



ORIGINAL ARTICLE

Early clinical trials in paediatric oncology in Spain: A nationwide perspective[☆]



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Abstract

Introduction: Cancer is the leading cause of death between the first year of life and adolescence, and some types of diseases are still a major challenge in terms of cure. There is, therefore, a major need for new drugs. Recent findings in cancer biology open the door

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Early phase clinical trials;
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to the development of targeted therapies against individual molecular changes, as well as immunotherapy. Promising results in adult anti-cancer drug development have not yet been translated into paediatric clinical practice. A report is presented on the activity in early paediatric oncology trials (phase I–II) in Spain.

Material and methods: All members of the Spanish Society of Paediatric Haematology Oncology (SEHOP) were contacted in order to identify early clinical trials in paediatric cancer opened between 2005 and 2015.

Results: A total of 30 trials had been opened in this period: 21 (70%) in solid tumours, and 9 (30%) in malignant haemopathies. A total of 212 patients have been enrolled. The majority was industry sponsored (53%). Since 2010, four centres have joined the international consortium of Innovative Therapies for Children with Cancer (ITCC), which has as its aim to develop novel therapies for paediatric tumours. A significant number of new studies have opened since 2010, improving the treatment opportunities for our children. Results of recently closed trials show the contribution of Spanish investigators, the introduction of molecularly targeted agents, and their benefits.

Conclusions: The activity in clinical trials has increased in the years analysed. The SEHOP is committed to develop and participate in collaborative academic trials, in order to help in the advancement and optimisation of existing therapies in paediatric cancer.

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PALABRAS CLAVE

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Medicina personalizada

Ensayos clínicos precoces en oncología pediátrica en España: una perspectiva nacional

Resumen

Introducción: El cáncer es la primera causa de muerte por enfermedad entre el primer año de vida y la adolescencia. Algunos tipos de enfermedad siguen constituyendo un reto en términos de curación. Existe por tanto una necesidad imperiosa de nuevos fármacos. Algunos descubrimientos recientes en la biología del cáncer abren la puerta al desarrollo de terapias dirigidas contra alteraciones moleculares concretas e inmunoterapia. Esto se ha traducido en resultados prometedores sobre todo en oncología de adultos, y en menor medida todavía en niños. Presentamos la actividad en ensayos clínicos precoces (fase I–II) en oncología pediátrica en España.

Material y métodos: A través de la Sociedad Española de Oncología y Hematología Pediátrica (SEHOP) contactamos a sus miembros para identificar los ensayos fase I–II en cáncer pediátrico abiertos entre 2005 y 2015.

Resultados: En este periodo se abrieron 30 ensayos: 21 (70%) en tumores sólidos y 9 (30%) en hemopatías malignas y se incluyó a 212 pacientes. La mayoría están promovidos por la industria farmacéutica (53%). Desde 2010, 4 centros se han integrado en el consorcio internacional ITCC cuyo objetivo es desarrollar nuevas terapias en cáncer infantil. Esto ha permitido ampliar el abanico de posibilidades terapéuticas. Los resultados de ensayos clínicos terminados muestran la contribución de los investigadores españoles, la introducción de terapias dirigidas y sus beneficios.

Conclusiones: La actividad en ensayos clínicos precoces ha aumentado en estos años. La SEHOP está comprometida a desarrollar y participar en ensayos clínicos académicos colaborativos, que favorezcan el avance en las terapias frente al cáncer infantil.

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Introduction

In Spain, a new case of cancer is diagnosed in 1 out of 6,500 children aged less than 15 years every year. This amounts to 1,100 new cases in children aged 0 to 14 years, while there are 450 in adolescents aged 15–19 years.¹

There have been enormous medical and therapeutic advances in paediatric cancer. In Europe, the mortality associated with childhood cancer decreased by 60% between the 1950s and the 1990s.² These figures have continued to improve since, although there has been a plateau in some diseases.¹ In Europe, the overall 5-year survival for all types

of cancer diagnosed between 2000 and 2007 was 77.9%.³ This success is due in large part to the development of multicentric clinical trials conducted by collaborative research groups.⁴

However, cancer continues to be the leading cause of death by disease from the first year of life and through adolescence¹: in 2014, cancer caused 29% of deaths in children aged 1–14 years, and 20% of deaths in adolescents aged 15–19 years.⁵

More specifically, the prognosis of certain diseases continues to be bleak, for instance in metastatic medulloblastoma, sarcoma or neuroblastoma, high-grade glioma or in patients with other types of cancer that recurs or is refractory to first-line treatment.

