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REVIEW ARTICLE

Novel Aspects of Late Neurological and Cardiovascular Complications in Adults with a History of Childhood Acute Lymphoblastic Leukemia

Aspectos novedosos sobre las complicaciones neurológicas y cardiovasculares tardías en adultos con antecedente de leucemia linfoblástica aguda infantil

Laritza Martinez-Contreras [1], **Adalberto Fortún-Prieto** [2], **Mirta Caridad Campo-Díaz** [3]

[1]University of Medical Sciences of Pinar del Río. "Abel Santamaría Cuadrado" General Teaching Hospital. Pinar del Río, Cuba.
[2]University of Medical Sciences of Pinar del Río. León Cuervo Rubio Teaching Clinical Surgical Hospital. Pinar del Río, Cuba.
[3]University of Medical Sciences of Pinar del Río. Pepe Portilla Pediatric Provincial Teaching Hospital. Pinar del Río, Cuba.

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ABSTRACT

Introduction: In recent years therapeutic advances have achieved an increase in the survival of childhood cancer, which leads to the development of long-term complications dependent on it or on the disease itself, being acute lymphoblastic leukemia the most common during childhood.
Objective: to update knowledge on late complications that may occur during adulthood in individuals who suffered from childhood acute lymphoblastic leukemia. Methods: relevant studies were selected from digital databases such as Medline, Virtual Health Library, SciELO, Research Gate, Google Scholar and digital books related to the subject. Of the 117 articles chosen, 30 were used, which constitute the bibliographic references of the work.
Development: Leukemia constitutes one third of all childhood cancer cases. Polychemotherapy and radiotherapy in pediatric patients with acute lymphoblastic leukemia may cause complications that appear years after the end of treatment and require diagnostic precision as well as therapeutic management to guarantee their quality of life during adulthood. Neurological and cardiovascular complications may be dependent on the disease or its treatment.

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Conclusions: Childhood acute lymphoblastic leukemia currently shows a high survival rate and cure criteria. The therapeutic actions used for this entity may cause long-term complications in these patients, as well as sequelae and involvement of various organs and systems, so medical follow-up is essential throughout life.

Keywords: Leukemia, Biphenotypic, Acute; Complications.

RESUMEN

Introducción: en los ultimos años los avances terapéuticos han logrado un aumento en la supervivencia del cancer infantil**,** lo que conlleva al desarrollo de complicaciones a largo plazo dependientes del mismo o de la propia enfermedad, siendo la leucemia linfoblástica aguda el más común durante la infancia.
Objetivo: actualizar los conocimientos sobre las complicaciones tardías que pueden producirse durante la edad adulta en individuos que padecieron leucemia linfoide aguda infantil. Métodos: se seleccionaron los estudios relevantes en bases de datos digitales como Medline, Biblioteca Virtual de Salud, SciELO, Research Gate, Google Scholar y libros digitales relacionadas con el tema. De los 117 artículos escogidos y se utilizaron 30, que constituyen las referencias bibliográficas del trabajo.
Desarrollo: la leucemia constituye una tercera parte de todos los casos de cáncer infantil. La poliquimioterapia y la radioterapia en los pacientes pediátricos con leucemia linfoblástica aguda pueden originar complicaciones que se presentan años después de finalizado el tratamiento y requieren de precisión diagnóstica, así como del manejo terapéutico que garantice su calidad de vida durante su edad adulta. Las complicaciones neurológicas y cardiovasculares pueden ser dependientes de la enfermedad o su tratamiento.

Conclusiones: la leucemia linfoblástica aguda infantil muestra en la actualidad una elevada tasa de supervivencia y criterio de curación. Las acciones terapéuticas que se utilizan para esta entidad pueden causar complicaciones a largo plazo en estos pacientes, así como originar secuelas y afectaciones a varios órganos y sistemas, por lo que es indispensable un seguimiento médico durante el transcurso de la vida.

Palabras claves: Leucemia Linfoblástica Aguda Infantil, Complicaciones en La Edad Adulta.

