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ORIGINAL

Pediatric oncology: past, present, and future

La oncopediatría: pasado, presente y futuro

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ABSTRACT

The infantile cancer has a marked importance in the environment of the pediatrics; since it is the second cause of mortality in the childhood. The oncopediatría has gone perfecting the diagnosis and the treatment protocols, getting better indexes of survival. At the present time, the advances in the technical diagnose and therapies facilitate a significant increment of survivors among the sick cancer infantojuveniles. He was carried out the present bibliographical revision with the objective of characterizing the evolution of the Oncopediatria. For the achievement of this objective 15 bibliographies were consulted. The improvement of the survival of the patients is not due to the improvements diagnose, therapeutic and assistance, to a decrease of the incidence. The future of the oncopediatría is directed to less toxic, more effective and more selective treatments; and to be able to identify the patients for their genetic profile predicting if they will respond or not to certain drug or outline.

Keywords: Evolution; Oncopediatria; Treatments.

RESUMEN

El cáncer infantil tiene una marcada importancia en el ámbito de la pediatría; ya que es la segunda causa de mortalidad en la infancia. La oncopediatría ha ido perfeccionando el diagnóstico y los protocolos de tratamiento, consiguiendo mejores índices de supervivencia. En la actualidad, los avances en las técnicas diagnósticas y terapéuticas posibilitan un incremento significativo de supervivientes entre los enfermos infantojuveniles de cáncer. Se realizó la presente revisión bibliográfica con el objetivo de caracterizar la evolución de la Oncopediatría. Para el logro de este objetivo fueron consultadas 15 bibliografías. La mejoría de la supervivencia de los pacientes se debe a las mejoras diagnósticas, terapéuticas y asistenciales, no a una disminución de la incidencia. El futuro de la oncopediatría está dirigido a tratamientos menos tóxicos, más eficaces y más selectivos; y poder identificar a los pacientes por su perfil genético prediciendo si responderán o no a determinada droga o esquema.

Palabras clave: Evolución; Oncopediatría; Tratamientos.

INTRODUCTION

Cancer accounts for more than 12 % of all causes of death worldwide. As life expectancy on the planet improves, the incidence of cancer increases due to multiple factors, such as increased exposure of individuals to

cancer risk factors, declining mortality and birth rates, with prolonged life expectancy and an aging population leading to increased incidence of chronic degenerative diseases, especially cardiovascular disease and cancer.[1]

The insidious rise in the incidence of cancer over the last century is why it is often regarded as a relatively new disease, a result of our modern industrial world. But this is far from the truth: scientists have found evidence of cancer dating back more than a million years.

The first case of cancer was recorded in ancient Egypt. It was found in the Edwin Smith Papyrus, which dates back to about 1600 BC. As for treatment, records speak of a kind of match to burn or cauterize unidentified tumors. It was Hippocrates (460-360 B.C.), the father of medicine, who first gave these tumors a name (karkinos, Greek for "crab"). Hippocrates believed that an imbalance in the body's four main fluids or humors caused the disease. In the case of cancer, he attributed it to an excessive concentration of black bile in the flesh and recommended diet, rest, and exercise to compensate for this imbalance. If this did not work, he recommended purging and sometimes surgery. This theory prevailed in ancient Greece and Rome.[2]

Later, Galen of Pergamon (129-216 A.D.) devised a classification of tumors and used the word oncos (Greek for "mass" or "inflammation") to describe them, which is why we call the study and treatment of cancer "oncology".[2]

After the fall of the Roman Empire, with medieval medicine, local folklore, herbology, and religious dogmas predominating over surgery, this changed with the arrival of the Renaissance and the invention of Gutenberg's printing press in 1450.[2]

By the early 17th century, the "father of German surgery," Wilhelm Fabricius, had begun to publish detailed accounts of his methods, which included extensive operations on cancers. The 19th century was the golden age of surgery, when disinfection and sterilization became increasingly common. In 1846, William Morton successfully demonstrated the use of anesthesia for surgery. This allowed increasingly radical surgeries on cancers. At the same time, microscopic study of tumors aided the understanding of the origins of cancer.[2]

