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Special article

Empowerment of patients and physicians’ role in the long-term follow-up survivors of childhood cancer☆

Protagonismo del paciente y papel de los médicos en el seguimiento a largo plazo de los supervivientes del cáncer infantil

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Introduction

Between 900 and 950 cases of cancer are diagnosed each year in Spain in children under 15 years of age and about 450–500 cases in adolescents aged 15–18 years, according to data from the Spanish Registry of Childhood Tumours. The incidence is stable and patterns in Spain are similar to those in Europe and the US.[1] Cancer is the leading cause of death due to disease in children and adolescents in Spain.

At present, most children and adolescents diagnosed with cancer in our healthcare setting will recover from it and will become long-term survivors. The latest report of the Spanish Registry of Childhood Tumours, where there are more than 15,000 registered cases, highlights the fact that about 75–80% of patients are alive 5 years after diagnosis[1] (Fig. 1). Survival rates in southern Europe are comparable to those in the north, central Europe and British Isles. In the last cohort, a survival rate of 82% was reached, similar to 81% in northern or central Europe.[2] This improvement in survival represents a progressive increase in the number of survivors, which means that the population between 25 and 35 years of age about one in 700 will be a survivor of childhood cancer or 1/1000 in the global adult population.[3]

The monitoring of children and adolescents with cancer will depend on each individual, the type of tumour and the treatment they receive. They should always be considered individually.[4] As suggested by Prof. D’Angio in the editorial published in *Lancet Oncology* in 2013, “Cure is not enough”.[5] The current goal is to cure with the highest possible quality of life, so a key message in the fight against childhood cancer is: “The cure is not enough, childhood cancer survivors need to be monitored”.[5]

The health of childhood cancer survivors

The population of survivors is a vulnerable group regarding sequelae associated to the disease itself or its treatment.[6] Most sequelae can be predicted and identified early during follow-up, but others do not appear until several years later. Survivor adaptation to late effects is generally good, 90% report good health, and most show very few psychological disorders. But the prolongation of survival adds risks that are little evaluated, especially in their interaction with other factors such as lifestyle, occupational and social trends and ageing.

Approximately, 70% of childhood cancer survivors experience at least one late effect due to the disease itself or the treatments, with consequences for their health and quality of life. In addition, 30–40% have a serious late complication, disabling or threatening for life. In an interesting study conducted in the USA[7] through surveys answered by almost 10,400 cancer survivors treated between 1970 and 1986, it was observed that 62% had at least one chronic disease. In comparison to his/her siblings, it was found that the risk of developing a chronic disease was 3.3 times higher. But if the most

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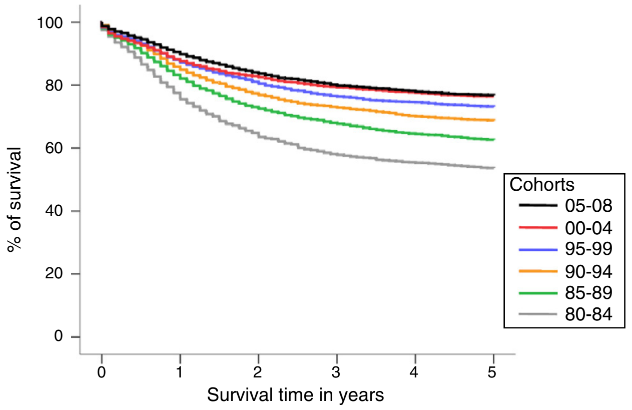

Fig. 1. Spanish Registry of Childhood Tumuors-Spanish Society of Pediatric Haematology and Oncology (RETI-SEHOP). All tumours. Survival 5 years after diagnosis by year of incidence cohorts. 0–14 years, 1980–2008. Not classifiable tumours according to the *International Classification of Childhood Cancer* (ICCC) such as myelodysplastic syndrome and other myeloproliferative diseases were excluded. Number of cases = 17,262.

serious or life-threatening diseases were analyzed, the relative risk was much higher (RR 8.2). 30 years from diagnosis it was observed that the risk of chronic disease was 73% and the risk of developing a severe, incapacitating disease or even death was 42%. Many patients also suffered 3 or more chronic conditions.

