haemorrhages, retinal changes, glaucoma
- Purulent postenucleation collections
- Post-radiotherapy changes: cosmetic changes (secondary orbital atrophy, atrophy of orbital fat and connective tissue -> eyes sunken into the orbit), radio-retinopathy and optic nerve atrophy, cataracts, dry eyes

The RB is a cancer with a major risk of developing a second malignancy. (14)

Monitoring (15)

Long-term monitoring of children treated for RB is recommended to detect early recurrence, second malignancy, and long-term side effects. The risk of recurrence or appearance of new tumours is minimal after 8-12 months after having finished the conservative treatment. (11)

- Oncological monitoring: RB survivors who have received chemotherapy or radiotherapy require oncological monitoring every 6 months for 5 years then on a yearly basis for their entire life. (15)
- Post therapeutic ophthalmic monitoring: The following ophthalmic monitoring scheme is recommended for children treated conservatively: evaluation under general anaesthesia at 3-4 weeks after diagnosis until 8-12 months after having finished the treatment, generally until around the age of 3 years; it is recommended ophthalmological examination every 6 months for children aged 3-9 years, annual examination for children aged 9-15 years and examination at 2-3 years for children > 15 years, for their entire life. For young children who do not cooperate, evaluation under general anaesthesia is recommended. (11)

Psychological support: Particular attention should be paid to the psychological support necessary for the social, school and professional classification of people with enucleation, those with visual impairment as well as those with significant late side effects (e.g. post-exposure to Carboplatin).

Practical information

The Paediatric Oncology Department within the Oncology Institute "Prof. Dr. Al. Trestioreanu" Bucharest has been an affiliated partner of the European Reference Networks

(ERN) since November 2019, being thus recognized as a European Reference Centre for solid tumours, including RB.

Functional collaboration relationships have been established with specialized clinics in Europe for conservative treatment of RB. Patients receive healthcare in another European state with the approval of the National Health Insurance Fund in the context of the European Directives on collaboration between Member States (Form S2-E112).

We recommend that all patients suspected of RB will be referred to the Paediatric Oncology Department of the Oncology Institute "Prof. Dr. Al. Trestioreanu" Bucharest for additional investigations, specialized treatment and, if necessary, immediate referral for conservative treatment in specialized centres.

Recommendations

- Genetic testing of the patient and people at risk in the family (parents, siblings, children).
- Informing families about the risk of hereditary transmission.
- Ophthalmologic monitoring of all children in families with a history of retinoblastoma.
- Routine determination of the red retinal reflex as an investigation
- Emergency ophthalmological evaluation performed by a physician with experience in paediatric ophthalmology for all children with leukocoria as well as for those with strabismus with sudden onset.
- Tumour biopsy is not recommended due to the risk of secondary dissemination and ocular destruction
- Guidance of patients with confirmed retinoblastoma in a centre specializing in retinoblastoma to complete investigations and specialized treatment
- The treatment is carried out centrally by an experienced multidisciplinary team, in specialized centres, where at least 5-10 newly diagnosed patients are cared for annually and has the possibility to collaborate with European clinics specialized in local therapies.
- In unilateral types group A-C as well as in bilateral types group A-C (D), conservative treatment of the eye and vision is preferred (local treatment +/- systemic chemotherapy).
- Recommended first-line chemotherapy: VCR + Carbo + VP16
- Long-term monitoring of children treated for retinoblastoma for early recurrence, second malignancy and long-term side effects

Bibliography:

1. J.Retinoblastoma-clinical-presentation-evaluation-and-diagnosis. https://www.uptodate.com updated Oct 2018

2. Fabian D et al. A Resource Manual for the Management of retinoblastoma updated September 2017.

3. Raport Registrul National al Cancerelor la Copil -SROHP, Octombrie 2019

4. Kohno S, Kitajima S, Sasaki N, Takahashi C. Retinoblastoma tumour suppressor functions shared by stem cell and cancer cell strategies. World J Stem Cells. 2016;8(4):170–84.

5. Lohmann DR, Gallie BL. Retinoblastoma. 2000 Jul 18 [Updated 2018 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993.

2020. Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

6. Skalet A, Gombos D, Gallie B, et al. Screening Children at Risk for Retinoblastoma. Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists. Ophthalmology 2018;125:453-458 ª 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND License

7. Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, et al and SIOP-PODC graduated-intensity retinoblastoma guidelines writing committee. CLINICAL PRACTICE GUIDELINES SIOP-PODC Recommendations for Graduated-Intensity Treatment of Retinoblastoma in Developing Countries. Pediatr Blood Cancer 2013;60:719–727. 2013 Wiley Periodicals, Inc.

8. Seema Kashyap, Rachna Meel, Neelam Pushker, Seema Sen, Sameer Bakhshi, et al Clinical Predictors of High Risk Histopathology in Retinoblastoma. Pediatr Blood Cancer 2012;58:356–361. http:// DOI.org/ 10.1002/pbc.23239

9. Red Reflex Examination in Infants Section of Ophthalmology Pediatrics 2002; 109; 980 DOI:10.1542/peds.109.5.980

10. PhotoTED Technique. https://wechope.org/retinoblastoma/white-eye-reflex/photo-red-technique/

11. National Retinoblastoma Strategy- Canadian Guidelines for Care. https://www.orpha.net/data/patho/Pro/en/retinoblastoma_canadian_guidelines_EN2009.pdf

12. Fabian I, Reddy A, Sagoo M. Classification and staging of retinoblastoma**.** COMMUNITY EYE HEALTH JOURNAL | VOLUME 31 | NUMBER 101 | 2018

13. J. Sanfilipo, S. C. Formenti, Tumours of the Eye and Orbit in Perez and Brady's Principles and Practice of Radiation Oncology 2019

14. Meel R, Radhakrishnan V, Bakhshi S. Current therapy and recent advances in the management of retinoblastoma in Indian J Med Paediatr Oncol. 2012 Apr-Jun; 33(2): 80–88. doi: 10.4103/0971-5851.99731

15. Nordiske retningslinjer for retinoblastom 2016 [Available from: http://www.nopho.org/member_pages/member_area/workinggroups/retinoblastom/Nordiske%20retningslinjer%20for%20utreding%20og%20behandling%20av%20Retinoblastom_v2_2016-05.pdf.

16. Abramson DH, Greenfield DS, Ellsworth RM. Bilateral retinoblastoma. Correlations between age at diagnosis and time course for new intraocular tumours. Ophthalmic Paediatr Genet. 1992;13(1):1–7.

17. Isidro MA, Roque M, Roque B. Retinoblastoma. https://emedicine.medscape.com/article/1222849-overview updated Dec 2019

8.10 RARE CHILDHOOD CANCERS

Childhood cancers are rare diseases. Very rare tumours in children include a heterogeneous group of tumours. This group of tumors comprices Group XI from ICCC-3. They are rarely found in current practice, even in large centres, which treat a large number of patients. Some of These cancers are so rare that study trials are difficult to start. They are defined as tumours with an incidence of less than 2 cases per 1 million children.

These tumours reflect specific epidemiological interests as they are more frequent in some parts of the world, such as adrenocortical carcinoma in Southern Brazil, thyroid carcinomas in Belarus and Ukraine, nasopharyngeal carcinoma in Africa and China and malignant melanoma in Australia and New Zealand. A combination of environmental and genetic factors may be responsible for these variations.

These tumors specific to young people, with low incidence(e.g.pulmonary blastoma, pancreatoblastoma are treated according to pediatric protocols. Adult-specific tumors (ovarian, digestive, ENT, bronchopulmonary, melanoma, carcinomas) are treated according to expert opinion in similar cases, similarly to cases published in the literature or according to treatment guidelines for adults. (1)

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma accounts for about a third of the upper respiratory tract cancers in children, it occurs extremely rarely under the age of 10 years and it is more common in the group 15-19 years of age. It is a condition associated with Epstein Barr virus infection. (2)

The biopsy is performed from the nasopharynx or the adenopathy. From a histological point of view, it is classified into three categories: type I keratinizing squamous cell carcinoma, type II non-keratinizing squamous cell carcinoma, type III undifferentiated carcinoma.

The onset symptoms are: epistaxis, nasal obstruction, headache, otalgia, trismus, cervical lymphadenopathy, altered nutritional status. The disease metastasizes to the lymph nodes, bone, lungs, liver.

Pre-therapeutic examinations include

- ENT examination performed by a specialist (direct rhinoscopy, posterior fibre optic rhinoscopy)
- Contrast enhanced MRI for head and neck, for evaluating the tumour extension in the soft tissues and/or cranial nerves, skull base or lymph nodes
- CT scan to assess the invasion of base of the skull
- Ophthalmological examination, examination of the auditory function (audiogram)
- +/- Neurological examination depending on symptoms
- Examination of the oral cavity, state of dentition +/- appropriate treatment before the start of the radiotherapy
- Assessment of distant metastasies
  - chest CT scan with contrast agents
  - or +/- FDG- PET- CT. Recommended examination in stage III and IV.
  - Other examinations depending on the clinical situation.

The effective treatment consists of radiotherapy and chemotherapy. The sequence of treatment and the total doses administered depend on the stage of the disease.

The prognosis is good; the 5-year survival exceeds 80%.

Treatment algorithm:

- T1, N0, M0: Only radiotherapy
- T1, N1-3; T2-4, N0-3: Induction chemotherapy followed by radiotherapy + concomitant chemotherapy
- T1-T4, N0-N3, M1: Platinum-based chemotherapy followed by radiotherapy, chemotherapy and concomitant radiotherapy, observation or palliative care, depending on the clinical situation

Total recommended doses: TD = 66 - 70, 2Gy (1.8 - 2 Gy/fr) in 6-7 weeks, on the primary tumour and the lymph node regions invaded or at risk and TD = 50 - 63 Gy (1.8-2 Gy/fr) for subclinical disease.

The total doses and the fractional dose vary depending on the clinical stage and the association with chemotherapy.

If the patient is placed on a clinical trial or chooses to be treated according to a specific protocol, the indications regarding the sequence of treatment, the irradiated volume and the total doses will be observed.

Radiotherapy technique: 3D CRT, IMRT (preferably), proton radiotherapy. The technique that allows the administration of the curative dose with respect to the dose to the organs at risk and the decrease of toxicity will be preferred, depending on the stage of the disease and the clinical situation.

Studies report that the 5 FU + DDP chemotherapy protocol is the most effective, being the standard treatment in most centres. DDP treatment is continued concomitantly with radiotherapy, weekly or every 3 weeks (days 1, 22, 43).

The addition of Docetaxel did not bring benefits. A variant with similar efficacy, but higher toxicity is the combination of DDP + EPI. (3)

The combination of interferon beta significantly prolongs survival. (4)

The refractory or relapsed/metastatic disease benefits from chemotherapy. The research on adults has shown efficacy of EBV cytotoxic T lymphocyte therapy and anti-PD-L1 monoclonal antibody therapy. (5, 6)

Follow-up: - First check-up 8 weeks after the end of the treatment (clinical examination, rhinoscopy, CT scan, MRI examination), EBV monitoring if the test was initially positive

- Subsequent examinations (clinical examination, lymph node regions, rhinoscopy) every 3-4 months for the first 2 years, every 6 months for another 3 years, annually throughout the entire life.
- PET-CT scan at 12 weeks if there is a clinical suspicion of persistence of the disease after the end of the treatment, suspicion of recurrence, or for the differential diagnosis of recurrence from post-radiotherapy changes
- Examination of the thyroid function starting from 6 months post-therapeutically

Esthesioneuroblastoma (olfactory neuroblastoma)

It is a rare tumour that occurs in the olfactory epithelium. It has a bimodal distribution with two peaks of incidence: between 11-20 years and 50-60 years. It is a distinctive type of PNET.

The symptomatology is represented by nasal obstruction, epistaxis, hyposmia, exophthalmos, nasopharyngeal mass with extension in orbits, sinuses, frontal lobe. It metastasizes to the lymph nodes.

Staging examinations:

- Contrast enhanced CT scan to identify possible bone invasion
- Contrast enhanced MRI: useful for assessing intracranial extension
- Chest CT scan or PET-CT to evaluate metastatic disease

Pre-therapeutically, the state of dentition and the state of nutrition are evaluated.

Esthesioneuroblastoma is staged according to the Kadish system (localized tumour = stage A, advanced locoregional stages= B and C, metastatic stage = D). Stage and histopathological grade are the most important prognostic factors.

Treatment:

- Surgery alone: for small lesions, with a low degree of differentiation, limited to the ethmoid

- Multimodal treatment: surgery, radiotherapy and chemotherapy for locoregionally advanced tumours or high degree of differentiation.

- Radiotherapy: TD = 50-60 Gy, (1.8 - 2 Gy/fr) on the primary tumour. For extensive tumours (Kadish C) elective cervical irradiation decreases the risk of recurrences at this level.

- Neodjuvant chemotherapy is given for inoperable or disseminated tumours. Effective cytostatic combinations include: DDP, VP 16, IFO, VCR, ACT-D, CTX, DOXO, IRI, DOCE.

Long-term monitoring of esthesioneuroblastoma is important, while late recurrences may occur even after 15 years. (7)

Thyroid cancer

It is found in the 15-19 age group, the incidence being 0.5-1.2 cases per million children under 14 years and 4.4-11 per million children between 15-19 years, increasing in Europe and USA. The incidence rate increases by 1.1% per year, due to the improvement of the diagnosis but there is also a real increase due to various environmental factors. It occurs more frequently in girls. (8)

Thyroid cancer is the most common form of cancer associated with radiation exposure. Risk factors are: radiation exposure (papillary carcinoma), genetic inheritance (medullary carcinoma: mutation of the RET proto-oncogene), family history. (8)

The most common histopathological type, 90%, is represented by the differentiated cancer (papillary type and follicular type). Undifferentiated, aggressive forms occur rarely: medullary thyroid carcinoma, anaplastic carcinoma. Numerous genetic and molecular changes have been identified, the most common in children being RET/PTC rearrangements (in papillary carcinomas). RET mutations are involved in the development of MEN2A, MEN2B and familial thyroid cancer. (8)

From a clinical point of view, the differentiated thyroid cancer is more aggressive at a young age. The lymph node invasion and the metastases are more common, the recurrence rate is higher. The factors for unfavourable prognosis are: male sex, voluminous and/or metastatic tumour, medullary type. However, the prognosis of the disease is good, even for the high-risk group. Overall survival at 30 years is over 95%. (8)

The pre-therapeutic evaluation includes: thyroid ultrasound (first-line diagnostic technique), thyroid scintigraphy, cervicothoracic CT scan, evaluation of the thyroid function, serum thyroglobulin level, calcitonin dosing (medullary carcinoma). TNM or AJCC staging is used.

The treatment of thyroid cancer follows the protocols used in adult patients and it consists of surgery (thyroidectomy with lymphadenectomy) and/or ablative therapy with radioactive iodine 131 I.

In case of recurrence, ablative therapy with I-131 and thyroid hormone replacement therapy is indicated.

For refractory disease or recurrence refractory to the treatment with I-131, chemotherapy has not been shown to be effective. The therapy with tyrosine kinase inhibitors (Sorafenib, Levatinib, BRAF inhibitor: Vemurafenib) has been shown to be effective. (9)

Post-therapeutic follow-up is done every 6 months for the first 5 years, then annually.

Midline carcinoma involving the NUT gene

It is an extremely rare and very aggressive disease, which is genetically characterized by rearrangements of the NUT gene, most often by creating a chimerism that encodes the formation of the BRD-NUT fusion protein. The tumour is of the epithelial type, and it develops in the epithelial structures of the midline (mediastinum, aerodigestive tract). It has the histological characteristics and the clinical features of an undifferentiated carcinoma. The average age at diagnosis is 16 years. The prognosis is very severe, the average survival being less than 1 year. Therapeutic options include: chemotherapy (cisplatin, taxanes, alkylating agents), surgery, radiation therapy. (10)

Pleuropulmonary blastoma (PPB)

It is an extremely rare and aggressive malignant disease that affects the lungs and/or pleura.

In about 2/3 of cases it is associated with the germline mutation of the DICER1 gene, a mutation highlighted in many other cancers, and there is often a familial association of PPB with cystic nephroma and other renal tumours. The following types have been identified:

- Type I occurs at a young age, it is characterized by a cystic structure and good prognosis;

Type Ir (suffix R meaning regression or non-progression) has cystic feature (and it is associated with the DICER1 mutation;) In PPB patients with Dicer1 mutation, family members should be offered genetic guidance and testing.

- Type II has both cystic and a solid component, the solid component appears blastomatous in microscopy, possibly anaplastic; it has a more severe evolution;

- Type III is a solid lesion, often anaplastic, with severe evolution.

The unfavourable prognostic factors are: inoperability and the Type III. The prognostic significance of the DICER1 mutation is unclear. (11)

From a clinical point of view, the disease is manifested by: fever, chest pain, respiratory failure. It is located peripherally but over time it may involve the pleura, mediastinum, heart, large vessels, diaphragm and can be complicated by pulmonary embolism. There is no standard therapy. Surgery can be performed on the primary tumour; adjuvant (or) chemotherapy for the residual tumour may be given. The adjuvant chemotherapy appears to lower the risk of relapse. The cytostatic agents and the used regimens are those of the protocols for rhabdomyosarcomas. (12)

Pancreatoblastoma

It represents 10-20% of all pancreatic cancers in children, the average age of onset being 5 years. Most cases occur sporadically. Children with Beckwith-Wiedemann syndrome have an increased risk of occurrence of pancreatoblastoma. It has also been associated with familial adenomatous polyposis syndrome. In some cases, mutations in the CTNNB1 and IGF2 genes have been identified. The tumour may secrete AFP which is then used as a tumour marker as well as ACTH or ADH, in which case the child has symptoms specific to hormonal disorders. The tumour metastasizes to the lymph nodes, liver, lungs. It has a good prognosis; the reported rate of long-term survival is 80%, the prognosis depending primarily on operability. The essential therapeutic act is the surgical one. For inoperable tumours, neo-adjuvant chemotherapy is administered, followed by adjuvant chemotherapy. The recommended protocol is PLADO (DDP + Doxo), administered similarly to the hepatoblastoma protocol. (13, 14)

Carcinoid tumor of the appendix

Carcinoid tumors are rare malignant neuro-endocrine tumors found mainly in the bowel and lung. They are the most common tumors of the appendix.

The clinical onset consists of abdominal pain, often with the appearance of acute appendicitis.

In carcinoid tumours of the appendix in children, the first therapeutic act is the surgical one, the appendectomy being sufficient for the vast majority of patients. Patients with tumours smaller than 2 cm, completely excised, without residual tumour are to be monitored. For patients with large tumours, with invasion in the mesoappendix or in the periappendicular fat, surgery can be completed, up to hemicolectomy. For high-risk patients (tumours larger than 2 cm, postoperative residue or positive lymphadenopathy) somatostatin analogs scan may be performed.

Survival is 100% in various studies, regardless of the extent of surgery. Biochemical and imaging monitoring has not been shown to be effective. (15)

Malignant melanoma

It is the most common skin cancer in children, with two thirds of cases occurring in the 15-19 age group. The risk factors are exposure to ultraviolet radiation, the presence of giant melanocytic nevi, xeroderma pigmentosum, neurocutaneous melanosis, immunodeficiency and immunosuppression, hereditary retinoblastoma and the particular phenotype (red hair, blue eyes, white complexion, dysplastic nevi or numerous melanocytic nevi, family history of melanoma).

The unfavourable prognostic factors are the advanced stage of the disease, age under 10 years, spitzoid morphology, ulceration. Patients with CNS melanoma, in the context of congenital melanocytic nevi syndrome, have a severe prognosis, mortality being 100%. (16)

Staging procedures includes biopsy or excision (0.5 cm margins for in situ lesion, 2 cm for thicker lesions), sentinel node technique for lesions thicker than 1 mm. Genetic alterations are similar to those encountered in adults, the most common being the BRAF somatic mutation (96%).

Histological confirmation of melanoma in children is difficult. There might be problems of over-diagnosis because of misinterpretation of benign Spitz nevus, or under-diagnosis because of reluctance to diagnose a malignant melanoma in a child. Evaluation by experienced pathologist is needed.

The treatment consists of surgical excision, which is the treatment of choice for localized melanoma. A sentinel node biopsy is also performed, if positive; followed by dissection of regional nodes.

The patients in the high-risk group can benefit from treatment with immune checkpoint inhibitors or BRAF/MEK inhibitors by extrapolating the experience in adults. There are currently no completed paediatric studies. This type of therapy can be given for metastatic, recurrent or progressive disease.

The standard therapy for adults, also recommended for children with malignant melanoma, is the combination of Ipilimumab and Nivolumab or Nivolumab alone. (17) Paediatric studies are underway, investigating the response to treatment with BRAF inhibitors, MEK inhibitors and PDL-1 inhibitors.

Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a rare but aggressive childhood cancer. The worldwide incidence has been estimated at 0.3/million/year with a bimodal peak under the age of 5 and after 10 years and they affect girls more frequently than boys. There is remarkable geographical

variation with the incidence in Southern Brazil, likely due to the high prevalence of a founder TP53 mutation in Brazil.

ACC commonly presents with virilization and Cushing syndrome and rarely with feminization and hyperaldosteronism. ACC can also be nonfunctional and diagnosed incidentally during the evaluation of abdominal pain, fatigue or other nonspecific symptoms. The majority of ACC are sporadic, but some are associated with a genetic defect. Individuals with the Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, multiple endocrine neoplasia type 1, and familial adenomatous polyposis have an increased risk of ACC.

Surgery is the mainstay of treatment. Even after complete resection, a high risk of recurrence of ACC remains. Good prognostic factors are: age < 4 years, tumor size < 4cm, early stage (I-II) and good quality of surgery. Despite multimodality approaches including mitotane (an adrenolytic drug), chemotherapy with cisplatin, etoposide and doxorubicin (CED), and radiotherapy, prognosis of pediatric ACC remains poor with an estimated 5-year survival rate ranging from 30 to 90%. (18)

Recommendations

- These cancers are so rare that study trials are difficult to start
- The tumours specific to young people, with low incidence (e.g. pulmonary blastoma, pancreatoblastoma) are treated according to paediatric protocols
- Adult-specific tumours (ovarian, digestive, ENT, bronchopulmonary, melanoma, carcinomas) are treated according to personal experience in similar cases, similarly to cases published in the literature or according to the treatment guidelines for adults

Bibliography

1. Ferrari A, Bisogno G, De Salvo GL, et al.: The challenge of very rare tumours in childhood: the Italian TREP project. 2007. Eur J Cancer 43 (4): 654-9.