In November 1895, German physics professor Wilhelm Röntgen discovered X-rays, and by the turn of the century, X-rays were increasingly being used to treat cancer. Radiotherapy as a cancer treatment was born. Along with surgery and radiotherapy, the 20th century scored another point in the battle against cancer: anticancer drugs, or chemotherapy. The first of these was nitrogen mustard, a toxic gas used with devastating effects in the trenches during the First World War.[2]

Childhood cancer is of increasing importance in the field of pediatrics; among other reasons, because it is the second leading cause of mortality in childhood.[3,4]

Pediatric Oncology emerged as a specialty within Oncology, as a logical consequence of the differences between childhood neoplasms and adult cancers, in terms of etiology, histology, and evolution.[5]

Until a few years ago, childhood cancer was considered a rarity by general practitioners and even by many pediatricians, especially at the primary care level. At that time, the causes of infant mortality were quite different from those of today. Infectious diseases, severe gastroenteritis with dehydration, neonatal pathology, prematurity, congenital malformations, etc., were the leading causes of death in infancy.[3,4]

Currently, cancer is the second leading cause of death in children over one year of age, surpassed only by accidents. In the first year of life, it is the third leading cause of death, surpassed only by mortality due to congenital malformations. The annual incidence for all malignant tumors in children under 15 years of age is 12,45 per 100 000 children.

According to the World Health Organization (WHO), about 400 000 children and adolescents aged 0-19 years are diagnosed with cancer each year. The incidence of cancer in children and adolescents fluctuates each year between 1,5 % and 2 % of all cancer diagnoses worldwide, and the mortality rate is approximately 3,6-3,8 per 10 000 population. The most common types of cancer in this population group are leukemias, brain cancer, lymphomas, and solid tumors such as neuroblastoma and Wilms' tumors.[6,7]

The average annual incidence in Europe is 140 cases per million children, but the disease represents the leading cause of death in children in developed countries.[1]

The worldwide age-adjusted rate (to the WHO standard population) was 132 per 100 000 inhabitants; for Cuba, it was 129 per 100 000. According to this figure and in a descending list of countries according to their cancer mortality rates, Cuba ranks 103rd among the 193 countries in the world reported in the report, and is below the world average. The Cuban population ranks 15th in the Americas and sixth in the Caribbean, preceded by Bolivia, Grenada, Peru, Uruguay, Jamaica, Antigua and Barbuda, Argentina, Paraguay, Honduras, Canada, Chile, Barbados, the United States, and the Dominican Republic, in that order.[8]

Therefore, we can affirm that, in Cuba, thanks to the development achieved by public health, these diseases behave similarly to those in the developed world. Cancer is the leading cause of death by disease in people from 1 to 18 years of age, after accidents. About 300 new cases are diagnosed each year, with some annual variations. These are treated in one of the nine countries' centers for oncohematological care. Of these, the majority (70 %) are leukemias, followed by lymphomas, and in third place, tumors of the central nervous system.[3,4,6]

In 2018, cancer was the leading cause of death by disease in Cuban children and adolescents aged one to 18 years, with an increase in mortality from 17 deaths in 2017 to 24 in 2018.[7]

In Villa Clara province, according to the latest Health Statistical Yearbook, a mortality rate from malignant tumors was diagnosed at 218,2 for a total of 1 696 cancer patients, 81 of them in children under 18 years of age.[9]

In 2018, in the municipality of Camajuaní, 131 patients were diagnosed with cancer, for an incidence rate of 220,5; of them, no patients were pediatric age.[10]

The history of the fight against cancer is the history of using the latest medical advances of each era. We are now entering what could potentially be the most interesting stage of this long struggle.

At present, advances in diagnostic and therapeutic techniques make it possible to achieve a significant increase in the number of survivors among children and youth cancer patients, up to 80 % five years after diagnosis. In Cuba, survival statistics are similar, even though approximately 50 % of the patients arrive at the specialized oncopediatric services of the country in advanced stages of the disease, especially from the provinces that do not have reference centers.[7]

The diagnosis, treatment, quality of life, and recovery of children and adolescents with cancer have evolved throughout history due to the development of research groups and projects in various countries. These groups allow an understanding of the different cancers, their evolution, and the use of new treatment techniques, as well as financing the welfare of these children. Due to the importance of documenting the development and evolution of Oncopediatrics, it was decided to carry out the following bibliographic review, which aims to characterize the evolution of Oncopediatrics.

