






REVIEW

Acute lymphoblastic leukaemia in children

Leucemia Linfoblástica Aguda en edad pediátrica

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ABSTRACT

The term cancer encompasses a group of diseases characterised by the development of abnormal cells that divide, grow and spread uncontrollably throughout the body. Acute lymphocytic leukaemia is a type of cancer of the blood and bone marrow. It is the most common form of cancer in children. The peak incidence is between two and five years of age. A literature review was conducted to characterise the development of acute lymphoblastic leukaemia in children. Journals and websites such as SciELO and Infomed were used, for a total of 17 references. The cause of acute lymphoblastic leukaemia is unknown. The treatment of patients with ALL is tailored to the patient's risk at diagnosis.

Keywords: Cancer; Leukemia; Acute Lymphoblastic Leukemia.

RESUMEN

El término cáncer engloba un grupo de enfermedades que se caracterizan por el desarrollo de células anormales, que se dividen, crecen y se diseminan sin control en cualquier parte del cuerpo. La leucemia linfocítica aguda es un tipo de cáncer de la sangre y de la médula ósea. Es la forma más frecuente de presentación del cáncer en la edad infantil. El pico de incidencia máximo se establece entre los dos y los cinco años de edad. Se realizó una revisión bibliográfica con el objetivo de caracterizar el desarrollo de la leucemia linfoblástica aguda infantil. Se utilizaron revistas, páginas web de sitios como SciELO e Infomed, para un total de 17 referencias. Se desconoce cuál es la causa de la leucemia linfoblástica aguda. El tratamiento de los pacientes con LLA está adaptado al riesgo del paciente al diagnóstico.

Palabras clave: Cáncer; Leucemia; Leucemia Linfoblástica Aguda.

INTRODUCTION

Cancer encompasses a large group of diseases characterized by the development of abnormal cells, which divide, grow, and spread uncontrollably in any part of the body.⁽¹⁾

Normal cells divide and die over a programmed period. However, the cancer or tumor cell ‘loses’ the ability to die and divides almost without limit. Such a multiplication in the number of cells eventually forms masses, called ‘tumors’ or ‘neoplasms,’ which can destroy and replace normal tissues in their expansion.⁽¹⁾

Cancer is the second leading cause of death in the world. However, survival rates are improving for many types of cancer thanks to improvements in the detection and treatment of cancer.⁽²⁾

Leukaemia is a blood disease in which the bone marrow produces abnormal white blood cells called leukemic blast cells or leukemia cells. These cells divide by reproducing themselves, leading to neoplastic proliferation of altered cells that do not die as they age or become damaged, accumulating and crowding out normal cells. This depletion of healthy cells can lead to difficulties transporting oxygen to tissues, healing infections, or controlling bleeding.⁽³⁾

Because it is a proliferation of immature, abnormal cells in the blood, leukemia is considered a blood cancer.⁽³⁾

Acute lymphocytic leukemia is a type of cancer of the blood and bone marrow, which is the spongy tissue inside the bones where blood cells are produced.⁽⁴⁾

The word 'acute' refers to the disease progressing rapidly and creating immature rather than mature blood cells. The word 'lymphocytic' refers to the white blood cells, called 'lymphocytes,' affected by this disease. Acute lymphocytic leukemia is also known as 'acute lymphoblastic leukemia.'⁽⁴⁾

Leukaemia was discovered at about the same time by two brilliant physicians who carried out careful studies on their patients and autopsies (Dameshek and Gunz 1964). The first to describe the disease was Velpeau in 1827, who observed a 63-year-old patient with fever, weakness, and an enormous abdomen growth. He found at autopsy an enormous liver and spleen (the spleen weighed 4 kg), and the 'blood was like oatmeal mush reminiscent of the consistency and color of red wine yeasts.' On the other hand, Barth (1856) studied 1839 a patient whose blood was analyzed by Donné (1844), who observed at autopsy under the microscope, 'mucous corpuscles very like pus cells.' According to this sequence, Donné would have been the first person to describe leukemic cells microscopically.⁽⁵⁾

Leukaemia was first described by Rudolf Virchow in 1845. During the 1930s, leukemia was frequently mentioned as a cause of illness and almost inevitable death.⁽⁶⁾

Virchow differentiated leukemia from leukocytosis in his work, describing two types of leukemia: splenic, associated with splenomegaly, and lymphatic, where enlarged lymph nodes were present. Years later, in 1857, there was another novel contribution by Friedreich, who described for the first time a form of leukemia that he called acute.⁽⁵⁾