Thus, there is a pressing need for new drugs.

These novel anticancer drugs are needed to improve survival and reduce the sequelae that result from multimodal treatment combining surgery, radiotherapy, chemotherapy and haematopoietic stem cell transplantation. Recently, the identification of particular molecular changes in specific tumours has led to the development of targeted therapies against them, which has come to be known as “precision medicine.”⁶ This has opened the door to strategies adapted to the presence of molecular changes or immunotherapy at the time of diagnosis or relapse, which are exclusive to oncology patients.

There is evidence of the usefulness of new targeted therapies in some paediatric solid tumours: ALK inhibitors for anaplastic large-cell lymphoma,^{7,8} Sonic-hedgehog signalling pathway inhibitors for medulloblastoma⁹ or BRAF inhibitors for high-grade glioma in patients with BRAF-V600E mutations.^{10,11}

In leukaemia, the best 2 examples correspond to chronic myelogenous leukaemia and acute lymphoblastic leukaemia, in which the discovery of the Philadelphia chromosome (t(9;22)(q34;q11)) allowed the identification of the BCR-ABL fusion protein, which plays an essential role in their pathogenesis. This finding has allowed the development of drugs such as imatinib, dasatinib or nilotinib that can kill leukaemia cells through the inhibition of ABL kinase activity, improving the prognosis of these patients.^{12,13}

Thus, continued investment in research and development of novel anticancer agents for paediatric cancer is of vital importance.

Motivated by the dearth of paediatric data for already authorised medicines, new legislation was introduced in Europe in 2007 regarding the regulation of medicines in paediatrics that refers to the “paediatric investigation plan” that pharmaceutical companies need to submit to the European Medicines Agency at the time of applying for authorisation of a new drug.¹⁴ Thus, whenever a pharmaceutical company gets a new drug authorised (usually for the adult population), it must be accompanied by a plan for paediatric development (as long as the drug is potentially useful in children). When paediatric investigation plans are completed satisfactorily, the medicine is eligible for a 6-month supplementary protection certificate, or in case of a so-called orphan medicinal product, for an extension of 2 years to the 10 years of market exclusivity for the already authorised indication.

The aims of this measure are¹⁵:

- To increase availability of new medicines authorised for use in children through generation of accurate safety and efficacy data and high-quality ethical paediatric clinical research
- To produce better information on existing paediatric medicines.

Despite the introduction of these initiatives in Europe in the past 15 years, the development of novel drugs for the treatment of paediatric cancer is still insufficient: 14 out of the 28 anticancer agents approved for adults have been waived for paediatric development, while 26 of them were relevant to childhood cancers.¹⁶ Thus, it is necessary for representatives of academic institutions, regulatory bodies, the pharmaceutical industry, parent organisations, patient rights advocacy groups and other charities to continue working and collaborating closely to facilitate children access to these new drugs.¹⁶

Generally speaking, the use of certain drugs in patients with refractory or relapsed cancer is not based on a solid foundation of scientific evidence, and most are not indicated for the paediatric age group. The off-label use of drugs that are only authorised in adults carries significant risks and does not help improve the scientific evidence on their use.¹⁷

Traditionally, the development of a new drug involves different phases (I through III) to evaluate its toxicity and safety (I), efficacy (II) and improvements in survival (III) in specific populations.¹⁸ Phase IV trials are postmarketing studies that seek to identify toxicities that were not observed previously and assess long-term efficacy. When it comes to oncology, the subset of patients that participate in early-phase trials (I and II) mostly consists of those who have relapsed after at least one course of treatment, or with refractory cancer. This is a long and costly process—usually more than 10 years from target identification in a laboratory to marketing with costs of up to 2000 million dollars per product.¹⁹ Fewer than 5% of medicines evaluated in phase I clinical trials gain market authorisation,²⁰ and only 1 out of 10 000 compounds ever reach the market.²¹

Along these lines, the Innovative Therapies For Children With Cancer consortium (ITCC; <http://www.itcc-consortium.org>) is an international organisation whose principal aim is to evaluate novel therapies for the treatment of cancer in children and adolescents. The ITCC provides the necessary accreditation to develop and implement clinical trials in childhood cancer, facilitates contact with academic or pharmaceutical industry sponsors, and opens new clinical research centres²² with the purpose of expediting access to these medicines for children.