2. Ayan I, Kaytan E, Ayan N: Childhood nasopharyngeal carcinoma: from biology to treatment. 2003. Lancet Oncol 4 (1): 13-21.

3. Cheuk DK, Billups CA, Martin MG, et al.: Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. 2011. Cancer 117 (1): 197-206.

4. Buehrlen M, Zwaan CM, Granzen B, et al.: Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. 2012. Cancer 118 (19): 4892-900.

5. Louis CU, Straathof K, Bollard CM, et al.: Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. 2010. J Immunother 33 (9): 983-90.

6. Ma BBY, Lim WT, Goh BC, et al.: Antitumor Activity of Nivolumab in Recurrent and Metastatic Nasopharyngeal Carcinoma: An International, Multicenter Study of the Mayo Clinic Phase 2 Consortium (NCI-9742). 2018. J Clin Oncol 36 (14): 1412-1418.

7. Porter AB, Bernold DM, Giannini C, et al.: Retrospective review of adjuvant chemotherapy for esthesioneuroblastoma. 2008. J Neurooncol 90 (2): 201-4.

8. Dermody S, Walls A, Harley EH: Pediatric thyroid cancer: An update from the SEER database 2007-2012.2016. Int J Pediatr Otorhinolaryngol 89: 121-6.

9. Iyer P, Mayer JL, Ewig JM: Response to sorafenib in a pediatric patient with papillary thyroid carcinoma with diffuse nodular pulmonary disease requiring mechanical ventilation. 2014. Thyroid 24 (1): 169-74.

10. Lemelle L, Pierron G, Fréneaux P, et al.: NUT carcinoma in children and adults: A multicenter retrospective study.2017. Pediatr Blood Cancer 64 (12).

11. Slade I, Bacchelli C, Davies H, et al.: DICER1 syndrome: clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. 2011. J Med Genet 48 (4): 273-8.

12. Bisogno G, Brennan B, Orbach D, et al.: Treatment and prognostic factors in pleuropulmonary blastoma: an EXPeRT report. 2014. Eur J Cancer 50 (1): 178-84.

13. Glick RD, Pashankar FD, Pappo A, et al.: Management of pancreatoblastoma in children and young adults. 2012. J Pediatr Hematol Oncol 34 (Suppl 2): S47-50.

14. Bien E, Godzinski J, Dall'igna P, et al.: Pancreatoblastoma: a report from the European cooperative study group for paediatric rare tumours (EXPeRT). 2011.Eur J Cancer 47 (15): 2347-52.

15. Njere I, Smith LL, Thurairasa D, et al.: Systematic review and meta-analysis of appendiceal carcinoid tumors in children. 2018. Pediatr Blood Cancer 65 (8): e27069.

16. Campbell LB, Kreicher KL, Gittleman HR, et al.: Melanoma Incidence in Children and Adolescents: Decreasing Trends in the United States. 2015. J Pediatr 166 (6): 1505-13.

17. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al.: Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. 2017. N Engl J Med 377 (14): 1345-56.

18. Gupta.N, Rivera M, Novotny P, Rodriguez V, Bancos I, Lteif A: Adrenocortical Carcinoma in Children: A Clinicopathological Analysis of 41 Patients at the Mayo Clinic from 1950 to 2017, Horm Res Paediatr 2018;90:8–18

8.11 HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN

8.11.1 AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

The use of high-dose chemotherapy, followed by autologous hematopoietic stem cell transplantation (aHSCT), in the treatment of chemosensitive tumours is based on the observation of a linear correlation between the response rate and the dose of chemotherapy used. The myelosuppression is the major adverse reaction to this dose, which requires reinfusion of hematopoietic stem cells in order to restore the hematopoiesis. The indication for autologous stem cell transplantation is described and detailed in the appropriate protocol that the child is following and should be discussed and described and concluded in a local or multidisciplinary team meetings.

Definitions (1)

The autologous hematopoietic stem cell transplantation (aHSCT) is a medical procedure that allows the administration of very high doses of chemotherapy (conditioning therapy), with the intention of destroying residual tumour cells followed by reinfusion of the patient's hematopoietic stem cells (previously harvested through the mobilization procedure) and continued by the grafting stage.

Classification of transplant procedures according to the level of recommendation

• Standard of care (S)

The indications classified as "standard of care" are well defined, and the results are equal or even superior to those of the treatment without transplantation. “Standard of care” transplantations can be performed in a specialized centre with experience in HSCT procedures and with an adequate infrastructure.

• Clinical option (CO)

The “clinical option” (CO) category is based on the fact that, for many indications, the number of patients is low and therefore randomized trials that compare the conventional treatments and HSCT are difficult to be performed. The results of the studies with a small number of patients who undergo HSCT confirm the efficacy and acceptable toxicity of the procedure. The current interpretation of existing data for the indications placed in this category supports HSCT as a valuable option for each patient, after careful discussion regarding the risks and benefits with the patient/family, but the value of HSCT requires further assessment for these patient groups. Indicated transplantations under this category should be performed in a specialized centre with major experience in HSCT procedures, with an appropriate infrastructure.

• Indications for development (D)

The indications for development are considered in cases where experience is limited in combination with the type of transplantation and when further research is needed in order to

define the role of HSCT. These transplantations should be performed in a clinical protocol. These protocols can be of different types, such as a randomized comparison of two or more therapeutic approaches, or a pilot study on a small number of patients performed in transplant units with recognized expertise in the management of that disease, or in that type of HSCT. The category also covers fundamentally new approaches to disease management that, at a different stage, may already be classified according to the "standard of care" or "clinical option". Protocols for "transplantations for development" must be approved by local research ethics commissions. The results of these studies are generally intended for presentation and/or publication for the medical society. Centres performing transplantations in the "developmental" category should meet the international standards.
(http://www.ebmt.org/1WhatisEBMT/Op_Manual/OPMAN16_Clinical%20Trials%20Guidelines.pdf)

- Generally not recommended (GNR)

The GNR category may include the stages of the disease that are so advanced that the chances of success are very low with conventional procedures. This category also includes HSCT for a disease in a phase or condition in which patients are not conventionally treated with HSCT.

The evaluation of the pretransplant patient with indication for autologous transplantation has as its main purpose the assessment of the disease status and the confirmation of the absence of the bone marrow involvement, in order to harvest hematopoietic stem cells (HSC) (see Table 1).

Table 1: EVALUATION OF THE PRE-TRANSPLANT PATIENT	
	Analysis type
Informed consent	
Immunohematology	ABO, Rh phenotype, Kell, Kidd, Duffy, MNSs
Laboratory	C-reactive protein
	Blood count, reticulocytes, peripheral blood smear
	Coagulation
	Liver, kidney, sideremia, ferritin, NSE, alpha fetoprotein tests
	Electrophoresis and immunoglobulin dosing
	Hormones (TSH T 3, T4)
	Virology (TPHA, CMV, HIV, HTLV, EBV, HSV, VSV, HAV)
	HCV, atg HBs, Hbe antibodies, HBc antibodies) + parasitology
	Complete urine tests
Hematological	Osteomedullary biopsy
	Cytogenetics - monitoring of specific anomalies
	Immunohistochemistry
Imaging examinations	Pulmonary radiography + sinuses
	Abdominal ultrasound
	CT scan (chest +/- abdomen +/- skull), PET – CT, MRI
Bacteriology	Exudate, urine culture, stool culture
Interdisciplinary	Pneumology + pulmonary function tests
	ENT
	Cardiology + heart ECG, Echo
	Ophthalmology
	Gynaecology + pregnancy test
	Dentistry
	Psychology and Psychiatry

HSCs mobilization chemotherapy

The mobilization of HSCs from bone marrow into peripheral blood in patients with an indication for autologous transplantation is achieved either from steady state or by chemotherapy, both are followed by growth factors (G-CSF). In most patients, after 12-14 days from the start of the procedure, a sufficient level of stem cells is obtained in the periphery to allow harvesting a graft of at least $2.5x10^6$ CD34/kg cells, which will allow adequate grafting. The mobilization protocols should be used according to the relevant treatment protocol and multidisciplinary team meetings.

Growth factors

After the completion of chemotherapy, treatment with G-CSF 10µg/kg/day, sc, with daily monitoring of leukocyte counts is initiated. When the value of leukocytes is > $1x10^9$/L, the number of CD34 cells in the peripheral blood is examined by flow cytometry. If CD34 ≥ 20/mmc, apheresis is initiated for HSCs harvesting.

Growth factors are also used after the infusion of the stem cells from day +5(7) an onwards until leucocyte recovery.

Indications for autologous transplantation

• Solid tumours

Neuroblastoma is the most common extracranial solid tumour in children, accounting for approximately 8% of all childhood cancers and accounting for 15% of childhood cancer mortality. The stratification in risk groups of the patients with neuroblastoma is based on the analysis of several factors – imaging examination, histology, cytogenetics, age at the time of diagnosis. Under the conditions of multimodal therapy with chemotherapy, radiotherapy, autologous hematopoietic stem cell transplantation, immunotherapy, differentiation therapy with isotretinoin, survival in types with increased risk of neuroblastoma is now approaching 50%. The SIOPEN group recommends autologous transplantation for the following situations:

- High risk types
- Localized types with n-myc amplification
- Chemosensitive metastatic recurrence in patients > 18 months with N-myc amplification who did not have a previous autologous HSCT

Ewing's sarcoma is a condition that occurs at any age, with maximum incidence in adolescents and young adults. The treatment is based on a multidisciplinary approach, which combines intensive neo-adjuvant and adjuvant chemotherapy, according to the risk group, surgery and/or radiotherapy. The role of high-dose chemotherapy is controversial, the indications being reserved for the following situations:

- Ewing's sarcoma - high-risk types
- Ewing's sarcoma relapse

Central nervous embryonal tumors like medulloblastoma are conditions in which the results of the treatment have improved by using craniospinal irradiation combined with chemotherapy, but with severe neurological complications in children <6 years. Chemotherapy regimens with autologous transplantation were evaluated to avoid long-term neurological sequelae. It is not clear whether single or in tandem autologous transplantation is superior in effectiveness and/or safety. Transplant indications refer to:

- Medulloblastoma – high-risk types and children younger than 4 years
- Medulloblastoma/pineoblasoma – infant types

- Atypical teratoid/rhabdoid tumour

Germ cell tumours (GCTs) have a cure rate for high-risk, recurrent and/or refractory forms of only 25% in the case of conventional chemotherapy. High-dose chemotherapy is used in the following situations:

- GCTs relapse
- GCTs refractory forms

• Hodgkin's lymphoma has an increased cure rate in children under the current protocol conditions. The indication for transplantation is made for the following situations:

- Partial remission or complete remission with positive PET
- Primary refractory but chemosensitive Hodgkin's lymphoma
- The first or another chemosensitive relapse

• Non-Hodgkin's malignant lymphomas. The studies evaluating autologous hematopoietic stem cell transplantation as being an effective therapy for refractory NHL in the paediatric population are limited. In recent years, there have been encouraging reports of aHSCT as a rescue therapy for paediatric patients with NHL and relapse to first-line therapy, but with chemosensitivity to second-line treatment. Transplant indications are reserved for:

- refractory, aggressive types of NHL, with no response to standard chemotherapy
- NHL with post-chemotherapy relapse

Recommendations

• The use of high-dose chemotherapy, followed by autologous hematopoietic stem cell transplantation in the treatment of chemosensitive tumours, is based on the observation of a linear correlation between the response rate and the dose of chemotherapy that was used.

• It is a procedure that has improved the prognosis in some high-risk, refractory or relapsed solid tumours groups, in some brain tumors (young children and infants to avoid irradiation) and in some malignant lymphomas (refractory or relapsed groups).

• The use of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation should only be performed in centres that are authorized and qualified for this procedure and prepared for the toxicity that this procedure implies.

Bibliography

1. Duarte, R.F., Labopin, M., Bader, P. *et al.* Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant* 54, 1525–1552 (2019). https://doi.org/10.1038/s41409-019-0516-2

2. Wingard JR, Gastineau DA, Leather HL, Snyder EL, Szczepiorkowsi ZM. Hematopoietic stem cell transplant – A handbook for clinicians 2nd Edition, 2015

8.11.2 ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

The decision to perform the transplantation procedure on a patient involves the attending physician, the doctor at the transplantation centre and the patient/family, after a careful analysis of the alternatives, the risks and the benefits of the procedure. The decision-making process for transplantation is a complex procedure and includes several factors in addition to the conditioning regimen and basic indication for transplantation. Some examples of such variables include general health and performance, comorbidities, disease risk/status (e.g. remission status and treatment capacity), graft and donor source. For some diseases (e.g. AML, ALL) the recommendations for transplantation are based on genetic characteristics. (1)

Definitions

The allogeneic transplantation is a complex medical procedure used in the treatment of malignant and non-malignant hematological diseases with the main objective of replacing abnormal hematopoiesis and/or restoring the affected immune system. Hematopoietic stem cell transplantation HSCT is defined as an treatment program that begins with a conditioning regimen, continues with the infusion of hematopoietic stem cells and then with the phase of hematopoiesis recovery or grafting of hematopoietic stem cells. Hematopoietic stem cells are harvested from the donor, somtimes after a mobilization procedure. (1)

Classification of hematopoietic stem cell transplantation procedures:

- **Donor source**
  - Transplant from HLA compatible family donor (MSD - matched sibling donor)
  - Transplant from unrelated donor (MUD - matched unrelated donor)
  - Transplant from haploidentical donor
- **Origin of stem cell source**
  - Peripheral stem cells transplantation
  - Bone marrow stem cell transplantation
  - Umbilical cord blood stem cell transplantation
- **intensity of conditioning therapy**
  - Transplant with myeloablative conditioning (MAC)
  - Transplant with non-myeloablative conditioning (NMA)
  - Transplant with reduced-intensity conditioning (RIC)
- The classification of transplant procedures according to the level of recommendation are described in chapter 8.11.1 Indications for autologous haematopoietic stem cell transplantation

The pre-transplant evaluation of the patient includes the investigations necessary to confirm the indication of the transplant (disease stage) and the potential comorbidities having an impact on the post-transplant evolution. (seeTable 1) (2)

Table 1 PRE-TRANSPLANT EVALUATION OF THE PATIENT (could vary according to disease)	
Informed consent	
Immunohematology	ABO group, Rh phenotype, Kell, Kidd, Duffy, MNSs tests on irregular antibodies and antiplatelet antibodies
Laboratory	HLA examinations
	C-reactive protein

	Blood count, reticulocytes, peripheral blood smear
	Coagulation
	Liver, kidney, sideremia, ferritin tests
	Electrophoresis and immunoglobulin dosing
	Hormones (TSH T3, T4)
	Virology (TPHA, CMV, HIV, HTLV, EBV, HSV, VSV, HAV)
	HCV, atg HBs, Hbe antibodies, HBc antibodies + parasitology
	Complete urine tests
Hematological examinations	Bone marrow aspirate/biopsy
	Citogenetics/molecular biology
	Immunophenotyping
	Specific tests for disease status monitoring (e.g. MRD)
Imaging investigations	Pulmonary radiography + sinuses
	Abdominal ultrasound
	CT scan (chest +/- abdomen +/- skull), PET – CT, MRI
	Heart ECG, Echo
Bacteriology	Exudate, urine culture, stool culture
Examinations	Pulmonary with ventilatory tests
	Cardiology
	ENT
	Ophthalmology
	Gynaecology + pregnancy test
	Dentistry
	Psychology/Psychiatry

In case of stem cell source from a MSD or another family donor , the evaluation of the hematopoietic stem cell donor is performed after obtaining the donation consent and confirming the HLA compatibility. Table 2 (2)

EVALUATION OF THE HEALTHY DONOR	
	Analysis type (could vary due to age of donor)
Informed consent	
Immunohematology	ABO group, Rh phenotype, Kell, Kidd, Duffy, MNSs
	tests on irregular antibodies and antiplatelet antibodies
Laboratory	HLA examinations
	C-reactive protein
	Blood count, reticulocytes, peripheral blood smear
	Coagulation
	Liver, kidney, sideremia, ferritin tests,etc.
	Electrophoresis and immunoglobulin dosing
	Hormones (TSH T 3, T4)
	Virology (TPHA, CMV, HIV, HTLV, EBV, HSV, VSV, HAV)
	HCV, atg HBs, Hbe antibodies, HBc antibodies
	Parasitology tests – toxoplasmosis, toxocara
	Complete urine tests
Imaging investigations	Pulmonary radiography + sinuses
	Abdominal ultrasound
	Heart Echo
Bacteriology	Exudate, urine culture, stool culture
Interdisciplinary	Cardiology + ECG
	Dentistry

Standard indications for HSCT in patients <18 years (3, 4)

According to the EBMT (European Group for Bone Marrow Transplant) data, more than 20% of allo-HSCTs are performed in patients under 20 years of age, however, at least one third of HSCT in children are performed for rare indications. Clinical trials to evaluate the results of HSCT in children have been limited by a small number of cases and disease-specific complications.

• *Acute lymphoblastic leukaemia (ALL)*

The indications for HSCT in children with ALL in complete remission 1 (CR1) are limited to the high-risk subpopulation, defined by most study groups as having an estimated event-free survival value (EFS) ≤ 50%. Risk factors that represent an indication for HSCT are known biological molecular markers or chromosomal abnormalities and biological factors, including a poor response to prednisone and resistance to initial chemotherapy, including persistence of minimal residual disease (MRD). Also, infants with very high risk ALL benefit from HSCT. All patients with early or very early bone marrow relapse have a severe prognosis when treated with conventional chemotherapy.

The HSCT indications of the AIEOP-BFM ALL 2009 study are practically maintained in the AIEOP-BFM ALL 2017 study, with the following modifications:

- TCF3-HLF: these patients have an indication for HSCT independently of the MRD response
- Non-remission at the end of induction (without CR d33)
- KMT2A-AFF1 with MRD positive day 33 and/or day 78
- Hypodiploidy below 44 chromosomes or DNA index below 0.8 with MRD positive day 33 and/or day 78
- IKZF1plus + MRD day 15 ≥10% + MRD positive day 33 and/or day 78
- IKZF1plus + MRD day 15 <10% + MRD positive day 78
- MRD positive at day 33 and/or day 78

Infants:

- Non-remission at the end of induction (without CR d33)
- Age under 6 months and leukocyte count over 300 $x10^9$/L at diagnosis
- Age under 6 months and unfavourable response to cortisone
- MRD positive at day 33 and / or day 78

• *Acute myeloblastic leukaemia(AML)*

AML in children is a rare and heterogeneous disease; the rate of EFS with intensive chemotherapy is around 60%. HSCT is not recommended as first-line therapy for low-risk patients. AML types FAB M0, M6 or M7 have very low chances with conventional chemotherapy and these types have indications for HSCT in CR1.

HSCT indications are represented by:

a. AML that associates cytogenetic abnormalities that predispose to relapse:

- 7/7q-, -5/5q-, 12p anomaly, inv (3)/t (3; 3) / abn (3q), CBFA2T3-GLIS2
- t(4; 11), t(5; 11), t(6; 11), t(10; 11), t(6; 9), t(9; 22), t(7; 12), t(11; 17), t (8; 16), t(3; 5)
- complex karyotype
- FLT3-ITD

b. AML with MRD-positive at the end of the induction treatment

c. Secondary AML (myelodysplastic syndrome, chronic myeloproliferative disorder, AML after previous cytostatic treatments)

d. AML in CR2 or any morphological remission after relapse

• *Myelodysplastic syndrome (MDS) / myeloproliferative disorder (MPD)*

The indications for transplantation in MDS / MPD are the following:

- Refractory cytopenia of childhood (RCC) with -7/7q-/- or ≥2 chromosomal aberrations
- RCC with any karyotype, less -7/7q- or ≥2 chromosomal aberrations that become transfusion dependent and neutrophils $<1x10^9/L$
- Refractory anaemia with excess blasts (RAEB)
-Refractory anaemia with excess blasts in transformation (RAEBT)
-AML-MDS
-relapse RAEBT post HSCT
- MDS secondary to previous chemotherapy treatment for malignancy
- MDS secondary to a previous condition (idiopathic aplastic anemia)
- chronic juvenile myelomonocytic leukaemia (JMML) with somatic mutations K-RAS, N-RAS, PTPN11, NF1
-First therapeutic line
-Relapse after HSCT

• *Chronic myeloid leukaemia (CML)*

It is currently accepted that all children and adolescents with chronic phase CML should be initially treated with tyrosine kinase inhibitors (TKI) first-generation (imatinib) or second-generation (dasatinib) and to be maintained with TKI therapy indefinitely if there is a good molecular response.

The indication for HSCT is discussed in the following situations:

- First chronic phase, after failure of TKI therapy (> / = 2^{nd} generation), with resistant mutation (e.g. T315I) or with intolerance to TKI therapy
- Progression to the accelerated or blastic phase, after obtaining complete morphological remission (<5% blasts in BM), with or without MRD
- Extramedullary determination of disease, with remission before HSCT

• *Acquired aplastic anaemia (AA)*

HSCT is the first therapeutic option in cases of aplastic anaemia in a paediatric patient with a compatible family donor and it is a therapeutic emergency.

The indications for HSCT are:

- AA severe or very severe types - first-line treatment if there is a compatible family donor
- AA severe or very severe types - second line treatment - post relapse – immune-suppressive treatment
- AA moderate types with relapse after immunosuppressive treatment

• *Congenital bone marrow failure syndromes (BMFS)*

BMFS are a heterogeneous group of conditions showing quantitative or qualitative abnormalities of one or more cell lines, caused by mutations in genes encoding structural proteins or elements of major cellular pathways - DNA repair, telomere length maintenance or ribosomal biosynthesis. HSCT is the only curative therapeutic method for bone marrow failure associated with the many abnormalities described in BMFS, but without a favourable impact on the risk of developing malignancies, associated with BMFS.

HSCT indications are represented by:

- Fanconi anemia - transfusion dependent
- Blackfan Diamond anaemia
- transfusion dependent
- no response to steroids

- cortisone dependent > 0.3 mg/kg/day
- post-transfusion alloimmunization
- progressive pancytopenia
- MDS / AML transformation
- Dyskeratosis congenita (DKC) - dependent on transfusions
- Severe congenital neutropenia - severe, recurrent infections
- Severe congenital thrombocytopenia

• *Hemoglobinopathies*

HSCT outcomes for thalassemia major have progressively improved by identifying Pesaro risk classes and developing new conditioning regimens and supportive therapies. The current HSCT indications are:

- beta thalassemia major
- sickle cell disease
- age <16 years
- compatible family donor
- complications occurrence: stroke > 24h, lung involvement, nephropathy, retinopathy, osteonecrosis, recurrent priapism, recurrent severe vaso-occlusive crisis, abnormal transcranial velocities Doppler, altered neuro-psychic function with MRI and angio-MRI with changes, post-transfusion alloimmunization.

