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The Importance of Early Diagnosis in Pediatric Oncology

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ABSTRACT

Childhood cancer has its own very different characteristics from adult cancer. The cells that suffer a mutation in the genetic material are unable to mature as they should and remain with similar characteristics to the embryonic cell, multiplying rapidly and in a disorderly manner.The main objective of this article is to describe some of the generalities of childhood tumors and to describe the warning signs that should prompt pediatricians to refer their patients to a specialist. This article is a systematic review, based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology, which seeks to identify the types of childhood cancer and treatment regimens established by the current literature on the subject. Cancer treatment begins with a correct diagnosis, which requires the participation of a reliable laboratory and imaging studies. Due to its complexity, treatment must be carried out in a specialized center and comprises three main modalities (chemotherapy, surgery and radiotherapy, when necessary), being applied rationally and individually for each specific tumour and according to the extent of the disease. The work coordinated by a multi-professional team is also a determining factor in the success of the treatment. Most of the symptoms of Childhood Cancer are much more likely to be caused by other reasons, such as an injury or infection. Even so, if your child has any of the symptoms mentioned in this article, consult a doctor so that the cause can be diagnosed and, if necessary, treatment started.

KEYWORDS: Childhood cancer, mutation in the genetic, correct diagnosis of cancer.

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INTRODUCTION

February 15th is the International Day Against Childhood Cancer. In Brazil, according to the National Cancer Institute (INCA), there are 12,000 new cases of childhood cancer every year. The most common types are leukemias, central nervous system tumors, lymphomas and solid tumors such as neuroblastoma, sarcomas and Wilms' tumor [1].

Cancer in childhood is a rare disease. The median percentage of pediatric tumors found in Brazilian population-based registries is close to 3%, which allows for an estimated 9,890 cases of pediatric tumors per year in the country. Despite this, its importance has been increasing, since in developed countries it is the leading cause of death by disease in childhood [1].

In addition, while adult cancer represents a loss of an average of 20 years of life, childhood cancer, when not cured, can represent a loss of 70 years of life. This has a huge personal, family and social cost [2].

In this context, pediatricians must be aware of the most frequent signs and symptoms of childhood cancers so that they can increase their patients' chances of being cured through early diagnosis [3].

While measures to improve adult cancer rates include prevention, which basically aims to reduce exposure to known carcinogenic risk factors such as smoking, environmental factors play a very small role in childhood. As a result, there are no effective primary prevention measures to prevent the development of cancer in the pediatric age group. As we cannot act at this point, secondary prevention, i.e. early diagnosis, becomes essential [4].

The main objective of this article is to describe some of the generalities of childhood tumors and to describe the warning signs that should prompt pediatricians to refer their patients to a specialist.

Childhood cancer has its own very different characteristics to cancer in adults. The cells that suffer a mutation in their genetic material are unable to mature as they should and remain with similar characteristics to the embryonic cell, multiplying rapidly and in a disorderly manner. This is why the tumor proliferates faster in children. On the other hand, it responds better to chemotherapy, with a chance of cure of 80%, according to INCA [5].

In the fight against the disease, the A.C.Camargo Cancer Center created the first Pediatric Oncology service in Brazil in 1964, as well as being the only institution in the country to operate on young patients with robotic surgery - a less invasive procedure with better recovery for children. The first cases involved the removal of tumors in the kidneys, with the same success that is achieved in adults, with the emphasis on shorter hospital stays and fewer side effects for small patients[6].

While cancer in adults is linked to ageing, smoking, alcohol and other exposure risks, cancer in children is not related to environmental and lifestyle factors. For this reason, early diagnosis is very important for successful treatment[7].

We should be on the lookout for some signs and symptoms, such as: Continuous and unexplained weight loss; Headaches with vomiting in the morning; Increased swelling or persistent pain in the bones or joints; Lump or mass in the abdomen, neck or any other location; Development of a whitish appearance in the pupil of the eye or sudden changes in vision; Recurrent fevers not caused by infections; Excessive bruising or bleeding, usually sudden; Noticeable pallor or prolonged tiredness[8].