The aim of this study is to describe the activity in early-phase clinical trials in paediatric cancer in Spain in the past 10 years, to evaluate the hurdles that we are facing, their potential solutions, and future challenges. This study will provide a reference for this field for future comparison, following the example of the BEST project of Farma Industry, an association that seeks to promote excellence in clinical research of medicines in Spain and to assess performance, efficacy and quality in the field (www.farmaIndustry.es).

Patients and methods

The Sociedad Española de Hematología y Oncología Pediátrica (Spanish Society of Paediatric Haematology and Oncology [SEHOP]; www.sehop.org) represents all paediatric oncology units in Spain. We contacted all the SEHOP members to identify phase I and II trials for solid tumours

and blood cancers initiated between 2005 and 2015. We chose this period because in Spain, early-phase trials in the paediatric population started to be conducted in 2005.

For each of the trials, we collected data regarding the type of trial (phase I or II), sponsor (academia or pharmaceutical industry), number of participating centres, enrolment period, type(s) of tumour(s) under study, drug under

Table 1 Ongoing paediatric phase I/II clinical trials for solid tumours in Spanish centres between 2005 and 2015.

Drug under study/name of clinical trial	Mechanism of action	Trial phase	Disease	Sponsor	Number of participating centres	Reference
CLDK378X2103	ALK-TKI	I	Solid tumours with ALK mutations	Industry	3	NCT01742286
Afatinib	Multi-TKI	I	Brain tumours and rhabdomyosarcomas	Industry	1	NCT02372006
BRIM-P: vemurafenib	BRAF-TKI	I	Melanoma	Industry	2	NCT01519323
Lenvatinib	VEGFR-TKI	I/II	Solid tumours	Industry	2	EudraCT: 2013-005534-38
Dabrafenib	BRAF-TKI	I/II	Solid tumours with <i>BRAF-V600E</i> mutation	Industry	2	NCT01677741
Abraxane (nab-placitaxel)	Cytotoxic agent	I/II	Solid tumours	Industry	3	NCT01962103
CELYVIR	Oncolytic virus	I/II	Solid tumours	Academia	1	NCT01844661
Haplo TPH + IL-15 NK	Haplo TPH + IL-15 NK	I/II	Solid tumours	Academia	1	NCT01337544
LTI ch14.18/CHO-IL2	Immunotherapy	I/II	Neuroblastoma	Academia	3	NCT01701479
Dinutuximab-IL2	Immunotherapy	II	Neuroblastoma	Academia	1	NCT02169609
BEACON	Cytotoxic agent ± antiVEGF mAb	II	Neuroblastoma	Academia	3	NCT02308527
Irinotecan/cisplatin	Cytotoxic agent	II	Brain tumours	Academia	1	NCT01574092
HERBY	Cytotoxic agent + radiotherapy + antiVEGF mAb	II	High-grade gliomas	Industry	10	EudraCT: 2010-022189-28
TEMIRI (temozolomide + irinotecan)	Cytotoxic agent	II	Medulloblastomas and high-grade gliomas	Academia	3	EudraCT: 2006-005476-40
TOTEM (topotecan + temozolomide)	Cytotoxic agents	II	Solid tumours	Academia	3	NCT00918320
Ipilimumab	Anti-CTLA-4 mAb	II	Melanoma	Industry	1	NCT01696045
Sunitinib	Multi-TKI	II	GIST	Industry	4	NCT01396148
GEIS-21 (gemcitabine + docetaxel)	Cytotoxic agents	II	Ewing sarcoma	Academia	8	NCT01696669
rEECur	Cytotoxic agents	II	Ewing sarcoma	Academia	17	EudraCT: 2014-000259-99
GEIS 29 (gemcitabine + rapamycin)	Cytotoxic agent + mTOR inhibitor mTOR	II	Osteosarcoma	Academia	15	NCT02429973
BERNIE	Cytotoxic agents + antiVEGF mAb	II	RMS and non-RMS soft tissue sarcomas	Industry	4	NCT00643565

Clinical trials that are no longer recruiting patients as of June 15, 2016 are presented in boldface.

