Paediatric oncology: Past, present and future

La oncología pediátrica: pasado, presente y futuro

Rafael Fernández-Delgado a, b

a Sección de Oncohematología Pediatrica, 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 and functional characteristics 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
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 prin-
ciples, the future of treatment depends on exact knowledge
of the specific molecular alterations of each tumour individu-
ally 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 mole-
cular 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 stud-
ed 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 pos-
sibility 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 cellu-
lar 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 patho-
logical 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 consider-
ation. On the other hand, analysis of minimal disseminated
disease in bone marrow and peripheral blood3 using mole-
cular 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 cir-
culating 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 paed-
iatric 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, accord-
ing 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 popu-
lations.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 chil-
dren 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 chil-
dren. 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
de Toledo J, et al. Nuevas estrategias terapéuticas para el
neuroblastoma basadas en el micro-RNA. An Pediatr (Barc).
2. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR-T cells forward.
3. Mussolin L, Rosolen A. Minimal disseminated disease in pediatric
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 Pedi-
5. Kowalczzyk JR, Samardakiewicz M, Pritchard-Jones K, Ladenstein
R, Essif H, Fitzgerald E, et al. European survey on standards of