METHODOLOGY

This article is a systematic review, based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology, which seeks to identify the types of childhood cancer and treatment regimens established by the current literature on the subject.

A search strategy was developed based on the evaluation of an objective on the subject in question, which forms the basis of the study.

The search descriptors were selected from the Descriptors in Health Sciences (DeCS) website and then combined with the Boolean operator "AND". The databases used for the search were: PubMed and the Virtual Health Library (VHL), where cross-sectional, cohort and case-control studies were evaluated, in Portuguese, English and Spanish.

In all, the result of the search in the databases using the descriptors, but without
application of filters, resulted in 221 articles available. After applying the following filters, PubMed: Portuguese, English and Spanish language and type of literature being a cross-sectional study. VHL: Portuguese, English, Spanish and type of literature being an observational study, a total of 65 articles were selected.

After pre-selecting the articles, a research protocol was created which clearly illustrated the aim of the study, the data collection process and the criteria involved in including the articles. After the analysis,
43 studies were excluded. Therefore, 22 articles were selected for this review.

The selection of material was based on the objective proposed by the study, with the inclusion criteria being articles that were related and relevant to the topic. Longitudinal, randomized, cross-sectional, case report and literature review studies were selected.

INITIAL ASPECTS OF THE APPROACH TO CHILDHOOD CANCER

The most frequent forms of cancer in childhood and adolescence are leukemias, especially acute lymphoid leukemia. Tumors of the Central Nervous System (CNS) are the most common solid malignant neoplasm [4].

In many cases, what makes it difficult to suspect and diagnose cancer in children and adolescents is the fact that its clinical presentation occurs through signs and symptoms that are common to other diseases that are more frequent in this age group, manifesting themselves through general symptoms that do not allow them to be localized, such as fever, vomiting, weight loss, bleeding, generalized adenomegaly, bone pain and pallor. Or through more localized signs and symptoms, which are also common in benign diseases, such as headaches, abdominal pain and osteoarticular pain[5].

The pediatrician must consider the possibility of malignancy in childhood not only because it is a potentially fatal disease, but because cancer is a potentially curable disease, depending on the type and stage of presentation. Studies indicate that the diagnosis of pediatric cancer is often delayed due to failure to recognize the presenting signs and also due to the fact that childhood cancer can mimic other common childhood diseases and even physiological processes of normal development [7].

Diagnosis at an early stage allows for less aggressive treatment, with greater chances of a cure and fewer sequelae from the disease or treatment[7].

Achieving high cure rates also requires medical care, correct diagnosis, referral to a treatment center and access to all prescribed therapy[3].

These are frequent signs:

a) Fever: this can be present in the diagnosis of various neoplasms, manifesting as a persistent fever with no determined origin. It should be considered in context and in association with other signs and symptoms.

b) Weight loss: this is one of the best indicators of health in childhood. Neoplasms induce catabolism, resulting in a change in weight. Weight loss of more than 10% in the six months prior to diagnosis associated or not with fever and night sweats are the so-called B symptoms associated with lymphomas.

c) Pallor: as a manifestation of anemia caused by medullary infiltration (as in leukemias), hemolysis or bleeding (associated with thrombocytopenia or intratumoral bleeding).

d) Abnormal bleeding: cutaneous manifestations of bleeding not associated with trauma such as petechiae or spontaneous bruising as signs of thrombocytopenia.

e) Generalized pain: due to tumor infiltration of the bone marrow or

bone marrow or metastatic processes.

f) Adenomegaly: common in childhood and usually associated with infectious processes. Neoplastic adenomegalies should be suspected when we see lymph nodes that are more than 3 cm in diameter, hardened, painless, adhered and without evidence of infection in the drainage area or in specific locations such as the supraclavicular.[6]

Algorithms have been developed in Brazil to aid in the early diagnosis of the most frequent childhood neoplasms, which can be easily applied by pediatricians in their daily practice. These algorithms were devised in a partnership between the Ministry of Health with the support of non-governmental institutions and are aimed at improving care for children with cancer in our country[5].