Recent studies in the US[8] show that the frequency of late complications continues to grow with the extension of follow-up and there is no evidence of a plateau effect yet. The systems most affected are the nervous system (39%), the endocrine system (32%), eyes and ears (22%) and genitourinary (17%). Cardiac, gastrointestinal, musculoskeletal, pulmonary disorders, impaired bone maturation and growth, neurocognitive (learning and memory difficulties) and psychological development (anxiety, depression), infertility and reproductive difficulties are also observed. In addition, these patients have a higher risk of developing secondary malignancies.[9] Unhealthy lifestyle habits (smoking, alcohol, unbalanced diet or sedentary lifestyle) may increase the risk of developing these complications. There have also been problems with the level of education, access to occupational life and quality of life.

According to the *Childhood Cancer Survivors Study*,[10] survivors have an 8.4 times greater risk of death at 5 years of completion of the treatment than the population control group, comparable by age and gender. Relapse or progression of the primary tumour is the leading cause of mortality, with 57% of deaths in this period. The second cause is second tumours, followed by heart and lung diseases in fourth place. Mortality remains stable at 30 years of diagnosis, significantly varying the distribution of causes; mortality by progression or recurrence of the primary tumour decreases, and those caused by secondary malignancies increase, which represent a 15.2 times higher risk when compared to the general population. The risk of death from cardiac causes is 7 times higher, 8.8 from lung causes and 2.8 times from other causes compared to the general population.

Since therapies used against childhood cancer have improved a lot since the 70s, the future health of patients who are in active treatment at present cannot be known, but complications are expected to be milder. Thus, the *Childhood Cancer Survivors Study* has recently published the reduction of late mortality rate in patients treated in the 90s compared to previous decades,[11] as revealed in their study of 5760 survivors of acute lymphoblastic leukaemia,[12] confirming that 25-year survival is lower than that of the general population and the 25-year cumulative mortality from diagnosis is 13%. The different cohorts were analyzed based on the date of diagnosis from 1970, finding that, in the most recent, the survival curve is a little better. Observing a higher rate of late complications in irradiated patients has led to completely omit radiotherapy or severely limit its indications in the design of new treatment protocols for acute lymphoblastic leukaemia. In addition, it was observed that a very large group of patients in this study, 92%, did not have any chronic illness or functional impairment.

Monitoring and follow-up of survivors

The optimal monitoring of survivors includes monitoring and assessment of present or expected adverse effects regarding the treatment received and the implementation of appropriate interventions to improve these sequelae. The regular monitoring of the survivors' health is recommended, with the following objectives:

1. Facilitate early diagnosis and proper treatment of late treatment complications and side effects.
2. Early detection of recurrences.
3. Screening and early detection of second tumours.
4. Allow detection and provision of adequate treatment of comorbidities.
5. Give the opportunity to implement preventive strategies such as diet modification, smoking cessation, lifestyle changes, etc.[8]

Survivors must be responsible and play a leading role in their health; to that end, they must have a screening and prevention plan that integrates their experience and their specific health needs.[13] This plan should be personal and adapted, related to several factors: patient's own characteristics (sex, race, age at diagnosis and follow-up), tumour type (location, treatment modalities), familial or genetic predispositions, lifestyle and health habits and comorbidities (previous diseases). In the last 20 years, numerous papers and books have been published in the scientific literature regarding survivors and morbidity, attracting the interest of institutions and research groups.[14,15] There are also numerous websites with relevant and reliable information that can be consulted, and major international groups that have studied the epidemiology of side effects and have developed follow-up guidelines:

- COG (Children Oncology Group): Long-Term Follow-up Program Resource Guide (www.survivorshipguidelines.org).
- Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/guidelines/fulltext/132/index.html).
- The British Childhood Cancer Survivor Study (BCCSS) (www.ukccg.org/public/followup/practicestatement/index.html).
- Dutch Childhood Oncology Group (DCOG LATER).

In Spain, the recommendations set out by the working group of side effects of the Spanish Society of Pediatric Haematology and Oncology (SEHOP).[14]

The largest project for the development of follow-up guidelines harmonized with scientific evidence which can be used universally was born in 2011 and is still in full progress. It is called the "*International Late Effects of Childhood Cancer Guideline Harmonization Group*" (www.ighg.org). Basically, this group brings together several European and American national groups, *The Cochrane Childhood Cancer Group* and *The PanCare SurFup Cosortium*. Its aim is to establish an integrated strategy and a common vision for the monitoring and treatment of late effects. They have already published several of these recommendations.[16,17]

Follow-up models

Although the need for follow-up programmes in the long term is clear, it is not easy to establish the ideal model nor the transition