DEVELOPMENT

Generalities of Pediatric Oncology

Cancer in pediatric age is rare, its annual incidence is 12,45 x 100 000 children; according to data provided by the RNTI-SEOP, the most frequent childhood cancer is acute leukemia (30 %). Almost 80 % of leukemias are acute lymphoblastic leukemias (ALL), and about 18 % are acute myeloblastic leukemias (AML). They are followed in frequency by central nervous system tumors (21,7 %), which account for almost a quarter of all childhood tumors, and lymphomas (12,7 %), which, in children under 15 years of age, are mostly non-Hodgkin's (62 %), including Burkitt's lymphoma. Eighteen percent of childhood tumors are embryonal, such as neuroblastoma (9 %) and Wilms tumor (5 %). Retinoblastoma (3 %), liver tumors (1 %), and germ cell tumors belong to this group. Malignant bone tumors account for 6 % of childhood cancers, the two most frequent being osteosarcoma and Ewing's tumor.[3,11]

There are differences between childhood and adult neoplasms. The predominant histologic type in childhood is sarcomas, instead of carcinomas in adults. Childhood cancers generally have deep anatomical locations, do not affect the epithelia, do not cause superficial hemorrhages, and do not cause exfoliation of tumor cells. All this makes using early detection techniques practically impossible in adult cancers. Thus, in most cases, the diagnosis of childhood cancer is made accidentally and often in advanced stages of the disease. On the other hand, most childhood tumors are susceptible to chemotherapy, in contrast to adult cancers.[3]

All pediatric oncology centers use the three classic tools for cancer treatment: surgery, radiotherapy, and chemotherapy.[5]

The authors agree with the different bibliographies discussed and state that surgery is the fundamental weapon for the treatment of solid tumors, mainly CNS tumors, hepatoblastoma, and bone and/or soft tissue sarcomas. Furthermore, radiant therapy, whose application has been restricted as a therapeutic resource due to the unacceptable sequelae it causes in childhood, has its precise indication in CNS tumors, and is limited only to some varieties of Rhabdomyosarcomas (RMS), Nephroblastomas, and advanced stages of Hodgkin's Lymphoma. We also emphasize that polychemotherapy used as adjuvant or neoadjuvant is undoubtedly the fundamental weapon for treating pediatric neoplastic diseases. Used at the Maximum Tolerated Dose (MTD) in very aggressive protocols, it becomes in some schemes a life-threatening alternative due to the toxicity that its use implies.

The evolution of the different types of treatment over time reveals notable differences between the past and the present and, above all, allows us to foresee a future in which new diagnostic and therapeutic approaches can increase survival and offer curative treatments for those diseases that are not currently curable.[12]

Beginnings of Pediatric Oncology

Due to the small number of patients, the need to organize cooperative groups that would allow prospective studies to be carried out to determine the efficacy of the various treatments became apparent. The birth of National and International Pediatric Oncology or Oncohematology Working Groups made it possible to create specific institutions to collect data and organize studies to increase knowledge about the various diseases.[12]

This motivated the need to group together as many patients as possible with a given neoplastic pathology

to investigate their characteristics and to be able to conclude with statistical significance. Thus, the National Wilms Tumor Study Group (NWTSG) was created in 1969 with the participation of more than 50 institutions in the United States and Canada that formed a multidisciplinary group of oncologists, surgeons, radiotherapists, pathologists, and statisticians that designed prospective, randomized, and controlled protocols. Over three decades, over 3000 children diagnosed with Wilms' Tumor were enrolled in 5 successive studies. The NWTSG succeeded in simplifying, economizing, and narrowing the treatment of Wilms' Tumor.[5]