Mortality from acute lymphoblastic leukemia (ALL) is currently a tracer indicator of access to and effectiveness of health care. It is one of the most common oncological diseases in the pediatric age group, accounting for 25 % of all childhood cancers. It accounts for 0,5-3 % of all malignant neoplasms worldwide. Several studies describe that more than 60 % of complications arise in the early phase of the disease. The most frequent causes of mortality were hemorrhages due to thrombocytopenia, infections, and neutropenic colitis.⁽⁷⁾

Of children with ALL, about 98 % achieve remission, and about 85 % of patients aged 1-18 years with newly diagnosed ALL who receive current regimens are expected to survive without long-term complications, and 90 % to survive to 5 years.⁽⁸⁾

In Mexico, between 5000 and 6000 children are diagnosed with cancer each year. About 5 out of 10 of these children are diagnosed with leukemia. Most children are diagnosed when the leukemia is in the late stages (about 70 % or 7 out of 10). In Peru, about 1300 children are diagnosed with cancer each year. Leukaemia accounts for 1 in 3 cases of childhood cancer. In Colombia, some 6218 children were diagnosed with cancer in 2018. Acute lymphoblastic leukemia is the most common childhood cancer in the country.⁽⁹⁾

In Cuba, acute lymphoblastic leukemia accounts for 23 % of cancer diagnoses in children under 15 years of age. Ninety-five percent of leukemias are acute (70,6 percent lymphoid). The relapse rate was 25,1 % in acute lymphoblastic leukaemia.⁽¹⁰⁾

The Oncohaematology service of the pediatric hospital in Villa Clara achieves an 80 % survival rate in children affected by acute lymphoblastic leukemia from the central provinces of Cuba.⁽¹¹⁾

ALL is a rapidly progressing cancer affecting lymphoid stem cells,⁽¹²⁾ Child and adolescent cancer survivors need close follow-up as side effects of cancer treatment may persist or present months or years later.⁽⁸⁾ The prognosis of children with ALL has improved dramatically in recent decades thanks to new drugs and risk-adapted treatment, although a small group of patients still fail treatment. For these patients, new strategies are needed.⁽¹³⁾

Because of the importance of knowledge about childhood cancer, especially ALL, which is the most common cancer in children, the research team was motivated to conduct a literature review.

Objective: To characterize the development of acute lymphoblastic leukemia in children.

DEVELOPMENT

Acute lymphoblastic leukemia is the most common form of childhood cancer. The peak incidence is between two and five years of age. In terms of gender, ALL slightly predominates in boys, especially in pubertal age. Geographical differences are notable in this disease. At the same time, in less developed countries, such as North Africa and the Middle East, T-lineage ALL and lymphomas predominate; in industrialized countries, B-lineage ALL is the most frequent hematological malignancy. This has been linked to the greater ease of exposure

to specific 'leukemogenic' environmental agents in industrialized countries. In countries with heterogeneous populations, a higher incidence of ALL has been observed in the white race.⁽¹³⁾

Some genetic factors, notably the presence of Down syndrome, are associated with an increased risk of ALL, but most patients do not have recognized hereditary elements. Genome-wide association studies have identified polymorphic variants in several genes (including ARID5B, CEBPE, GATA3, and IKZF1) that are linked with increased risk of ALL or specific ALL subtypes.⁽¹⁵⁾

Rare germline mutations in PAX5 and ETV6 are associated with familial ALL.⁽¹⁴⁾ Few environmental risk factors are associated with ALL in children. Increased rates of the disease have been linked to exposure to radiation and certain chemicals, but these links explain only a tiny minority of cases.⁽¹⁵⁾

The pathogenesis of ALL involves abnormal proliferation and differentiation of a clonal population of lymphoid cells. Studies in the pediatric group have identified genetic syndromes that predispose to a minority of ALL cases, such as Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, and Nijmegen decomposition syndrome. Other predisposing factors include exposure to ionizing radiation, pesticides, certain solvents, or viruses such as Epstein-Barr and human immunodeficiency virus. However, in most cases, it appears as a *de novo* malignant neoplasm in previously healthy individuals. Chromosomal aberrations are the hallmark of ALL but are not sufficient to give rise to leukemia.⁽¹⁴⁾

The research team suggests that the risk of ALL is highest in children under 5 years of age. The risk then slowly declines until the mid-twenties but then rises again after age 50.

