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REVIEW

Oncopediatría de precisión: logros, perspectivas y desafíos actuales

Precision pediatric oncology: achievements, prospects, and current challenges

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ABSTRACT

Precision oncology is based in that the final cause in the genesis of the cancer is in genetic mutations, its knowledge allows to establish identification strategies and application of the preventive boarding, diagnosis and therapeutic more effective. In their bigger one he/she leaves it has not applied in the attention of the pediatric cancer. Inside their purposes in this field meet the integration of the genetic-molecular information with the available information in other databases to identify susceptible reveilles of personalized treatments. He/she was carried out a bibliographical revision with the objective of characterizing the medicine of precision like novel and promising applicable science to the diagnosis and treatment of the cancer in pediatric ages. For the achievement of the objective 22 bibliographies were consulted. You concluded that, through the use of tools genómicas of new generation, the oncología of precision has arrived to the pediatric practice at the moment outlining new opportunities and challenges.

Keywords: Precision Medicine; Precision Pediatric Oncology; Genes; Therapy.

RESUMEN

La oncología de precisión se basa en que la causa final en la génesis del cáncer se encuentra en mutaciones genéticas, su conocimiento permite establecer estrategias de identificación y aplicación del abordaje preventivo, diagnóstico y terapéutico más efectivos. En su mayor parte no se ha aplicado en la atención del cáncer pediátrico. Dentro de sus propósitos en este campo se encuentran la integración de la información genético-molecular con la información disponible en otras bases de datos para identificar dianas susceptibles de tratamientos personalizados. Se realizó una revisión bibliográfica con el objetivo de caracterizar la medicina de precisión como novedosa y prometedora ciencia aplicable al diagnóstico y tratamiento del cáncer en edades pediátricas. Para el logro del objetivo fueron consultadas 22 bibliografías. Se concluyó que, a través del uso de herramientas genómicas de nueva generación, la oncología de precisión ha llegado actualmente a la práctica pediátrica planteando nuevas oportunidades y desafíos.

Palabras clave: Medicina de Precisión; Oncopediatría de Precisión; Genes; Terapéutica.

INTRODUCTION

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.[1]

Later, Galen of Pergamon (129-216 AD) 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".[1]

After the fall of the Roman Empire, medieval medicine, local folklore, herbology, and religious dogmas predominated over surgery; this changed with the advent of the Renaissance and the invention of the Gutenberg printing press in 14501.

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, the microscopic study of tumors aided the understanding of the origins of cancer.[1]

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 World War.[1]

Cancer is a disease caused by cells that lose their standard control mechanisms and show disordered growth. These can develop from any tissue, and as they multiply, they form a mass that can invade adjacent organs and spread throughout the body.[2]

Cancer is the second leading cause of death in the world today, a disease that affects more than 32 million people globally and is expected to increase by up to 70 % in the next 20 years.[2]

In 2019, a total of 25,035 new cases of malignant tumors were diagnosed in Cuba, with a death rate of 223 per 100 000 inhabitants, of which 89 were in children under 14 years of age.[2]

In the province of Villa Clara, according to the latest Health Statistical Yearbook, the mortality rate for malignant tumors was 218,2 per 100 000 inhabitants, for a total of 1 696 patients with cancer, of which 81 were in children under 18 years of age.[3]

In 2018, in the municipality of Camajuaní, 131 patients were diagnosed with cancer, for an incidence rate of 220,5; of them, of them no pediatric patients.[4]

The history of the fight against cancer has been one of using the latest medical advances of each era. Now, we are entering what could potentially be the most interesting stage of this long struggle.

The sequencing of the human genome in 2000 revolutionized medicine and produced a new understanding of an individual's genetic structure. This made it possible to determine the molecular basis of many diseases and, on that basis, to make a more accurate diagnosis.[5]

Its impact on the treatment of cancer patients has made it possible to make therapeutic decisions in a personalized manner, based on the genomic and molecular characteristics of each patient's tumor. This is what is known as precision medicine or personalized medicine.[6]

Precision oncology is based on the concept that the final cause in the genesis of cancer is genetic mutations. These mutations cause both activation of oncogenes, which escape normal control mechanisms, and inactivation of tumor suppressor genes, which are involved in controlling cancer development. Changes or mutations in these genes alter the mechanisms of DNA transcription and translation. Eventually, this leads to the failure of certain proteins to perform their function properly, leading to the development of a tumor.[7]