• *Primary immunodeficiencies*

Primary immunodeficiencies (PID) are genetic disorders characterized by nonspecific (innate) or specific (adaptive) immunity abnormalities. Recurrent, persistent opportunistic infections are the classic hallmarks of PID, which are associated with phenomena of autoimmunity and predisposition to malignancy. HSCT is indicated in many cellular immunodeficiencies that affect innate or adaptive immunity, of which severe combined immunodeficiency (SCID) is the most severe, with progression to death in infants or young children.

Indications of HSCT in PID:

-SCID

-Chronic granulomatous disease with severe, frequent infections

- Haemophagocytic lymphohistiocytosis (HLH)

HLH - familial form, in the first complete remission

HLH - secondary form, at relapse

• *Malignant lymphomas*

Most children and adolescents with malignant lymphomas are cured with conventional chemotherapy, only a few patients are eligible for HSCT:

- Malignant lymphomas (Hodgkin's or non-Hodgkin's) with chemosensitive relapse (complete or partial response) after autologous haematopoietic stem cell transplantation, without massive disease determination
- Primitive lymphomas refractory to chemotherapy treatment

• *Metabolic diseases*

Most metabolic diseases with indication for HSCT are lysosomal storage diseases; but posttransplant evolution is frequently affected by lack of grafting. Cord cell transplantation has favourable results in patients with Hurler syndrome.

• *Refractory solid tumours* - indications in clinical trials. In general, HSCT in children with solid tumours should be explored only in prospective studies in experienced centres.

Side effects of HSCT

The type and severity of side effects from HSCT are influenced by the degree of HLA matching between donor and recipient, the condition and age of the patient and the chemotherapy regimen.

- *Short term toxicities of Allogeneic Stem Cell Transplant*

The the more common short term side effects are the bone marrow suppression, the infections (bacterial, viral and fungal), mucositis (very common and debilitating) , the veno-oclusive disease of the liver, interstitial pneumonia syndrome (occurring several months after treatment), the graft-versus-host disease (GVHD) that can develop within days or as long as 3 years after transplantation.

The Graft Failure occurs when bone marrow function does not return.

- *Long-Term Side Effects of Allogeneic Stem Cell Transplant*

Specific and late side effects are related to the vulnerability of the developing organism - hormonal deficiencies, growth retardation, dental and skeletal lesions, cataracts, infertility, as well as the high risk of malignancies especially in congenital syndromes with chromosomal fragility.

Table 3 HSCT indications for children

Disease	Disease status	MSD	MUD	Alternative donor
Malignant hematological disorders				
AML	CR1 low risk	GNR		
	CR1 high risk / very high risk	S	S	CO
	CR2	S		
	>CR2	S	CO	CO
ALL	CR1 low risk	GNR		
	CR1 high risk	S	S	CO
	CR2	S	S	CO
	>CR2	S	S	CO
CML	Chronic phase, TKI failure gen 2, 3	S	S	CO
	Accelerated phase, blast phase,> CP1	S	S	CO
NHL	CR1 low risk	GNR		
	CR1 high risk	CO		
	CR2	S	S	CO
HD	CR1	GNR		
	Relapse, CR2	CO		
MDS/MPD		S	S	CO
Non-malignant hematological disorders				
SCID		S		
Chronic granulomatous disease		S	S	CO
Kostmann syndrome		S	S	CO
Hemoglobinopathies (major thalassemia, sickle cell disease)		S	CO	CO
Acquired aplastic anaemia		S	S	CO

Fanconi anaemia (FA)	S	S	CO
Blackfan Diamond anaemia	S	S	CO
Metabolic diseases: MPS-1H Hurler	S	S	CO
Metabolic diseases: MPS-1H Hurler Scheie	GNR	GNR	GNR
Metabolic diseases: MPS-VI Maroteaux-Lamy	CO	CO	CO
Metabolic diseases: Osteopetrosis	S	S	S
Metabolic diseases: others	GNR	GNR	GNR
Solid tumours			
High risk neuroblastoma	CO	CO	D
Neuroblastoma >CR1	CO	D	D
Germ cell tumour	CO	CO	CO
Ewing's sarcoma increased risk or > CR1	D	D	D
Soft tissue sarcoma or > CR1	D	D	D
Wilms' tumour	GNR	GNR	GNR
Osteosarcoma	GNR	GNR	GNR
Brain tumours	GNR	GNR	GNR

Recommendations

- The allogeneic transplantation (HSCT) is a complex medical procedure used in the treatment of malignant and non-malignant hematological diseases with the main objective of replacing malignant or otherwise abnormal or restoring the affected hematopoiesis and/or restoring the affected immune system
- It is recommended as the first line treatment in hematological malignancies for diseases with an increased risk of recurrence or refraction, or in case of relapses
- HSCT is a highly toxic procedure and should only be perfomed in national and specifically trained centres
- Specific and late side effects are related to the vulnerability of the developing organism - hormonal deficiencies, growth retardation, dental and skeletal lesions, as well as the high risk of malignancies especially in congenital syndromes with chromosomal fragility

Bibliography

1. Duarte, R.F., Labopin, M., Bader, P. *et al.* Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant* 54, 1525–1552 (2019). https://doi.org/10.1038/s41409-019-0516-2

2. Wingard JR, Gastineau DA, Leather HL, Snyder EL, Szczepiorkowsi ZM. Hematopoietic stem cell transplant – A handbook for clinicians 2nd Edition, 2015

3. Guidelines for Hematopoietic Stem Cell Transplantation (HSCT) in Childhood MDS and JMML for Patients enrolled in EWOG-MDS Studies, www.skion.nl

4. AIEOP-BFM ALL 2017 International collaborative treatment protocol for children and adolescents with acute lymphoblastic leukemia, www.uni-kiel.de

9. SUPPORTIVE TREATMENTS

9.1 MANAGEMENT OF INFECTIONS

Prophylactic strategies in paediatric oncology

Children receiving intensive myelosuppresive chemotherapy are at risk for invasive infections depending on the integrity of the various components of the immune system and the virulence and number of infectious agents to which the child is exposed. The risk of infection depends on several factors: the type and stage of the malignant disease, the type of cancer treatment, cutaneous and mucosal integrity, length of hospitalization, nutritional status, foreign bodies, ventriculo-peritoneal shunt, gastrostomies . (1)

The following axioms must be taken into account when assessing infection in children with cancer:

- the fever must be considered of infectious etiology until proven otherwise
- the symptoms and signs characteristic to infection are often absent
- severe leukopenia and granulocytopenia, especially below 500 neutrophils/mmc, increase the risk of infections
- low virulent microorganisms can cause severe infections
- bacterial infections should be treated immediately with antibiotics administered parenterally in maximum dosage

Antibacterial prophylaxis is especially aimed at the prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infection and varicella-zoster infection

Otherwise, antibacterial and antifungal prophylaxis is not routinely practiced, except in children with acute leukaemia at onset, children undergoing stem cell transplantation, situations where the protocol of the centre should be followed.

Management of febrile neutropenia

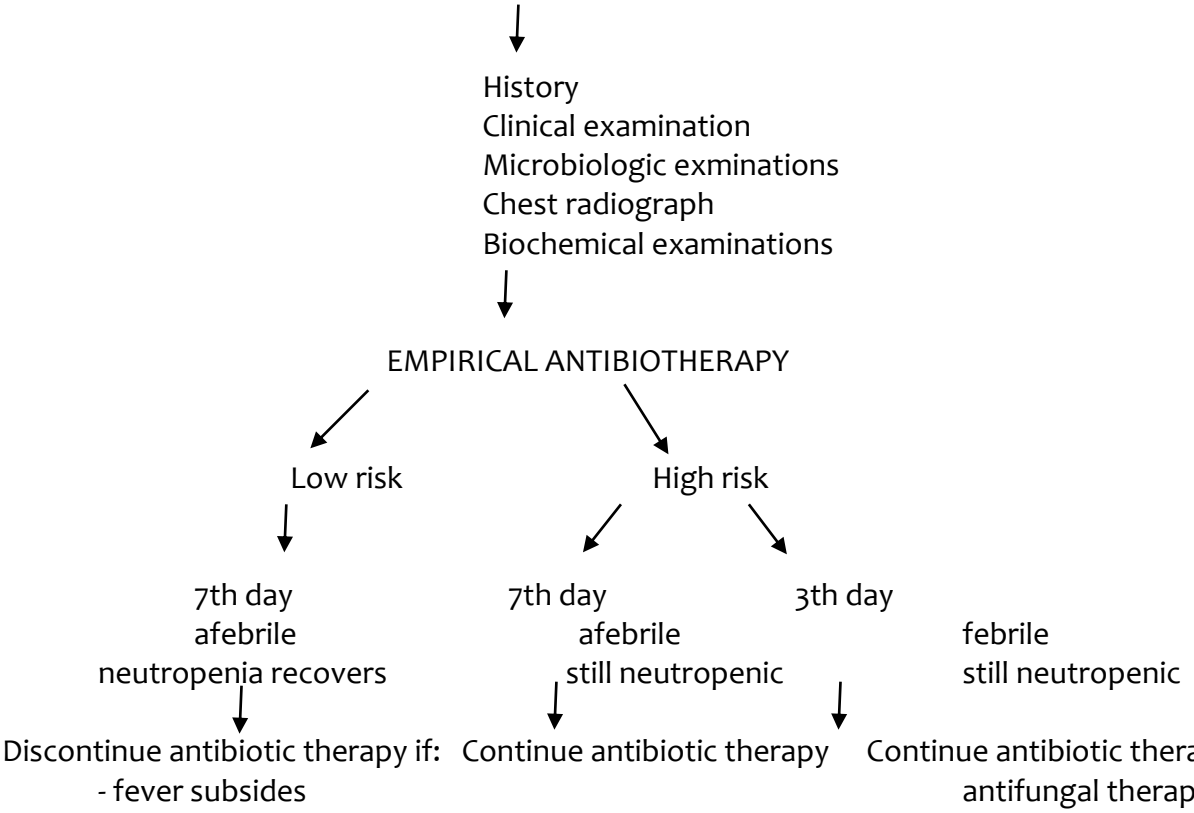
When assessing febrile cancer patients, it is important to place them in risk groups. The grade of neutropenia is the most important risk factor.

Criteria for determining the risk grade (2)

Low risk	High risk
Granulocytes below 500/mmc	Granulocytes below 100/mmc
The patient has a solid tumour or leukaemia undergoing maintenance treatment	Patients with ALL undergoing induction treatment, or AML and lymphoma patients and patients undergoing stem cell transplant
Absence of associated morbid conditions	It is associated with fever: - hypotension

	- altered mental status - respiratory failure - dehydration - abdominal pain - haemorrhage - heart disorders - cellulite - renal or hepatic failure
Fever of unknown origin	- proven bacteremia - pneumonia or other severe infection - general condition changed at the onset of fever and neutropenia

Evaluation of patients with febrile neutropenia (2)



The empirical antibiotic therapy is initiated promptly, immediately after the neutropenic patient has developed fever.

Studies have shown that the etiological agent is bacterial in 85-90% of cases. (3, 4)

The antibiotics used in the empirical antibiotic therapy must meet the following conditions:

- broad spectrum, the infection may be due to both gram-positive and gram-negative bacteria
- maximum dosage
- low toxicity, taking into account the toxicity of previous therapy, pre-existing conditions, the toxicity of other concomitant drugs, NB aminoglycosides should not be given to patients receiving platin products.

- administration as easily as possible, parenterally (i.v.)
- most protocols associate two or more antibiotics
- previous microbial history (MRSA/VRE/ESBL) of the patient should be taken into consideration when choosing antibiotics
- the microbial load in the respective health unit and the local results on antibiotic resistance are taken into account

Recommendation on the use of various regimens of antibiotics according to risk factors, symptoms and findings:

I. Low risk group

- First line antibiotherpy:

-oral antibiotherapy (Ciprofloxacina or amoxicilina/acid clavulanic)
-parenteral antibiotherapy – ceftriaxona or amoxicilina/acid clavulanic

- Second line antibiotherapy:

- carbapaname (meropenem, imipenem)
- ciprofloxacina or ceftazidim i.v.
- aminoglicozid
- Vancomicina, Teicoplanina, Linezolid

II. **High risk group** The first and second line antibiotics are the same. The antibiotic therapy continues until the neutrophyl count exceeds 500/mmc.

Antifungal therapy

Empirical antifungal therapy is required if the patient is still febrile after 3 days of broad-spectrum antibiotic treatment. This is OK but is not reflected in the figure above! The most effective drug is Amphotericin, if available. (3, 4)

- Liposomal Amphotericin B is also effective in CNS infections, nefrotoxic: should be used in precausions in children who have reduced renal function.
- Fluconazole administered from day one i.v. appears to be comparable in efficacy to Amphotericin in most candida albicans infections; it is inactive against Aspergillus sp. In case of prophylactic use interactions with Vincristin should be recognised.
- Voriconazole: active against Candida, Aspergillus sp. Serum levels should be monitored.
- Itraconazole: very effective in Candida infections
- Caspofungin: effective in invasive candidiasis and invasive aspergillosis. It is not administered in CNS infections
- Ketoconazole po as prophylactic treatment or for cutaneous and mucosal infections

Management of patients with central venous catheter and bacteremia

Criteria for immediate removal of the central venous line:

- evidence of local infection
- persistent positive blood cultures
- recurrent positive cultures with the same pathogen
- positive cultures for: Candida sp., polymicrobial infections, Vancomycin-resistant enterococci

Criteria for removal of the central venous line:

- catheter-related bloodstream infection with Pseudomonas aeruginosa or Mycobacterial infection
- alteration of the general condition in a patient with positive blood cultures
- positive blood cultures with: staphylococcus aureus, streptococcus viridans, bacillus sp., Candida

Pneumocystis carinii infection

Prophylaxis is performed with Cotrimaxazole (Trimetoprim/Sulfa) at a dose of TMP 5 mg/kg/day, administered 3 consecutive days, each week. (3, 4)

For the treatment of Pneumocystis carinii infection, Cotrimaxazole can be administered at a dose of TPM 20 mg/kg/day or Pentamidine at a dose of 4 mg/kg/day in a 3-hour perfusion.

Antiviral treatment [3, 4]

In children with cancer, varicella has a severe course with significant mortality. For patients with varicella, the treatment with Aciclovir 20mg/kg/day is recommended until the incubation period is over, especially if the patient is not vaccinated. In case of varicella-zoster infection during cancer treatment, the patient should receive Aciclovir therapy. Some authors recommend immunization against varicella before the start of chemotherapy.

Acyclovir treatment is associated with the combination of antibiotics in case of severe mucositis or vesicular lesions: Aciclovir p.o. 200-800 mg/day. In case of varicella, Aciclovir 1500 mg/sqm/day iv is administered for minimum 5 days (until the lesions are dry and crusted).

Evolution, monitoring during hospitalization

- monitoring the management of the infectious process
- treatment should be re-evaluated daily to optimize efficacy, to prevent resistance and to avoid toxicity

Recommendations:

- Fever must be considered of infectious etiology until proven otherwise in all cancer patietns
- High risk patients with fever should without interruption start broad spectrum iv antibiotics after obtaining cultures and thereafter be moitored closely to follow the progression of the infection, and make changes in the treatment also with high focus on fungal treatment.
- Clinically stable patients with fever but without neutropenia do not always require empirical antibiotic therapy. Antibiotic treatment will be started after obtaining the results of the cultures.
- Duration of the antibiotic treatment:

- in patients with negative cultures, without neutropenia, at least 48 hours afebril = STOP
- in patients with positive cultures: antibiotic therapy lasts at least 10 days or 14 days in those with a central venous catheter

- In case of severe systemic infection, iv immunoglobulins should be considered.

Bibliography

1. Alexander SW, Walsh TG, Friedfeld AG and Pizzo P, Infectious complications in Pediatric Cancer Patient, In: Pizzo PA, Poplack DG, Principles and Practice of pediatric Oncology, Lippincott Williams&W 2016

2. Freifeld AG, Pizzo PA. The outpatient management of febrile neutropenia in cancer patients. Oncology 10: 599-612, 2016

3. Hughes WT, Armstrong D, Bodey GP et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clinical infectious Diseases 34:730-751, 2002

4. Lawrence J Wolff, Arnold J Altman, Roger L. Berkow, F. Leonard Johnson – The Management of Fever and Neutropenia, In: Arnold J Altman, Supportive Care of Children with cancer, 25-38, 2014

9.2 GROWTH FACTOR TREATMENT (G-CSF)

G-CSF stimulates the granulocytopoiesis and it is administered in order to decrease the incidence of febrile neutropenia and severe neutropenia, to shorten the duration of hospitalization, to reduce the risk of infection, to improve the tolerance to cytotoxic chemotherapy.

G-CSF indications in paediatric haematology and oncology are as follows:

- Use in the primary prophylaxis of neutropenia, in order to increase the intensity of the dose of chemotherapy;
- Prophylactic use in patients in whom the expected incidence of post-chemotherapy neutropenia is greater than or equal to 40%. It accelerates the myeloid recovery when the expected duration of severe neutropenia is 7 days or more;
- Use as secondary prophylaxis for patients who have previously developed an episode of febrile neutropenia;
- After high-dose chemotherapy with autologous progenitor stem cell support in order to accelerate the myeloid recovery;
- Mobilization of peripheral blood progenitor cells for harvesting before the autologous stem cell transplantation;
- To increase the number of granulocytes in patients with aplastic anaemia, myelodysplastic syndromes, congenital neutropenia or other congenital neutropenic diseases

(It should be noted that in acquired aplastic anaemia and severe congenital neutropenia (especially Kostmann's syndrome) the use of G-CSF has been associated with an increased incidence of MDS and AML. (1, 2)

Dose and duration

The treatment is initiated at a dose of 5 μg/kg/day sc or iv, being more effective with the sc administration. The iv administration is recommended in case of severe thrombocytopenia (platelets $<10x10^9$/l), the sc administration being contraindicated. Before harvesting stem cells prior to autologous transplantation, doses higher than 10 μg/kg/day sc or iv are used. (1, 2)

The G-CSF treatment is initiated at least 24 hours after the last dose of chemotherapy. For the chemotherapy induced neutropenia, G-CSF is administered up to the values of the neutrophil count >1000 /μl. For congenital neutropenia, the goal is to maintain neutrophils at values ~ 750/μl.

In some treatment protocols the use of growth factor is part of the protocol with specific doses, start and stop criteria, and in other protocols its use is according to the institutional own procedures.

G-CSF is generally well tolerated; transiently, it can cause fever, bone pain, nausea, decrease of platelets count. (3) The treatment is associated with a 20% reduction in febrile neutropenia and a shorter hospital stay; but without influencing the mortality associated with an infectious process. (4)

Recommendations:

The use of G-CSF is justified:

- as primary prophylaxis of neutropenia
- as secondary prophylaxis of neutropenia
- after high-dose chemotherapy with cell support
- for the mobilization of progenitor cells

Bibliography

1. Anurag K. Agrawal, James Feusner. Supportive care of patients with cancer. In: Philip Lanzkowsky, Jeffrey M.Lipton, Jonathan D.Fish. Lanzkowsky's Manual of Pediatric Hematology and Oncology Sixth Edition 2016; 620-655

2. Anurag K.Agrawal, Caroline A.Hastings, James Feusner. Hematologic supportive care for children with cancer. In: Philip A.Pizzo, David G.Poplack. Principles and practice of pediatric oncology Sixth Edition 2011; 1152-1189

3. Hrishikesh M. Mehta, Michael Malandra, Seth J. Corey. G-CSF and GM-CSF In Neutropenia. J Immunol. 2015 August 15; 195(4): 1341–1349

4. Lillian Sung, Paul C. Nathan, Beverly Lange, Joseph Beyene, and George R. Buchanan. Prophylactic Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor Decrease Febrile Neutropenia After Chemotherapy in Children With Cancer: A Meta-Analysis of Randomized Controlled Trials. J Clin Oncol 2014; 22 (16): 3350-3356

9.3 TRANSFUSION INDICATIONS

The transfusion activity has evolved over the last two decades, especially in terms of improving safety measures to reduce the risk of infections transmitted through blood products. However, the indication for substitution should be made so that the blood components are transfused only when necessary and only with the appropriate component for each patient.

As a general rule, all World Health Organization (WHO) guidelines are followed for prescribing blood products regarding ABO and Rh group compatibility as well as centre-specific internal protocols (https://www.who.int/bloodsafety/transfusion_services/d044.pdf). (1)

The neoplastic disease in children is one of the most common pathologies associated with an increased need for transfusions. The mechanisms involved in this increased need are multifactorial and relate to both the disease and the chemotherapy and radiotherapy treatment that inhibits haematopoiesis. Poor nutrition, spontaneous bleeding or various manoeuvres and interventions complete this picture.

Irradiation of blood products

Indication for irradiation of blood products:

For the following groups of patients there are clear recommendations for prescribing blood products (RBC concentrates, apheresis platelet concentrate, standard platelet concentrate/mass (PM)), irradiated with 25Gy:

- all patients diagnosed with Hodgkin's lymphoma - permanently
- all patients treated with chemotherapy protocols containing purine-fludarabine analogue, cladribine (2-cda), deoxycoformycin, clofarabine, nelarabine and bendamustine - permanently
- all patients treated with antithymocyte globulin (ATG) - permanently
- all patients treated with alemtuzumab (Campath) - permanently
- all patients who have had an allogeneic bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT)
- all cases subjected to a haploidentical donor transplant procedure
- newborns who received blood components in utero - up to 6 months of age
- children with severe T lymphocyte immunodeficiency syndromes: combined immunodeficiency, severe combined immunodeficiency, 22q11 deletion syndrome (DiGeorge syndrome), Wiskott-Aldrich syndrome.
- where blood products from relatives are being used.

Granulocyte mass transfusions must be irradiated.

No need to irradiate the fresh frozen plasma (FFP) or the cryoprecipitate.