ALL starts in the bone marrow (the soft part inside certain bones where new blood cells are formed). Most often, leukemia invades the blood very quickly. Sometimes, these cells can also spread to other body parts, such as the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles (in men).⁽¹⁶⁾

Other cancers that begin in lymphocytes are called lymphomas (non-Hodgkin's lymphoma or Hodgkin's lymphoma). Although leukemias, such as ALL, mainly affect the blood and bone marrow, lymphomas mainly affect the lymph nodes or other organs (but can also affect the bone marrow). Sometimes, it can be difficult to tell whether a cancer of the lymphocytes is leukemia or lymphoma. Generally, the disease is considered leukemia if at least 20 % of the bone marrow comprises cancerous lymphocytes (called lymphoblasts or simply blasts).⁽¹⁶⁾

On the other hand, acute lymphocytic leukemia (ALL) does not usually form tumors. It usually affects the entire bone marrow of the body and, in some cases, by the time it is detected, has already spread to other organs, such as the liver, spleen, and lymph nodes.⁽¹⁶⁾

In ALL, very immature leukemic cells accumulate in the bone marrow, destroying and replacing those that produce normal blood cells. The leukemic cells are transported through the bloodstream to the liver, spleen, lymph nodes, brain, and testes, where they can continue to grow and divide. However, ALL cells can accumulate anywhere in the body. They can spread to the lining of the brain and spinal cord (leukemic meningitis) and also cause anemia, liver and kidney failure, and damage to other organs.⁽¹⁶⁾

This research team believes that the primary methods used to determine ALL in children are physical examination, patient history, complete blood count, and bone marrow aspiration.

In the case of a child with suspected leukemia, a good anamnesis should be carried out in search of signs and symptoms compatible with hematopoietic failure or extramedullary infiltration. The examination should be exhaustive. The presence of ecchymosis, petechiae, lymphadenopathy, skin pallor, etc., should be explored, the liver and spleen should be palpated, a good neurological examination should be performed, and, in males, the testicles should always be palpated. In most patients diagnosed with ALL, the first thing that is done and which confirms suspicions is a haemogram. This shows leukocytosis at the expense of lymphoblasts in approximately 50 % of cases, anemia in 80 %, and thrombopenia (with less than 100 x 10⁹/L platelets) in 75 % of cases. Lymphoblasts are usually seen under the microscope in the peripheral blood smear (although they do not always appear). The definitive diagnosis of acute leukemia should always be made by morphological, molecular, and cytogenetic analysis of the OM aspirate. Treatment should never be initiated without obtaining an OM sample. At least 25 % of blasts in the OM will confirm the diagnosis. The ALL subtype will be defined by morphological, molecular biology, and cytogenetic studies of the aspirate. The cerebrospinal fluid examination should always be performed on all leukemia patients at diagnosis to rule out initial CNS involvement. An initial chest X-ray will allow us to determine the existence of a mediastinal mass. Other studies performed at diagnosis are abdominal ultrasound, cardiological study (before treatment, which includes cardiotoxic drugs), blood biochemistry (including LDH, uric acid, calcium, phosphorus, transaminases, etc.), coagulation study, serology (viral hepatitis, HIV, herpes, CMV, etc.) and immunoglobulins. If the patient presents with fever, cultures of blood, urine, and any suspicious lesions should be obtained and appropriate antibiotic treatment initiated.⁽¹³⁾

According to Lassaletta Atienza A.⁽¹³⁾, the initial symptoms at diagnosis usually result from lymphoblast infiltration of the bone marrow, which is anemia, thrombopenia, leukopenia, bone pain, etc. Although Caywood E.⁽¹⁸⁾ states that, like all leukemias other symptoms or signs are being very tired, weak or pale, swollen lymph nodes, recurrent infections (such as bronchitis or tonsillitis), fever, night sweats, easy bruising or petechiae

(small red spots on the skin caused by easy bleeding), abdominal pain (caused by the accumulation of cancerous blood cells in organs), and pain in the abdomen (caused by the accumulation of cancerous blood cells in organs).

Different types of treatment are available for children with acute lymphoblastic leukaemia (ALL). Some treatments are standard, and others are being evaluated in clinical trials.

When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment. Treatment of children with ALL should be planned by a team of doctors who are experienced in treating childhood leukaemia.⁽¹⁷⁾

Children with acute lymphoblastic leukemia are treated with chemotherapy. These special medicines are used to kill cancer cells. Which drugs and how they are combined depends on the subtype of acute lymphoblastic leukemia the child has and how aggressive the disease is. How the cancer responds to initial treatment is also essential in choosing which type of chemotherapy to use.⁽¹⁸⁾

Doctors can administer chemotherapy through a vein (intravenous route) by injecting it into a muscle (intramuscular route), by mouth (oral route), in pill form, or through a lumbar puncture (intrathecal route) to inject the drug directly into the cerebrospinal fluid, where the cancerous white blood cells are concentrated. The goal of treatment is remission, which is when cancer cells are no longer detected in the patient's body. Maintenance chemotherapy is then used to keep the child in remission and prevent the cancer from returning. The child receives maintenance chemotherapy for a period of 2 to 3 years.⁽¹⁸⁾

Another treatment for this type of leukemia is known as stem cell transplantation, which involves destroying cancer cells, normal bone marrow cells, and immune system cells using high-dose chemotherapy and/or radiotherapy, introducing stem cells from a donor into the patient's body, and rebuilding healthy blood and immune systems with the new stem cells.⁽¹⁸⁾

According to the AEAL Forum⁽¹⁷⁾, Stem cell transplantation is rarely used as an initial treatment for children and adolescents with ALL. It is most often used as part of the treatment of relapsed ALL. But Caywood E.⁽¹⁸⁾ suggests that children with aggressive types of acute lymphoblastic leukemia may require it.