This has its antecedent in the so-called evidence-based medicine that uses information from genes, proteins and the environment of an individual to prevent, diagnose and treat a disease, is a new concept that refers to the adaptation of medical treatment to the individual characteristics of each patient and makes it possible to establish strategies for identifying and applying the most effective preventive, diagnostic and therapeutic approach, is an approach to cancer treatment targeted to the genetic markers of their specific cancer, not limited by tumor type or location allowing a percentage of patients with different tumors to receive treatments targeted to molecular or genomic alterations that cause tumor development with greater specificity and therefore greater efficacy and lower toxicity compared to conventional therapies.[6,8,9]

Since its launch in 2016, the initiative has provided late-stage cancer patients with recommendations and access to targeted therapies that could prolong life.[9]

The sequencing of the first cancer genomes dates back to 2006. Since then, advances in molecular diagnostic techniques, based, among other things, on Next-Generation Sequencing, have led to shorter times and lower costs.[7]

Thanks to this and other significant advances in genomics, imaging scans, bioinformatics, and related disciplines, studies incorporating the essential principles of precision medicine have been designed. These include: Lung-MAP, ALCHEMIST, and NCI-MATCH. All three aptly illustrate how precision medicine influences how cancer research is conducted. Next-generation genomic sequencing and analysis are performed to determine whether a patient's tumor has a mutation or mutations that align with approved or investigational targeted therapies.[5]

Given the challenge imposed by Genomic Medicine and the initiative of some countries to implement precision or personalized medicine programs, within the framework of the Cuba Salud 2018 convention, the Cuban Society of Human Genetics, in conjunction with the National Center of Medical Genetics and the Directorate of Science and Technique of MINSAP organized the meeting Precision Medicine in Cuba: Challenges and Perspectives, which addresses the global panorama of precision medicine in the era of genomic medicine and the perspective of our country.[10]

Research such as the aforementioned has led to a better understanding of cancer genetics. However, the clinical application of this knowledge for childhood or pediatric cancer has been significantly delayed because studies have been conducted only in adults. In an article recently published in the journal Science, Jaclyn Biegel, MD, of Children's Hospital Los Angeles (CHLA), and Alejandro Sweet-Cordero, MD, of the University of California, San Francisco, surveyed the landscape of this young field of medicine, and present opportunities for the use of genomic information to move toward a new era of care for children with cancer.[11]

The annual incidence of pediatric cancer in developed countries is 140-160 new cases per million children aged 0-14 years. Despite having a higher cure rate than in adults, pediatric cancer is the leading cause of death from disease in children over one year of age.[12]

It is estimated that 20 % of pediatric cancers arise in children who have a genetic predisposition to malignancy. Therefore, clinical genetic assays developed to inform prognosis and treatment decisions for adult cancers have not been as applicable in pediatrics.[11]

But this story is changing; precision medicine is coming to pediatrics. In 2020, a German oncologist at the University of Heidelberg, Cornellis M. Van Tilburg, presented a study investigating this strategy in children with difficult-to-treat tumors, developing resistance to therapy, or high-risk tumors. The result showed that when it is possible to identify those "molecular targets" against which specific drugs are developed, survival without disease progression increases substantially.[13]

For the first time, children may benefit from a novel strategy that was only being studied and applied in adults. Thus, there is a tremendous opportunity to change outcomes in children with cancer by using this comprehensive approach, which includes genomic medicine as a central component in their care.[11,13]

Due to the encouraging results offered by this novel branch of medicine to pediatric oncology and its impact on the field of contemporary medicine, it was decided to conduct the present literature review to characterize precision medicine as a novel and promising science applicable to the diagnosis and treatment of cancer in pediatric age. The novelty of the subject and its scarce bibliographic treatment constitute the primary motivations. The lack of bibliographic documentation on the subject was the main problem faced.

Objective

To characterize precision medicine as a novel and promising science applicable to the diagnosis and treatment of pediatric cancer.