In some cases, findings of clinical syndromes on physical examination and family history data indicate the need for more careful investigation (Pollack, 1993). An example is the presence of anuria, hemihypertrophy and Beckwith-Wiedemann Syndrome (FIGURE 1) with Wilms[7] tumor.

Wilms' tumor (FIGURE 2) or nephroblastoma is a tumor of the kidneys that typically occurs in children and is rare in adults.

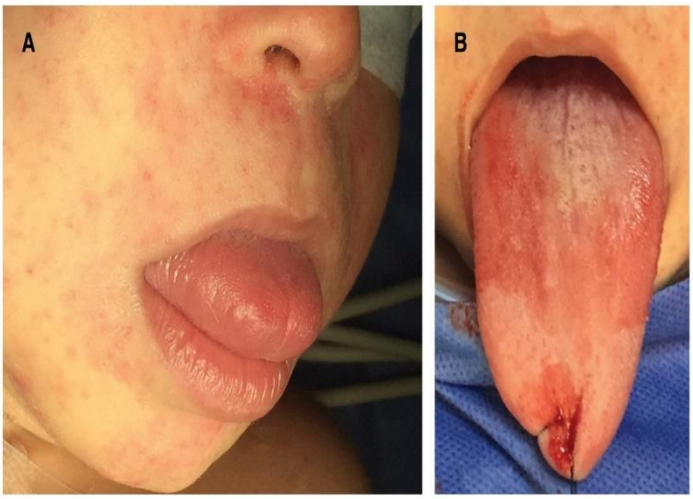


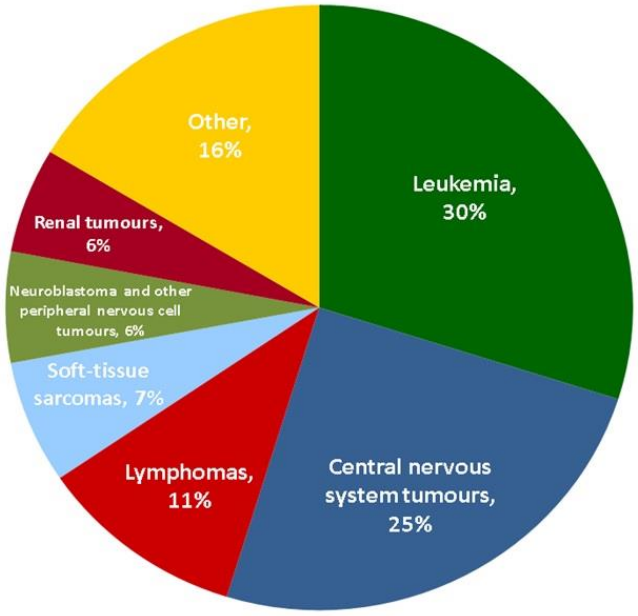
Figure 1. A) The extra-oral photograph shows the dermatological diagnosis: miliaria rubra and secondary traumatic purpura. B) The clinical photograph shows the length of the lingual body. Source: gi-bin/new/resumenI.cgi

Figure 2. Nephroblastoma Note the prominent septa subdividing the sectioned surface and the protrusion of tumor into the renal pelvis, resembling botryoid rhabdomyosarcoma.
Source: teachmepaediatrics.com(2023).

INCIDENCE OF CHILDHOOD CANCER IN THE WORLD

There are many different types of childhood cancer (GRAPH 1). Cancers that affect children can be quite different from cancers that affect adults, as they tend to occur in different parts of the body than adult cancers.

The most common type of cancer is leukemia, which accounts for around a third of all cases in both boys and girls.



Source: childhood-cancer-statistics, 2023.