Clinical trials are research studies that offer patients promising new treatments that are not yet available to the general public. Doctors decide whether a child is a good candidate to participate in a clinical trial.⁽¹⁸⁾

Late effects of cancer treatment may include the following:⁽¹⁷⁾

Physical problems, such as heart, blood vessel, liver, or bone problems, and fertility problems. The risk of heart late effects can be decreased by various strategies, such as when dexrazoxane is given with chemotherapy drugs called anthracyclines.

Mood changes: feelings, thinking, learning, or memory. Children under 4 years of age who received radiation therapy to the brain are at increased risk for these effects.

Second cancers (new cancers) or other conditions, such as brain tumors, thyroid cancer, acute myeloid leukemia, and myelodysplastic syndrome.

The research team recommends that pediatric ALL patients' initial evaluation and subsequent treatment should occur in specialized pediatric haemato-oncology centers. Treatment is targeted to different risk groups and comprises induction, intensification (consolidation), and maintenance phases.

Treatment of childhood ALL usually consists of three phases:⁽¹⁷⁾

- Remission induction: This is the first phase of treatment. The goal is to destroy the leukemic cells in the blood and bone marrow. This puts the leukemia into remission.
- Consolidation/intensification: this is the second phase of treatment. It begins once the leukemia is in remission. The goal of consolidation/intensification therapy is to destroy any remaining leukemia cells in the body that may cause a relapse.
- Maintenance is the third phase of treatment. The goal is to destroy any remaining leukaemic cells that could regenerate and cause a relapse. Maintenance treatments are often given at lower doses than those used in the remission induction, consolidation, or intensification phases. The cancer is more likely to return if the drugs prescribed by the doctor in maintenance therapy are not taken. This phase is also called continuation therapy.

During treatment, the primary care pediatrician must follow up on the different problems that may occur, such as:⁽¹³⁾

- Fever: any patient with acute leukemia who presents fever during treatment should be evaluated in a hospital center. Remember that these are immunocompromised patients: The first thing to do is assess the patient's general condition in case urgent measures are required. The second thing to do is check if the patient is neutropenic or needs blood products. Always draw blood cultures. Remember that these patients are carriers of central venous catheters that may be the source of the fever. If there is febrile neutropenia, the chemotherapy treatment will be suspended, and empirical treatment intravenous with broad-spectrum antibiotherapy will be started.
- Toxicity of treatment: Chemotherapy and radiotherapy present numerous adverse effects, such

as side effects produced by antibiotics, antiemetics, antihistamines, etc. Patients usually present myelosuppression of variable degree that may require haemoderivatives. Mucositis is frequent after treatment with methotrexate. Alopecia (which occurs in almost 100 % of patients) is reversible. Anthracyclines can cause cardiomyopathy. Corticoids (used for prolonged periods) cause obesity, a decrease in mineralization, etc. In addition, there is a higher rate of bone necrosis, especially in adolescents.

- Disease: every patient with acute leukemia should be closely monitored. Physical examination (including palpation of the male testicles) and analytical examination should be done frequently. Whenever a relapse is suspected, a bone marrow evaluation of the cerebrospinal fluid should be performed (as isolated CNS relapses occur).

The research team believes that receiving the news that one's child has cancer is terrible, and cancer treatment is often very stressful for any family. There are many resources available to help them through this challenging situation. In addition, treatments for these sick children must continue to be refined, and follow-up care is critical.

CONCLUSIONS

Acute lymphoblastic leukemia occurs when the body makes too many lymphoblasts (a type of white blood cell). It is the most common type of cancer in childhood. The disease develops quickly and gets worse rapidly. The cause of acute lymphoblastic leukemia is not known. However, some risk factors may increase a child's chances of developing the disease. Confirmation of the diagnosis is made by morphological, cytogenetic, and molecular study of the bone marrow aspirate. Treatment of patients with ALL is adapted to the patient's risk at diagnosis and comprises three phases: induction, intensification (consolidation), and maintenance. The total duration is two years.

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