DEVELOPMENT

Genetics of cancer

Cancer arises from genetic changes, including DNA mutations, present at birth or acquired over time. Many adult cancers are initiated by mutations acquired through exposure to substances such as tobacco smoke and radiation, or simply by aging. Tumors can contain hundreds of sequence alterations, and identifying which changes drive tumor growth and the impact of their response to treatment can be difficult.[11]

Personalized cancer medicine involves selected treatments tailored to each patient's individual genetic characteristics and tumors' molecular characteristics.[14]

Given the genetic heterogeneity and complexity of many tumors, there is significant variability in response to treatment depending on the altered molecular pathway. For this reason, knowledge of the tumor's molecular profile is key to choosing the most appropriate therapy. In recent years, significant progress has been made in the molecular characterization of different types of cancer, which constitutes a very valuable tool to be applied in precision medicine.[12]

In addition to identifying the genetic alterations causing the tumor, it is essential to determine whether

these are somatic or germline. Although only 5-10 % of cancers are hereditary, several types of germline cancers are caused by known mutations. In these cases, the diagnosis and prognosis are different and require genetic counseling since, in addition to increasing the likelihood of carriers developing cancer, it can also affect other members of their family and be transmitted to their offspring.[12]

While current treatment of childhood cancers results in high overall cure rates, relapse of high-risk disease is associated with a poor prognosis.[15]

Precision oncology has not yet been applied in pediatric cancer care, unlike in adult cancer, where it has improved outcomes.[15]

In contrast to tumors in adult ages, pediatric malignancies usually develop from a minimal number of mutations, only some of which overlap with those seen in adult cancers.[11]

At the molecular level, pediatric cancers differ from adult cancers in the type and frequency of genetic alterations. Most pediatric tumors originate in developing tissues during early organ formation.[12]

Until very recently, it was technically impossible to know in detail the genetic identity of each tumor. However, today, we have massive sequencing to characterize the most relevant genetic alterations and integrate these into clinical trial databases that allow us to determine the clinical utility of these alterations.[16]

Impact of precision medicine

Through massive sequencing techniques, it is possible to evaluate the patient from multiple aspects. In only two decades, the study of DNA has gone from being able to be studied by targeted sequencing of one or a limited group of genes with laborious techniques and high use of human resources to the possibility of studying the entire genome at a cost and in a time that can currently be implemented in clinical practice.[17]

17 Massive sequencing makes it possible to detect point mutations, insertions, deletions, copy number variations, and translocations in addition to them. Also of notable importance in the cancer study is the use of NGS (Next Generation Sequencing) in detecting somatic variants in subpopulations of tumor cells, which are, therefore, present in a low proportion in the tumor sample. These subclonal mutations, undetectable by Sanger sequencing, are responsible in some cases for relapse or resistance to treatment in some tumors.[12]

In the following, we describe the main NGS sequencing strategies in cancer diagnosis, as well as their advantages and disadvantages:[12]

Gene panel sequencing: These contain primers or probes for a known group of genes and allow targeted sequencing for a given pathology. Although many commercial panels are available, they can also be designed "à la carte." They allow sequencing of known mutations (hot spots), complete genes, and detection of copy number variations and translocations.[12]

- Advantage: Their design is optimized, allowing the sequencing of genes of interest with high coverage and read depth. This makes detection of very low-frequency variants feasible, as well as rapid and reliable analysis.[12]
- Disadvantage: Currently, commercial oncology panels are oriented to adult cancer, not including relevant regions in childhood cancer. Moreover, as they are targeted to known regions, they do not allow the discovery of new genes potentially involved in cancer.[12]

The use of "panels" that allow the study of a limited number of genes for the study of known mutations is currently more cost-effective for clinical practice when the diseases under study involve a limited number of genes and mostly known mutations. This study usually requires germline DNA and is typically obtained from the blood of affected patients, with some diseases requiring the concomitant study of their progenitors.[17]

Whole exome sequencing (WES): the exome is the part of the genome corresponding to the coding regions (exons) capable of being expressed and giving rise to proteins. It corresponds to approximately 1,5 % of the genome and is the most important functional part of the genome.[12]

In other words, only the protein-coding sequences of the genome are studied in the study of the exome.[17]

At the technical level, there are different approaches to exome sequencing, such as prior amplification of exons by polymerase chain reaction or their capture using specific probes.[12]

- Advantage: the identification of genes and variants potentially involved in the disease that have not been previously described.
- Disadvantage: Due to the larger number of regions to be sequenced, more reads are required than sequencing a panel of genes, making it economically more feasible to use a shallower read depth. This results in the loss of the ability to detect subclonal mutations. In addition, its analysis and interpretation are more complex due to the large number of variants detected (approximately 40 000), so in cancer, it is advisable to determine which of these variants are somatic by paired sequencing in blood and tumor.[12]

