



EDITORIAL

Paediatric oncology: Past, present and future[☆]



La oncología pediátrica: pasado, presente y futuro

Rafael Fernández-Delgado^{a,b}

^a Sección de Oncohematología Pediátrica, Hospital Clínico Universitario, INCLIVA, Valencia, Spain

^b Universitat de Valencia, Valencia, Spain

Childhood cancer treatment has improved spectacularly in the last 25 years, with an increase in overall cure rates from 20% to 30% in the late 1970s to over 75% today. However, we must not fall into complacency and assume that the problem is largely solved. Cancer is one of the main causes of mortality in the paediatric age group and there is considerable room for improvement, which society must address.

The development of the various types of treatment over time reveals very marked differences between past and present, and above all it allows us to foresee a future in which new diagnostic and therapeutic approaches will succeed in increasing survival and may offer curative treatments for those diseases where they do not currently exist.

The introduction of chemotherapy, in the middle of the last century, ushered in an era of improvement in the prognosis of malignant diseases in children. A number of drugs were used with varying degrees of success in a range of cancer types, generally in empirical combinations, achieving partial or total remission and increased survival in certain tumours. The diagnostic tools used were primarily derived from conventional radiology. Cytological and histological studies, the basis of diagnosis, gradually enabled us to get to know the morphological structure of the diseased tissue, and subsequently its functional characteristics, through the use of more suitable staining techniques.

The initial successes, given the small number of patients, highlighted the need to organise cooperative groups that

would enable prospective studies to be performed to discover the efficacy of the various treatments. The establishment of national and international Paediatric Oncology or Oncohaematology working groups made it possible to create specific institutions for collecting data and organising studies to increase knowledge of the various diseases. Thus the Spanish Paediatric Oncology Society was found in 1977, although national and international meetings on the subject had been taking place since 1969. The establishment of the current Spanish Register of Childhood Tumours in 1979 has provided us, since then, with a firm structure for knowledge of the specific situation of childhood cancer in Spain.

Currently, cure rates of over 85–90% are attained in some diseases (lymphoblastic leukaemias, lymphomas, Hodgkin's disease, Wilm's tumour, etc.). Other groups of diseases, however, do not show the same therapeutic success and have a poor initial prognosis (tumours of the central nervous system, bone tumours, mesenchymal tumours, etc.). In both groups there is potential for improvement.

In the former, the aim must be to limit early and late toxicity by "de-escalating" the treatment, making it more comfortable and caring, prioritising outpatient treatment and improving palliative care (pain, infections, digestive toxicity). It is not just a matter of increasing the survival rate but of making a qualitative leap, improving the quality of life for patients and survivors and reducing the sequelae of the disease and its treatment.

In the second group the aim lies in making better use of the means available and finding new therapeutic tools to enable us to improve the prognosis. In this connection, we have known since the end of the last century that cells in probably all malignant diseases show specific molecular

[☆] Please cite this article as: Fernández-Delgado Cerdá R. La oncología pediátrica: pasado, presente y futuro. An Pediatr (Barc). 2016;85:59–60.

E-mail address: Rafael.Fdez-delgado@uv.es

alterations that can be therapeutic targets for drugs that act preferentially on the tumour and not on normal tissues, reducing toxicity. Examples of this type of drug are imatinib, which has been used for years in chronic myeloid leukaemia, but also dasatinib, ibrutinib, crizotinib and others, some of which are still in the experimental stage. This therapeutic strategy looks set to occupy an important place in the future of childhood cancer treatment. As well as these generic principles, the future of treatment depends on exact knowledge of the specific molecular alterations of each tumour individually and how these alterations develop in the course of treatment. For this purpose the exome of the tumour cells in each patient needs to be sequenced, drawing the molecular footprint and adapting the treatment to the specific alterations. This type of therapeutic approach, known as "precision medicine", must be applied at least to patients with more complex diseases. Epigenetics is also being studied as a form of diagnostic and therapeutic approach, as the study by Boloix et al. included in this issue of *Anales* shows.¹