When to start and stop irradiation of blood products:

- for patients who have had an allogeneic bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT)
- from the initiation of conditioning chemotherapy/radiotherapy
- throughout the prophylaxis of graft-versus-host disease (PBSCT) or up to a lymphocyte value > $1x10^9/l$
- permanently if chronic immunosuppression is required or if PBSCT is present

- for bone marrow (BM) or peripheral blood stem cell (PBSC) donors - starting 7 days before/during harvesting

- for patients undergoing BM or PBSC harvesting - starting 7 days before/during harvesting

- for patients undergoing an autologous BMT or PBSCT

- from the initiation of conditioning chemotherapy/radiotherapy

- continues for up to 3 months after transplantation or 6 months after transplantation if total body irradiation (TBI) has been used in conditioning

Blood components

Red blood cells

Indications for RBC transfusion: Correction of anaemia due to disease or treatment:

- hemoglobin (Hb) value of≤ 7g/dl (2, 3, 4, 5)

- the patient's treatment protocol will always be observed and the Hb value must be maintained according to the protocol

- in children undergoing radiotherapy, the aim is to maintain Hb level around 10 - 12g/dl

- in the context of onset of symptoms caused by anaemia, transfusion is also indicated at higher Hb values

- precautions should be taken in patients with hyperleukocytic leukaemia

- treatment of anaemia caused by haemorrhage:

in case of active haemorrhage the indication for transfusion is made on clinical grounds

the local protocol for major haemorrhage will be followed

Dose: Dose in ml = 3 x weight (kg) x desired increase in Hb (in g/dl)

Usual - 10-20ml/kg

Administration: - maximum 5ml/kg/hour

If the calculated volume is <200 ml, units for small volume transfusions (paediatric units) are indicated.

If the calculated volume is > 200ml, the prescribed dose can be rounded to the nearest value of an adult unit.

Precautions: in patients with hyperleukocytic leukaemia (> $50x10^9$/ l), the administration of RBC increases the risk of aggravating the leukostasis

- a value of Hb ≥ 6 g/dl is considered satisfactory

- a maximum of 5 ml/kg should be administered within 4 hours if a transfusion is urgently needed

Transfusion reactions: internal reporting and reaction protocols will be followed

Validity and storage:

- valid for 35 days (or 14 days after irradiation)

- stored at 4° C (+/- 2° C); the transfusion should be initiated within 30 minutes after the unit is removed from the refrigerator.

Platelets

Indications for PM or platelets concentrate transfusion in case of thrombocytopenia associated with malignant pathology:

- Prophylactic - see table 1

- Active haemorrhage - see table 1

- platelet count is indicated > $50x10^9$ / l- or > $100x10^9$ / l if haemorrhage is in a critical area (lungs / CNS)

- always in patients with thrombocytopenia and active haemorrhage (6)

Dose: If the child weighs <20 kg, 10 ml/kg is transfused in 30 minutes

- If the child weighs > 20 kg, one unit of platelets concentrate is transfused

Double doses may be required in the following circumstances: - active haemorrhage
- sepsis / DIC
- splenomegaly.

Precautions:

The effectiveness of the transfusion should always be assessed, either clinically (the haemorrhage stops) or by assessing the increase in the platelet count above baseline and calculating the increment.

Deficient platelet increase is practically defined as follows: failure to increase platelet count > 20-30x10^9 /l in 1 hour or 10-20x10^9/l in 24 hours post-transfusion. If this situation occurs, it is necessary to exclude an associated immune pathology and test HLA antibodies. If HLA antibodies are identified, identical HLA platelets should be administered. (6, 7, 8)

Validity and storage: 5 days at 22 ° C (+/- 2 ° C) with gentle continuous stirring.

Platelet transfusion is NOT prophylactically indicated in the following situations:

- Hemodynamically stable patients with chronic, stable, severe thrombocytopenia by:
  - alloimmunization
  - immune thrombocytopenia
  - thrombotic thrombocytopenic purpura
  - aplastic anaemia
  - myelodysplastic syndrome

These patients have an indication for platelet transfusion in case of haemorrhage.

- Bone marrow aspirate and bone biopsy
- Insertion of intravenous cannula (7)

Table 1 (7)

Platelet count x 10^9/l	Indications for transfusion with platelet concentrate
< 10	-Prophylactically in clinically stable paediatric patients - in chemotherapy -Prophylactically in paediatric patients in critical condition but without active haemorrhage -**Brain tumours, bladder tumours or necrotic tumours require prophylaxis at higher platelet levels**
< 20	-During bone marrow transplantation (BMT) -Chemotherapy treatment or BMT associated with: fever, sepsis, minor bleeding, mucositis, DIC without active haemorrhage -Critical patients with risk factors for haemorrhage (sepsis, kidney failure, medication) -Insertion of nasogastric tube
< 30	-Lumbar puncture associated with chemotherapy administration -Intramuscular injections (e.g. Erwinia asparaginase) -Insertion of a non-tunneled central venous catheter -Brain tumours: - with ventriculoperitoneal shunt or Omaya reservoir - after complete tumour resection and chemotherapy and radiotherapy treatment - residual tumour and chemotherapy and radiotherapy treatment

< 50	-Lumbar puncture with chemotherapy administration at initial diagnosis in acute leukemia -The patient is subjected to an invasive manoeuvre (insertion of a tunneled central venous catheter) -Moderate active haemorrhage (including DIC-associated haemorrhage) -Brain tumours with: - history of cerebral haemorrhage - treatment with an anti-angiogenesis agent (Bevacizumab)
< 80 -100	Surgery on the eye or central nervous system -Active haemorrhage in the brain, lungs or life-threatening haemorrhages

Fresh frozen plasma (FFP)

Indications:

- Correction of coagulopathy in:

DIC/severe sepsis

severe liver disease

major haemorrhage

severe vitamin K deficiency (vitamin K is also administered)

reversal of the effect of vitamin K antagonists (if prothrombin complex concentrate is not available) - No recommendation

deficiencies of coagulation factors if no specific concentrate is available (e.g. factor V deficiency)

- FFP is usually given to correct a coagulopathy if a child is bleeding or requires surgery
- Occasionally, FFP is justified for the correction of very severe coagulopathy (or which progresses rapidly) in the absence of haemorrhage/surgery, e.g., onset of leukaemia (especially acute myeloid leukaemia AML).
- FFP should not be administered as a volume expander. (8)

Dose: 10-15 ml/kg

Administration: rate of 10-20 ml/kg/hour; in children with weight > 20 kg, one unit is administered (250ml)

Validity and storage: can be stored for 3 years at -25° C

Once thawed, the unit can be stored in the refrigerator (4° C) for 24 hours before transfusion.

Cryoprecipitate

Indications: Correction of low fibrinogen levels from:

- DIC/severe sepsis
- severe liver disease
- major haemorrhage
- congenital hypofibrinogenemia / afibrinogenemia (if there is no fibrinogen concentrate)
- correcting a low level of fibrinogen if a child is bleeding or needs surgery

Occasionally, the use of cryoprecipitate is justified to correct a level of fibrinogen that is very low (or rapidly decreasing) in the absence of haemorrhage/surgery, for example, onset of leukaemia (especially AML) or as a rich source of factor VIII and von Willebrand factor if the factor concentrate is not available.

Dose: initially 5 ml/kg in 30 minutes; young children may need 10 ml/kg

Validity and storage: can be stored for 3 years at -25° C.

Once thawed, it should be stored at room temperature and used in 4 hours.

Granulocytes

There is insufficient evidence to recommend the prescription of granulocyte transfusions. It is sometimes used in patients with sepsis and severe neutropenia who do not respond to antibiotic treatment and granulocyte colony stimulating factor. (6, 8)

Recommendations:

- A restrictive red blood cell transfusion strategy (Hb of 7 g/dl as transfusion threshold) in paediatric patients with hemodynamically stable disease
- Thrombocytes must be always administered in case of bleeding and thrombocytopenia. It is suggested that for most stable children prophylactic platelet transfusions should be administered when the platelet count is below $10x10^9$/l, excluding patients with immune thrombocytopenia, thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome and heparin-induced thrombocytopenia who should only be transfused with platelets for life-threatening bleeding. (9)
- Blood components should be irradiated prior to transfusion in line with the above guideline and as per ref. (10).

Bibliography

1. Safe Blood and Blood Products –World Health Organization - reprinted 2009
2. Lacroix J[1], Demaret P, Tucci M.Red blood cell transfusion: decision making in pediatric intensive care units. Semin Perinatol. 2012;36(4):225-31. doi: 10.1053/j.semperi.2012.04.002.
3. Valentine SL, Bembea MM, Muszynski JA, Cholette JM, Doctor A, Spinella PC, Steiner ME, et al.Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI), Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Pediatr Crit Care Med. 2018;19(9):884.
4. Lightdale JR, Randolph AG, Tran CM, Jiang H, Colon A, Houlahan K, Billet A, Sloan S, Lehmann LE. Impact of a conservative red blood cell transfusion strategy in children undergoing hematopoietic stem cell transplantation; Biol Blood Marrow Transplant. 2012; 18(5):813.
5. Jun Teruya. Red blood cell transfusion in infants and children: Indications. Section Editors: Donald H Mahoney, Jr, MD. Adrienne G Randolph, MD, MSc; Deputy Editor: Carrie Armsby, MD, MPH, Literature review current through: Jan 2020. | UpToDate
6. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
7. Clinical Practice Guidelines – Blood Product Prescription – The Royal Children´s Hospital Melbourne
8. Paediatric Haematology & Oncology : Supportive Care Protocols – 4th Edition – A collaborative publication from Great Ormond Street Hospital for Children, The Royal Marsden, University College London Hospitals – NHS Foundation Trust
9. Guidelines on transfusion for fetuses, neonates and older children Helen V. New,1,2 Jennifer Berryman,3 Paula H. B. Bolton-Maggs,4 Carol Cantwell,2 Elizabeth A. Chalmers,5 Tony Davies,6 Ruth Gottstein,7 Andrea Kelleher,8 Sailesh Kumar,9 Sarah L. Morley10 and Simon J. Stanworth,11 on behalf of the British Committee for Standards in Haematology - British Journal of Haematology, 2016, 175, 784–828
10. Transfusion guidelines for neonates and older children. Brenda E S Gibson, Audrey Todd, Irene Roberts, Derwood Pamphilon, Charles Rodeck, Paula Bolton-Maggs, Geoff Burbin, J Duguid, F Boulton, H Cohen, N Smith, D B L McClelland, M Rowley, G Turner, British Commitee for Standards in Haematology Transfusion Task Force: Writing group - British Journal of Haematology 2004, 124, 433–453

9.4 PAIN MANAGEMENT

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

The goal of palliative care is to achieve the best possible quality of life. Many aspects of palliative care should be applied early in the course of disease, in conjunction with the curative treatment, but they are very important in the terminal phase of disease. The pain control should begin with the diagnosis of cancer in children and it should continue throughout the disease. The analgesic therapies must be combined with appropriate psychological, physical, and supportive approaches to this issue.

Each pain episode, whether acute or chronic, requires a correct assessment, establishing the specific etiology and therapy.

Pain is one of the most common symptoms in cancer patients and has a negative impact on patient's quality of life. The prevalence of pain in childhood malignancies is 78% at diagnosis, between 25-50% during the curative treatment and 47-88% during the terminal phase of the disease. (1)

Causes of pain:

- pain at the onset of the disease - subsides soon after initiating therapy
- pain caused by diagnostic and therapeutic procedures
- pain due to the complications of the disease or treatment (peripheral neuropathy, myelopathy, infections, stomatitis, ileus, bladder, phlebitis)
- the evolution of the disease - the pain in the terminal stages

Pain assessment of a child is difficult, and this is why a number of case-by-case strategies are used to develop an effective treatment plan. The best way to assess the pain in children is to invite the child to report data about the pain he/she is feeling. However, the method is limited by the child's inability to communicate due to: the preverbal stage of development, cognitive impossibility or emotional disorders.

Pain assessment methods

- behavioural changes (0-3 years): facial expression, crying, body movements, physiological parameters (heart rate, respiratory rate, oxygen saturation)
- self-reporting (3-7 years): faces pain scale, colour analog scale (CAS), visual analog scale (VAS)
- self-reporting (7-18 years): interviews, questionnaires, faces pain scale, numerical rating scale, visual analog scale (VAS)

Principles for the management of pain

The analgesia in chronic pain is performed in accordance with the principles established by the WHO for the treatment of pain in children. (2) The escalation of the treatment is done in steps, from mild analgesics to strong analgesics. The transition from one stage to another is made only in case of therapeutic failure or inefficiency of the drugs from the previous stage.

Analgesia in chronic pain is based on four key concepts:

- on the WHO scale

- by the clock - the treatment is administered according to a regular schedule and not as needed, the doses being supplemented in case of intensification of pain or intermittent pain

- the oral route should be used whenever possible

- individualized - the dose should be based on the particularities of the child: it is not a standard dose, suitable for all children

Currently, the three-step ladder has been abandoned for children in favour of a two-step approach. (5) However, as new data on the safety and efficacy of tramadol or other weak opioids in the treatment of pain in children emerge, the two-step strategy may be reviewed.

• The treatment of mild pain (Pain score <4 on a numerical scale): Paracetamol and Ibuprofen are drugs recommended in the treatment of mild pain in children. There are insufficient studies regarding the efficacy and safety of other non-steroidal anti-inflammatory drugs (NSAIDs) in the paediatric population. Non-steroidal anti-inflammatory drugs may cause gastrointestinal side effects and renal toxicity.

• Treatment of persistent moderate and severe pain (Pain score 4-6 and Pain score ≥7): a strong opioid is recommended.

Morphine is the drug of choice for the treatment of severe pain in children. It is usually appropriate to start using immediate-release preparation, then proceeding to the twice-daily prolonged-release preparation once the patient's daily requirement is established. The oral/iv morphine ratio is 3/1. For breakthrough pain additional doses of immediate-release morphine are recommended. Rescue doses of opioid may be calculated as 1/6 of the total daily opioid requirement (4). There is no specific or maximum dose for morphine.

The two-step approach considers the use of low doses of strong opioid analgesics for the treatment of moderate pain, following the same titration recommendations.

Fentanyl is an alternative to morphine in patients with renal failure as it metabolizes to inactive metabolites in the liver and it has shorter half-life.

Oxycodone has similar properties to morphine, but vomiting and hallucinations are less common.

Methadone has a prolonged half-life and requires extremely careful dose adjustments to achieve pain management. It is rarely used in children.

Switching opioids and/or route of administration are recommended in the presence of an inadequate analgesic effect or in order to minimize side effects.

Adjuvant pain medications have a primary indication other than for pain management. They may be used with analgesics for enhance pain relief (6). The most commonly used are:

- antidepressants: amitriptyline in neuropathic pain

- anticonvulsants (carbamazepine, gabapentin, clonazepam) in neuropathic pain

- corticosteroids (dexamethasone) in bone pain, for raised intracranial pressure in CNS tumours, neuropathic pain, pain caused by spinal cord compression or hepatic capsular retraction

- NMDA antagonists (ketamine, methadone) improve analgesia in neuropathic pain

- bisphosphonates in the treatment of pain associated with bone metastases in adolescents

Other types of pain treatment include:

- palliative radiation therapy

- pain procedures (surgical, radiological, infiltrations, nerve blocks, neuroaxial delivery of analgesia, evacuation of collections)

- complementary and alternative therapies

Opioid side effects and their treatment:

- constipation is the most common side effect of opioids: diet, laxatives

- nausea and vomiting: antiemetics

- excessive sedation - most often, it disappears spontaneously, without reducing the dose; dextroamphetamine may be administered

- respiratory depression: opioid dose is reduced by 50%

- respiratory arrest: naloxon

- urinary retention: catheterisation, a decrease in dose of opioid, change of opioid or of the route of administration

- allergic reactions, pruritus: antihistamines

- euphoria, confusion, hallucinations: neuroleptic drugs - haloperidol or change of the opioid

- myoclonus, seizures: benzodiazepines

- drug tolerance: increase of the dose

Evolution, monitoring:

- monitoring the control of pain episodes

- monitoring the side effects of opioids

Under current legislation, treatment with morphine and other strong opioids can be initiated and continued by any physician, regardless of the specialty, including the family doctor.

Recommendations

- There are methods to assess the child's pain regardless of age
- It is recommended to use the analgesic treatment in two steps according to the child's level of pain severity
- Paracetamol and Ibuprofen are the medicines of choice for mild pain in children
- For moderate and severe pain, a strong opioid is recommended
- Adjuvant therapy is recommended on any step of the ladder

Bibliography

1. Berde CB, Billett AL, Collins JJ, Symptom management and supportive Care, In: Pizzo PA, Poplack DG, Principles and Practice of pediatric Oncology, Lippincott Williams&Wilkins, 2016

2. World Health Organization, Cancer Pain Relief and Paliative Care in children, Geneva:WHO, 1998

3. Michelle Koh, Finella Craig, Joanne Wolfe – Palliative care for children with advanced cancer, In: Michael C.G. Stevens, Hubet N. Caron, Andrea Biondi, Cancer in children – Clinical management, 118-127, 2012

4. William T. Zempsky, Neil L. Schechter, Arnold J Altman, Steven J. Weisman – The Management of Pain, In: Arnold J Altman, Supportive Care of children with cancer, 200-220, 2014

5. World Health Organization. (2012). Persisting pain in children package: WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. World Health Organization. Disponibil la: https://apps.who.int/iris/handle/10665/44540

6. Bennet M – Palliative medications: drugs for neurophatic pain, Euro J Palliat Care, 17, 167-169, 2010

9.5 PSYCHOLOGICAL SUPPORT

Psychological response to illness

Cancer diagnosis is a significant source of stress for the sick person and the family, which makes it a risk factor in the occurrence of psychological difficulties associated with the disease and an increased vulnerability to stressors not associated with the disease. Cancer diagnosis significantly changes a person's life, from the point of view of emotions, as well as family, profession, and social life.

Each person reacts in a particular way when facing the disease depending on the individual characteristics and situational factors. The impact of the events is influenced by the type and severity of the disease, age at diagnosis, income, education, gender, treatment, social support available. (1) The moment of diagnosis is accompanied by a high level of distress, behavioral problems, anxiety, depression, feelings of guilt based on speculation about the cause of the disease. (2) Distress varies over time, decreasing for some and increasing for others.

Emotional reactions to illness

The psychological response to stress in children, as well as in adults, is a complex process involving cognitive, emotional, and behavioural reactions. (3, 4)

• *Emotional reactions:*

- anxiety: before the diagnosis, associated with medical procedures, related to the evolution of the disease (possibility of relapse, unfavourable evolution, even if the prognosis and evolution are favourable, the patient dwells on the idea of "limitation of life/ life threat" because of the disease onset), thoughts about death

- depression: caused by the loss of control, of independence, of an active role, of the uncertainty of the future, because of the restriction/limitation in manifestations, repeated and prolonged hospitalizations, mutilating surgeries

- anger: towards the "unjust fate", towards the state of depersonalization

- loneliness: related to experiencing the disease, to the fact that the patient often feels misunderstood, he/she feels that a distance has intervened between him/her and the healthy people which is difficult or impossible to overcome

- helplessness: determined and maintained by the dependence on other people, the characteristics of the disease (pain, functional impairment, long-term disabilities, loss of independence, dependence on other people, etc.)

- hopelessness: pessimism concerning disease evolution

• *Cognitive reactions:* impaired memory, decreased ability to concentrate, increased rate of errors and confusion, decreased ability to decide, inhibitions and blockages, reduced tolerance to criticism, etc.

• *Behavioural reactions:* passivity/ aggression, intolerance, disagreement, change in appetite, deterioration of interpersonal relationships, alcohol and tobacco consumption, etc.

Methods of psychological assistance

Adaptation to the disease mainly involves: coping with the disease, with all the problems that may occur, coping with treatment, developing a good communication framework with the medical team, adapting to one's life change caused by the disease. (3)

The process of adaptation to the disease, with its consecutive changes, is a long process, which intensely requires the adaptive resources of the sick person, of the family, with particular manifestations and feelings in every moment accompanying the disease:

- suspicion of having cancer
- confirmation of diagnosis
- treatment of the disease
- end of treatment
- monitoring the response to treatment
- relapses
- palliative care/care in the terminal phase

Adaptation is an effort to find an acceptable balance between contradictory constraints, rather than trying to overcome the danger posed by the disease. (4)

Some patients manage very well their own resources, others need specialized help, adapted to their individual needs and characteristics. There is no one-size-fits-all psychological treatment for all patients. There are various therapeutic ways to provide the necessary psychological support, useful in the short term, to deal with crises or in the long term, to provide the necessary support:

- individual psychotherapy
- group psychotherapy
- counselling
- crisis intervention

Regardless of the type of intervention used, the aim is:

- increasing the psychological adaptation to the disease, the therapeutic compliance
- improving the emotional response
- improving the quality of life of both patients and their families

• *Communication*

Communication with the patient, with his/her family, is an important element, which cannot be replaced by any other therapeutic method of intervention.

The way the diagnosis is communicated produces, in the patient and family, reactions that will determine the entire course of the disease. Emotional adaptation begins on the day of the diagnosis. (3) Effective communication is associated with psychological adjustment, adherence to treatment, lower levels of negative emotions.

The following are considered basic elements of communication with the patient/family:

- providing information adapted to the level of understanding of each person
- providing the appropriate amount of information to each patient
- providing basic information and information on specific topics
- repetition of information
- listening carefully to the patient
- providing opportunities for asking questions, providing answers to questions
- patient involvement in the decision-making process regarding the care plan
- emotional support

• *Psychological counselling*

The issues that can be addressed through counselling in cancer patients are related to two main issues: finding out that they are suffering from a serious illness and treatment-related problems. (5)

- *Adaptation to hospitalization and the condition of being a patient*
- *Reducing the stress induced by medical procedures*
- *Pain control*
- *Emotional support, the opportunity to express their fears, feelings*
- *Play therapy, therapies through artistic creations (playroom)*
- *Counselling the family*

The parent is a helpful resource for his/her child. The parent's anxiety level correlates positively with the child's anxiety level. Interventions aim at:

- reducing the parent's anxiety
- teaching the parent to resort to behaviours that help the child cope with the situation
- open communication as a couple, development of common goals, support
- finding solutions to practical problems, to concrete needs regarding childcare

• *Counselling siblings*

The siblings of the sick child may face feelings of jealousy over the attention paid to the sick sibling, difficulties at school, feelings of sadness, anger, guilt, fear of the possible death of the sick sibling, difficulty coping with comments about the sick sibling's illness.

It is necessary and useful to provide them with age-appropriate information about their sibling's medical condition, to be encouraged to talk openly about their feelings, to be involved in decisions about family life.