INTRODUCTION

Worldwide, approximately 12,7 million new cases of cancer are diagnosed each year. It is predicted that by 2030 this figure will rise to 21,3 million and will have a greater impact on low-income populations.[1] In Cuba there are an average of 300 new cases per year.[2]

During the last decades, the advances achieved in the treatment protocols of oncologic diseases in pediatrics have achieved an increase in the survival of childhood cancer, reaching rates close to 80 % at five years. This fact leads to the appearance of long-term complications depending both on the underlying disease and on the side effects of the treatment, which can damage different organs and appear many years after the disease has subsided.[3]

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There are several therapeutic procedures that are part of the oncological treatment protocols, and most of them, if not all, have the ability to cause chronic complications, which often appear in adulthood years after the successful completion of the treatment of the malignant disease during childhood. The two most commonly used options in these diseases are chemotherapy and radiotherapy, and in both of them complications have been described which, when late, can be identified during adulthood once the underlying disease has been overcome.

Among the cytostatic drugs, alkylating agents have been associated with cardiac and pulmonary problems, an increased risk of secondary cancer (including central nervous system tumors). These drugs may increase the risk of chronic heart failure, myelodysplastic syndromes and acute myeloid leukemia.

Radiation therapy, used for the purpose of destroying cancer cells, when used in the head and neck region may cause learning difficulties (cognitive impairment), growth hormone deficiency, hypothyroidism or hyperthyroidism, hearing loss, ophthalmologic problems such as cataracts or glaucoma, dental abnormalities, brain or thyroid tumor and osteoporosis. Some children who receive cranial radiation therapy may not reach puberty at the appropriate age.

A small percentage of them experience premature puberty, while in other children puberty is significantly delayed. Radiation therapy to the chest can cause lung damage (scarring, inflammation), heart damage (scarring, inflammation, coronary heart disease), as well as osteosarcoma, breast or thyroid cancer, hypothyroidism or hyperthyroidism. In boys, radiation therapy to the testicles can cause fertility problems, while in girls, abdominal irradiation can have the same effect, including ovarian failure or premature menopause.

The effect of radiation therapy on the ovaries and testes depends on the age of the child, the dose used and its location. Radiation therapy administered to the whole body can potentially cause gonadal failure and fertility disorders in people undergoing hematopoietic stem cell transplantation.[1]

Between 40 and 60 % of patients who received chemotherapy during pediatric age present endocrine disorders, the most frequent sequela being hypogonadism (83 %), followed by hypothyroidism (56 %) and growth hormone deficiency (50 %). Radiotherapy is the main risk factor for the development of hormonal dysfunction; its impact will depend on the site where it was received, the total dose, the patient's age, the number of sessions and the scheduling of tissue recovery time between doses.

Gonadal dysfunction due to chemotherapy in women may manifest as delayed puberty, infertility or premature menopause and may be dependent on damage to the hypothalamic-pituitary axis or the reproductive organ. Hypogonadotropic hypogonadism due to lesion of the hypothalamus is frequent in patients who have undergone cranial irradiation, showing a decrease in gonadotropic hormones (LH and FSH).[2]

Cardiac muscle lesions are generally related to cumulative doses of anthracyclines, including doxorubicin and daunorubicin. Children appear to have less tolerance to multiple chemotherapeutic drug doses than adults. When these drugs are combined with chest radiotherapy, there is a risk of heart failure with lower doses of these drugs.

Drugs that block mitosis to prevent cell division, such as vincristine, have been associated with the presence of peripheral neuropathy.

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The most common type of malignant disease in childhood is leukemia, followed by central nervous system tumors, lymphomas, soft tissue sarcomas, neuroblastomas and kidney tumors.[4,5]

Leukemias are a group of diseases characterized by the infiltration of neoplastic cells of the hematopoietic system into the bone marrow, peripheral blood and other tissues, all of which are caused by a group of alterations, especially genetic, which result in the affectation or loss of the mechanisms that regulate these processes.[6]

Leukemias are classified as lymphoid or myeloid according to their morphology and acute or chronic according to their clinical behavior. Acute lymphoblastic leukemia (ALL) is more frequent in children, representing 80 % of all leukemias, with a survival rate of over 90 % in some subtypes.[7] The highest incidence of the disease is found between two and five years of age; its origin is considered multifactorial and among the factors for its development are genetic and environmental. The most frequent clinical manifestations are asthenia, anemia, fever, bleeding, infections, bone and/or joint pain, hepatosplenomegaly and lymphadenopathy, among others.