Around 1 in 410 boys under the age of 15 develops cancer, compared to 1 in 471 girls [8].

For both boys and girls, the incidence was highest in the first five years of life, decreasing to a minimum between the ages of 5 and 9, and increasing again slightly between the ages of 10 and 14 [9].

From the age of 14, the prevalence of cancer continues to increase throughout adulthood. For the most common types of cancer, the rates and frequency of diagnosis are generally similar to other countries in Europe, North America, Australia and New Zealand [10].

This data helps doctors and analysts to compare on a global scale[11].

Globally, 80% of children diagnosed between 2013 and 2023 survived for at least five years [12].

There was a marked increase in survival between these periods for children with lymphoma, brain and spine tumors and kidney tumors, as well as for children aged 1 year and older when diagnosed with neuroblastoma [13].

The highest survival rates, over 95% at five years after diagnosis, were found for Hodgkin's lymphoma, various types of non-malignant intracranial tumors, retinoblastoma, fibrosacroma, synovial sarcoma, germ cell tumors of the testis and ovary and thyroid carcinoma [14].

Survival also exceeded 90% for precursor lymphoblastic leukemia (the most frequent of all childhood cancers), Wilms' tumor, germ cell tumors in locations other than the testicles and ovaries and malignant melanoma [15].

Cancer is rare in children, but thousands of new cases are diagnosed every year [15].

Thanks to improved research and treatment, survival has increased greatly over the last 50 years [11].

This is a huge improvement on the 1960s, when only around 3 in 10 children (30%) with cancer were successfully treated [9].

Collecting and analyzing solid data is an important part of the work. Reliable data on the incidence and survival of the population makes a difference to everyone affected by childhood cancer [5].

Firstly, it helps the families of children with cancer to better understand the disease, which can make a real difference when they are dealing with something that is so emotionally difficult [9].

It is also essential for doctors treating children with cancer to help them determine the resources needed to provide children suffering from cancer with the treatment and care they need [8].

Pathophysiology and forms of treatment for the most common types of Childhood Cancer.

ACUTE LEUKEMIA

This is the main malignant neoplasm of childhood. Great advances have been made in recent years both in treatment and in understanding the biology of these diseases, making the case of childhood acute lymphocytic leukemias a true success story [11].

Cure rates, which before the advent of modern chemotherapy (around the 1950s) were 0%, have now risen to survival rates of over 80%.

This result is due to improved understanding of the pathology, adaptation to treatment and supportive care such as antibiotic therapy, but also to the joint efforts of patients, doctors and families who have participated in various cooperative study groups [12].

To put it simply, in order to make an early diagnosis of these pathologies we should request a blood count for any child who presents with symptoms of abnormal bleeding, fever, fatigue, pallor, bone pain, hepatosplenomegaly, generalized lymphadenomegaly. With the result in hand, any child who shows an alteration in two or more blood series should be referred to a referral service as a matter of urgency [10]. This is summarized in FIGURE 3.