CTLA-4, cytotoxic T-lymphocyte antigen 4; GIST, gastrointestinal stromal tumour; HSCT, haematopoietic stem cell transplantation; IL, interleukin; mAb, monoclonal antibody; RMS, rhabdomyosarcoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Source: www.clinicaltrials.gov/www.clinicaltrialsregister.eu.

Table 2 Ongoing paediatric phase I/II clinical trials for blood cancers in Spanish centres between 2005 and 2015.

Drug under study/name of clinical trial	Mechanism of action	Trial phase	Disease	Sponsor	Number of participating centres	Reference
LANK-2	NK cell therapy + cytotoxic agents	I	Acute lymphoblastic and myeloid leukaemia	Academia	2	NCT02074657
HNJ-NKAES-2012	NK cell therapy + cytotoxic agents	I	T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma	Academia	1	NCT01944982
Dacogen	Hypomethylating agent+ cytotoxic agent	I/II	Acute myeloid leukaemia	Industry	3	NCT01853228
Brentuximab	mAb anti-CD30	I/II	Anaplastic large-cell lymphoma and Hodgkin lymphoma	Industry	1	NCT01492088
Carfilzomib	Proteasome inhibitor ± cytotoxic agent	I/II	Acute lymphoblastic leukaemia	Industry	1	NCT02303821
Nilotinib	TKI	II	Ph+ chronic myelogenous leukaemia	Industry	3	NCT01844765
Dasatinib	TKI	II	Ph+ chronic myelogenous leukaemia	Industry	6	NCT00777036
Moxetumomab	Anti-CD22 mAb	II	Acute lymphoblastic leukaemia and lymphoblastic lymphoma	Industry	2	NCT02227108
Inter-B-NHL-RITUX 2010	Rituximab (mAb anti-CD20) ± cytotoxic agents	II	Primary mediastinal B-cell lymphoma	Academia	30	NCT01516580

Clinical trials that are no longer recruiting patients as of June 15, 2016 are presented in boldface.

mAb, monoclonal antibody; NK, natural killer; TKI, tyrosine kinase inhibitor.

Source: www.clinicaltrials.gov/www.clinicaltrialsregister.eu

investigation, mechanism of action and number of patients enrolled in the trial. We updated these data on December 1, 2015. We checked whether trials were still recruiting patients in June 15, 2016.

When further information was needed, we resorted to the clinical trials registry of the United States National Institutes of Health (www.clinicaltrials.gov), the European Union Clinical Trials Register (www.clinicaltrialsregister.eu) and the Spanish Register of Clinical Trials of the Agencia Española del Medicamento y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices [AEMPS]; <https://reec.aemps.es>).

Results

Centres with units devoted to early-phase clinical trials: The role of the ITCC consortium

Since 2010, 4 Spanish hospitals have joined the ITCC consortium: the Hospital Universitari La Fe in Valencia; the Hospital

Universitari Vall d'Hebron in Barcelona, the Hospital Niño Jesús in Madrid and the Hospital Sant Joan de Déu in Barcelona. Other centres that are members of the SEHOP have also partaken in some of the studies described here, most of them phase II trials: La Paz, Gregorio Marañón and Doce de Octubre hospitals (Madrid), Hospital Santa Creu i Sant Pau (Barcelona), Hospital Virgen del Rocío (Seville), Hospital Virgen de la Arrixaca (Murcia), Hospital de Cruces (Bilbao), Hospital Son Espases (Palma de Mallorca), Hospital Clínico (Valencia), Hospital Universitario de Canarias (Tenerife), Hospital Miguel Servet (Zaragoza), Hospital Central de Asturias (Oviedo), Hospital Regional Universitario (Malaga) and Hospital General Universitario (Alicante).

Paediatric oncology clinical trial portfolio

Tables 1 and 2 list the early-phase clinical trials in patients with solid tumours and blood cancer, respectively, initiated between 2005 and 2015 in Spain.

Table 3 Clinical trials conducted between 2010 and 2015 by specific disease groups.

Clinical trials		2010	2015
Brain tumours	High-grade glioma	◆	◆
	Low-grade glioma		◆
	Medulloblastoma	◆	◆
	Other brain tumours		◆
Leukaemia, lymphoma	ALL		◆
	AML		◆
	CML	◆	◆
	Lymphoma		◆
Solid tumours	Osteosarcoma		◆
	Ewing sarcoma		◆
	Rhabdomyosarcoma	◆	◆
	Other sarcomas	◆	◆
	Neuroblastoma		◆
	Melanoma		◆
	Other solid tumours		◆

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myelogenous leukaemia.