Due to the increased survival rate that has been achieved with the new therapeutic protocols for this disease, it is possible that many pediatric cancer survivors reach adulthood with a history of oncologic treatment during childhood, particularly for ALL, which requires greater attention at acrtual times, as long-term therapeutic toxicity in this clinical entity, whether from radiotherapy or chemotherapy, can cause involvement in different organs and systems, which is often not identified by physicians not directly involved in the care of these diseases and in fact, have become their attending physicians, both in community and hospital care.[5]

With the aim of updating knowledge on late complications that may occur in adulthood among individuals who suffered ALL during pediatric age, a documentary review was performed in which relevant studies were located and selected in the electronic databases Medline, Virtual Health Library, SciELO, Research Gate, Google Scholar and in digital books. The search terms used were: precursor cell lymphoblastic leukemia-lymphoblastic lymphoma, lymphoblastic leukemia. We found 117 papers published in the last 5 years on related topics. Of these, 26 were chosen and made up the sample, by addressing the topic long-term complications of ALL treatment.

DEVELOPMENT

Leukemia is a clonal, uncontrolled, malignant proliferation of hematopoiesis precursor cells with varying degrees of differentiation, which accumulate in the bone marrow with suppression of normal hematopoiesis, invade the peripheral blood and other organs and tissues.

ALL is a clonal proliferation that develops from one or more hematopoietic cells of lymphoid lineage with blockage at a more or less early stage of differentiation, dependent on the occurrence of different oncogenic events. Several genetic factors have been proposed to explain its occurrence, including trisomy 21, constitutional abnormality of the p53 tumor suppressor gene (Li-Fraumeni syndrome) or neurofibromatosis type 1, among others.[8]

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Among the environmental risk factors, its frequency is known in survivors of the atomic explosion in Japan in 1945, with a peak incidence eight years after the explosion and its relatively high incidence in children treated for a first cancer with radiotherapy, however, there is so far no argument to associate exposure to magnetic fields with an increased risk of the disease.

Current treatment protocols include the use of chemotherapy, radiotherapy, bone marrow transplantation, supportive care and adequate hygienic, sanitary and isolation conditions to avoid complications.

Chemotherapy constantly involves the intensive use of multiple drugs during the three phases of treatment (induction, consolidation and maintenance). The purpose of chemotherapy is to destroy the malignant cells and stop their multiplication, achieving total resolution and clinically evident disease-free survival.[9]

With improved biological characterization of the different types of leukemia, optimization of diagnostic techniques, adjustments in classification systems, application of risk-adapted treatments, increased surveillance, early detection of side effects and new supportive treatments to reduce toxic deaths, the prognosis of children with cancer has improved from less than 10 % in the early 1960s to 80 % in the late 1990s, with a current cure rate of more than 75 % in ALL patients.[10,11,12]

These survival rates make it necessary to address new clinical and psychological problems in the follow-up of these patients. Polychemotherapy and radiotherapy can cause organic sequelae related to growth and development, thyroid, sexual and reproductive function, bone affectation, intellectual capacity, cardiopulmonary and gonadal function, in addition to the appearance of secondary neoplasms attributable to them and other affectations in different apparatus and systems.[13]

Neurotoxicity

Radiation and chemotherapy treatment of ALL in pediatric ages causes alterations at the level of the central nervous system that are directly related to the structural damage, intensity and duration of treatment. Most studies,[14,15,16] have reported abnormalities in the white matter of these patients, although there is also evidence of alterations in the gray matter. Irradiation of nervous tissue induces, together with vascular changes and elimination of periventricular progenitor cells, early apoptosis of oligodendrocytes and damage to myelination.

It has also been reported that chemotherapy alters folate metabolic pathways, resulting in subclinical demyelination, is related to excitatory amino acid production, and causes changes in dopamine and serotonin synthesis. Patients with ALL who have received chemotherapy have decreased bilateral connectivity between the parietal and temporal lobes, as well as between the left parietal lobe and the right hippocampus.

These neurological alterations are responsible for the cognitive deficits observed in these patients, which persist for many years, even after treatment has been completed. Studies that have analyzed cognitive deficits in children with ALL show that they present a heterogeneous pattern of cognitive impairment, but the most common deficits are slowing of processing speed, worsening of verbal skills, deficits in working memory and sustained attention, as well as alterations in executive functioning, in particular, cognitive flexibility, verbal fluency and inhibition capacity, and even slight decreases in IQ. The most important variables seem to be

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age at disease diagnosis, sex, having received cranial radiation, as well as the time and intensity of treatments.