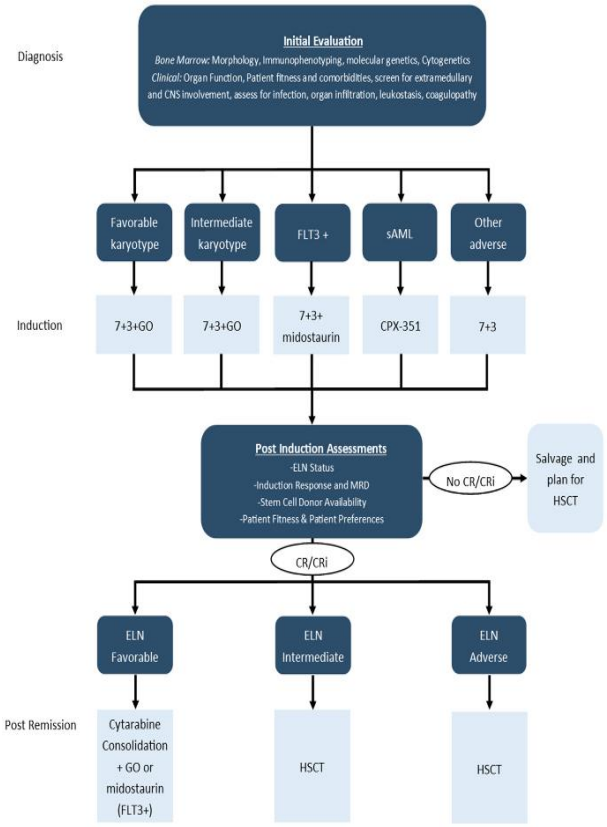


Figure 3. Overview of frontline intensive treatment of AML.Source: Stubbins et.al, 2022 [20].

LYMPHOMAS

These are among the three most common neoplasms in childhood. They basically affect the lymph nodes, but can also affect the spleen, liver or bone marrow. They are divided into two large groups: Hodgkin's disease and non-Hodgkin's lymphomas [15].

As some lymphomas grow very quickly, a patient with suspicious adenomegaly (FIGURE 4) should be referred quickly to a specialized service [16].

It is important to remember that the use of corticosteroids for more than 48 to 72 hours in both lymphomas and leukemias can hinder or even prevent the diagnosis of these pathologies, and should not be prescribed until the patient has been properly assessed by a specialist [17].

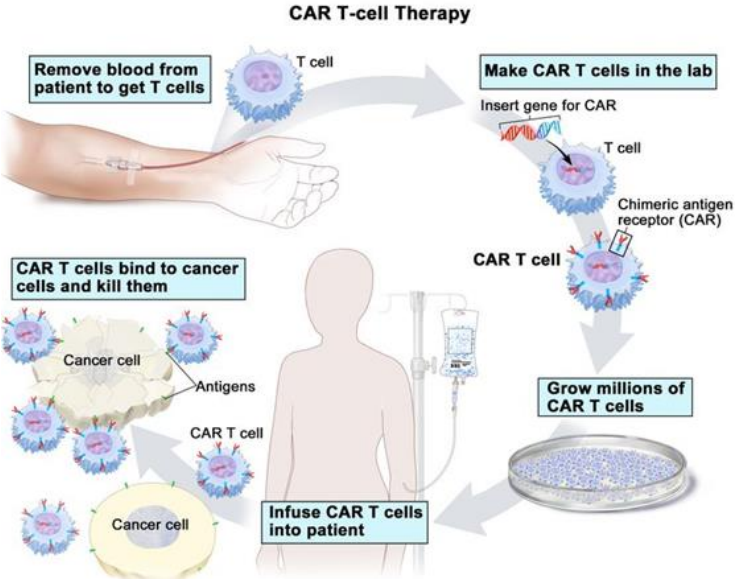


Figure 4. Lymphoma treatment regimen. Source: National Cancer Institute (2023).

CAR T-cell therapy. A type of treatment in which a patient's T cells (a type of immune cell) are altered in the laboratory to bind to cancer cells and kill them. Blood from a vein in the patient's arm flows through a tube into an apheresis machine (not shown), which removes the white blood cells, including the T cells, and sends the rest of the blood back to the patient. Then the gene for a special receptor called a chimeric antigen receptor (CAR) is inserted into the T cells in the laboratory. Millions of CAR T cells are grown in the laboratory and then administered to the patient by infusion. The CAR T cells are able to bind to an antigen on the cancer cells and kill them [18].

CENTRAL NERVOUS SYSTEM TUMORS

CNS tumors represent one of the most frequent neoplasms in childhood. Unfortunately, the morbidity of these diseases and their treatment can be extremely significant in terms of physical deficits, as well as neuropsychological or neuroendocrine sequelae [19] (FIGURE 5).