Two years later, in 1971, the European group of the International Society of Pediatric Oncology (SIOP) created a similar chapter for treating nephroblastoma using different strategies depending on the characteristics of the study population, but achieving identical results. In line with this trend, similar groups were organized for the study and treatment of other solid tumors such as those of the Central Nervous System (CNS), Rhabdomyosarcoma, Ewing Sarcoma, Hepatoblastoma, Neuroblastoma, Hodgkin's Lymphoma, etc., publishing their results and suggesting the optimal treatment for each of these neoplasms.[5]

Coordinated national and international groups capable of designing studies, formulating hypotheses, and creating treatment protocols have emerged over the years. Thanks to the ongoing collaboration of pediatric oncologists, definitive conclusions have been reached on various aspects of childhood cancer. It is the systematic use of treatment protocols that has most improved cancer cure rates in children, with 70 % of children diagnosed surviving. The protocols to be used are multicenter, based on other previous protocols of proven usefulness, and their toxicity and the benefits obtained must be evaluated.[3]

The diagnostic tools used were mainly derived from conventional radiology. Cytological and histological studies, the basis of the diagnosis, made it possible to determine the morphological structure of the diseased tissue and, subsequently, its functional characteristics through the most suitable staining techniques.[12]

Molecular biology, with all its avalanche of knowledge, has allowed us to understand many enigmas concerning tumorogenesis. It is not in vain that the last Nobel Prizes in medicine, physiology, physics, and chemistry awarded by the Swedish Academy have been for work related to the problem of cancer.[5]

In the 1950s, Watson and Crick's description of the double helix structure of DNA and the possibility of denaturing it, i.e. separating the two strands by heat or by modifying their pH and being able to make a mirror complementary strand with synthetic oligonucleotides, gave a glimpse of the enormous possibilities that hybridization offers, thus giving birth to the era of recombinant DNA or genetic engineering.[5]

In addition, a better understanding of the intricate mechanism of the cell cycle has made it possible to identify proteins that intervene antagonistically, those that favor mitosis (oncogenes) and those that interrupt the process (tumor suppressor genes), which has made it possible to define cancer as a genetic disease caused by stimulation of oncogenes, inhibition of tumor suppressor genes or failure of the genes responsible for DNA repair.[5]

When the proteins involved in programmed cell death (apoptosis) were discovered, the tricks and stratagems used by neoplastic cells to evade it became apparent. Indeed, when the death messengers reach the membrane receptors of normal and neoplastic cells, the latter refuse to die, evading the message in their intention to eternalize themselves. A better knowledge of the enemy's characteristics is a fundamental requirement to defeat it in battle. We now know that the neoplastic cell accumulates mutations in its genome, activates oncogenes, inactivates suppressor genes, modifies the cell cycle, alters its phenotype, grows and proliferates without control, inhibits the mechanisms of apoptosis, and eludes the immune system. Based on all this knowledge, new strategies could be developed to defeat cancer: using monoclonal antibodies as selective therapy to block tyrosine kinase receptors has been very effective in certain types of leukemias and sarcomas of the gastrointestinal tract. - Knowledge of the factors that influence tumor angiogenesis, the mechanism by which the neoplastic cell can grow and metastasize, has made it possible not only to develop antiangiogenic drugs, but also to identify a new target: the vascular endothelium of the vessels from the healthy tissues that supply the tumor. This has given rise to a new treatment modality, the so-called metronomic therapy, consisting of prolonged, uninterrupted, low-dose administration of different chemotherapy agents.[5]

At the beginning, when surgery was the only therapeutic procedure available, survival at two years ranged from 0 to 20 % with high perioperative mortality.[2] Before the application of radiotherapy and chemotherapy, surgery was the only possible treatment for solid tumors; however, only a small percentage of patients with localized tumors were cured.9 Radiotherapy began to be used systematically in pediatric pathology in the 1950s, and the first positive results were seen in Hodgkin's Disease and Wilms' Tumor.[3]

Chemotherapy initially began to be used in relapses as a last resort. It was first used in monotherapy and then as polychemotherapy. Once its usefulness was proven, it was added as a third therapeutic weapon to be administered after surgery and/or radiotherapy.[3]