Late radiotherapeutic neurotoxicity can show variable clinical behavior ranging from asymptomatic to focal neurological symptoms such as seizures and cranial nerve palsies. Findings on MRI studies show that necrosis is the anatomopathologic process involved. Other late effects that may occur are:

- Vascular malformations: cerebral cavernous alterations are the most frequent, with an incidence of 57 % in survivors of childhood leukemia treated with cranial radiotherapy. They may be asymptomatic or manifest with seizures or hemorrhage. Surgical treatment should be reserved for those patients presenting with refractory seizures, recurrent hemorrhage or progressive neurological deterioration.
- Calcifications: Mineralizing microangiopathy occurs as a result of radiation-induced damage to small and medium vessels, with hyalinization, fibrinoid necrosis, endothelial proliferation and calcium deposition. Computed axial tomography is the best imaging test for its diagnosis, showing calcium deposition located mainly in the basal ganglia and subcortical white matter.
- Secondary neoplasms: showing a variable cumulative incidence ranging from 4-15 % depending on the follow-up period.
- Cerebral atrophy.
- Hormonal disorders due to alteration of the hypothalamic-pituitary axis.
- Methotrexate neurotoxicity: Methotrexate is an essential component of ALL chemotherapy that inhibits cell replication by blocking the enzyme dihydrofolate reductase, thus preventing the conversion of folic acid to tetrahydrofolic acid. It can be administered both intravenously and intrathecally to treat the disease and prevent recurrence in the central nervous system. The exact pathophysiological mechanisms of neurotoxicity induced by this drug are unclear.

Risk factors for the development of its toxicity include high doses of chemotherapy, intrathecal administration, associated irradiation and young age. Its most relevant clinical manifestations include cognitive disorders (more related to intravenous administration). In the image obtained by nuclear magnetic resonance a pattern corresponding to a diffuse and progressive periventricular leukoencephalopathy can be observed.[17,18] On the other hand, executive functions can also be damaged, which are the processes of association of ideas and those that allow the resolution of complex behaviors, which when affected limit initiative, motivation, the formulation of goals, action plans and the self-control of behavior, all of them related to frontal lesions.[19]

In patients treated with ALL, the incidence of a second malignant neoplasm is 62,3/100 000 cases annually and among them, those of the central nervous system constitute a small group, however, they are the secondary malignant tumors that occur most frequently in survivors of lymphoblastic leukemia during childhood, and are mostly associated with cranial radiotherapy.[20] Glioma is the most common tumor, followed by ependymoma, lymphoma and meningioma. It has been suggested that loss of immune surveillance and genetic components are the main etiological factors for its occurrence, with seizures, headache and sensory disturbances being the most characteristic manifestations.

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Cardiotoxicity

The effects of chemotherapy generally occur acutely during treatment; however, anthracycline-dependent cardiotoxicity has been described up to 20 years after the use of anthracyclines.[21] This recently defined clinical entity, if it produces signs of heart failure, is a marker of poor prognosis in cancer survivors who have received treatment with these drugs. In the coming years, the population of cancer survivors will grow, so the risk of cardiac death and sudden death will increase by 5,9 and 3,9 times respectively with respect to the population that did not receive cancer therapy.[22] It has been reported that 15 to 25 years after cancer diagnosis, surviving children had 8,2 times the frequency of cardiac death, 15 times the frequency of developing heart failure and 10 times the frequency of ischemic coronary disease.[23]

Anthracyclines are among the most frequently used antineoplastic drugs, and their use has allowed an increasing number of patients with childhood acute leukemia to achieve complete remission and greater long-term event-free survival. However, their use can lead to complications that affect quality of life or put it at risk, cardiotoxicity being one of the most serious. There are three clinical forms of cardiotoxicity caused by anthracyclines: acute or subacute, chronic and late.

The acute or subacute form is rare and appears during the course of treatment or in the hours and days following, is generally transient and is characterized by electrocardiographic alterations with nonspecific changes in the ST segment, lengthening of the QT interval, tachycardia and extrasystoles; it may also manifest as pericarditis or myocarditis.

Chronic cardiotoxicity manifests after the first year of treatment and is characterized by structural alterations in myocytes and/or myocardial fibrosis. In the case of late cardiotoxicity, as already mentioned, it can even appear up to 20 years after treatment, presenting with arrhythmias and ventricular dysfunction leading to heart failure.