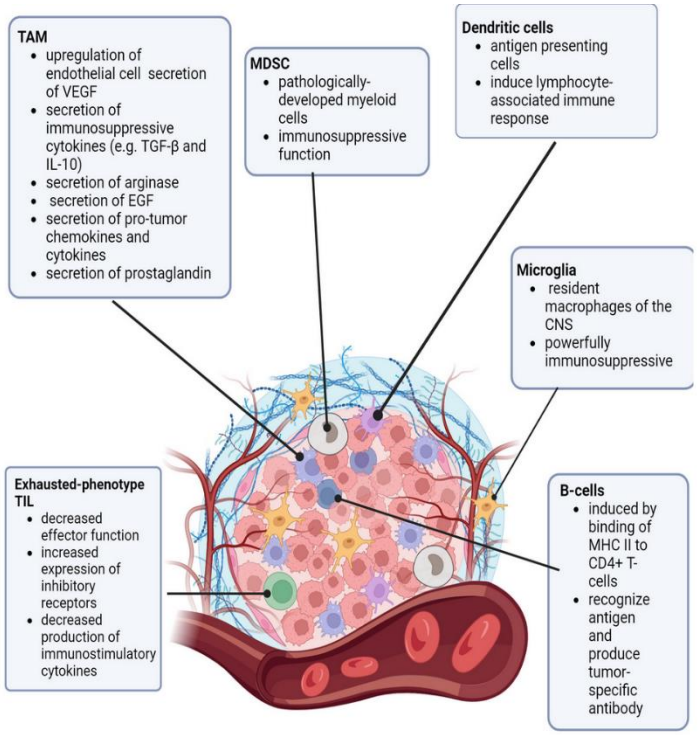


Figure 5. The tumor microenvironment of the pediatric CNS. Source:frontiersin.org/journals/immunology/articles/ (2024).

In this case TAM (tumor-associated macrophage), MDSC (myeloid-derived suppressor cell), VEGF (vascular endothelial growth factor), TGF-β (transforming growth factor β), IL-10 (interleukin 10), EGF (epidermal growth factor), CNS (central nervous system) MHC (major histocompatibility complex), CD4 (cluster of differentiation 4), TIL (tumor infiltrating lymphocyte) [20].

In addition, the mortality rate caused by these tumors is among the highest among pediatric cancers. The optimal treatment of these children represents a major challenge, requiring a multidisciplinary group of specialists including a neurosurgeon, pathologist, neuroradiologist, radiotherapist and oncologist [20].

Early diagnosis is also extremely important in this case, as it can clearly reduce not only mortality, but also the morbidity linked to the disease and its treatment [21].

The most frequent symptoms are those linked to intracranial hypertension, such as headache, vomiting or altered sensory perception. In younger children, the symptoms of hypertension may be later due to the presence of a fontanel. In these patients, regular measurement of the head circumference at routine visits is essential, and its alteration can be an early warning sign [22].

EARLY DIAGNOSIS

Pediatric cancer is not a preventable disease. Although several studies point to the existence of potential risk factors due to the child's intrauterine exposure, there is no scientific evidence that makes the association between the disease and environmental factors clear. Therefore, the prevention of childhood cancer is still a challenge for the future and the current emphasis in the approach to this cancer should be on its early diagnosis and timely referral for timely and quality treatment, which allows for higher cure rates [6].

Cancer in children and adolescents has characteristics that make it different from cancer in adults. It originates predominantly from embryonic cells, has a short latency period and generally grows rapidly, making it very important for the best results to be obtained if the diagnosis is promptly suspected and the patient is quickly referred for treatment [2].

What makes it difficult in many cases to suspect and diagnose cancer in children and adolescents is the fact that its clinical presentation occurs through non-specific signs and symptoms that are common to other benign diseases that are more frequent in childhood, manifesting as general symptoms that do not allow them to be localized, such as prolonged fever, vomiting, weight loss, bleeding, generalized adenomegaly, generalized bone pain and pallor. Or through more localized signs and symptoms, such as headaches, vision changes, abdominal pain and osteoarticular pain [7].