Systemic polychemotherapy began in the 1970s, and since then, the efficacy of the combination of vincristine, ifosfamide, actinomycin D, and etoposide has been demonstrated.[3]

The advent of chemotherapy in the middle of the last century ushered in an era of improved prognosis for childhood malignancies. Most cancers are sensitive to chemotherapy. The treatment with chemotherapy obeys

precise protocols for its execution, which requires a health team specialized in this type of treatment. The diagnosis should be definitively confirmed before treatment is started.[1,12]

In the past, surgery and radiotherapy were widely used in the treatment of non-Hodgkin lymphomas; today, chemotherapy is used almost exclusively in most protocols. Until the mid-1970s, the long-term survival of these patients was poor, not exceeding 20 %. The introduction of a combination of polychemotherapy changed the results obtained, mainly thanks to the initial work of Wollner.[3]

Different drugs were used with varying success in various types of cancer, generally in empirical combinations, achieving partial or total remissions and increases in survival in certain tumors.[12]

Until thirty years ago, acute leukemia was considered an inevitably fatal disease. Temporary remissions could be achieved, but could not be sustained. However, new treatment strategies have been developed to increase the survival rate.[3]

In the 1960s, and largely thanks to the experience accumulated in the treatment of leukemias, systematic treatment with chemotherapy associated with surgery and radiotherapy began to be introduced in the treatment of solid tumors.[3]

From the early 1970s, adjuvant chemotherapy began to be used in an attempt to control subclinical metastatic disease. The results of these studies also led to the administration of neoadjuvant chemotherapy. Rosen's studies using high-dose methotrexate demonstrated that a shrinkage of the primary tumor was possible prior to surgery, making more conservative surgery possible, resulting in increased survival. Furthermore, neoadjuvant chemotherapy facilitates evaluating the histological response to chemotherapy in the surgical specimen, which has been consolidated as a decisive prognostic factor. Patients with more than 90 % tumor necrosis have an excellent prognosis with survival rates of around 90 %.[3]

We have seen how different techniques (surgery, chemotherapy, radiotherapy, etc.) have been used for years to treat pediatric patients. These techniques are not a thing of the past; they are still being used and perfected today. Below, we will provide more information on this subject.

Oncopediatrics today

The probability of surviving a cancer diagnosed at pediatric age depends on the country of residence: in high-income countries, more than 80 % of children with cancer are cured, but in many middle- and low-income countries, the cure rate is only 15 % to 45 %.[6]

These lower cure rates may be due to delayed diagnosis or detection of the disease when it is already at an advanced stage, lack of accurate diagnosis, lack of available treatments, abandonment of therapeutic guidelines, death due to toxicity (side effects) caused by drugs, and preventable recurrences.[6]

In 2018, WHO launched, together with partners, the Global Initiative on Childhood Cancer, which provides governments with technical and leadership assistance to establish and sustain quality programs for children with cancer. This initiative aims to achieve a survival rate of at least 60 % worldwide by 2030, nearly doubling the current rate and thus saving an additional one million children's lives over the next ten years.[6]

Carcinogenesis is a multistage process with four defined events: initiation, promotion, conversion, and progression. With biomarkers, molecular epidemiology can monitor gene events from exposure to disease onset and assess the interaction between a biological system and a chemical, physical, or biological environmental agent. The causes of childhood cancer are unknown, and the prevention of childhood cancer is not possible. Early detection programs for Neuroblastoma have not shown an impact on the survival of affected children. There are childhood cancers that are associated with genetic transmission related to specific chromosomal alterations, such as retinoblastoma, Neuroblastoma, and Wilms' Tumor.[2]

There is no doubt about the development currently achieved in the diagnosis and treatment of oncopediatric diseases, which has led to an increase in survival in the last 20 years, with 80 % of these children reaching adulthood. In Cuba, statistics on this subject are similar to those reported in the world in general.[13]