Support from collaborators

- specialized psychosocial support (psychological support groups)
- schooling in hospital

Bibliography

1. Barraclough J.: Cancer And Emotion A Practical Guide To Psycho-Oncology, John Wiley & Sons., Chichester, 1999, cap. 1, 4, 9

2. Ollendick T., Hersen M.: Handbook Of Child Psychopatology, Plenum Press, New York, 1998, cap. 18

3. Guex P.: An Introduction To Psycho-Oncology, Routledge, London, 1994, cap. 2, 6, 10, 12

4. Băban A.: Psihologia Sănătății - Curs universitar, Editura Presa Universitară Clujeană, Cluj-Napoca, 1999, cap. 1, 4 (Health Psychology - University course, Cluj University Press Publishing House, Cluj-Napoca, 1999, chap. 1, 4)

5. Davis H., Fallowfield L.: Counselling And Communication In Health Care, John Wiley&Sons, Chichester, 1991, cap. 16

9.6 TERMINAL CARE

"How people die remains in the memory of those who will live on"
Cecily Saunders

Palliative care (PC) is an integrated part of all active childhood cancer treatment from the time of diagnosis, using a holistic approach focused on the needs of the patient and his/her family. The assessment of physical, psychological, spiritual, social needs aims to control pain and symptoms, providing psychological, social, spiritual assistance to ensure the quality of life of the patient and his/her family. (1)

Fortunately, cases of children dying of cancer or other progressive diseases are rare compared to those of adults. The purpose of this chapter is to present some practical recommendations for the correct assessment of the terminal phase (TP), regarding the prognostic staging and the treatment measures that should be taken at this stage.

Terminal care

Terminal care (TC) is part of the palliative care (PC) offered in the last days of life when it is obvious that the patient can no longer benefit from curative therapy. This episode(stage) in the evolution of the disease continues to be a challenge both for the medical staff who face the ethical and medical problems at the end of life, and for the family, that faces the imminent loss of a loved one.

The terminal care in children encounters difficulties related to: age and cognitive level, the child's expectations, pre-existing experience and behaviour of others, emotional state and fear of death, educational and cultural factors, the presence or absence of mother or family and last but not least, the existence of uncontrolled symptoms. (2)

The treatment will be applied taking into account what the patient and family can accept.

Standards and objectives in terminal care - Primary intervention

The palliative treatment in the terminal phase, in both children and adults, must be individualized and will take into account the following objectives:

Discuss the care plan with the patient and the family and document the findings in the observation sheet:

- The objectives of care - maintaining comfort
- The place where the child prefers to be cared for at the end of life
- Sharing concerns about medical issues

Involvement of the family in care (3):

Each family must be helped to decide on an end to the life plan and must receive care and support to achieve this. Professionals will be open and honest with families when approaching the end of life, terminal care being recognized as a difficult communication problem. The communication of the palliative treatment is based on a good dialogue between the doctor, the patient and his/her family. When treating children, the doctor has a responsibility to communicate with the family. It is always a difficult and exhausting process for parents to become aware and accept that their child's life can no longer be saved. (4, 5)

Joint planning with the family and the professionals involved should take place as soon as possible and it should be adjusted throughout the disease according to its evolution. The advance care plan, a written care plan (Advance Care Planning), must be agreed on and shared with the family. It must cover all aspects (treatment in hospital, in hospice or at home; provision of emergency services; decisions on resuscitation methods; parenteral nutrition; terminal sedation, etc.). The care plan must be modified according to the evolution of the disease and it must be applied by the multidisciplinary team.

The transition from the curative treatment to the palliative treatment which aims in particular at controlling pain and controlling symptoms, providing a good quality of life at the end of it. All the decisions on terminal care should be made in full transparency with the patient's parents and the patient if the patient is mature enough to understand.

There have been debates on the issue of terminal sedation and whether it can be included in the palliative treatment from an ethical point of view. Experience indicates that terminal sedation is a backup solution for children, because the goal is to maintain the child's consciousness as much as possible, which is important for the relationship between the parent and the child. In some cases, terminal sedation may be the best option for the child and the decisions on this issue will be made as a team. (4)

Patients with terminal cancer will not be subjected to cardio-pulmonary resuscitation, but the decision is made within the team that includes the family. The decision will be clearly recorded in the patient observation sheet and must be reiterated when a re-assessment is made. The documentation must include the treatment to be administered, the medical justification for the decision, the information provided to the parent and the patient's wishes.

The development of a symptom management plan for the last 24 hours includes:

- access to medicines - Emergency medication kit for the terminal patient, containing ampoules of morphine, haloperidol, levomepromazine, scopolamine butyl bromide, midazolam
- adequate management of the main symptoms: pain, nausea and vomiting, dyspnoea, psychomotor agitation, bronchial hypersecretion
- change of oral medication with medication administered subcutaneously, intravenously or intrarectally

Discontinuation of inappropriate, unnecessary interventions (e.g. blood tests, iv treatments)

There is no cardio-respiratory resuscitation (the doctor discusses the issue of non-resuscitation with the family and it is recorded in the observation sheet).

Intensification of comfort measures:

- skin care (e.g. positioning, anti-decubitus mattress)
- care of the oral cavity every 4 hours, to keep the oral cavity and lips moist

Religious support, the presence of the priest and the practice of rituals that have meaning for the patient and his/her family. Emotional and spiritual support will be available for the child and family.

The oncologist, the doctor with palliative care competence or the family doctor are the ones who manage the control of the symptoms at the end of life. They must be properly qualified and experienced in this regard. If the family wished, the child should be cared for at home during the terminal stages of the disease. The terminal treatment is followed in collaboration with the paediatric department, the family doctor and the home care team (if it exists).

Open discussions about the time of death and after, providing support during the mourning period.

The child's family doctor is responsible for the final part of the treatment in cases where a child dies at home. People who have known the family for a long time are the ones who have to be with the family in the terminal phase (5).

The management of the symptoms - Practical recommendations

- Pain;

Most children who die of cancer suffer and they need treatment to control their pain.

Sometimes it is necessary to initiate pain treatment well before the terminal phase. The main goals of terminal care treatment are comfort and pain control. (see chapter The treatment of pain)

- Psychomotor agitation

Benzodiazepines can be given to reduce anxiety and, if necessary, to improve the effectiveness of painkillers. Midazololam can be administered s.c. at 4-6 hours or by continuous perfusion.

- Bronchial hypersecretion

Avoid administration of excess fluids, limit the amount of fluid by perfusion and the administration of bolus scobutyl is indicated.

- Dyspnoea

Dyspnoea is a symptom of the terminal phase that produces anxiety. Oxygen will only be used if it alleviates the child's difficulty of breathing. At this stage, oxygen saturation is not measured. It is contraindicated to administer oxygen to asymptomatic patients, only to increase oxygen saturation. Benzodiazepines in combination with opioids are indicated to reduce symptoms in this situation.

- Nausea and vomiting

Oral or parenteral antiemetics and/or haloperidol are recommended, with progressive dose escalation. Levomepromazine can be used as an alternative.

- Transfusions

The transfusions are administered after an individual evaluation and they are rarely indicated, only to the extent that low haematological values have a clinical input.

Other interventions: treatment of infections, fluid supplementation and proper nutrition should be considered depending on the symptoms and anticipated life expectancy. This stage may be accompanied by anxiety, seizures. Anxiolytic medications may be needed and may improve analgesic effects. Benzodiazepines are the best for this purpose. It is also the group of drugs used to control seizures. Consciousness is often reduced in the terminal phase.

Psychological support

Emotional and spiritual support should be available to the child and family. Supporting the family to achieve their desired goals must begin with the diagnosis and continue until the end of life and the period of mourning.

The treatment will be applied taking into account what the patient and family can accept.

Recommendations:

- Allow the family and the child to spend time together
- Adapt the communication to the level of understanding of the family
- Make sure the family understands the signs and symptoms of imminent death and that they are supported during this process
- Counsel the family and explain what a "good death" means: minimal suffering for the child, family and caregiver, in accordance with the wishes of the patient and the family
- Assess the risk of pathological mourning and provide support
- Ask for the support of the priest - before, at death and during the period of mourning
- Evaluation of anticipatory mourning manifestations / risk of complicated mourning
- Respond to family emotions with empathy

Bibliography

1. Joanne Wolfe, SarahFriebert, Joanne Hilden. Caring for children with advanced cancer Integrating palliative care. Pediatr Clin N Am 49. 2002. 1043–62

2. Charlotte Mellor, Emma Heckford,Jo Frost. Developments in paediatric palliative care. Peadiatrics and Child Health Care. Vol 22, Issue 3, 115-20

3. Hinds PS, Drew D, Oakes LL, Fouladi M, Spunt SL, Church C, Furman WL, End-of-life care preferences of pediatric patients with cancer. J Clin Oncol. 2005. 23(36):9146-54.

4. Bernacki RE, Block SD; American college of Physicians High Value Task Force. Communication about serious illness care goals: A review and synthesis of best practices. JAMA Intern Med 2014; 174:1944-2003.

5. Powazki R, Walsh D, Hauser K, et al. Communication in palliative medicine: A clinical review of family conferences. J Palliat Med2014;17:1167-77.

10. LEGISLATIVE PROVISIONS

Children's rights to health care insurance

Prior to any diagnostic or therapeutic procedure, it is mandatory to obtain informed consent from the legal representatives of the minor patient.

We face too many cases where parents refuse or abandon the treatment of children with cancer, unknowingly assessing that the disease is deadly anyway. We consider that it is necessary to highlight the way in which the Romanian law regulates this problem.

Being a matter of major importance, all the situations are set out in detail in Law no. 272/2004 regarding the protection and promotion of children's rights.

According to this law, the child has the right to benefit from the best possible health state and the medical and recovery services necessary to ensure the effective implementation of this right. This right is guaranteed by the Romanian state.

It is mandatory for the parents to seek medical assistance in order to ensure that the child is in the best possible health that he/she could reach and to prevent situations which endanger the child's life, its growth and development.

In the exceptional situation in which the child's life is in imminent danger, or there is a risk of serious consequences for his/her health or integrity, the doctor has the right to perform those medical acts of strict necessity to save the child's life, even without having the consent of the parents or another legal representative thereof.

Cancer is considered to be a serious disease, and the disabled child has the right to special care, adapted to his/her needs. The state provides monthly allowances for the parent who cares for the child with severe disabilities, to come to the aid of all families for the transition through therapy, recovery and social reintegration. The legislative framework is represented by Law no. 448/2006 on the protection and promotion of the rights of persons with disabilities and the amendments introduced by the Emergency Ordinance no. 60/2017 for the amendment and completion of Law 448/2006. Given the child's right to treatment and care, stipulated by the law, every effort must be made to limit the phenomenon of non-compliance and in each case the support of the competent authorities must be requested, starting with the General Directorate of Social Assistance and Child Protection.

Regarding the rights of the child with a serious illness, in the hospital, the following are mentioned:

- Child care is performed without discrimination
- The child should be accompanied by a parent or caregiver
- The state provides free transportation for the treatment of the child and for the person caring for him/her, depending on the clinical condition, the transport being carried out by ambulance or public transport.

- Children with cancer are encouraged to continue their studies (at school, hospital school, home schooling), as required by the clinical situation.

- The connection between the hospital and the family doctor is essential; it is made both by medical letter and by direct contact in special situations.

An unresolved issue is the decision not to apply unnecessary, heroic treatments in the event of death of the terminal patient, the DNR decision (do not resuscitate). There is a legislative vacuum that must be filled by the involvement of specialists; as for now, the doctor undertakes the responsibility to act according to his/her conscience in each situation, in accordance with the opinion of the family, but not being supported by legislation.

11. VACCINATION IN CHILDHOOD CANCER

Immunocompromised children are a special category of patients who require close monitoring. Primary immunodeficiencies are congenital and include humoral, cellular, combined, and phagocytic deficits (e.g., X-linked agammaglobulinemia, SCID, chronic granulomatous disease).

Secondary immunodeficiencies are acquired, and this category is represented by children with neoplasms or under immunosuppressive treatment (chemotherapy, radiotherapy, corticotherapy, biological medication), with hematological diseases, autoimmune diseases, HIV, anatomical or functional asplenia, chronic diseases such as chronic kidney disease, diabetes. The children in these categories are more vulnerable to infections compared to immunocompetent ones, so vaccination is often necessary, but with some guidelines. The laboratory tests that assess humoral immunity are: immunoglobulin subsets and the level of specific antibodies (tetanus, diphtheria, pertussis), and those that assess cellular immunity are: absolute lymphocyte count, lymphocyte subsets (CD4/CD8) and T lymphocyte proliferation. (1)

The decrease of the defence of the body against infections in children with cancer under treatment is caused by the combination of damage to the body's barriers (skin, mucous membranes) and myelosuppression. The specific/adaptive immune system, represented by lymphocytes and antibodies is always affected, and the consequences are varied and unpredictable. There is a decrease in the number and function of B lymphocytes, with the impairment of humoral immunity which is reflected by the decrease in Ig A, Ig G and Ig M (9-50% of cases); Cellular immunity is also affected by a decrease in the number of T lymphocytes, which causes a poor response to vaccination during treatment; memory cells persist. (2, 3)

Different types of cancer in children require treatment with different combinations of chemotherapeutic agents. Therapy is risk-stratified according to patient-related factors, disease extent, and molecular biology and it varies in intensity for each type of cancer. Depending on the treatment regimen, the number and function of T and B lymphocytes decrease during treatment, mostly with complete quantitative and qualitative recovery at 6 months after the end of chemotherapy, in some cases up to 1 year. (4) The immunosuppression in children with cancer is caused by the following factors: young age, underlying disease (leukaemia, lymphoma, etc.), type, intensity and duration of chemotherapy, drugs (e.g. steroids), other types of treatment (splenectomy, thymectomy, radiotherapy). (3)

During the period of low intensity treatment and after the end of the chemotherapy, the normalization of the specific or adaptive immune system occurs. NK cells and B lymphocytes are reconstituted in the first 3 to 6 months after the end of the chemotherapy. Immunoglobulins may be decreased during treatment, and their normalization occurs gradually within the first 6 months. Abnormalities of Ig G subclasses and decreased levels of specific antibodies may persist for more than 1 year after the end of chemotherapy in a large percentage of children. Helper T lymphocytes (CD4) may be decreased up to 12 months after treatment, and cytotoxic T lymphocytes are usually normalized within the first 3 to 6 months. (4, 5)

Classification of immunocompromised patients: (6)

Patients with high levels of immunosuppression:

- chemotherapy for cancer
- severe combined congenital immunodeficiencies (SCID)
- corticosteroid therapy more than 20 mg/day or 2 mg/kg/day for children under 10 kg, for more than 14 days
- Biological therapy: anti TNF alpha (adalimumab, infliximab, etanercept), anti Interleukin 6 (Tocilizumab) or anti -human antigen CD20 monoclonal antibody (Rituximab)
- The first months after hematopoietic stem cell transplantation; for a longer period depending on the type of bone marrow transplant (longer period for allogeneic versus autologous), donor type and stem cell source, post-transplant complications as well as graft-versus host disease (GVHD)
- The first 2 months after any solid organ transplant
- HIV infection with CD4 T lymphocytes below 200/mm3 for children over 5 years of age and with a percentage of CD 4 T lymphocytes below 15% for children under 5 years of age

Patients with low immunosuppression:

- Daily therapy with lower doses of corticosteroids than the higher levels of immunosuppression (less than 20 mg/day, or less than 2 mg/kg/day for children under 10 kg) or therapy on alternative days
- MTX below 0.4 mg/kg/week, azathioprine below 3 mg/kg/day or 6 MP below 1.5 mg/kg/day
- Asymptomatic HIV infection and CD4 T cell count between 200-499/mm3 for children over 5 years of age and with a percentage of CD4 T cells between 15-24% for children under 5 years of age

Basic principles of immunization in immunocompromised children: (5)

- Determining the immune status
- Careful assessment of risks versus benefits (safety and efficacy)
- Live virus vaccines are contraindicated
- Inactivated vaccines are safe and they play an important role
- Partial post-vaccination protection is better than total lack of protection
- Consider testing for antibodies to evaluate the response to the vaccine
- Vaccination of contacts and medical care staff
- Compliance with current vaccination recommendations
- Administration of vaccines before immune suppression when possible

Practical vaccination advice for immunocompromised patients (6)

- *For patients in whom immunosuppressive medication is scheduled, live virus vaccines should be administered more than 4 weeks before immunosuppression and not less than 2 weeks before starting the medication; inactivated vaccines can be given at least 2 weeks before medication*
- Certain vaccines can be administered to children even if they are moderately immunosuppressed, especially if this immunosuppression is long-lasting; e.g. inactivated vaccines during maintenance chemotherapy in acute leukaemia
- Patients receiving treatment with TNF alpha antagonists or monoclonal antibodies against B lymphocytes (Rituximab) may be vaccinated with live or inactivated virus vaccines at least 6 months after stopping the treatment.

- Patients receiving high doses of corticosteroids daily (more than 20 mg/day or 2 mg/kg/day for children under 10 kg, for more than 14 days) may be vaccinated with inactivated viruses, when indicated, even if the vaccine response is weaker.

- Vaccines with live viruses are contraindicated during high-dose corticosteroid therapy; they can be administered first 4 weeks or more after the end of the treatment

- Patients receiving low doses of corticosteroids daily (less than 20 mg/day, or less than 2 mg/kg/day for children under 10 kg) or therapy on alternative days may be vaccinated with live virus vaccines during corticosteroid therapy.

- Patients that have received immunoglobulins or blood products may be vaccinated with live virus vaccines first 3 months or more after administration, as the vaccine antigen may be inactivated by antibodies from the infusion of immunoglobulins or blood products

- It is recommended that vaccination should not be performed if the absolute number of neutrophils is below 500/mm3, as any adverse reaction such as post-vaccination fever will result in hospitalization and the need for antibiotic therapy.

Recommended vaccines during chemotherapy (2, 3, 5, 7) (see Table 1)

- Inactivated virus vaccines (Hepatitis A, Hepatitis B, Hemophillus, pneumococcus, meningococcus, diphtheria-pertussis-tetanus DPT) **can be administered** during maintenance treatment, but with unpredictable response.

- **Vaccines with live viruses** are **contraindicated** during chemotherapy: oral polio vaccine, anti measles, mumps, rubella, (MMR), rotavirus, chickenpox, live attenuated influenza vaccine (LAIV)

- **Vaccines with live bacteria** are **contraindicated** during chemotherapy: BCG vaccine, Salmonella Typhi vaccine

- **The inactivated influenza vaccine** is recommended to be performed annually, before the flu season, in children over 6 months of age, if the absolute number of neutrophils and lymphocytes is over 1000/mm3, 2-3 weeks after the last chemotherapy treatment.

Table 1. Vaccination recommendation during chemotherapy (7)

The moment of chemotherapy	Vaccination recommendation
Chemotherapy or in the first 6 months after the end of chemotherapy	➢ Vaccination is not recommended; the administration of inactivated vaccines must be assessed on a case-by-case basis in relation to the social and epidemiological conditions which increase the risk of vaccine-preventable diseases. ➢ Vaccines with live viruses and bacteria are absolutely contraindicated
6 months after the end of chemotherapy or later	➢ Starting a new vaccination schedule in children under one year of age who have not been vaccinated or who have received only one dose of vaccine ➢ Revaccination following the usual vaccination for older children

For children completely vaccinated with the primary schedule, the antibody titer is checked and then a booster dose is given OR a booster dose is given to all (without checking the antibody titer).

For children incompletely vaccinated with the primary scheme, the following applies: if they have not been previously fully vaccinated, it is recommended to start a new vaccination

schedule according to age; if partially vaccinated, booster is given and complete immunization is continued. (2, 3)

A recent feasibility study demonstrated post-chemotherapy immunological recovery earlier than 6 months and recommends re-vaccination in non-transplanted children who are in remission even at 3 months after the end of chemotherapy. (8)

National Immunization Program in Romania according to the National Institute of Public Health Order MS 978/2019 (see table 2)

Table 2. National Vaccination Calendar 2019 for immunocompetent children (9)

Vaccine type	**Age of administration**	**Comments**
Calmette Guerrin Vaccine (BCG)	The first 2-7 days after birth	In the maternity ward
Hepatitis B vaccine (Hep B)	The first 24 hours	In the maternity ward
Diphtheria-tetanus - acellular pertussis-poliomyelitis-Haemophilus B-hepatitis B vaccine (DTaP-Hib-IPV-Hep B)	2+4+11 months	Family doctor
13 Serotypes pneumococcal conjugate vaccine	2+4+11 months	Family doctor within the available funds
Measles, mumps, rubella (MMR) vaccine	12 months and 5 years	Family doctor
Diphtheria-tetanus - acellular pertussis-poliomyelitis vaccine (DTaP-IPV)	6 years	Family doctor
Diphtheria-tetanus - acellular pertussis vaccine for adults (DTaP)	14 years	Family doctor
Human papillomavirus vaccine (HPV)	11-14 years	Family doctor At the request of parents

Other recommended vaccines that are not mandatory in Romania are: rotavirus, varicella, hepatitis A, influenza, HPV, meningococcal. The flu vaccine is recommended for population groups at risk established by the World Health Organization (medical staff, the chronically ill, the elderly and pregnant women), and the MMR vaccine should be applied to outbreak contacts.

WHO is responsible for vaccinating immunocompromised patients? (10)

The specialty doctors /specialists treating immunocompromised patients have a responsibility to ensure that patients receive the appropriate vaccines (where necessary).

The specialty doctors /specialists treating immunocompromised patients have a responsibility to ensure that immunocompetent persons caring for or living with an immunocompromised patient are informed of the required vaccination and they receive the appropriate schedule.

WHEN is the best time to get vaccinated? (10)

- vaccination should be carried out before the beginning of the treatment regimen (if possible)
- live vaccines should be administered more than 4 weeks before immunosuppressive treatment and should be avoided within the first 2 weeks from the start of the treatment
- inactivated vaccines should be given more than 2 weeks before the start of immunosuppressive therapy

Vaccination recommendations for children with cancer receiving chemotherapy (4, 10, 11)

- The inactivated influenza vaccine (IIV) can be given annually to children over 6 months of age with haematological neoplasms or solid tumours, except for those receiving intensive chemotherapy (e.g. induction or enhancement chemotherapy for acute leukaemia) or receiving anti B cell antibody treatment (Rituximab).
- The live attenuated influenza vaccine (LAIV) is not recommended for children receiving chemotherapy (even if it is maintenance chemotherapy); this vaccination can be given after more than 3 months from the end of the chemotherapy.
- The pneumococcal conjugate vaccine (PCV13) is recommended for all children newly diagnosed with haematological neoplasms or solid tumours before and during chemotherapy if they have not been vaccinated before and if they are at risk of preventable infections with this vaccine. The pneumococcal polysaccharide vaccine (PPSV23) can be given to children over 2 years of age at least 8 weeks after PCV13.
- Inactivated vaccines (other than influenza vaccine) recommended in immunocompetent children (Hib, hepatitis A, B, DTP, HPV, meningococcal conjugate, inactivated polio), may be considered in children receiving maintenance chemotherapy; doses of vaccine given during chemotherapy cannot be considered effective unless there is evidence of a protective antibody titer; administration is preferred at more than 2 weeks before the start of chemotherapy
- Vaccines with live viruses (MMR, varicella, rotavirus, oral polio vaccine) should not be given during chemotherapy

In Tables 3 and 4 we present the scoring system used for vaccination recommendations of children with oncological diseases receiving chemotherapy and the indication of vaccines during and after chemotherapy.