However, although the technology to perform these studies in adequate depth is advancing rapidly, and the time will eventually come when the study of the genome or exome will be cost-effective, at present, in our

environment, these studies tend to be performed mainly for discovery or research purposes, with more limited applications in clinical practice.[17]

Whole genome sequencing (WGS) covers an individual's entire genome, including chromosomal and mitochondrial DNA.[12]

- Advantage: allows identification of non-coding variants associated with disease. Its main application is in research.[12]
- Disadvantage: It is expensive and requires a great deal of analysis since the non-coding regions of the genome are less conserved and present a greater number of variants. In addition, it requires very high-performance sequencers, which are not available in most laboratories of research centers or hospitals in our country. Therefore, it is less accessible in routine diagnosis.[12]

When these three techniques mentioned above are used for the study of pediatric cancers, the need to study tumor DNA is added, in addition to germline DNA, since these studies are key not only for the diagnosis of certain types of tumor, but also (more frequently) for risk assignment through the identification of different "biomarkers" that make it possible to anticipate, for example, a worse response to treatment.[17]

Transcriptome sequencing or RNA seq (whole transcriptome sequencing [WTS]) allows quantitative information to be obtained on the genes expressed at a given time.[12]

- Advantage: It allows the study of RNA transcripts, their isoforms, post-transcriptional modifications, gene fusions, mutations, and changes in gene expression. Different RNA populations (total RNA, small RNA, transfer RNA, and ribosomal RNA) can be sequenced.[12]
- Disadvantage: The results obtained are tissue-specific and dependent on time and reading depth. Their analysis and interpretation are highly complex, and it is recommended to use expression in healthy tissue as a control.[12]

In oncology, the study of RNA plays an important role, and it is also possible to study it thoroughly using the transcriptome or the targeted research of specific transcripts of interest for each tumor.[17]

Interpretation of genetic data obtained by Next Generation Sequencing

Correctly interpreting the genetic variants or changes detected is key in precision medicine. Detecting these variants consists of identifying differences in an individual's DNA sequence when compared to a reference DNA. However, determining variants by itself is insufficient, and interpretation by specialists who can accurately assess their molecular and clinical implications is necessary for an optimal approach.[12]

There are databases of variants detected in the healthy population (polymorphisms) and pathogenic variants for the interpretation of variants. In the case of unknown variants, bioinformatics programs that provide in silico pathogenicity predictions are used. To detect pathogenic variants and exclude polymorphisms, we use several parameters:[12]

- Allelic frequency in our population.
- Coverage.
- Variant location.

In addition to these parameters, it is essential to highlight the importance of recording all the variants found when sequencing different samples with the same technology in the laboratory's database. This allows easy detection of intrinsic errors of the technology (repeated in all samples) and frequent population polymorphisms, greatly facilitating data analysis and interpretation.[12]

It is important to establish the variant's categorization: benign, probably benign, pathogenic, probably pathogenic, or of uncertain clinical significance.[12]

Perhaps the most paradigmatic case in current pediatric oncology is medulloblastoma, a tumor that, thanks to these studies of gene expression and, to a lesser extent, mutations, could be subclassified into at least four molecular subtypes with different clinical behavior, cell of origin, and specific treatment.[17]

In pediatric cancer, we found the limitation that most of the variants are not described in the databases, making it necessary to use in silico predictors with programs that predict the pathogenicity of the mutations based on different aspects.[12]

The authors agree that the availability of this large amount of data has improved genetic sequencing, which has allowed the development of epigenetics and proteomics. Before 2004, a cancer patient received treatment based on cytostatics that had limited efficacy but innumerable side effects. Now, we can select the most appropriate therapy for each patient, reduce complications and side effects, and, for this latter reason, increase patient adherence to treatment.