A total of 30 trials have been launched: 21 (70%) in patients with solid tumours and 9 (30%) in patients with blood cancers.

Of the trials for solid tumours, 3 (14%) are separate phase I trials, 6 (29%) are parallel phase I/II trials, and 12 (57%) are separate phase II trials. Six (28%) are assessing tyrosine kinase inhibitors (TKIs), 6 (28%) cytotoxic agents, 3 (14%) a combination of cytotoxic agents with a monoclonal antibody (mAb), 2 (9%) a combination of 2 immunotherapy drugs for neuroblastoma, 1 (5%) a mAb for melanoma, 1 (5%) the combination of a TKI with a cytotoxic agent for osteosarcoma, 1 (5%) an oncolytic virus (Celyvir^{23,24}) and 1 (5%) a combination of interleukin-15-stimulated natural killer cells and haploidentical hematopoietic stem cell transplantation. Two trials (10%) focused on tumours with specific molecular changes, 14 (66%) on specific types of tumours and 5 (24%) were for solid tumours of any type. Half of the trials were sponsored by pharmaceutical companies and the other half by academic institutions; 15 (72%) focused exclusively on the paediatric population (age <18 years), 4 (19%) included young adults up to age 21 years and 2 (9%) included paediatric as well as adult patients.

Of the blood cancer trials, 2 (22.2%) were phase I trials, 3 (33.3%) were phase I/II trials, and 4 (44.5%) phase II trials; 2 (22.2%) studied a TKI, 2 (22.2%) a mAb, 2 (22.2%) cell therapy with and without chemotherapy, 1 (11.1%) a combination of a mAb with cytotoxic agents, 1 (11.1%) a hypomethylating agent and 1 (11.1%) a proteasome inhibitor. Two trials (22.2%) focused on diseases with specific molecular changes and 7 (77.8%) on specific blood cancers. Most are sponsored by the pharmaceutical industry ($n=6.66\%$). They are all exclusively focused on the paediatric population under 18 years.

Table 3 shows the considerable increase in the options available for the groups of diseases for which clinical trials have been available in the past 5 years in Spain.

Enrolment in paediatric cancer clinical trials

A total of 212 patients were enrolled during this period: 179 (84%) in solid tumour clinical trials and 33 (16%) in blood cancer clinical trials.

Completed clinical trials

The findings of completed trials and of ongoing trials whose intermediate results have been made available demonstrate the positive contribution of Spanish researchers, the introduction of targeted molecular therapies in the paediatric population and the benefits that patients may derive from these new drugs (Table 4).^{8,10,23,25-31}

Discussion

This article describes the activity in the development of new treatments for paediatric cancer in Spain.

Children with cancers that are high-risk or carry a poor prognosis continue to have difficulty accessing new drugs. The number of trials opening in Spain has increased in the past 5 years, probably as a result of hospitals joining the ITCC, changes in legislation applying to paediatrics and institutional efforts to establish units devoted to these trials staffed by physicians, research nurses, project managers and data managers.

Between 2010 and 2014, 4 centres have joined the ITCC, a consortium established in 2003 that comprises 9 European basic research laboratories and 47 paediatric oncology centres with the necessary resources to carry out phase I and II clinical trials in paediatric oncology. One of the aims of the consortium is to develop novel therapies for paediatric malignancies in collaboration with pharmaceutical companies, regulatory bodies and patient and parent associations.²² Since 2007 the number of drugs in early phase trials being run by the ITCC has grown from one in 2007 to 12 in 2013, with half of these trials being conducted to comply with the regulatory requirements of a paediatric investigation plan; this has significantly improved access of European children to novel therapies.¹⁵ For Spain, being actively involved in the ITCC allows us to participate in international collaborative trials, which facilitates access to promising therapies to our patients.