Table 3 Scoring system used for vaccination recommendations (12)

Level of recommendation	Quality of evidence
A. Strong evidence for efficacy and substantial clinical benefit; strongly recommended	I: Evidence present in at least one controlled, randomized, well-executed trial
B. Strong or moderate evidence for efficacy, but limited for clinical benefit; generally recommended	II: Evidence present in at least one well-executed but non-randomized trial; cohort or case-controlled analytical studies (preferably more than one centre); multiple studies serialized over time
C. Insufficient evidence of efficacy or evidence does not outweigh possible adverse effects; optional	III: Evidence from the opinion of the authorities based on clinical experience; descriptive studies; reports of expert committees
D. Moderate evidence against efficacy or adverse effects; generally not recommended	
E. Strong evidence against efficacy or adverse effects; never recommended	

Table 4 The level of indication and recommendation of vaccines in children during and after chemotherapy (12)

Vaccine	The period of chemotherapy Indication level, Recommendation	After chemotherapy Indication level, Recommendation	Remarks
Poliomyelitis inactivated	C III, optional, it is delayed if the number of lymphocytes is below 1000 /mm3	B II, recommended, booster or vaccination 6 months after the end of chemotherapy	
Diphtheria and pertussis	C III, optional, it is delayed if the number of lymphocytes is below 1000 /mm3; passive immunoprophylaxis and antibiotic prophylaxis in case of epidemic	B II, recommended, booster or vaccination 6 months after the end of chemotherapy	
Tetanus	C III, optional, it is delayed if the number of lymphocytes is below 1000 /mm3, passive immunoprophylaxis, washing and disinfection of wounds, antibiotic therapy as needed	B II, recommended, booster or vaccination 6 months after the end of chemotherapy	
Hepatitis A virus	C III, optional, vaccination for seronegative patients before starting chemotherapy in endemic areas; alternatively passive immunoprophylaxis	C III, optional, booster or vaccination 6 months after the end of chemotherapy	
Hepatitis B virus	B II, recommended, vaccination for seronegative patients before starting chemotherapy in endemic areas; alternatively passive immunoprophylaxis	B II, recommended, booster or vaccination 6 months after the end of chemotherapy	4 weeks between the first and second dose of vaccine and 3 months between the third and fourth dose of vaccine
Measles, mumps, rubella (MMR)	D III, not recommended, not administered under the age of 12 months; passive immunoprophylaxis in case of contact; vaccination of seronegative family members	B II, recommended, booster or vaccination at 6 months after the end of chemotherapy; it is not administered under the age of 12 months	If the patient received a dose before chemotherapy, he/she should receive 2 doses later, with the second dose at 6 months after the end of chemotherapy.
Measles (epidemic)	C III, optional, if there is an epidemic, patients can be vaccinated if they have an adequate level of CD4+ lymphocytes	B II, recommended, booster or vaccination at 6 months after the end of chemotherapy; it is not administered under the age of 12 months	Adequate CD4+ level: higher than 750/mm3 (children under 12 months); higher than 500/mm3 (1-5 years); higher than 200/mm3 (children over 6 years of age)

Varicella	C II, optional, it is postponed if the absolute number of lymphocytes is between 700-1200/mm3 or if the patient is not in continuous remission for 12 months or if he/she undergoes radiotherapy; It is not administered under the age of 12 months Vaccination of family members at risk; post-exposure prophylaxis in the first 96 hours after the contact with specific immunoglobulins (0.2 ml/kg, max. 10 ml); after 96 hours of contact Aciclovir 4 x 20 mg/kg/day (7-21 days)	B II, recommended, is not administered under the age of 12 months Booster or vaccination at 6 months after the end of chemotherapy	It is not recommended if the absolute number of neutrophils is below 500/mm3 or lymphocytes below 700/mm3, corticosteroid therapy over 7 days with doses higher than 2 mg/kg/day combined with other immunosuppressive treatments It can be given during maintenance chemotherapy in acute lymphoblastic leukaemia
Haemophilus Influenzae	C III, optional, is not administered under the age of 2 months, it is recommended before splenectomy; it is delayed if the number of lymphocytes is below 1000/mm3	B II, recommended, is not administered under the age of 2 months Booster or vaccination at 6 months after the end of chemotherapy	
Pneumococcus	C II, optional, vaccination before splenectomy is recommended; it is delayed if the number of lymphocytes is below 1000/mm3	B II, recommended booster or vaccination at 6 months after the end of chemotherapy	The pneumococcal polysaccharide vaccine (PPSV23) is not effective under the age of 2 years. It is performed at least 8 weeks after administration of the pneumococcal conjugate vaccine. The pneumococcal conjugate vaccine (PCV13) can be given to infants over 6 weeks of age.
Meningococcal	C III, optional, is recommended before splenectomy; it is delayed if the number of lymphocytes is below 1000/mm3; it is not recommended under the age of 2 years	B II, recommended booster or vaccination at 6 months after the end of chemotherapy; booster after 3 years if vaccinated	The meningococcal B vaccine available in Romania can be administered after the age of 10 years. The meningococcal conjugate vaccine A,

		between 2-6 years of age	C, W, Y (MCV4) available in Romania can be administered to infants over 6 weeks of age.
Inactivated influenza virus (IIV)	B II, recommended, early autumn vaccination; it is delayed if the number of lymphocytes is below 1000/mm3; vaccination of family members with inactivated influenza virus	B II, recommended, vaccination in the autumn season at 3 months after the end of intensive chemotherapy	It is not administered to infants younger than 6 months of age
Human papilloma virus (HPV)	No data	C III; it is not administered under 9 years of age; booster or vaccination 6 months after the end of chemotherapy	If there was no previous vaccination or incomplete vaccination has been given, 3 doses will be given at 6, 8 and 12 months after the end of chemotherapy.
Rotavirus	contraindicated	No data	

Vaccination in children with hematopoietic stem cell transplantation (HSCT)

Children with hematopoietic stem cell transplantations have severe immunosuppression for a long time after transplantation, from several months to several years. Immunological reconstitution after autologous hematopoietic stem cell transplantation occurs faster than after allogeneic transplantation. Innate immunity is restored weeks and months after bone marrow transplantation; instead, the deficiency of the adaptive immune system, in particular the decrease in CD4+, causes a prolonged immunodeficiency. B lymphocyte counts may return to normal 3 months after the transplantation in patients without GVHD, but their function restores over a longer period of time. Immunoglobulin levels begin to normalize in 6 months after the transplantation, with slower recovery of the IgG2 subclass. T lymphocyte recovery is evident in 6-12 months after transplantation. (4)

Immunity to vaccine-preventable diseases (tetanus, poliovirus, MMR, encapsulated bacteria) decreases up to 1-4 years after bone marrow transplantation. As a result, patients who have been vaccinated before a bone marrow transplant should be routinely revaccinated after the transplant. (4)

The factors influencing vaccine immunogenicity in bone marrow transplant patients are: type of transplant, time after transplantation, chronic GVHD, age, number of vaccine doses, current vaccine. (4)

Vaccination recommendations in children after bone marrow transplantation (1, 4, 10)

• ***Inactivated influenza vaccine (IIV)*** is recommended annually to children over 6 months of age, at 6 months after transplantation and subsequently annually, for life; it can also be given 4 months after the transplantation if a flu epidemic is declared; children aged 6 months to 8 years receiving the flu vaccine for the first time should have two doses

• ***Pneumococcal conjugate vaccine*** *PCV13* is recommended at 3-6 months after transplantation, 3 doses, with a 4-week dose interval. For patients without chronic GVHD, a dose of pneumococcal polysaccharide vaccine PPSV23 may be given at 12 months after transplantation; for patients with chronic GVHD disease the fourth dose of PCV13 vaccine can be given at 12 months after transplantation

• ***Hib vaccine*** *(Hemophillus influenza type b)* is recommended at 6-12 months post-transplantation, 3 doses, with at least a 4 weeks interval between doses.

• ***Meningococcal conjugated vaccine*** *MCV4* is recommended 6-12 months after transplantation in children aged 11-18 years, with a revaccination at the age of 16-18 years for those who received the initial dose of vaccine after transplantation at the age of 11-15 years.

• ***DTaP vaccine*** is recommended at 6 months after transplantation, 3 doses

• ***Hepatitis B vaccine*** is recommended at 6-12 months post-transplantation, 3 doses

• ***Inactivated polio vaccine*** is recommended at 6-12 months after transplantation, 3 doses

• ***HPV (human papilloma virus) vaccine*** can be administered optionally at 6-12 months after transplantation, for females, aged 11-26 years, 3 doses.

• The ***MMR vaccine*** can be given more than 24 months after the transplant, to children and adolescents with no anti-measles antibodies, no chronic GVHD disease or immunosuppression and at 8-11 months after the last dose of intravenous immunoglobulins; two doses should be given

• The ***varicella vaccine*** can be given more than 24 months after the transplant for children with no anti-varicella antibodies, no chronic GVHD disease or immunosuppression and at 8-11 months after the last dose of intravenous immunoglobulins; two doses should be given

• **live virus vaccines are contraindicated in transplantation patients with active GVHD disease, and during any immunosuppressive therapy**

• Are contraindicated BCG vaccination (except for specific circumstances, highlighting immunological reconstitution), rotavirus, live intranasal attenuated influenza vaccine

• The administration of vaccines is contraindicated at least 3 months after the administration of intravenous immunoglobulins

Vaccination recommendations for immunocompetent patients living with an immunocompromised person (4, 5, 10)

• Inactive vaccines included in the vaccination schemes for both children and adults can be administered to immunocompetent patients

• The annual flu vaccine is recommended for family members over 6 months of age; if live attenuated influenza vaccine (LAIV) is administered, it has a potential for transmission for 1-2 weeks after vaccination and the contact with the immunocompromised person should be avoided

• The oral polio vaccine should not be administered

• MMR vaccination in all children over 12 months of age who come into contact with the immunosuppressed patient

• Immunization of all contacts at risk of varicella

• Vaccination against rotavirus for infants aged 2-7 months, avoiding contact with the immunocompromised person for 2-4 weeks post-vaccination

• Immunization of non-immunized medical staff for TB, hepatitis B, MMR, varicella, influenza

Bibliography

1. General Best Practice Guidelines for Immunization: Alterated Immunocompetence; https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.pdf

2. Battista A., Ruggiero A., Cocia P., Arena R., Attina G., Riccardi R., Vaccination în children with cancer: a debate, Cent. Eur. J. Med.2012;7(2): 137-141

3. Fadoo Z., Vaccination Guidelinesin Immunocompromised Children, SIOP PODC Supportive Care Education , ICON 2016https://siop-online.org/wp-content/uploads/2015/11/ICON-2016-Vaccination-Guidelines-în-immuno-compromised-children.pdf

4. PatelS., Heath P., Skinner R., Vaccinations for Pediatric Treated With Standard Dose Chemotherapy and Haematopoietic Stem CellTransplantation (HSCT) Recipients, CCLG FINAL Version 10-12-14, Review date september 2017 https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/Vaccinations_for_Children_treated_with_Standard-Dose_Chemotherapy_and_HSCT_Recipients-Sept_2014-FINAL_CCLG.pdf

5. Naqvi A., Fadoo Z., Alvi S., Vaccination Guidelines for Children with Cancer and Hematopoietic Stem Cell Transplantation Living în Resource Poor Countries, Pediatr Blood Cancer 2010; 54:3-7.

6. Kimberlin DW., Brady MT., Jakson MA., Long SS., RedBook: 2015 Report of the Committee on Infectious Diseases. 30th ed., American Academy of Pediatrics, Chapter title: Immunization in Immunocompromised Children: 74-89

7. RuggieroA., Battista A.,Cocia P., Attina G., Riccardi R., How to Manage Vaccination în Children with Cancer, Pediatr Blood Cancer 2011; 57(7):1104-108

8. Han JH., Harmoney KM., Dokmeci E., et al, Dynamic re-immunization of off-treatment childhood cancer survivors: An implementation feasability study, PLOS ONE 2018, 13(2):e0191804,1-8

9. Calendarul National de Vaccinare https://cnscbt.ro/index.php/calendarul-national-de-vaccinare

10.Rubin LG., Levin MJ., Ljungman P., et al , 2013 IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host, Clin Infect Dis2014;58(3):309-18

11.Brumboiu MI.,Bocsan IS., Vaccinuri și Vaccinari în Practica Medicala, Editura Medicala Universitara Iuliu Hatieganu 2005, Cap. Vaccinarile la gazde imunodeprimate: 138-172

12.Cesaro S., Giacchino M., Fioredda F. et al, Guidelineson Vaccination în Pediatric Haematology and Oncology Patients, Bio Med Res Int.2014:707691

12. FOLLOW-UP OF CHILDREN WITH CANCER, SIDE EFFECTS OF ONCOLOGICAL THERAPIES

12.1 ACUTE TOXICITY OF ONCOLOGICAL TREATMENTS

The acute toxicity of cytostatic agents is due to the antiproliferative effect it exerts on normal tissues (bone marrow, mucosal epithelium). The low therapeutic index of cytostatic agents due to the non-selective mechanism of action causes an increased incidence of severe toxicity. The acute toxicity caused by most cytostatic agents includes: myelosuppression, nausea and vomiting, alopecia, oro-intestinal mucositis, liver and kidney function involvement, allergic reactions, local skin ulcers after extravasation. These toxic effects occur within hours to weeks after the administration of the cytostatic agents and they are usually reversible.

Some cytostatic drugs have a unique toxicity that is specific to an organ or a tissue, as well as cardiotoxicity caused by anthracyclines; hemorrhagic cystitis associated with cyclophosphamide and ifosfamide; peripheral neuropathy occurring after the administration of Vincristine, Cisplatin; nephrotoxicity caused by Cisplatin and ifosfamide; ototoxicity caused by Cisplatin; coagulopathy caused by Asparaginase. Organ toxicity is more worrying as it may require dose limitation in subsequent courses, or may cause long-term sequelae in curable patients. (1)

The toxicity of tyrosine kinase inhibitors (TKI) differs from the conventional toxicity of the cytostatic agents. The tyrosine kinase inhibitors (TKI) do not usually cause myelosuppression, and acute toxicity includes anorexia, fatigue, nausea, vomiting, diarrhoea, abdominal pain, edema, hypertension, rash. TKI can cause thyroid dysfunction and cardiotoxicity (1).

In acute lymphoblastic leukaemia, according to the ALL study groups (Ponte din Legno Toxicity Working Group or PTWG), 14 acute non-infectious toxicities were defined: mucositis, central and peripheral neuropathy, osteonecrosis, thromboembolism, sinusoidal obstruction syndrome, endocrinopathy (cortisone-induced adrenal insufficiency and hyperglycemia), nephropathy caused by high doses of methotrexate, toxicity caused by asparaginase (hypersensitivity, pancreatitis, hyperlipidemia, coagulation disorders), specific toxicity associated with host genome variants, risk of secondary malignancy (2). In ALL, the non hematological toxicity is primarily represented by infections, followed by hepatotoxicity and gastrointestinal toxicity (3).

Adverse event (AE) reporting is an important aspect in oncology. These may reflect the toxicity of the chemotherapy or may be a sign of the underlying disease. The assignment of symptoms can be difficult due to the fact that it cannot be established with certainty whether they are caused by the disease itself, by the treatment, by the comorbidities or the combination of the three. (4, 5)

According to the Common Terminology Criteria for Adverse Event (CTCAE version 5, 2017) published by the National Cancer Institute (NCI), adverse events are classified in 5 grades (6):

1 = mild, minor, asymptomatic, usually does not require intervention or medication

2 = moderate, usually symptomatic, requires minimal, local, non-invasive interventions

3 = severe, with multiple symptoms, requires hospitalization or prolongation of the hospitalization

4 = life threatening, with emergency intervention

5 = death

The haematological toxicity associated with chemotherapy is well known.

Leukopenia with neutropenia (1): The risk of infection in children with cancer is directly proportional to the severity and duration of neutropenia: ANC <200/mm3 risk of bacteremia/sepsis; ANC <500/mm3 risk of severe infections (pneumonia, cellulite, etc.). It starts on day 3 and it is maximum between days 7-14 of the chemotherapy cycle. Febrile neutropenia: ANC <1000/mm3 and fever over 38.3 degrees Celsius at a determination or over 38 degrees persistent over one hour.

Neutropenia is the most common haematological toxicity and it can cause severe infections. The chemotherapy predisposes children to severe infections through myelosuppression and the cytotoxic effect on digestive tract cells. The degree and duration of neutropenia is the most important risk factor for infection. Patients with haematological malignancies have a higher risk of developing neutropenia compared to solid tumours due to the intensity of the used chemotherapy regimens. Early-onset neutropenia is more common during induction in ALL and AML.

Anaemia is common in children with cancer. The decreased erythrocyte production is associated with nutritional deficiencies, inadequate response to erythropoietin, tumour infiltration in the bone marrow, and chemotherapy. In addition to transfusions, the erythropoietin treatment can be used: 150 U/kg/dose, 3 administrations per week subcutaneous, Hb can increase by 1-2g% in patients receiving moderately aggressive chemotherapy.

The thrombocytopenia is an adverse effect of chemotherapy and it is more common in children with haematological malignancies. (7, 8)

Gastrointestinal toxicity

Table 1- Classification of cytostatic agents according to the emetogenic risk (9, 10)

Increased emetogenic risk ≥ 90%	Carboplatin Cisplatin Dacarbazine Procarbazine	Dactinomycin Cyclophosphamide ≥ 1g/m2 Cytarabine 3g/m2/doza Methotrexate ≥ 12 g/m2
Moderate emetogenic risk 30-90%	Cyclophosphamide <1g / sqm Oral cyclophosphamide Ifosfamide Cytarabine 200 mg-3 g/m2 Daunorubicin Doxorubicin Epirubicin	Oral etoposide Imatinib Oral temozolomide Oral vinorelbin Methotrexate ≥250 mg-12 g / m2 Intra-spinal therapy (MTX, Hydrocortisone, Cytarabine) Irinotecan Lomustine

	Idarubicin Busulfan Clofarabine	Melphalan ≥ 50 mg / m2
Low emetogenic risk 10-30%	Cytarabine <200 mg / m2 Etoposide Oral busulfan Oral fludarabine 5 Fluorouracil Gemcitabine	Methotrexate ≥ 50 mg / m2-250 g / m2 Mitomycin Mitoxantrone Nilotinib Paclitaxel Topotecan
Minimal emetogenic risk <10%	Asparaginase Bleomycin Oral chlorambucil Cladribine Dasatinib Erlotinib Fludarabine Hydroxyurea	Oral mercaptopurine Methotrexate <50 mg / m2 Rituximab Oral thioguanine Vinblastine Vincristine Vindesine Vinorelbine

• Nausea and vomiting induced by chemotherapy are some of the most common side effects of chemotherapy in children (70%). (8) (see table 1)

Classification of emesis:

- Acute emesis: it appears a few minutes after the start of chemotherapy and it disappears in the first 24 hours.

- Delayed emesis: occurs 24 hours after the initiation of chemotherapy and may be present in 80% of patients; it is usually more severe on the third day and it can last up to 7 days

- Anticipative emesis: occurs before the chemotherapy in patients who have had emesis in previous cycles

Treatment of chemotherapy-induced nausea and vomiting according to the 2016 MASCC / ESMO guideline (8, 10, 11):

- serotonergic antagonists (of 5-hydroxytryptamine-3/5-HT3 receptors): odansetron, granisetron, palonosetron

- palonosetron is second-generation 5-HT3 receptor antagonist with good nausea control compared to odansetron in children with high or moderate emetogenic chemotherapy risk.

- neurokinin 1 receptor antagonist (aprepitant), a new drug approved in the USA and Europe for the treatment of nausea and vomiting in children with high and moderate emetogenic chemotherapy risk

- dexamethasone

Prophylaxis of nausea and vomiting (8, 10, 11):

- chemotherapy with low emetogenic risk: 5HT3 antagonists (recommendation level II B)

- chemotherapy with high or moderate emetogenic risk: 5HT3+ Dexamethasone + aprepitant antagonists (recommendation level II B)

- the oral aprepitant is not always available in liquid form and may not be an option for all children with highly emetogenic chemotherapy, in which case the combination of 5HT3 antagonist and dexamethasone is used (recommendation level II B)

• Chemotherapy-induced diarrhoea (12)

It is caused by the combination of mechanical and biochemical disturbances caused by the effects of cytostatic agents on the intestinal mucosa. It occurs more frequently after the administration of Topoisomerase inhibitors (Irinotecan), high doses of methotrexate or 5 Fluorouracil. The differential diagnosis with Clostridium difficile-induced enterocolitis, subacute intestinal obstruction, steatorrhea is required.

Management:

- clinical evaluation, weighing, hydration status
- laboratory tests (blood, stool cultures, exclusion of Clostridium difficile toxins)
- diet, oral or parenteral hydration
- if the patient is neutropenic, prophylactic antibiotic therapy is considered
- if diarrhoea is considered non-infectious, loperamide should be considered.

• Oral and gastrointestinal mucositis is caused by high-dose chemotherapy and radiotherapy. (2, 13, 14)

The oral mucositis is the inflammation of the oral mucosa, erythema and ulcers that can be exacerbated by local factors, as well as secondary infections and mucosal lesions and can lead to a poor nutritional status. Chemotherapeutics drugs that can cause oral mucositis: CTX, DOXO, VCR, VP16, IFO, MTX, DDP, Carbo, IRI, 5 FU, Vin

- The signs of gastrointestinal mucositis are abdominal pain, diarrhoea or constipation, nausea or vomiting, and oral and intestinal mucositis may not coincide. They usually occur 10-14 days after the chemotherapy and they disappear in 5 to 10 days.