These advances are accompanied by an extraordinary improvement in diagnostic possibilities, from imaging techniques to those of cellular recognition, many of them within the reach of most centers, although in all cooperative studies, a centralized review is necessary. Magnetic resonance has been refining the normal and pathological images of the organism. It is currently accompanied by isotopic methods with radioactive glucose that make it possible to determine the metabolic activity of the tissues, differentiating between normal and pathological, and representing a tool of great value in extension studies. This technique (positron emission tomography [PET]) has already proved valuable in some pediatric tumors, and its definitive application in other diseases is under study. On the other hand, the study of "minimal disseminated disease" in bone marrow or peripheral blood using molecular biology techniques makes it possible to know more accurately the extent of the disease and to assume, as generalized, an alteration that, with conventional methods, could be defined as localized and therefore treated suboptimally. This technique is directly related to what is called "liquid biopsy", which consists of the search for circulating DNA from tumor cells using PCR techniques, clearly improving diagnostic precision.[12]

All this has changed the perception of the pediatrician who is not dedicated to the care of children with cancer. A pediatric oncology patient is not a condemned patient. Still, the repository of a life to fight for, and the intercurrences that occur during the disease and its treatment, are now a therapeutic objective. In contrast, until a few years ago, they were considered a pitiable complication.[12]

Therapeutic advances in childhood cancer have been enormous in recent decades. These advances have led to a decrease in mortality, almost 60 % from the 1960s to the end of the last century. In recent years, this downward trend has continued. Despite this, cancer remains the leading cause of death from disease from the first year of life through adolescence.[11]

In recent years, we have witnessed a spectacular advance in the results obtained in childhood cancer treatment. In fact, in a few pediatric specialties, there has been an improvement in therapeutic results during the last two decades that is comparable to that obtained in pediatric oncology. Until thirty years ago, acute leukemia was considered an inevitably fatal disease. Temporary remissions could be achieved, but could not be sustained. Today, acute lymphoblastic leukemia, which is the most frequent variety of leukemia in childhood, has a long-term survival of more than 70 %, which means that most patients can be cured definitively.[3]

Similar progress has been made in the treatment of solid tumors. In the beginning, when surgery was the only therapeutic procedure available, two-year survival ranged from 0 to 20 % with high perioperative mortality. Radiotherapy began to be used systematically in pediatric pathology in the 1950s, and the first positive results were seen in Hodgkin's disease and Wilms' tumor.[3]

With modern chemotherapies, long-term survival in non-Hodgkin lymphoma is around 70 %, a notable advance compared to the results of previous decades. In patients who are refractory to treatment or who suffer relapses, the technique of bone marrow transplantation has become very widespread, since chemotherapy offers very few possibilities in these patients.[3]

Over the last 20 years, the survival of children with rhabdomyosarcoma has progressively improved, with survival rates of 70 % in the Intergroup Rhabdomyosarcoma Study III (IRS III).[3]

Over the last 20 years, the combined use of chemotherapy, radiotherapy, and surgery in coordinated and generally multicenter studies has significantly increased the long-term survival of childhood tumors. Analysis of this progress leads to interesting conclusions. These are due not only to therapeutic and diagnostic discoveries and innovations, but above all to the progressive design of new controlled clinical protocols that have made it possible to resolve dilemmas and select the most appropriate guidelines for each neoplasm and, within each of them, for the specific situation of each patient.[3]

The authors can affirm that the improvement in survival has not been due to a decrease in incidence but to diagnostic, therapeutic, and care improvements in general—that is, to the increase in the effectiveness of care.

Recently, hyperfractionated radiotherapy has begun to be used, which reduces the sequelae produced by irradiation. Still, it has not yet been shown to improve disease control and survival results.[3]

Neuroblastoma is unfortunately the exception in the advances achieved in the treatment of childhood neoplasms in recent decades. Only complete surgical excision guarantees definitive control of the disease, and this can only be achieved in localized forms without regional extension, which includes a minimal number of patients. In tumors with large locoregional extension and in the metastatic forms that constitute the majority of cases, radical surgery is usually not possible or is useless in the presence of bone metastases. In these cases, surgery should be limited to the performance of a biopsy, which is essential for histological diagnosis and biological and molecular study. Chemotherapy has a vital role in the treatment of disseminated neuroblastoma.[3]