In some cases, these difficulties lead patients to seek medical attention several times over the course of weeks or months, always with the same complaint or with a worsening of the situation that led them to seek health care in the first place, and the patient can be diagnosed in unfavorable clinical conditions, with many complications that make treatment and its outcome difficult [18].

It is therefore essential that professionals at all points in the Health Care Network are trained to contextualize clinical findings with age, gender, association of symptoms, time of evolution and other data, so that a correct suspicion can be made and the case managed quickly and effectively [11].

Here are some general recommendations for the pediatrician and/or Family Health team doctor for handling a suspected case (NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE, 2023).

- ✓ Value information from caregivers (parents), bearing in mind that they are often the best observers of children's health status.
- ✓ Be available to reassess your patients whenever necessary. If the problem continues unresolved or does not improve to the expected standard, the opinion of another professional is recommended.
- ✓ In the stages of suspected diagnosis, interact with other professionals from the ESF, teachers and psychologists, as well as doctors from various specialties, such as ophthalmologists, neurologists, neurosurgeons and orthopedists (in Primary Care, we don't find specialists, so perhaps it would be nice to point out that specialists are at the middle level of care. Discussing suspected cases directly with specialists can help indicate the need

for early referral).

- ✓ Refer the child with a suspected diagnosis of malignant neoplasia (cancer) for evaluation at a specialized health care service with specialists in pediatric onco-hematology.
- ✓ Interact with the pediatric oncologist during all stages of treatment, supporting the patient and their family.
- ✓ Decide which children need diagnostic investigation. In these cases, a good history, a detailed physical examination and some laboratory and imaging tests can help to elucidate the case.
- ✓ Carry out the investigation without alarming family members ahead of time, but share with parents your concern about the possibility of a more serious illness, so that they don't miss the necessary appointments and tests.
- ✓ Dealing with the fear of diagnosis and the "cancer taboo". Some parents will want to have a test to rule out the possibility of cancer. Others won't want to talk about it. The doctor can also often be uncomfortable talking about it. This can lead to parents feeling continually anxious and requiring many visits to various pediatricians.

TREATMENT

Cancer treatment begins with a correct diagnosis, which requires the participation of a reliable laboratory and imaging studies. Due to its complexity, treatment must be carried out in a specialized center and comprises three main modalities (chemotherapy, surgery and radiotherapy, when necessary), being applied rationally and individually for each specific tumour and according to the extent of the disease [15].

The work coordinated by a multi-professional team is also a determining factor in the success of the treatment [21].

FINAL CONSIDERATIONS

Most of the symptoms of Childhood Cancer are much more likely to be caused by other reasons, such as an injury or infection. Even so, if your child has any of the symptoms mentioned in this article, consult a doctor so that the cause can be diagnosed and, if necessary, treatment started.

Some children may have a greater chance of developing a specific type of cancer due to alterations in certain genes inherited from one of their parents. These children should have regular medical follow-up to assess the signs of the disease and carry out specific tests to diagnose it early.

Survival in pediatric cancer is related to various factors, including those related to the patient, such as gender, age, as well as the location, extent and type of tumor.

However, issues inherent to the organization of the health system - which may involve greater or lesser ease and timeliness of diagnosis, referral for treatment, quality of treatment and social support - also contribute to determining different chances of survival.

In Brazil, it has been seen that improved medical training in the early diagnosis of pediatric cancers has also improved patients' access to appropriate treatment. Curricular changes in medical schools with an emphasis on learning primary care according to the guidelines of the World Health Organization are also enabling an improvement in this regard (SUS).

Through educational policies, paediatricians and primary care doctors who are previously sensitized and aware of the main warning signs will be able to make an earlier diagnosis and quickly refer children with cancer to specialized centers, thus allowing for better chances of a cure and a better quality of life for them. It remains to be remembered that "only those who think about cancer make a cancer diagnosis".

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