Classification as an adverse event according to NCI CTCAE v.5 is separate for oral mucositis (stomatitis) and for each type of gastrointestinal mucositis: pharyngitis, esophagitis, gastritis, colitis, rectal and anal mucositis. (6)

Preventive measures:

- daily examination of the oral cavity
- avoid foods that can cause irritation of the oral mucosa, avoid spices
- elimination of dental problems
- rigorous oral hygiene
- washings with physiological serum, Sodium bicarbonate, Chlorhexidine

Treatment:

- antifungal drugs: Nystatin, Fluconazole, Posaconazole
- oral or intravenous antiviral drugs (Acyclovir)
- local disinfectants: Tantum Verde - Benzydamine, Gel X (zinc and taurine gluconate), Anaftin gingival gel
- treatment of local and systemic analgesic pain (parenteral nonsteroidal anti-inflammatory drugs, neuroleptics, opioids)
- granulocyte stimulating factor in case of severe neutropenia
- treatment with probiotics (Lactobacillus) for diarrhoea in intestinal mucositis
- other: iv glutamine, cryotherapy, laser therapy, recombinant keratinocyte growth factor

• Hepatic toxicity secondary to chemotherapy occurs most commonly as an unpredictable and idiosyncratic reaction, and pre-existing liver disease increases this risk (15). Hepatotoxicity is one of the most common acute post-chemotherapy toxicities in ALL and it occurs most frequently in the induction and reinduction stage. (2. 3)

Although the grading system with liver enzymes and bilirubin is frequently used in practice, their increase does not always reflect liver dysfunction.

Drug Induced Liver Injury (DILI):

- Grade 1: (mild): isolated increased ALT or ALP
- Grade 2: (moderate): increased bilirubin and coagulopathy
- Grade 3: (severe): requires hospitalization
- Grade 4: liver failure, encephalopathy, kidney failure
- Grade 5: death or liver transplant

Liver failure: increased liver enzymes, increased ammonia, increased bilirubin, LDH, prolongation of prothrombin time. Clinical presentation of hepatotoxicity secondary to chemotherapy includes: asymptomatic patient, increased liver enzymes, cholestasis, steatosis, progression to fibrosis and liver cirrhosis.

Veno occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) is a complication of hematopoietic stem cell transplantation, PEG-asparaginase, maintenance treatment with 6MP in ALL.

Chemotherapy drugs with hepatic metabolism requiring dose reduction: MTX, ACT-D, IFO, Gem, VP 16, IRI; PCB, 6MP, ARA-C, CTX, sorafenib, crizotinib.

Chemotherapeutic drugs used with extreme caution, especially in patients with pre-existing liver function impairment: anthracyclines, vinca alkaloids, imatinib, erlotinib, nilotinib, ruloxitinib (2, 3, 15)

Cardiovascular toxicity (16)

Cardiovascular toxicity can be a short-term or long-term complication of the chemotherapy. Some drugs such as anthracyclines and other biological agents cause significant irreversible heart dysfunctions.

Cardiovascular side effects produced by chemotherapy: left ventricular dysfunction, heart failure, myocardial ischemia, hypertension, arrhythmias, QT prolongation.

Cardiotoxicity classification:

• Type I- irreversible heart damage (destruction of myocardial cells):

- Anthracyclines - may also cause acute, reversible toxicity, immediately after infusion, with transient decrease in myocardial contractility; the risk of cardiotoxicity increases with the maximum cumulative dose 400-550 mg/m2 (for Doxo)

Alkylating agents: CTX over 1.5 g/m2, IFO over 12.5 g/m2, Paclitaxel

• Type II-reversible heart damage (mitochondrial cell dysfunction): monoclonal antibodies: bevacizumab, trastuzumab; tyrosine kinase inhibitors: sunitinib, sorafenib.

Cardiovascular risk assessment before initiation of chemotherapy with reversible or irreversible cardiotoxic potential (recommended level):

- Careful clinical evaluation and detection of comorbidities (I A)
- Determination of the risk of cardiotoxicity based on the cumulative dose of anthracycline (I A)
- ECG - QT interval extension (I B)
- Echocardiography - measurement of LV ejection fraction (I A)
- Specific biological markers: troponin and BNP (brain natriuretic peptides), with increased values in cardiotoxicity (III B)
- Treatment of pre-existing heart disease (I A)

Cardiotoxicity prophylaxis in all high-risk patients: Dexrazoxane, conversion enzyme inhibitors, beta-blockers, Carvedilol (III B)

Cardiovascular monitoring during and after chemotherapy with reversible or irreversible cardiotoxic potential (recommended level):

- cardiac monitoring at 3, 6, 9 months during treatment, then at 12 and 18 months after initiation of treatment (I A)

- determination of serum troponin and BNP to identify patients at risk of cardiotoxicity, in particular for anthracyclines, at the beginning and during the treatment for each cycle (III B)

- performing echocardiography with measurement of the ejection fraction (EF) of the left ventricle, if the EF is between 40-50% continue the treatment with anthracyclines, then re-evaluation after 3 weeks; if the EF drops below 40%, the chemotherapy is stopped (II B)

Treatment of cardiotoxicity:

- Subclinical cardiotoxicity with increased cardiac troponin: conversion enzyme inhibitors to prevent left ventricular EF decrease (II A)

- Left ventricular dysfunction or heart failure: treatment of heart failure (II A)

Dermatological toxicity: alopecia, hypersensitivity reactions, erythema multiforme, pruritus,

photosensitization (erythema, edema, blisters, hyperpigmentation, desquamation), necrosis at the site of administration after extravasation.

The chemotherapeutic drugs with extravasation effect are classified according to the lesions they cause in: blistering, irritating and non-blistering. (17) (see Table 2)

Table 2- Classification of cytostatic agents according to the lesions caused after extravasation

Blistering	Irritating	Non-blistering
DNA binding	Alkylating agents	Asparaginase
Alkylating agents	Ifosfamide	Bleomycin
Mechlorethamine	Dacarbazine	Bortezomib
Bendamustine	Melphalan	Cladibrina
Anthracyclines	*Other anthracyclines*	Cytarabine
Doxorubicin	Liposomal	Gemcitabine
Daunorubicin	Doxorubicin	Fludarabine
Epirubicin	Liposomal daunorubicin	Interferon
Idarubicin	*Topoisomerase II inhibitors*	Interleukin 2
Antibiotics	Etoposide	Methotrexate
Dactinomycin	Teniposide	Monoclonal antibodies
Mitoxantrone	*Antimetabolites*	Pemetrexed
Non DNA binding	Fluorouracil	Cyclophosphamide
Vinca alkaloids	Platinum salts	
Vincristine	Carboplatin	
Vinblastine	Cisplatin	
Vindesine	Oxaliplatin	
Vinorelbine	*Isomerase type I inhibitors*	
Taxanes	Irinotecan	
Docetaxel	Topotecan	
Paclitaxel		

A differential diagnosis is required with other chemotherapeutic agents, correctly administered, which cause local reactions besides extravasation (see Table 3).

Table 3: Chemotherapeutic agents that cause local reactions besides extravasation (17).

Local skin reactions	Chemical phlebitis
Asparaginase Cisplatin Daunorubicin Doxorubicin Epirubicin Fludarabine Melphalan Vinorelbine	Carmustine Cisplatin Dacarbazine Epirubicin 5 Fluorouracil Gemcitabine Vinorelbine

Management of extravasation according to ESMO 2012 guide (17).

General measures: recommendation level V-A (recommended):

- prompt identification of extravasation
- initiation of non-specific measures: removal of the granule, aspiration of the extravasated solution
- use of the extravasation kit, marking the extravasation area

Specific measures:

- use of subcutaneous corticosteroids is not recommended (V-C)
- for blistering or irritant cytostatic agents:
- anthracyclines, antibiotics, alkylating agents: local: application of cold dry compresses for 20 minutes, 4 times a day, for 1-2 days; neutralization with specific antidotes (see table)
- non- blistering cytostatic agents: cold dry compresses
- vinca alkaloids, taxanes, platinum salts: dispersion - application of hot dry compresses for 20 minutes, 4 times a day, for 1-2 days and dilution
- administration of agents that increase resorption
- for vinca and taxane alkaloids: hyaluronidase.

Immune system toxicity (18)

Postinfusion reactions of cytostatic agents can be:

- *Immune-mediated allergic hypersensitivity reactions* with immediate onset 1-6 hours after administration (typically Ig E-mediated) or with late onset, at any time, from 1 hour after administration to several days (delayed T-cell-dependent allergic mechanism)
- *Non-mediated immune reactions*: pseudoallergic (anaphylactoid) with mast cell degranulation: cytokine release syndrome (CRS); it manifests through nausea, headache, tachycardia, hypotension, rash; idiosyncratic reactions (rarer, unrelated to the pharmacological action of the drug) and intolerances. CRS treatment: short-term cessation of perfusion, antihistamines, corticosteroids, antipyretics; after remission of symptoms the perfusion can be resumed at a slower rate at half the initial rate.
- *Anaphylaxis / anaphylactic shock* Treatment of the anaphylactic shock: stopping the administration of the medication, maintaining the venous approach, initiating resuscitation manoeuvres, oxygen, adrenaline, administration of physiological serum in bolus, antihistamines combination of H1 and H2 antagonists, corticosteroids: methylprednisolone 1-2 mg/kg; vasopressors in case of hypotension.

Neurological toxicity (2)

Central neurotoxicity: seizures, encephalopathy (PRES- posterior reversible encephalopathy syndrome), stroke-like syndrome caused by high doses of Methotrexate (MTX

SLS), steroid-induced psychosis, with time determination of neurocognitive deficits. Other CNS toxicities: intracranial haemorrhage, cerebral thrombosis, transverse myelitis.

- *MTX SLS (stroke-like syndrome related to HDMTX*) is characterized by neurological deficits and hemiparesis, speech difficulties or impaired consciousness, which occurs after 2-3 weeks (usually 2-14 days) after the administration of high doses of intravenous MTX or after the administration of intrathecal MTX. Treatment with dextromethorphan or aminophylline.

- *PRES (PRES- posterior reversible encephalopathy syndrome)* is a clinical and radiological entity, which occurs most frequently in the first month of treatment of ALL. It is usually caused by chemotherapy, high blood pressure and corticosteroid therapy; it is manifested by headache, altered mental status, seizures, visual disturbances. MRI shows vasogenic edema in the posterior region of the brain; the affected areas are hypodense in T1 and hyperdense areas in T2.

- *Transverse myelitis* is a rare complication in children with hematological malignancies. It occurs as a result of the malignant infiltration or as a result of intensive chemotherapy: HDARA-C, MTX,

- *Psychosis secondary to corticosteroid* therapy requires tranquilizing medication, and in severe cases antipsychotics (Risperidone).

- *Peripheral motor and sensory neuropathy*, is usually caused by Vincristine, and it is generally completely reversible.

Other post-chemotherapy toxicities: (2)

- Renal toxicity: renal failure (HDMTX, DDP), acute haemorrhagic cystitis (CTX. IFO)
- Endocrinopathy: hyperglycemia, diabetes mellitus (cortisone-induced, L-ASP), cortisone-induced adrenal insufficiency
- Bone toxicity: cortisone-induced osteonecrosis, fractures, osteoporosis
- CVC-induced central or peripheral venous thromboembolism, immobilization, infections, L-ASP and corticosteroid therapy, genetic risk factors for thrombophilia

Recommendations

- The acute toxicity of cytostatic agents is due to the antiproliferative effect it exerts on normal tissues
- Organ toxicity is more worrying as it may require dose limitation in subsequent courses, or may cause long-term sequelae

Bibliography

1. Pizzo AP., Poplack DG., Principles and Practice of Pediatric Oncology, Seventh Edition 2016, General Principles of Chemotherapy:244-254

2. Schmiegelow K., Muller K., Mogensen S., et al., Non-infectious chemotherapy associated acute toxicities during childhood acute lymphoblastic leukemia therapy, F1000 Research 2017;6:1-14

3. Zawitkowska J., Lejman M., Zaucha-Prazmo A., et a.l, Grade 3 and 4 Toxicity Profiles During Therapy of Childhood Acute Lymphoblastic Leukemia, In Vivo 2019;33:1333-1339

4. Russel JS., Colevas D., Adverse event monitoring in oncology clinical trials, Clin. Invest 2013; 3(12):1157-1165

5. Gipson DS., Kirkendall ES., Gumbs-Petty B. et al, Developmentof a Pediatric Adverse Terminology, Pediatrics 2017;139 (1):1-7

6. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

7. Ozdemir ZC., Kar YD., Turhan AB., Bor O., Assessment of Hematological Toxicity in Children with Acute Lymphoblastic Leukemia, Receiving Treatment with ALL IC BFM 2009 Protocol, Open Acces Library Journal 2017; 4(e3807):1-13

8. Ruggiero A., Rizzo D., Catalano M., Coccia P.,et al., Acute chemotherapy induced nausea and vomiting in children with cancer: Still waiting for a common consendus treatment, Journal of International Medical Research 2018, 46(6):2149-2156

9. https://www.pogo.ca/_media/File/guidelines/POGO%20Emetogenicity%20Classification%20Guideline%20Final-rev%20250111.pdf

10. Roila F., Molassiotis A., Herrstedt J., et al., 2016 MASCC and ESMO guideline update for the prevention of chemotherapy and radiotherapy induced nausea and vomiting and nausea and vomiting in advanced cancer patients, Annals of Oncology 2016; 5:119-133

11. Dupuis LL., Sung L., Molassiotis A., et al.,2016 updated MASCC/ESMO consensus recommendations: Prevention of acute chemotherapy induced nausea and vomiting in children, Support Care Cancer 2017; 25:323-331

12. https://tvscn.nhs.uk/wp-content/uploads/2014/09/Cancer-Children-Diarrhoea-Guidelines-v2.1-Nov-2015.pdf

13. Peterson DE., Boers Doets CB., Bensadaoun RJ., Herrstedt J., Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up, Annals of Oncology 2015; 26(5):139-151

14. https://www.nice.org.uk/guidance/ipg615/documents/overview

15. Grigorian A., O Brien C., Hepatotoxicity Secondary to Chemotherapy, Journal of Clinical and Translational Hepatology 2014; 2: 95-102

16. Curgliano G., Cardinale D., Suter T., et al., Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines, Annals of Oncology 2012; 7:155-166

17. Perez Fidalgo JA.,Garcia Fabregat L., Cervantes A., et al., Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines, Annals of Oncology 2012;7:167-173

18. Rosello S., Blasco I., Fabregat G., et al., Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines, Annals of Oncology 2017; 28:100-118

12.2 LATE SIDE EFFECTS OF ONCOLOGICAL TREATMENT

As a result of the progress of paediatric oncology, the survival over 5 years now can reach more than 75%. As a result of cancer treatment, about half of the survivors will have a chronic health problem.

The term "late side effect" means the persistence of physical or psychological symptoms for more than 5 years after the onset of cancer. The most common side effects are cardiac, endocrine, musculoskeletal, pulmonary, neurological, psychological effects and secondary neoplasms. The follow-up of cancer survivors aims to prevent, diagnose and treat late side effects, as soon as they appear. (1)

Effects on the cardiovascular system

The most common cardiovascular diseases induced by the oncological treatment are valvulopathies and the occurrence of coronary heart disease at young age. The cytostatic agents such as anthracyclines, cyclophosphamide, especially in combination with chest radiotherapy may cause heart involvement. The cumulative dose of cytostatic agents is important because cardiotoxicity increases rapidly over a certain dose. Anthracycline-induced cardiomyopathy is a progressive disease, manifested by signs of congestive heart failure, it rarely occurs up to limited cumulative doses, which depend on the administered drug. Chest irradiation induces thickening, fibrosis, calcification of the heart valves with valvular insufficiency followed by their stenosis, this effect occurs gradually, over time, even up to 20 years after radiotherapy was delivered. The interdisciplinary communication between the oncologist, the cardiologist and the family doctor are essential in the care of cancer patients treated with potential cardiotoxic therapy. Clinical examination, ECG, echocardiography with measurement of the fractional shortening (normal value over 29%) and the left ventricular ejection fraction (normal value over 55%), as well as cardiac biomarkers (troponin) are used in the screening of cardiac involvement.

In the prevention and minimization of the cardiotoxic effect of the anticancer treatment, the patient must be evaluated cardiologically at the beginning, at 3-6 weeks during the treatment and after the end of the treatment at intervals of 2-5 years, indefinitely. Early diagnosis and treatment can improve the prognosis of cardiac side effects. Cardioprotective treatment may include the use of digoxin to increase ventricular contractility (although it is less and less commonly used), diuretics to decrease water and sodium retention, decrease the afterload with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, the use of cardioprotection with Dexrazoxane, the use of protocols without anthracyclines when heart disease requires it. Heart transplantation in selected cases is a rare option. (2)

Endocrinological side effects

Endocrinological complications are common after cancers treated in childhood, occurring in 20-50% of cases. The endocrinological follow-up is of major importance for their early recognition and treatment. The risk factors include radiation therapy to susceptible organs and alkylating cytostatic agents. The most common endocrinological sequelae are those of the hypothalamic-pituitary axis, disorders of puberty, thyroid dysfunction, gonads, osteoporosis, obesity and diabetes. Growth hormone deficiency occurs after the involvement of the

hypothalamic-pituitary region by tumour invasion, surgery or radiation therapy. The growth hormone treatment can improve the slow linear growth. The cranial irradiation can lead to early puberty with the onset of puberty before the age of 8 in girls and the age of 9 in boys. The hypersecretion of steroid hormones accelerates bone maturation leading to premature cessation of growth in length. Skeletal maturation can be investigated by bone age assessed on the basis of radiography of the fist and left hand. Hormone examinations to determine the serum level of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol and testosterone are used to assess early puberty. In some cases, cranial irradiation leads to hypogonadotropic hypogonadism.

ACTH (adrenocorticotropic hormone) deficiency is usually transient and it occurs after the prolonged treatment with glucocorticoids in pharmacological doses. Central hypothyroidism due to decresed level of TSH (thyroid stimulating hormone) may occur after cranial irradiation, but not after chemotherapy. The thyroid gland is frequently affected in cancer survivors, with hypofunction occurring much more often than hyperfunction. Primary hypothyroidism occurs mainly after neck region irradiation, craniospinal irradiation or after total body irradiation (TBI). As hypothyroidism can occur late, even after 25 years from the irradiation, endocrinological follow-up is recommended throughout life. Therapy-induced hyperthyroidism is much less common. Autoimmune thyroiditis and thyroid cancers can occur after the irradiation of the thyroid gland. (9)

Gonadal dysfunctions occur due to gonadotropin deficiency as well as direct injury to the testicles and ovaries. In the male gonad, germ cells and Sertoli cells form seminiferous tubules where the spermatogenesis takes place and Leydig cells synthesize the testosterone, which is responsible for inducing puberty with secondary sexual characters. Germ cells and Sertoli cells are much more sensitive to radiotherapy and some cytostatic agents (alkylating agents: cyclophosphamide, procarbazine), frequently leading to infertility. Leydig cells are more resistant, however the radiotherapy with doses > 24 Gy leads to hypoandrogenism. In women, the loss of the ovarian function before puberty is manifested by delayed puberty and primary amenorrhea, and after puberty by secondary amenorrhea and menopausal symptoms. The early loss of the estrogen production leads to osteoporosis and coronary heart disease. The myeloablative therapy with high doses of busulfan, melphalan, thiotepa as well as pelvic, abdominal and spinal irradiation can induce ovarian failure in women. Osteoporosis and osteopenia with consecutive fractures are the result of the underlying disease, of the prolonged corticosteroid therapy and of cytostatic agents such as methotrexate. Investigation by DEXA (dual energy X ray absortiometry) remains the preferred instrument for measuring osteodensity. Avoiding smoking, exercise, vitamin D and calcium are important in preventing osteoporosis. (3)

Obesity and overweight occur especially after leukaemia and brain tumours. Surgery in the Turkish saddle area, irradiation of the hypothalamic-pituitary area, corticotherapy and female sex favour the appearance of obesity. The increased parasympathetic tone by inducing hyperinsulinemia also favours the formation of adipose tissue. Diabetes occurs 2 times more often in cancer survivors by developing insulin resistance. (3)

Musculoskeletal side effects

Osteonecrosis (synonyms: aseptic necrosis, avascular necrosis) occurs as a result of altered bone blood circulation. It occurs more often in the epiphyses of long bones (femur, humerus). The risk factors are the treatment with high and long doses of corticosteroids, irradiation and transplantation of hematopoietic cells. It usually occurs during or immediately after these treatments, but can sometimes occur late. Arthralgia, arthritis and impaired function are the main signs of the disease. Simple radiography, bone MRI, bone scintigraphy, rarely bone biopsy can be used for diagnosis. The therapy involves the treatment of pain, the use of orthoses to

reduce the weight on the affected joint, physical therapy, electrical stimulation to induce osteosynthesis, rarely surgery. Swimming is recommended.

Amputation is sometimes inevitable for the treatment of cancers. The late effects of amputation can be skin changes of the residual limb (erythema, blisters), phantom pain, stress from changing body image, back pain, weight gain through inactivity, diabetes due to obesity and lack of physical activity. To prevent these side effects it is recommended to proceed to the correct hygiene of the residual limb, the frequent washing of the textile parts of the prosthesis, the evaluation of the prosthesis every 6 months if the patient is still growing and every 1 year for the others.

Scoliosis and kyphosis occur frequently after surgery on the spine or local irradiation with > 20 Gy, in the case of tumours of the spine or in paraspinal tumors. If the angle of scoliosis exceeds 10 degrees and 50 degrees in kyphosis, orthopedic consultation is recommended.

In the case of conservative limb surgeries (limb sparing procedures), there may be differences in the length of the extremities, bone lesions at the insertion sites of the prosthesis, muscle contractions, obesity, chronic pain. Orthopedic control is recommended every 6 months when the patient is growing, then less often. (4)

The **pulmonary side effects** are usually related to treatment with bleomycin, carmustin, lomustin, busulfan and pulmonary irradiation. Bleomycin, especially in the cumulative doses exceeding 400 mg/m^2 and in combination with pulmonary radiotherapy, smoking, exposure to elevated oxygen levels, determines interstitial pneumonia and/or pulmonary fibrosis, respectively ARDS (acute respiratory distress syndrome) in adults. Annual medical check-ups, regular lung function tests, annual influenza vaccination, pneumococcal vaccination, avoidance of inhalation of oxygen in high concentration and for long periods (hours) are recommended. (4)

Fatigue

Fatigue is one of the most common symptoms in cancer. The causes are related to the presence of malignant tumor, oncological treatments and comorbidities. The diagnosis of fatigue is established by 2-3 targeted questions or by using specific questionnaires. Laboratory examinations help to clarify the etiology. Psychological consultation is essential.

