European Journal of Cancer (2013) 49, 2392–2402

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.com

A comparative analysis of paediatric dose-finding trials of molecularly targeted agent with adults' trials

Xavier Paoletti [a,*], Birgit Geoerger [c], François Doz [d,e], André Baruchel [f,g], François Lokiec [h], Christophe Le Tourneau [b,i]

[a] *Biostatistics department, Institut Curie, Paris, France*
[b] *INSERM U900, Institut Curie, Paris, France*
[c] *Department of Paediatric and Adolescent Oncology, Institut Gustave Roussy, University Paris-Sud IX, Vectorology and Anticancer Therapeutics, CNRS UMR 8203, Villejuif, France*
[d] *Paediatric Department, Institut Curie, Paris, France*
[e] *University Paris Descartes, Sorbonne Paris Cité, France*
[f] *Paediatric Hemato-Immunology Department, Hôpital Robert Debré, Paris, France*
[g] *University Paris Diderot, Sorbonne Paris Cité, France*
[h] *Pharmacology Department, Institut Curie – René Huguenin Hospital, St. Cloud, France*
[i] *Clinical Trial Unit, Department of Medical Oncology, INSERM U900, Institut Curie, Paris, France*

Available online 27 March 2013

KEYWORDS
Dose-finding
Design
Pharmacokinetics
Paediatrics
Clinical development
Phase I trial

Abstract ***Background:*** Dose-finding phase I trials in children are usually carried out once clinical data have already been accumulated in the adult population. The objectives, place and role of paediatric dose-finding trials are investigated in the era of molecularly targeted agents (MTAs).

Methods: Phase I paediatric oncology trials of MTAs approved in adults before June 15th, 2012 were reviewed. The recommended phase II dose (RPIID) was compared to the body surface area (BSA)-adjusted approved dose in adults. Toxicity profile was compared to the findings from the corresponding adult phase I trials.

Results: Fifteen MTAs out of a total of 25 MTAs approved in the adult population have been evaluated in 19 single-agent phase I paediatric trials. Trials included a median of 30 children with a median of four dose levels. The paediatric RPIID ranged between 90% and 130% of the BSA-adjusted approved dose in adults for 70% of the trials (75% of compounds). Overall, 63%

* *Corresponding author*: Address: Biostatistics Department, INSERM U900, Institut Curie, 26, rue d'Ulm, 75005 Paris, France. Tel.: +33 1 56 24 56 47; fax: +33 1 40 20 10 40.
E-mail address: xavier.paoletti@curie.net (X. Paoletti).

0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.02.028

of children did not receive an optimal dose. The most marked discrepancy involved sunitinib. Safety profiles described in phase I paediatric trials were usually similar to those reported in the adult population.

Conclusions: These data suggest that dose-finding studies might not be necessary for all the MTAs in children. Except in the case of a narrow therapeutic index, early-phase trials validating pharmacokinetics, pharmacodynamic markers and efficacy findings from adults while controlling for toxicity appear to be a possible alternative to accelerate drug development in paediatric oncology.

1. Introduction

Despite the high cure rate in most childhood cancers, some diseases still have a poor prognosis and several active treatments are associated with severe sequels. The clinical development of novel agents is therefore of primary importance in paediatric oncology.

New drugs undergo a rigorous sequential development process before they can be recommended for paediatric use.[1] However, evaluation of safety and efficacy is challenging in view of the low incidence of paediatric cancers.[2] Clinical development of new drugs usually follows a similar process to that established in adults. Phase I trials are designed to identify the optimal dose for subsequent evaluation of efficacy in phase II and III trials.

Phase I trials in the paediatric population present specificities: (1) the toxicity profile, the recommended phase II dose (RPIID) and pharmacokinetic/pharmacodynamic (PK/PD) parameters are generally already known from the adult population, (2) the patient population is heterogeneous in terms of age, therefore amplifying potential variability[3], and (3) the ethical issue of parents who consent for their children knowing that the primary objective of the study is to evaluate toxicity. In view of these aspects, the optimal design of dose-finding studies and the best way to use information from adults are regularly reassessed.

A landmark paper compared the conduct of phase I trials in children published between 1990 and 2004 and their corresponding phase I trials in adults. They found that the maximum tolerated dose (MTD)[4] in children ranged between 80% and 160% of the MTD established in adults in 80% of trials, supporting 80% of the RPIID in the adult population as a safe starting dose for phase I trials in the paediatric population.[5] However, this study mainly involved cytotoxic agents administered as single agents. Molecularly targeted agents (MTAs) display different toxicity profiles, predominantly non-haematologic toxicities.[6] Importantly, the efficacy of MTAs may not always increase with the dose[7] and the therapeutic index may be larger. The notion of optimal biological dose has then been coined.

This paper scrutinises the findings of phase I clinical trials of MTAs in children. We compared all published data obtained from phase I paediatric trials of MTAs approved for clinical use in adults to data obtained in the adult population. Based on our findings, we suggest methodological considerations for the design of early-phase trials in a paediatric cancer population.

2. Patients and methods

2.1. Literature review

MTAs were defined as agents triggering extra- or intra-cellular targets that differ from those of cytotoxic agents (DNA, tubulin or cell division machinery).[8] The list of oral or intravenous MTAs approved by the US Food and Drug Administration (FDA) and/or European Medical Agency (EMA) for the treatment of solid tumours or haematologic malignancies was obtained from the National Cancer Institute (NCI) and EMA websites (http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted and http://www.ema.europa.eu/) as of 15th June 2012. Full length reports of phase I paediatric trials were identified by searching the National Library of Medicine using the following keywords in addition to the name of the drug: 'paediatric', 'children', 'phase I', 'cancer' and 'trial'. Finally, the proceedings of the American Society of Clinical Oncology and the American Society of Hematology meetings were also scrutinised. When no single-agent phase I trial could be found, combination trials were used if dose escalation only involved the agent of interest. Phase I trials in adults of the compound investigated in children were similarly searched.

2.2. Data extraction

Data were extracted by XP and validated by B.G., A.B. (paediatric studies) and C.L.T. (adults' studies). Objectives and end-points were extracted from the method sections of each publication. The following data were recorded for each phase I paediatric trial: drug type, dose regimen, route of administration, number of patients included, median age and range, tumour types, number of dose levels, number of patients assessable for toxicity, clinical responses, dose-limiting toxicities (DLTs) and toxicity profile as assessed by the authors, MTD or maximum administered dose (MAD) when the MTD was not reached and RPIID. If no RPIID