Most of the early-phase clinical trials in paediatric oncology and haematology that have opened in Spain have been sponsored by the pharmaceutical industry ($n=16$; 53%). Only one third of the total focus on blood cancers. This is possibly due to the fact that the overall cure rate with first-line treatment is high for leukaemias and lymphomas, and that a significant percentage of patients that relapse achieve full remission for the second time and eventually a cure with conventional chemotherapy or hematopoietic stem cell transplantation. Thus, the target paediatric population for new drugs for blood cancers is smaller. Recruitment is further complicated by the stringent inclusion and exclusion criteria, the challenges involved in transferring patients from their original hospitals to the centres where these new therapies are available, and the natural history of the disease, which sometimes does not allow delays in treatment initiation. These factors also apply to solid tumour patients,

Table 4 Summary of some of the completed trials.

Clinical trial ^[Ref]	Results
Ceritinib (LDK 378) ⁸	22 patients aged less than 18 years with relapsing/refractory tumours with ALK mutations/changes. Patients were treated with increasing doses of ceritinib RP2D: 510 mg/m ² . Pharmacokinetics comparable to those in adults 2 DLTs at doses of 560 mg/m ² /day. Frequent AEs: diarrhoea, vomiting, nausea, elevated ALT 6 objective responses: 2 of 2 patients with LCAL and 4 of 7 patients with MT/IMT
Dabrafenib ¹⁰	27 patients aged less than 18 years with relapsing/refractory tumours with BRAF mutations/changes. Patients were treated with increasing doses of dabrafenib RP2D: 4.5 mg/kg/day for patients >12 years and 5.25 mg/kg/day for patients <12 years 1 TLD at 4.5 mg/kg/day. Frequent AEs: hypotension, skin rash, DIC, fever and arthralgia 23 objective responses: 6 of 8 patients with high-grade glioma, 14 of 15 with low-grade glioma, 2 LCH, 1 other type of solid tumour
Abraxane (nab-paclitaxel) ²⁵	64 patients aged less than 18 years with relapsing/refractory solid tumours except brain tumours Patients were treated with increasing doses of nab-paclitaxel RP2D: 240 mg/m ² 2 TLD at doses of 120 mg/m ² and 270 mg/m ² (dizziness and neutropaenia, respectively) 5 partial responses
Celyvir ²³	14 patients aged less than 18 years with refractory or relapsed neuroblastoma Weekly infusion of autologous pluripotent mesenchymal stem cells carrying an oncolytic virus (range, 4–70) Total cells (min, 70 × 10 ⁶ , max 2.640 × 10 ⁶) and viral particles (min, 1.80 × 10 ¹² ; max, 5.280 × 10 ¹³) No serious adverse events 4 objective responses: 1 stable disease, 2 partial remissions and 1 full remission
Haplo + IL-15 NK cell ³¹	6 patients aged less than 18 years with refractory sarcoma and relapsed adrenal gland carcinoma DLI of haploidentical NK cells obtained by immunomagnetic separation in GMP conditions and stimulated with IL-15 overnight. Total infused cells 11 × 10 ⁶ /kg (3–27 × 10 ⁶ /kg) No serious adverse events associated with NK cell infusion 4 objective responses: 1 stable disease, 2 partial remissions and 1 highly favourable partial remission
LTI ch14.18/CHO-IL2 ²⁶	97 patients aged less than 21 years with high-risk neuroblastoma Pharmacokinetics of ch14.18/CHO in cycle 1: C _{max} = 12.2 ± 0.4 µg/mL, t ^{1/2} = 8.4 ± 1.1 d, AUC = 145.3 ± 5.8 µg d/mL 1-year and 4-year PFS: 54.4% ± 06.9% and 32.3% ± 06.9% versus 19% ± 02% and 8% ± 03% of historical controls 1-year and 4-year OS: 94.2% ± 03.2% and 60.9% ± 09.0% versus 56% ± 03% and 14% ± 04% of historical controls
GEIS-21 ²⁷	43 patients with Ewing sarcoma aged less than 40 years in first-line treatment 22 SR patients and 21 HR patients Chemotherapy with mP6, surgery and radiation in SR patients and window evaluation of gemcitabine/docetaxel in HR patients 4-year EFS and OS in SR patients were 67% and 74%, respectively 4-year EFS and OS in HR patients were 67% and 42%, respectively EFS and OS were significantly higher in the under-18 years group
TEMIRI ²⁸	66 patients aged less than 18 years with relapsing/refractory medulloblastoma Patients were treated with temozolomide on days 1–5 and irinotecan on days 1–5 and 8–12 every 21 days The most frequent toxicities were haematologic and gastrointestinal (diarrhoea) The objective response rate was 33%, and 68% showed clinical improvement
TOTEM ²⁹	38 patients aged less than 18 years with relapsing/refractory neuroblastoma L patients were treated with temozolomide on days 1–5 and topotecan on days 1–5 and 8–12 every 28 days The most frequent toxicity was haematologic 1-year PFS and OS were 42% and 58%, respectively
BERNIE ³⁰	154 patients aged less than 18 years with metastatic rhabdomyosarcoma 80 were randomly allocated to the chemotherapy-only arm, and 74 to the chemotherapy + bevacizumab arm The toxicity profile was similar in both groups EFS was similar in both groups (12.5% vs 18.9%, P = .71) OS was similar in both groups (42.2% vs 32.3%, P = .32)