Secondary malignancies

The secondary cancer occurs more frequently in those who have been successfully treated for a neoplasm during childhood or adolescence. The treatment with alkylating agents (cyclophosphamide), epipodophyllotoxins, anthracyclines, stem cell transplantation can induce the occurrence of secondary leukaemia, especially non-lymphoblastic leukaemia, in the first 10 years after the treatment. Radiotherapy could induce secondary solid tumours after 8-10 years after the completion of treatment, in the irradiated field (breast cancers, CNS tumors, bone and soft tissue sarcomas, skin cancers, thyroid cancer, colon and rectum cancer). It is recommended to follow these patients up, so that different screening methods detect these secondary malignancies in the initial stages with higher chances of cure. (4)

The late effects induced by radiotherapy depend on:

- Tumour location
- Direct action on irradiated healthy and tumour tissues
- Total dose, fraction dose, irradiated volume, type of radiotherapy (photons, protons), energy used
- Association with chemotherapy: type of chemotherapy, dose intensity, cumulative dose, sequentiality of treatment

- Association with surgery, type of surgery and topography
- Concomitant radiotherapy/chemotherapy treatments

A special mention is needed regarding **visual and cognitive disorders**, as a result of irradiation of the central nervous system. The first of them appear after irradiation at the level of sensitive structures of the ocular system (lens, optic nerve, optic chiasm). In such cases, an ophthalmological consultation is recommended. Cognitive disorders may affect memory, orientation, affect, etc. There are side effects that are harder to notice because they are nonspecific and less pronounced than the others. There is no specific treatment for these problems.

The use of modern radiotherapy techniques (modulation of radiation beam intensity, IMRT, proton irradiation), total dose reduction, fraction dose, renouncing at radiotherapy in the treatment of some cancers (early stages with complete response in Hodgkin's lymphomas; prophylactic cranial irradiation in ALL in patients without risk of CNS involvement, or prophylactic pulmonary irradiation) are some methods to reduce the number and intensity of late effects.

Bibliography

1. Dreyer Z.E., Blatt J., Bleyer A: Late Effects of Childhood Cancer, in: Pizzo P.A., Poplack D.G: Principlesand Practice of Pediatric Oncology, Lippincott Williams andWilkins, Philadelphia, 2002, pg. 1431-1463.

2. Curigliano G, Lenihau D, Fradley M et al: Management of cardiac disease in cancer patientsthroughoutoncologicaltreatment: ESMO consensusrecommendations. Annals of Oncology 2020, Vol 31(2): 171-190.

3. Chemaitilly W., SklarCh.A: Endocrine complications in long-termsurvivors of childhoodcancers. Review. Endocrin-Related Cancer 2010, 17: 141-159.

4. Children'sOncology Group: Long-termFollow-UpGuidelines for Survivors of Childhood, Adolescent andYoung Adult Cancers. www.survivorshipguidelines.org.

12.3 LONG – TERM FOLLOW-UP OF SURVIVORS

Until 1970, most children with cancer died because of the disease. The progress in the multimodal therapy (chemotherapy, radiotherapy, surgery) supported by effective supportive therapy have led to a significant and continuous increase in survival rates. Currently, overall long-term survival exceeds 80% in developed countries. Consequently, we are facing a large, ever growing number of childhood cancer survivors. They can experience a variety of physical and psychosocial side effects, which predispose them to increased morbidity and mortality compared to the general population. Therefore, survivors of childhood malignancies require long-term medical follow-up in order to detect early side effects and to apply appropriate treatment. (1)

Late complications of childhood cancer and cancer treatments can affect any organ or system. Vital organ dysfunctions, growth and developmental disturbances, neurocognitive and intellectual disorders have been identified, as well as an increased risk of developing a new malignancy. The psychological disorders following going through illness and the oncological treatment affecting the former patient, his/her family and company, they can cause difficulties in regard to family school and social reintegration, sometimes requiring interventions for career guidance.

The monitoring of long-term side effects until the age of 18 is performed in paediatric medical departments (up to 25 years in some centres), usually in the departments where they have benefited from the treatment of oncological disease, so that they can be taken over by the records of oncology or haematology centres for adults. Sometimes the family doctor is involved in solving the difficulties faced by the survivor. A real benefit is brought by the help of the support groups.

A patient who had a type of childhood cancer should be followed throughout life. Long-term follow-up of survivors should be performed in centres dedicated to this purpose, according to specific requirements, being adapted to the underlying disease, the type of oncological treatments applied and the side effects of the therapy. (1)

Childhood cancer survivors are to be referred to these follow-up centres. They will be informed about the history of the malignant disease and the possibility of side effects. Being informed, they must agree to collaborate for long-term follow-up. Patients at high risk for late side effects, such as former patients with brain tumours, are especially targeted.

This is a problem that is not yet solved in Romania, but it is provided in the European multinational program Childhood and Adolescent Cancer Survivor Care (PanCare), a program to which all European countries must adhere. One of the objectives of this program is to develop a document "Survivorship Passport" which includes information about the diagnosis of cancer, the therapy received by the patient and the long-term risks. The patient will have the document with him/her in order to provide the relevant medical information as needed.

Bibliography

1. American Academy of Pediatrics Section on Hematology/Oncology: Long-Term Follow-Up Care for Pediatric Cancer Survivors. Pediatrics. 2009; 123(3):906-915. doi:10.1542/peds.2008-3688

13. THE ELABORATION OF THE GUIDE FOR DIAGNOSIS, TREATMENT AND FOLLOW-UP OF CHILDHOOD CANCERS

The elaboration of the first National Guide for Diagnosis and Treatment of Childhood Cancers was possible within the programme Challenges in Public Health at European Level, funded by the EEA Financial Mechanism 2014-2021, within the project: "Increasing performance in the diagnosis and treatment of childhood cancers by improving the technical equipment, the purchase of modern equipment, the training of medical staff and the development of recommendations".

Specialists from Romania, who treat cancer in children, were involved in developing the materials. In order to achieve the proposed goal, the authors carried out a thorough research work. The result of this collective work is the creation of the first national guide for diagnosis, treatment and follow-up of childhood cancers.

The activity was carried out with the support and guidance of paediatric oncology experts from paediatric oncology centres in Norway, as well as specialists in medical management from the Norwegian Directorate of Health. Some of the authors had the chance to participate in study visits to paediatric oncology centres in Oslo, for discussions with Norwegian specialists on how to use the guides.

The material was structured in such a way as to include epidemiological issues, diagnosis, treatment and follow-up principles, with references to the side effects of the therapy. The most comprehensive chapter includes a concise presentation of childhood cancers, illustrating the current state of knowledge and the management to be followed for each case, in terms of diagnosis, therapy and monitoring. Each of the subchapters contains the "Recommendations" box. This collective activity was an exciting experience. The paediatric oncologists in Romania understood the importance of this project and developed good quality materials, showing a serious professional quality, openness to additional work and ability to collaborate. The guide will be translated into English and made available to the Norwegian Health Directorate.

Access to the guide as well as to all the protocols underlying the preparation of the materials will be accessible on the SROHP website.

Having documented the needs for the correct care for patients, we have the possibility to provide the authorities with data that will make possible a correct funding and development of the paediatric oncology network in Romania. This refers to inaccessible or very expensive investigations as well as therapies that cannot be applied in the country.

For diseases that cannot be treated in Romania, or for therapeutic sequences that are not yet available in Romania, patients should be referred to centres abroad. The indications for each of the diseases specify what we can do in Romania and for which patients the health system must provide funding for treatment abroad.

To sum up, the most pressing issues for the next period, for which we request the support of the Romanian Ministry of Health, are summarized as follows:

- Providing a constant supply of mandatory medication used in pediatric oncology

- Providing more possibilities to use MRI (more equipment!) in the work up for diagnosis and in follow up after childhood cancer as it is clearly documented that this has an effect on late effects (no X-rays!) and second malignancies

- Access must be provided to genetic and molecular diagnostic centers, in order to complete the oncological diagnosis of children with cancer

- To ensure the children's access to radiotherapy in departments with expertise in delivering radiotherapy to pediatric patients. It is imperative to create the optimum conditions for young or non-compliant children to receive radiation therapy under sedation

- Organizing palliative care and terminal care services at a national level

- Organizing the national follow-up network for childhood cancer survivors

- For diseases that cannot be treated in Romania, or for therapeutic approaches that are not yet accessible in Romania, patients must be referred to centers abroad. A special note should be made for access to proton therapy in cases with precise indication for this type of therapy.

- There must be an effort to make it possible for Romania to take part in European trials on equale terms as other EU- countries, trials mainly conducted through SIOPs European branch. To be able to do so will require safe, constant supply of drugs used in the trials and possibility to carry through the necessary tests to stratify patients into the trial arms.

- As knowledge about childhood cancer in the general population are somehow scarce, there should be a nationwide information campaign about childhood cancer and the success of treatment of children with cancer, to help parents of all social classes and educational levels to understand the importance of the early diagnosis and proper therapy

- Solving the unclear situation of the adolescents and young adults dealing with cancer. The following groups of patients need to have access to especially designed units of oncology: patients who start the oncological treatment as children and continue it beyond the age of 18; paediatric oncology patients who relapse beyond the age of 18; young adults who are diagnosed with childhood-specific types of cancer. For all these patients, the best chance for long term survival is provided by treatment options conducted according to pediatric protocols

New treatments for cancer are developing rapidly. That is why we propose the revision of the National guide for diagnosis and treatment in childhood cancers periodically, at intervals of 3-4 years, or when therapeutic progress requires it.

ABBREVIATIONS

3D CRT: conformational radiotherapy
AA: acquired aplastic anemia
ACTH: adrenocorticotropic hormone
AD: antidiuretic hormone
AE: adverse event
AFP: alpha-fetoprotein
aHSCT: autologous haematopoietic stem cell transplantation
AIEOP: Italian Association of Pediatric Hematology and Oncology
AJCC: American Joint Committee on Cancer
AL: acute leukaemia
ALCL: anaplastic large cell lymphoma
ALK: anaplastic lymphoma kinase
ALL: acute lymphoblastic leukemia
allo-HSCT: allogeneic hematopoietic stem cell transplantation
ALP: alkaline phosphatise
AML: acute myeloid leukaemia
ANC: absolute neutrophil count
AP: anterior-posterior
aPTT: activated partial thromboplastin time
ARDS: acute respiratory distress syndrome
AT III: serum antithrombin III
ATG: antithymocyte globulin
ATO - arsenic trioxide
ATRA: all-trans Retinoic Acid
BAL: biphenotypic acute leukaemia
B-ALL: B-cell Acute Lymphoblastic Leukemia
BCG: bacillus Calmette–Guérin vaccine
BCP-ALL: B-cell precursor acute lymphoblastic leukaemia
BFM: Berlin-Frankfurt-Münster
BM: bone marrow
BMB: bone marrow biopsy
BMFS: bone marrow failure syndrome
BMT: bone marrow transplantation
BNP: brain natriuretic peptides
BSA: body surface area
CAR: chimeric antigen receptor
CAS: colour analog scale
CGH: comparative genomic hybridization

CML: chromic myeloid leukemia
CMML: chronic myelomonocytic leukemia
CMV: cytomegalovirus
CNL: chronic neutrophilic leukemia
CNS: central nervous system
CO: clinical option
COG: Children's Oncology Group
CR: complete remission
CRP: C-reactive protein
CRS: cytokine release syndrome
CsA: cyclosporine
CSF: cerebrospinal fluid
CT: computer tomography
CTCAE: Common Terminology Criteria for Adverse Event
CVC: central venous catheters
D: Indications for development
DIC: disseminated intravascular coagulation
DILI: drug induced liver injury
DKC: Dyskeratosis congenita
DLBCL: diffuse large B-cell lymphoma
DLI: donor lymphocyte infusion
DM: diabetes mellitus
DS: differentiation syndrome
EBMT: European Group for Bone Marrow transplant
EBV: Epstein Barr virus
ECG: electrocardiogram
Echo: echocardiogram
EDTA: ethylene diamine tetraacetic acid
EEG: electroencephalograph
EF: ejection fraction
EFS: event free survival
EFV:ventricular ejection fraction
EGIL: The European Group for the Immunological Classification of Leukaemias
ENT: ears, nose and throat
EpSSG – The European paediatric Soft tissue Sarcoma Study Group
ESMO: European Society of Medical Oncology
EsPhALL: European Intergroup Study on Post Induction Treatment of Ph+ ALL
ESR: erythrocyte sedimentation rate
ETMR: embryonal tumour with multilayered rosettes
FAB: French-American-British
FC: flow cytometry
FDG: fluorodeoxyglucose
FEV: forced expiratory volume
FFP: fresh frozen plasma
FIGO: Federation of Gynaecology and Obstetrics
FISH: fluorescent in situ hybridization
FNAB: fine needle aspiration biopsy
Fr: fraction
G-banding: Giemsa banding

G-CSF: granulocyte-colony stimulating factor
GCTs: germ cell tumours
GNR: generally not recommended
GOT: glutamic-oxaloacetic transaminase
GPOH: German Pediatric Oncology and Hematology
GPT: Glutamic pyruvic transaminase
GVHD: graft-versus host disease
Hb: hemoglobin
HbF: fetal haemoglobin
HBV: hepatitis B viruse
HCG: human chorionic gonadotropin
HCT: hematopoietic cell transplantation
HCV: hepatitis C viruse
HGG: high grade gliomas
HIV: human immunodeficiency virus
HL: Hodgkin's lymphoma
HLA: human leukocyte antigen
HLA: major histocompatibility complex
HLH: hemophagocytic lymphohistiocytosis
HR: high risk
HSC: hematopoietic stem cells
HSCT: hematopoietic stem cell transplantation
HVA: homovanillic acid
ICD: O: International Classification of Diseases for Oncology
ICP: increased intracranial pressure
IDRFs: image-defined risk factors
IFRT: involved Field Radiotherapy
IMRT: intensity-modulated radiation therapy
INPC: International Neuroblastoma Pathology Classification
INR: International Normalized Ratio
INRGSS: International Neuroblastoma Risk Group Staging System
INSS: International Neuroblastoma Staging System
INTERFANT: International Collaborative Treatment Protocol for the Infants Under One Year
IPF: immature Platelet Fraction
IR: intermediate risk
IRS – Intergroup Rhabdomyosarcoma Study
ITD: internal tandem duplication
iv: intravenous
JMML: juvenile chronic myelomonocytic leukaemia
LAIV: live attenuated influenza vaccine
LAP: leukemia-associated phenotypes
LCH: Langerhans cell histiocytosis
LDH: lactate dehydrogenase
LGG: low Grade gliomas
LR: low risk
LTS: life threatening symptomps
LV: left ventricle
MAC: myeloablative conditioning
MDD: minimal Disseminated Disease

MDS: myelodysplastic syndromes
MEN: multiple endocrine neoplasia
MGG: May-Grünwald-Giemsa stain
MIBG: metaiodobenzylguanidine
MKI index: mitosis-karyorrhexis index
MLL: mixed lineage leukemia
MMR: measles, mumps, rubella
MPAL: mixed-phenotype acute leukaemia
MPD: myeloproliferative disorders
MR: moderate risk
MRD: minimum residual disease
MRI: magnetic resonance imaging
MSD: match sibling donor
MUD: match unrelated donor
NB: neuroblastoma
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
NF: neurofibromatosis
NHL: nonHodgkin's lymphoma
NK cell: natural killer cell
NMA: non-myeloablative conditioning
NMDA: N-methyl-D-aspartate
NOS: non otherwise specified
NRSTS – non-rhabdomyosarcoma soft tissue sarcomas
NSAIDs: nonsteroidal anti-inflammatory drugs
NSE: neuron specific enolase
NUT: nuclear protein in testis
OG: observation group
OS: overall survival
PBSC: peripheral blood stem cell
PBSCT: peripheral blood stem cell transplantation
PCR: polymerase chain reaction
PCT: polychemotherapy
PCV: pneumococcal conjugate vaccine
PET-C: positron emission tomography
PGR: prednisone good response
Ph1: Philadelphia chromosome
PID: primary immunodeficiencies
PM: platelet mass
PNET: primitive neuroectodermal tumors
po: orally
PPB: pleuropulmonary blastoma
PPR: prednisone poor response
PR: partial remission
PRD: prednisone
PRETEXT: PRE Treatment Extension
PT: prothrombin time
PTLD: posttransplant lymphoproliferative disease
RAEB: refractory anemia with excess blasts

RAEBT: refractory anemia with excess blasts in transformation
RB retinoblastoma
RBC: red blood cells
RCC: refractory cytopenia of childhood
RECIST: response evaluation criteria in solid tumors
RIC: reduced-intensity conditioning
RMS - rhabdomyosarcoma
RO: risk organs
RS: risk sites
RT: radiotherapy
S: standard of care
sc: subcutaneous
SCID: severe combined immunodeficiency disease
SD: stable disease
SIOP: Internațional Society of Paediatric de Oncology
SIOPE: European Society of Paediatric de Oncology
SIRS: systemic inflammatory response syndrome
SKY: spectral karyotyping
SMS: the superior mediastinal syndrome
SOS: sinusoidal obstruction syndrome
SR: standard Risk
SROHP: Romanian Society for Paediatric Oncology and Haematology
SVCS: the superior vena cava syndrome
TBI: total body irradiation
TD: total doze
TdT: deoxynucleotidyl transferase terminal
TKI: tyrosine kinase inhibitor
T-LBL - T-lymphoblastic lymphoma
TLS: tumour lysis syndrome
TNM: Tumor-Node-Metastasis
TSH: thyroid stimulating hormone
TT: thrombin time
VAS: visual analog scale
VMA: vanillylmandelic acid
VOD: veno occlusive disease
VZV: varicella-zoster virus
W: weight
WHO: World Health Organization
WLI: whole lung irradiation

Cytostatics:
- 5FU: 5 Fluorouracil
- 6MP: 6Mercaptopurina
- 6TG: 6Thioguanina
- ACT-D= Actinomicin D
- ARA-C: Citarabina
- Bleo: Bleomicina
- Carbo: Carboplatina
- CTX= Ciclofosfamida

- Dauno: Daunorubicina
- Dexa: Dexametazona
- DDP=Cisplatin,
- Doce= Docetaxel
- DOXO= Doxorubicin
- DTIC: Dacarbazina
- EPI= Epirubicina
- GEM=Gemcitabina
- HDAraC: Citarabină în mare
- HD-MTX: Metotrexat în doză mare
- HU: Hidroxiuree
- IDA: Idarubicina
- IFO: Ifosfamida
- IRI: Irinotecan
- MTX: Metotrext
- PCB: Procarbazina
- PRD: Prednison
- Top70:Topotecan
- VP 16= Etoposid
- VBL: Vinblaston
- VCR - Vincristin
- VDS: Vindesine
- Vin= Vinorelbina
- TEM:Temozolomida

AUTHORS

1. Foreword	Cosnarovici Rodica Voichița
2. Introduction	Cosnarovici Rodica Voichița
3. Epidemiology	Cosnarovici Rodica Voichița
4. Screening, early diagnosis, pathways	Cosnarovici Rodica Voichița
5.1 General symptomatology	Sava Cristian Nicolae
5.2 Investigations	Sava Cristian Nicolae
5.2 Pathology	Sava Cristian Nicolae
6. Genetics in childhood cancers	Balint Gib Loredana Simona
7.1 Principles of surgical treatment	Vidlescu Ruxandra
7.2 Principles of chemotherapy	Vidlescu Ruxandra
7.3 Principles of radiation therapy	Cernea Dana Michaela
7.4 Oncological emergencies in childhood cancer	Sava Cristian Nicolae
7.5 Lymph node enlargement	Horvath Maria Adriene
8.1.1 Acute lymphoblastic leukemia	Jinca Cristian Marius
8.1.2 Acute non-lymphoblastic leukemia	Radu Letiția Elena
8.1.3 Chronic mieloid leukemia	Jercan Cristina Georgiana
8.1.4 Juvenile chronic mielo-monocitic leukemia	Jercan Cristina Georgiana
8.1.5 Non Hodgkin's Lymphoma	Bică Ana Maria
8.1.6 Hodgkin's Lymphoma	Chinceșan Mihaela Ioana
8.1.7 Histiocytosis	Blag Cristina Lucia
8.2.1 Ependymoma	Dragușin Simina Maria, Dragomir Monica Desiree
8.2.2 High grade glioma	Iaru Oana, Dragomir Monica Desiree
8.2.3. Low grade glioma	Iaru Oana, Dragomir Monica Desiree
8.2.4 Medulloblastoma	Badoi Monika, Dragomir Monica Desiree
8.2.5 Embrional brain tumours	Badoi Monika, Dragomir Monica Desiree
8.2.6 Germ cell brain tumours	Drinca Olivia, Dragomir Monica Desiree
8.2.7 Primary brain lymphoma	Comșa Codruța Ulpia, Dragomir Monica Desiree
8.2.8 Craniopharyngioma	Drinca Olivia, Dragomir Monica Desiree
8.2.9 Benign tumours of the central nervous system	Comșa Codruța Ulpia, Dragomir Monica Desiree
8.2.10 Metastases of the central nervous system	Cosnarovici Rodica Voichița
8.3 Soft tissue sarcomas	Mihuț Emilia
8.4.1 Osteosarcoma	Olteanu Elena Diana

8.4.2 Ewing Sarcomaof bone	Olteanu Elena Diana
8. 4.3 Benign bone tumors of oncological importance	Olteanu Elena Diana
8.5 Kidney tumours	Pruteanu Doina Paula
8.6 Neuroblastoma	Boeriu Estera, Oprisoni Licinia Andrada, Balint Gib Loredana Simona
8.7 Hepatic tumours	Vidlescu Ruxandra
8.9 Germ cell tumours	Pruteanu Doina Paula
8.9 Retinoblastoma	Comșa Codruța Ulpia, Dragomir Monica Desiree
8.10 Rare childhood cancers	Cosnarovici Rodica Voichița
8.11.1 Autologous hematopoietic stem cell trasnplantation	Coliță Anca
8.11.2 Allogeneic hematopoietic stem cell transplantation	Coliță Anca
9.1 Management of infections	Mihuț Emilia, Cosnarovici Rodica Voichița
9.2 Growth factor treatment	Chinceșan Mihaela Ioana
9.3 Transfusion indications	Oprișoni Licinia Andrada
9.4 Pain management	Mihuț Emilia
9.5 Psychological support	Șomlea Corina, Mihuț Emilia
9.6 Terminal care	Boeriu Estera
10.Legislative provisions	Cosnarovici Rodica Voichița
11.Vaccination of children with cancer	Voda Daniela Mariana
12.1 Acute toxicity of oncological treatment	Voda Daniela Mariana
12.2 Late side effects of oncological treatment	Horvath Maria Adriene
13.Long -term follow-up of survivor	Cosnarovici Rodica Voichița
14. The elaboration of the guide for diagnosis treatment and follow-up of childhood cancers	Cosnarovici Rodica Voichița