Objectives of precision medicine in pediatric oncology:[18]

1. Molecular-genetic analysis of tumors in children with cancer using next-generation massive DNA

sequencing technologies.[18]

2. The confirmation and validation of identified alterations by alternative techniques.[18]
3. The integration of molecular-genetic information with the information available in other databases (pharmacological, clinical trials, etc.) to identify targets for personalized treatments.[18]

Application of precision medicine to the field of health care. Therapeutic opportunities

During the last decade, most treatments in pediatric oncology with molecular targets have been tested in unselected populations. There are currently few biomarker-targeted therapies for clinical use in pediatric oncology. The most prominent are drugs that have been developed for other pathologies in adults, such as ALK kinase inhibitors, used in non-small cell lung cancer with ALK gene translocation, which have also demonstrated efficacy in anaplastic large cell lymphomas and inflammatory myofibroblastic tumors (with ALK translocation) and neuroblastomas (with ALK mutation), and ALK inhibitors (with ALK mutation) BRAF in melanoma is also effective in pediatric gliomas with the BRAF V600E mutation. ALK and BRAF analysis in tumor tissue is part of the standard diagnostic protocol in most pediatric oncology centers. However, consecutive marker analysis is incompatible with clinical practice due to the limited amount of tumor available, which is mainly obtained by core needle biopsy at the time of diagnosis, the time required for each analysis, and the overall cost of the process.[12]

The availability of massive sequencing techniques has made it possible to identify new therapeutic targets that allow treatment directed at a specific molecular pathway or even the repositioning of certain drugs. In addition, these techniques allow the pharmacogenomic study of particular patient populations and can predict response or increased toxicity. For targeted therapies, new-generation studies will enable the identification of biomarkers mainly recognized from information from adult oncology. Identifying these biomarkers showed us that their expression may not be tumor-specific.[17]

It is hoped that the use of exome or genome studies will enable the diagnosis of patients who have been undiagnosed for long periods of time, a process referred to as the "diagnostic odyssey".[17]

The rapid development of high-throughput technologies and bioinformatics support enables unprecedented tumor analysis at the molecular level. The ability to study biological phenomena at an omic level is expected to continue to lead to significant advances in precision medicine, as well as in the identification of new potentially treatable alterations and less frequent genomic alterations for which targeted therapies already exist and which may improve the prognosis of our patients.[12]

Incidentalomas

Necessarily, when studying such a high number of genes in a patient and sometimes in a family, unexpected results may appear in the germline study when unexpected mutations are detected, and the pediatrician must be prepared for their management, as they may involve sensitive information. Most of the time, this scenario can be anticipated and is usually included in the informed consent if the family wishes to know these incidental results, but not all situations can be foreseen. The right of the different family members to access this information must be respected, and the patient's wish to reach adulthood must be contemplated at.[17]

Studies

Despite all the technological and research advances, since 2007, only 18 drugs have been developed with indications in pediatric oncology, compared to the more than 150 produced in adult oncology. This is partly due to the strict regulatory framework for developing new drugs in each country. For example, age under 18 is an exclusion criterion in many clinical trials, which is necessary for a new drug to be administered to patients. This leads to the systematic exclusion of the pediatric population from many research studies and slows the development of new medicines for children's and adolescents' diseases. In addition, among the drugs that have finally reached pediatric indications, there is sometimes a delay of more than a decade since the indication was obtained in adults compared to the pediatric population. Added to this is the low incidence of childhood cancer compared to adult cancer.[7]

Implementing new treatment strategies for these diseases and transferring advances in research to daily clinical practice are necessary. Regulatory agencies must be involved in developing drugs for the pediatric population, and countries must collaborate to implement clinical trials in which pediatric patients can be included, regardless of their country of origin.[7]

The Individualized Therapy for Recurrent Malignancies in Childhood registry, also known as INFORM, was developed by a consortium of pediatric oncologists and genomics researchers to develop precision approaches. It shows drug-based approaches to evaluate their efficacy in relapsed, refractory, or high-risk therapeutic pediatric cancers.[19]

The results of this work show that it is possible to identify precision targets in recurrent pediatric cancers that can guide clinical decision-making on treatment approaches. This registry has opened up the genomic

landscape in pediatric oncology. It provides a unique source of information to help match new drugs or drug schedules with appropriate biomarkers in specific pediatric patient populations.[19]

The INFORM registry brings together clinical and molecular data collection of fresh tumor material from pediatric patients with refractory, relapsed, or progressive malignant disease.[19]

A new study by researchers at the Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorders Center in the United States points to advances in precision medicine, in which diagnosis and treatments are targeted to the genetic susceptibilities of individual cancers to the point where it can now affect the care of most children with brain tumors. The scientists applied clinical tests on more than 200 tumor samples. This is the most extensive study of genetic abnormalities in pediatric brain tumors. In the process, most of the samples were found to have genetic irregularities that could influence how the disease was diagnosed and/or treated with approved drugs or agents being evaluated in clinical trials.[20]