Immunotherapy has not been lagging behind. From non-specific stimulation of the immune system by continuous administration of BCG, which has been used for over 40 years, to current approaches to CAR-T technology, there has been a succession of effective treatments, prominent among which are monoclonal antibodies directed against antigens expressed by tumour cells. Experience with anti-CD20, anti-CD33 and others has shown their efficacy in the treatment of lymphoid or myeloid proliferations. More recently the possibility of engineering T lymphocytes to produce a chimeric receptor (chimeric antigen receptor [CAR])² for an antigen expressed by tumour cells and thereby provoking a cellular immune response, killing tumour cells, has opened up a new therapeutic strategy for diseases considered resistant to conventional treatments.

These advances have been accompanied by a remarkable improvement in diagnostic possibilities, from imaging to cell recognition techniques, many of which are within reach of most hospitals, even though centralised review becomes necessary in all cooperative studies. Magnetic resonance has progressively improved the precision of normal and pathological images of the body and is currently accompanied by isotopic methods using radioactive glucose that make it possible to determine the metabolic activity of tissues, differentiating between the normal and the pathological and constituting a very valuable tool in extension studies. This technique (positron emission tomography [PET]) has already proved valuable in some paediatric tumours and its definitive application to other diseases is under consideration. On the other hand, analysis of minimal disseminated disease in bone marrow and peripheral blood³ using molecular biology techniques enables us to obtain more accurate knowledge of the extent of the disease and to consider as

generalised an alteration that might have been defined as localised using conventional methods and therefore treated suboptimally. This technique is directly linked to what has been called "liquid biopsy", which involves looking for circulating DNA from tumour cells using PCR techniques, which clearly improves diagnostic precision.

All this has changed the perception of paediatricians who do not specialise in the care of children with cancer. A paediatric cancer patient is not a doomed invalid but someone with a life to be fought for, and the intercurrents that arise during the course of the illness and its treatment are now a therapeutic objective, whereas until a few years ago they were regarded as a regrettable complication. The majority of Paediatric Intensive Care Units express this view, according to the survey presented by García-Salido et al.⁴

By the same line of argument, these possibilities for improvement cannot be applied exclusively to select populations.⁵ We must not forget that the main objective of paediatric oncology is to try to ensure that no child dies of cancer, that is, to cure the highest possible number of children suffering from malignant diseases. Although medicine is increasingly capable of defining the prognostic factors that influence a patient's chances of survival, as paediatric oncologists we know that the main prognostic factor in a given community is the financial investment society is able to assign to the diagnosis and treatment of cancer in children. This investment must be equitably distributed, so as to give children from all geographical areas access to the best care. While remaining aware of the need to stratify care management (health care resources must be allocated sequentially to cover the needs of an entire geographical area), associations of parents and relatives of children with cancer must be firm in demanding equal quality. Only on this basis will we, as doctors, and society at large keep faith with the people we are devoted to: children suffering from malignant diseases.

References

1. Boloix A, París-Coderch L, Soriano A, Roma J, Gallego S, Sánchez de Toledo J, et al. Nuevas estrategias terapéuticas para el neuroblastoma basadas en los micro-RNA. *An Pediatr (Barc)*. 2016;85:109.e1-6.
2. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR-T cells forward. *Nat Rev Clin Oncol*. 2016;13:370-83.
3. Mussolin L, Rosolen A. Minimal disseminated disease in pediatric non-Hodgkin lymphoma. *J Carcinog Mutagen*. 2013;5:1-2.
4. García-Salido A, Nieto-Moro M, Iglesias-Bouzas MI, González-Vicent M, Serrano-González A, Casado-Flores J. Paciente crítico onco-hematológico. ¿Hacemos lo que deberíamos hacer? *An Pediatr*. 2016;85:61-9.
5. Kowalczyk JR, Samardakiewicz M, Pritchard-Jones K, Ladenstein R, Essiaf S, Fitzgerald E, et al. European survey on standards of care in pediatric oncology centres. *Eur J Cancer*. 2016;61:11-9.