Between 3 and 25 % of patients treated with anthracyclines develop chronic and late cardiotoxicity and it is reported that the chronic form is the most frequent and corresponds to signs of cardiomyopathy.[22] Restrictive cardiomyopathy is that which appears in pediatric patients many years after the end of treatment. The risk of heart failure is therefore a threat that accompanies the child throughout life after successful antineoplastic treatment.

The pathogenic mechanism of anthracycline cardiotoxicity is complex and not fully understood. Sarcoplasmic and mitochondrial reticulum injury; modification of myofibril structures and function. The pathogenic mechanism of anthracycline cardiotoxicity is complex and not fully understood. Sarcoplasmic and mitochondrial reticulum injury has been described; modification of myofibril structures and function; modification of coupling, excitation and contraction, as well as altered calcium influx, apoptosis and loss of cardiac muscle regeneration. These phenomena are triggered by the production of reactive oxygen species in addition to the degradation of myofilaments, with a decrease in myocyte sarcomeric proteins.

These events result in dysfunction and hypertrophy of surviving myocytes, with limited cardiac muscle regeneration capacity and a reduction in the number of myocytes with increased fibrosis, leading to a process of ventricular remodeling. The administration of anthracyclines generates a dose-dependent lesion on the myocyte accompanied by early diastolic and late systolic dysfunction. The consequences of cardiotoxicity may be expressed clinically or subclinically.[24]

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Approximately 65 % of childhood cancer survivors treated with anthracyclines have subclinical myocardial dysfunction, with cardiovascu¬lar disease being the main cause of morbidity and mortality due to cardiotoxicity, after cancer recurrence and secondary neoplasms, and its intensity is classified based on the deterioration of left ventricular ejection fraction:

Grade I: reduction in ejection fraction of 10 % to 20 % from baseline.
Grade II: reduction greater than 20 % or decrease below normal (p < 55 %).
Grade III: appearance of symptoms of congestive heart failure.

Although it is not sensitive for early detection of subclinical cardiac involvement and is influenced by changes in preload and afterload leading to transient changes in it, left ventricular ejection fraction is the parameter usually used for decision making. Determination of the degree and rate of deformation has emerged as promising techniques and could play an important role in the early detection of ventricular dysfunction. At baseline, global longitudinal strain improves the risk stratification of ventricular dysfunction due to cardiotoxicity with respect to ejection fraction. The combined determination of the degree of global longitudinal strain and troponin I improves the negative predictive value for the development of clinically evident ventricular dysfunction.[23]

Toxic effects can also be expressed as the appearance of acute coronary syndrome, hypertension, thromboembolic events, pericardiopathies, valvulopathies, arrhythmias and alterations of the QT interval.

Radiotherapy can also produce cardiotoxic side effects, such as myocardial fibrosis, cardiomyopathy, early coronary disease, as well as valvular and electrophysiological dysfunction. This type of toxicity depends on acute damage and inflammation, leading to long-term myocardial fibrosis. The risk of these adverse effects increases two to six times in patients receiving high-dose thoracic irradiation. Radiation cardiotoxicity is dose-dependent and is related to the area of the heart exposed, the radiological technique used and the age of the patient, with greater incidence in younger individuals. Patients receiving more than 1 500 to 3 500 cGy show an increased risk of heart disease; higher doses are associated with myocardial ischemia up to 12 years after treatment.[25]

Although a variety of complications related to both the disease itself and its treatment may be present in adults who have had ALL during childhood, the highest incidence falls on chronic neurologic and cardiovascular disturbances, mostly related to two aspects of the treatment protocol, chemotherapy and radiation therapy. Cancer survivors have a higher risk of developing a second malignancy compared to the general population.[26]

The frequency of these complications and the need for their identification and adequate treatment require a high index of suspicion and adequate scientific preparation of all medical professionals who care for the adult population to identify them through timely diagnostic workup in apparently healthy individuals who survived a malignant disease during childhood, particularly ALL, which is by far the most frequent neoplasm with the highest survival rate at this stage of life.

Conflict of Interest
The authors declare that there is no conflict of interest.

Authorship Contribution
LMC: Contributed Conceptualization and design of the work. Drafting of the manuscript. Performed bibliographic search. Revision and final drafting of the article.
AFP: Conceptualization and design of the work. Drafting and critical revision of the manuscript.
MCCD: Critical revision of the manuscript.

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