Australian researchers have shared a new breakthrough against childhood cancer in the scientific journal Nature Medicine. It aims to benefit children suffering from cancers with poor prognoses: rare tumors, relapsed patients, or patients with refractory cancers, by identifying new treatments specifically targeted to each child's cancer. The program uses genomic analysis (Whole Genome Sequencing, WGS), RNA analysis, and methylation profiling. The study was performed on a total of 250 children with different types of aggressive cancers. With the analysis of all patients, they could identify 968 mutations. The results were truly satisfactory, since 93,7 % of the children carried at least one mutation in both germline and somatic chromosomes. Of the 250 subjects, 71,4 % had mutations that could be used as therapeutic targets, and 5,2 % obtained a diagnosis different from the initial one, thus ensuring a better viewpoint for their future treatment.[21]

Currently, studies are being carried out in academic centers and cooperative groups, where genetic material is obtained from the tumor for study by exome (or sometimes genome) and transcriptome in search of new pharmacologically modulatable therapeutic targets. Patients who demonstrate them receive targeted treatment if the drug is available and has been studied in pediatrics, at least in initial phases8. However, for now, only patients in very advanced stages of their disease have been studied, and the impact of these treatments did not have the expected outcome.[17]

The authors consider that precision oncopediatrics offers hopeful diagnostic and therapeutic options for pediatric cancer, especially highly aggressive and recurrent cancers, given the results obtained in these and other studies. Still, it is also necessary to carry out different studies, broaden the spectrum and focus of attention, to get new results and perfect those received so far, to find specific and individualized treatments for pediatric cancer, extending and improving the quality of life of infants who suffer from it.

Advantages of precision medicine applied to oncopediatrics:[7]

- Molecular characterization has made it possible to classify tumors better, understand their pathophysiology, and determine genetic factors with prognostic implications.[7]
- Researchers have been developing molecules that target certain molecular alterations that recur in cancer and have managed to radically change the prognosis of some diseases. The development of these drugs initially requires preclinical research to first demonstrate the involvement of a biomarker in the development of the disease and the activity of the molecule under study in the pathology with that biomarker.[7]
- It is more precise, scientific, safe, and effective, with a strong emphasis on prevention. Knowledge of a patient's genetic profile will also lead to the identification of some of the predisposing factors to a disease. Prevention, based on genetic data, thus becomes a new medical tool.[22]
- It has the potential to detect the onset of the disease early, increase patients' adherence to their treatment by reducing the side effects of a drug, improve their overall health, and obtain an overall view of the disease, the prognosis, and the care required.[22]
- It allows the correct prescription from the beginning of treatment.[14]
- It also has an essential impact on the field of pharmaceutical research by improving the selection of potential targets for the discovery of new drugs, by reducing the cost and duration of clinical trials, and by preventing already approved drugs from being withdrawn from the market because of their side effect or toxicity.[22]
- From the public health point of view, personalized or precision medicine increases efficiency since, by knowing the molecular profiles, treatments that are of no benefit to the patient will be discarded, avoiding unnecessary expenses and complications that compromise the quality of life.[14]
- Its adoption by physicians offers substantial advantages such as: permanent updating of their knowledge; progression in their understanding of scientific methods and in being more critical when using data; increasing their confidence in management-related decisions; improving their ability to use bibliographic information sources and their reading habits, and reinforcing the cohesion of clinical teams by establishing an objective framework of operation.[22]

Skeptics and detractors

However, on its slippery path to becoming a strategic proposal to be sponsored by health systems, it must face more than a few skeptics and detractors. Some are skeptical, stating: "If the leap from a person-centered system to a disease-centered system is problematic enough, the leap to a gene-centered system is irrational".[22]

Other detractors assert: "The utopian promise that medicine will cease to be a practice with uncertainty and become an exact science is undoubtedly attractive but, at present, it only represents techno-scientific smoke sold by industry to naive politicians to introduce, at a price of gold, new drugs and obtain, at a low price, the millions of data generated by the healthcare system".[22]

On the other hand, others denounce and denounce the fact that it will aggravate inequity between groups and countries and will never solve the problems of population morbidity and mortality, which are fundamentally caused by the well-known social determinants.[22]

Having said this, it is to be understood that the postulates of precision medicine and evidence-based medicine (EBM) will be under permanent scrutiny by the scientific community about: their conceptual and logical rationality, their empirical support, and above all the realism of their final proposals and the adjustment of the means they propose, all of this, apart from the economistic or commercial management paradigms that threaten to invade it continuously.[22]

The authors consider that personalized and precision medicine does not represent a new paradigm or an emerging approach with respect to previous currents of medical reasoning, such as evidence-based medicine, but rather a continuity of its promoters in the search for greater scientific certainty applied to individual patients in medicine.