Immunotherapy has not been left behind. From the non-specific stimulation of the immune system, used more than 40 years ago, through the continuous administration of BCRs, to the current approaches of CAR-T technology, a path of effective treatments has been followed, among which monoclonal antibodies directed against antigens expressed by tumor cells stand out. Experiments with anti-CD20, anti-CD33, and others have shown their efficacy in treating lymphoid or myeloid proliferations. More recently, the possibility of inducing in T lymphocytes an achimeric antigen receptor (CAR) for an antigen expressed by tumor cells, thus provoking a cellular immune response that induces tumor death, has inaugurated a new therapeutic strategy for diseases considered refractory to conventional treatments.[12]

The group of authors wishes to emphasize the current situation, where new antineoplastic agents have been incorporated with the possibility of administering megatherapy thanks to the resource of stem cell transplantation (autotransplantation of bone marrow).

We would also like to emphasize that current techniques have allowed progress in the treatment of pediatric oncology patients. For the future, we plan to continue researching and creating new programs and alternatives to cure the disease in children who suffer from it.

Future of Oncopediatrics

The possibility of detecting genetic and molecular alterations in tumor cells may make it possible to individualize the risk of patients and, consequently, to use treatments that are just as effective, but less toxic.[3]

Since the end of the last century, it has been known that the cells of probably all malignant diseases present specific molecular alterations that can be therapeutic targets for drugs that would act preferentially on the tumor and not on normal tissues, decreasing toxicity. Examples of this type of drug are imatinib, used for years in chronic myeloid leukemia, but dasatinib, ibrutinib, crizotinib, and others, some still in the experimental phase.[12]

This therapeutic strategy promises to occupy an essential place in future childhood cancer treatment. In addition to these generic principles, the future of treatment depends on the exact knowledge of the specific molecular alterations of each tumor individually, and the evolution of these alterations during treatment.[12]

This type of therapeutic approach is known as "precision medicine".[10] The concept of precision medicine refers to obtaining information from a person's genes, proteins, and characteristics to determine the diagnosis or treatment of the disease.[14]

In oncology, applied precision medicine allows for individualized genomic analyses that can be key to diagnosis and treatment. However, pediatric oncology has not yet fully benefited from precision medicine. One reason is that, at diagnosis, pediatric cancer patients tend to have a lower frequency of genomic mutations compared to adults with cancer. In addition, there are a limited number of assays and very few test candidates.[14]

Progress in genetic and molecular research will determine the possibility of establishing prognostic factors based on these findings, as is already the case in neuroblastoma and rhabdomyosarcoma. Identifying oncogenes or tumor suppressor genes, as occurs in retinoblastoma, may open the way to molecular diagnosis and even offer the possibility of genetic counseling.[3]

In recent decades, progenitors obtained from umbilical cord blood for transplantation from unrelated donors have been consolidated, especially in pediatric units, and umbilical cord banks have been established worldwide. Precursor cells in cord blood have a different composition and functionality than those in bone marrow and peripheral blood, which results in less graft-versus-host disease, even when HLA disparity exists. Disadvantages include, on the one hand, the availability of a single unit in each procedure (single use), the possibility of transmitting congenital diseases not detected by family history or laboratory tests, or the disparity in size with the recipient.[15]

The authors would like to point out that the future of the battle against cancer will be fought by identifying risk factors, performing early detection tests, changing lifestyles, administering drugs that prevent disease progression, and genetic profiling.

It should be noted that treatments will be less toxic, more effective, and selective, and we will be able to identify patients by their genetic profile, predicting whether or not they will respond to a particular drug or scheme using a new discipline: Oncopharmacogenetics.[15]

CONCLUSIONS

Childhood neoplasms were rare in the last century. Due to the few existing patients, a consensus was reached to carry out research projects in collaboration with several countries worldwide. The diagnostic means have been improved, as well as the treatments and treatment protocols, and have managed to improve the patients' quality of life. The improvement in patient survival is due to diagnostic, therapeutic, and care improvements, not to a decrease in incidence. The future of oncopediatrics is directed towards less toxic, more effective, and selective treatments, and being able to identify patients by their genetic profile, predicting whether or not they will respond to a particular drug or regimen.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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