AE, adverse event; AUC, area under the curve; DIC, disseminated intravascular coagulation; DLI, donor lymphocyte infusion; DLT, dose-limiting toxicity; EFS, event-free survival; GMP, good manufacturing practice; HR, high risk; IMT, inflammatory myofibroblastic tumour; RP2D, recommended phase II dose; LCH, Langerhans cell histiocytosis; IL, interleukin; LCAL, large-cell anaplastic lymphoma; MT, myofibroblastic tumour; NK, natural killer; OS, overall survival; PFS, progression-free survival; SR, standard risk.

and in specific nervous system diseases or sarcomas, there are even fewer clinical trials.

For all the above reasons, paediatric cancer as a whole constitutes a “small” market with few incentives for the pharmaceutical industry.³²

We believe that these groups of “orphan” patients should benefit from academic clinical trials. From our paediatric haematology and oncology society,³³ and in collaboration with other scientific societies, such as the Grupo Español de Investigación en Sarcomas (Spanish Sarcoma Research Group [GEIS]), we aim to develop and participate in collaborative academic clinical trials to promote therapeutic advances and the optimisation of existing therapies for rare diseases like childhood cancer, which are not usually the target of pharmaceutical companies. Our duty as researchers is to improve on study design to add adaptability and flexibility, and to develop trials on the basis of solid scientific evidence so that they target populations that are more likely to show a favourable response.³⁴ In this regard, the Sociedad Española de Oncología Médica (Spanish Society of Medical Oncology) took an important initiative in addressing a manifesto to policymakers requesting support for independent academic clinical research.³⁵

An added difficulty is the lack of funding for clinical development in academic settings. This poses barriers to participation in international academic clinical trials, as the costs of opening the trial at the local and national levels must be assumed nearly in full by participating countries. Few not-for-profit organisations fund paediatric cancer research programmes or have specific agendas to support clinical trials. The recent Royal Decree 1090/2015 regulating drug clinical benefits non-commercial clinical research studies through exemption of fees or reduced fees and by simplifying the costly and complex bureaucracy involved in opening such trials. Lack of funding does not only ail this side of the Atlantic. In the United States, 60% of the funding for biomedical research comes from the biopharmaceutical industry,³⁶ followed by the National Institutes of Health, which contributes another 25%. However, funding from the pharmaceutical industry is nearly nonexistent in paediatric cancer, so that research in the field depends on the National Institutes of Health, private institutions and charities.³²

On the bright side, the favourable outcomes observed in samples selected based on molecular findings and treated with targeted therapies such as ALK or BRAF inhibitors^{8,10,11} or with the use of anti-GD2 mAb in high-risk neuroblastoma²⁶ are encouraging, so we must remain optimistic. Such evidence ought to stimulate investment in basic and clinical research and help patients be referred more easily to centres that can offer new therapies that may be beneficial.

The experience of 2 of the largest early-phase clinical trial units in paediatric oncology in Europe, the Royal Marsden (London, United Kingdom)³⁷ and Gustave Roussy (Villejuif, France)³⁸ proves that implementing these therapies in the context of everyday paediatric oncology practice is possible and safe for patients, while allowing a significant percentage of paediatric cancer patients to benefit from these treatments.

Clinical trials are a necessary and indispensable means to evaluate new treatments that can provide robust and solid data on their safety and efficacy, which is as beneficial to the

scientific community as it is to patients. The evaluation of new anticancer drugs in children and adolescents must comply with current legislation, avoiding off-label use^{17,39} and in the context of clinical trials approved by ethics committees and conducted in adherence to good clinical practice principles.

Conflict of interests

The authors have no conflict of interests to declare.

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