Challenges

Once again, every effort must be made to optimize inter-institutional relations, taking advantage of the technology available in related centers and avoiding duplication in the purchase of high-cost equipment.[17]

Training human resources capable of handling these technologies is a significant challenge for countries like ours. These technologies have integrated bioinformatics professionals as another actor within the healthcare team. Specialists in these disciplines trained in genomics are needed. Clinical pediatricians and specialists should have a deeper knowledge of this discipline that is emerging as a component of daily practice in the near future.[17]

Future perspectives

However, it is necessary to promote the implementation of new treatment strategies for these diseases and to transfer advances in research to daily clinical practice. Despite the improvement in survival rates in recent decades, childhood cancer continues to be the leading cause of death from childhood disease in high-income countries. This is compounded by the short- and long-term side effects of cancer treatments.[7]

The involvement of regulatory agencies in the development of new drugs for the pediatric population is necessary. This would allow the study of drugs based on the mechanism of action rather than by pathology, so that patients with rare diseases such as pediatric cancer can be included in the studies. Similarly, collaboration between countries facilitates the implementation of international clinical trials in which pediatric patients can be included regardless of their country of residence.[7]

It is interesting to note that much support is being devoted to the development of this therapeutic discipline to achieve its maximum development and guarantee access to the drugs resulting from research, development, and innovation.[14]

There are now international platforms for collaboration between clinicians and researchers, industry, regulatory agencies, and patients that aim to improve the development of new drug targets in childhood cancer. Working together, these bodies are responsible for detecting current problems and limitations in research and seeking solutions to improve strategies so that the most significant number of patients can benefit from advances and so that children and adolescents with cancer can be included in trials for the study of new drugs.[7]

Likewise, we must not forget that most patients diagnosed with childhood cancer reside in low-income countries, so it is essential to improve diagnostic and treatment strategies for these patients, as well as to increase cooperation between countries to favor their inclusion in clinical trials to increase the survival of the majority of children and adolescents with cancer worldwide.[7]

In an international collaborative framework, the development of new therapies opens the way to improving the survival rates of patients diagnosed with childhood or adolescent cancer. Similarly, we must work to reduce the toxicity profile of cancer treatments without compromising cure rates; our aim is not only to achieve a cure, but also to ensure that survivors reach adulthood in good physical, psychological, and social health, and thus achieve an adequate quality of life.[7]

Let us remember that medical care is expensive and that the vast majority of patients with so-called chronic, degenerative, and non-communicable diseases consume resources on a large scale. It would be very opportune

and convenient to consolidate a new health care model based on predictive, personalized, and more efficient medicine, which mainly guarantees prudent resource management but with the best desired efficacy.[14]

Precision medicine and oncology in Cuba

On April 26, 2018, the Precision Medicine in Cuba: Challenges and Perspectives meeting took place and was attended by representatives of the National Health System and BioCubaFarma reference institutions. High-level foreign representatives from Spain and the USA also participated. The morning session dealt with the global panorama of precision medicine in the era of genomic medicine. The afternoon session dealt with Precision Medicine in Cuba: Strengths and Challenges—finally, Dr. C. Beatriz Marcheco, Director of the National Center of Medical Genetics and President of the Society of Human Genetics, presented the proposal of Precision Medicine in Cuba: Strengths and Challenges.[10]

Our country's strategy in precision medicine is focused on improving the health of the population as the main evaluation criterion. It will involve integrating all the human and institutional capacities available in the country and will imply the development of our own capacities, technology transfer, and human resource training. The meeting became a space for fruitful exchange in which the main components of the Cuban strategy were discussed.[10]

CONCLUSIONS

The present work allowed us to understand that there are highly differentiated types of cancer whose effects on each patient are different and often change during the disease. In response to this, precision oncology was born. This, through the use of new generation genomic tools, has now reached pediatric practice, posing new opportunities and challenges, bringing multiple benefits to patients and their families, transcending the limits of pure research and achieving the individuality of the patient and their disease, not only for diagnosis and therapy, but also for prediction and prevention.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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