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EDITORIAL

Advances and challenges in the fight against childhood cancer☆

Avances y retos en la lucha contra el cáncer infantil

I. Astigarraga

Servicio de Pediatría, BioCruces Health Research Institute, Hospital Universitario Cruces, Departamento de Pediatría, Universidad del País Vasco UPV/EHU, Barakaldo, Bizkaia, Spain

Cancer is the leading cause of death by disease among children and adolescents in many countries around the world. Most children with cancer live in countries with limited health care resources. As a result of the gradual decrease in child mortality from infections and malnutrition, the fight against cancer has become a worldwide public health priority.[1] In the last decade numerous international initiatives have been developed to improve the care of children with cancer, research and professional training. Many countries have provided financial and political support for developing national strategies, establishing registers, authorising centres, defining care standards and formulating adapted protocols, as well as specific social and economic support programmes for families.[2] Mexico is a good example of the benefits of national plans to combat acute lymphoblastic leukaemia (ALL) (since 2006) and other malignant neoplasms (2008), with a very positive impact in increasing survival rates and reducing treatment default.

The distribution of types of tumours is very different in children and adults. Leukaemias (especially ALL) are the most common neoplasms in children, followed by brain tumours. Biological behaviour is also different in children and adults, even in tumours with similar histology or in children of different ages. Clinical research on these types of cancer, as in the articles by Estrada-Padilla et al.[3] and by Pardal-Souto et al.[4] in this journal, is very important for advancing our knowledge of childhood cancer.

Research aimed at ascertaining the possible causes that give rise to malignant transformation of cells is complex. Cancer can be considered a genetic disease which develops from alterations in DNA that allow a normal cell to be transformed into a tumour cell. In the last five years many advances have been made thanks to the Pediatric Cancer Genome Project,[5] which has made it possible to discover numerous somatic mutations that lead to the development of cancer in children. Mutations, epigenetic alterations and changes in RNA expression have been identified in leukaemias, brain tumours and other solid tumours. It has also been found that many cancers are heterogeneous, composed of different clones of malignant cells together with other normal and immune system cells. These biological discoveries at the level of genes, proteins or pathways implicated in childhood cancer are making it possible to conduct clinical trials to discover new drugs. Despite the progress made, many children are still dying of cancer, and innovation in safe and effective new therapies is insufficient. Moreover, access to these new treatments is not equitable between different countries.

Genomic advances have demonstrated the importance of these factors in the development of childhood leukaemias.[5] Although a clear relationship has been established between certain genetic diseases and a higher risk of leukaemia, most patients have no known genetic predisposition. There is a clear correlation between clonal chromosomal abnormalities, biological properties of leukaemic cells and clinical features, and therefore various genetic markers are used

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E-mail address: itziar.astigarraga@osakidetza.net

as prognostic factors to adjust the intensity of treatment.[6] Certain molecular alterations such as the BCR/ABL fusion gene, originating from the t(9;22) translocation, are therapeutically important. The discovery of this molecular defect made it possible to develop a new treatment, imatinib, which has achieved very good results in some types of leukaemia. Interesting immunotherapy-related applications have recently been produced, such as the generation of transduced lymphocytes with chimeric antigen receptors (CARs).

Leukaemias are the result of genetic and environmental factors, of a multifactorial character.[6] Events occurring prenatally, even at the progenitor germ cell level, can produce effects that are manifested after variable latency periods. In research on childhood leukaemias, the study of genetic determinants is especially important. In the article by Estrada-Padilla et al.[3] published in this journal, on 120 children with ALL and 120 controls, the finding of a larger number of minor phenotypic variants in cases of leukaemia suggests the hypothesis of the influence of prenatal events and altered phenogenesis, although the aetiopathogenic value of the observed phenotypic variants cannot be established. The prenatal origin of ALLs has also been proposed in other studies that observe concordant leukaemia in monozygotic twins[6] or a finding of preleukaemic cells in 63% of dried blood samples from neonatal screening of patients with ALL, strongly associated with hyperdiploidy and low birth weight. Although these findings are interesting, the process of oncogenesis is very complex and is influenced by other epigenetic factors that regulate gene expression and by environmental agents.

Low-grade gliomas are the most common brain tumours in the paediatric age group, and the retrospective review of 111 cases conducted by Pardal-Souto et al.[4] is very representative of the clinical behaviour of these tumours. The importance of germline genetic factors in brain tumours was also observed, since 7 children showed tumour-predisposing genetic disorders (neurofibromatosis type I and tuberous sclerosis). The prognosis depends essentially on resection of the tumour, and all the children that underwent complete surgical excision (31 children) survived. However, many tumours are located in areas of the brain where it is impossible to operate or where surgery is associated with high morbidity, as in the brainstem, optic pathway or spinal cord, and therefore other adjunctive treatments such as radiotherapy or chemotherapy were needed. Although overall survival (88.3%) was favourable, follow-up was short and it is likely that other children will die from tumour progression and that the observed sequelae will increase.

The articles published in this journal on leukaemias and gliomas[4] confirm the need to make further progress in studying the biological behaviour of childhood cancer in search of more effective and safer new therapies. Within the Pediatric Cancer Genome Project[5] interesting discoveries have been made in type T leukaemias and in gliomas. Few mutations have been observed in this family of brain tumours, but genetic changes have been identified in BRAF, RAF1, FGFR1, MYB, MYBL1, H3F3A and ATRX. Animal models have also been developed that indicate the importance of the MAPK/ERK and PI3K pathways as therapeutic targets, as they can be blocked by specific inhibitors.[7] In the last few years clinical trials have been instituted with new agents which act specifically on the pathways that are altered in each tumour, although it is not yet known how effective and safe the results will be in the long term.

An interesting recent development is that the new drugs are applied to all the tumours that share alterations in the same metabolic pathway, even if they have different histologies. For example, alterations in MAPK/ERK are observed in low-grade gliomas, histiocytosis, melanomas and other tumours, so RAF inhibitors (dafrafenib, vemurafenib) or ERK inhibitors (trametinib) are being analysed in trials that include different types of tumours. These are good examples of drugs developed from research on mechanisms basic to molecular therapy. In addition, they represent a change in the way childhood tumours are managed, classically based on histological types, and allow us to ''dream'' of a more individualised form of treatment with better survival rates and fewer adverse effects.

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