CLINICAL INVESTIGATION

Challenges of developing new drugs for childhood cancers

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New anticancer drugs are developed separately in children because of potential differences in drug disposition, tissue/organ sensitivity to the drug's toxic effects and pathogenesis and tissue of origin of childhood cancers compared with cancers in adults. The focus of new drug development for childhood cancers has shifted to molecularly targeted drugs that selectively inhibit cell-signaling pathways responsible for the malignant phenotype. This new era of drug development will require a process for selecting new agents to study in children, based on target expression and new clinical trial end points and designs that determine the dose based on a therapeutic effect rather than toxicity. For new orally administered agents, pediatric liquid formulations are essential to accurately dose and study new agents in young children.

Keywords: childhood cancer • dose • end points • formulation • molecularly targeted drugs • pharmacokinetics • toxicity • trial design

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Conventional cytotoxic chemotherapy has had its greatest impact in the treatment of childhood cancers. The 5-year survival in children with cancer has improved to 80%, and most of these children are cured of diseases that were once uniformly fatal [1]. However, cure comes at a cost – acute toxicities of current dose-intensive chemotherapy regimens can often be life-threatening. In addition, survivors of childhood cancer can suffer from long-term sequelae that include infertility, secondary cancers, deafness and other neurological impairments, and organ damage, such as cardiomyopathy and renal glomerular and tubular dysfunction [2,3]. The search for new, less toxic anticancer drugs for childhood cancers is a high priority for pediatric oncologists.

The clinical development of anticancer drugs is summarized in Table 1. Traditionally, dose is determined by toxicity rather than by a therapeutic effect of the drug in Phase I trials. The severity of each toxicity is graded using standardized criteria (National Cancer Institute Common Terminology Criteria for Adverse Events [101]). The recommended dose for subsequent trials is the maximum tolerated dose (MTD), which is the dose level below the dose at which a third or more of the patients experienced a dose-limiting toxicity that was defined in the protocol to be unacceptably severe.

New anticancer drugs are studied separately in children because the ontogeny of excretory organs impacts drug disposition and tissue/organ sensitivity to the toxic effects of anticancer drugs can be age-dependent. In addition, the pathogenesis and tissue of origin of childhood cancers differ substantially from cancers in adults [4]. The approach to clinical drug development in children is similar to the approach in adults (Figure 1), but noteworthy differences include:

- Pediatric Phase I trials are most often conducted at multiple institutions,

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Table 1. Phases of the clinical drug-development process for anticancer drugs.

	Phase I	Phase II	Phase III
Objective	Define the MTD Describe the PKs Describe toxicity profile	Describe antitumor activity spectrum	Demonstrate efficacy (clinical benefit)
Eligibility	All tumor types	Tumor specific	Tumor specific
End point	Toxicity quantified by grading criteria (CTCAE)	Percentage decrease in tumor size	Survival
Design	Dose escalation	Two-stage with early stopping for futility	Randomized

The optimal dose is defined as the MTD based on severity of ensuing toxicity. This dose is used in the Phase II and III trials. Response in Phase II is quantified by measuring the percentage change in the longest diameter of a tumor and then categorizing the percentage change as a complete response, partial response, stable disease or progressive disease.
CTCAE: Common Terminology Criteria for Adverse Events; MTD: Maximum tolerated dose; PK: Pharmacokinetic.

usually within organized consortia such as the NIH-funded Pediatric Phase I and Pilot Consortium, to ensure more rapid accrual to the trials;

- The 'rolling six' Phase I clinical trial design [5,6], which is better suited for multi-institutional Phase I trials because of its flexible, concurrent enrollment of up to six patients per dose level, is gradually replacing the traditional 3 + 3 Phase I trial design;
- Pediatric Phase I trials are conducted after completion of Phase I trials in adults. The starting dose for the pediatric trials is usually 80% of the adult MTD [7] and the dose is escalated in 25–30% increments until the MTD is defined in children;
- Pediatric Phase II trials are also multi-institutional studies that typically include multiple tumor types, which are enrolled independently.

Meta-analyses comparing the outcomes of Phase I trials conducted in children and adults using the same dosing schedule support the need for separate Phase I trials in children, rather than scaling the adult dose for children. For 14 cytotoxic drugs studied in the 1970s and early 1980s in patients with solid tumors, the MTDs in children were an average of 130% of the MTDs in adults, with a range of 66–280% (the MTD were lower in children than adults for only one drug) [7]. This meta-analysis led to the recommendation of using 80% of the adult MTD as the starting dose for pediatric Phase I trials. In a more recent analysis of 32 pediatric solid tumor Phase I trials of cytotoxic agents that were also studied in adults [8], the MTD in children was lower than the adult MTD in a third of the trials and the MTDs in children ranged from 35 to 173% of the MTDs in adults. Drug clearances in children were compared with clearances in adults in a subset of these clinical trials [8]. Although drug clearance in children correlated with clearance in adults, the ratios of pediatric to adult clearance ranged from 6 to 220%.

Anticancer drug development has been revolutionized by our rapidly expanding knowledge of the pathogenesis of cancers at a genetic and molecular level. This has led to the discovery of new classes of molecularly targeted anticancer drugs that are transforming our approach to cancer treatment. Their pharmacological effects selectively and reversibly inhibit cellular signaling pathways that are involved in the malignant transformation of cancer cells and this enhanced selectivity may translate into more favorable toxicity profiles and therapeutic indices. The acute toxicities of these agents appear to differ substantially from conventional cancer chemotherapy. However, we are not yet able to assess their long-term effects, which may impact on growth and development in young children.

The focus of new drug development for childhood cancers has shifted to molecularly targeted drugs, but our approach to the clinical development of these new agents currently follows the traditional model used for conventional cytotoxic drugs, with toxicity-based dosing and tumor response used to define drug activity. For molecularly targeted drugs to fully realize their potential to be a less toxic approach to control tumor growth, invasion and metastatic spread, a new approach to clinical drug development, including innovative clinical trial end points and designs, is required. This review focuses on these new challenges to developing molecularly targeted drugs for childhood cancers, as well as the long-standing challenges of performing clinical research in children with rare diseases.

Drug discovery & selection

The primary and often only criterion for selecting

new cytotoxic drugs to develop in childhood cancers has been the successful completion of Phase I trials in adults. This ensures that the drugs are safe in humans and that there would be a potential path towards US FDA approval in adults with a common form of cancer. This pragmatic approach to drug selection is rational for cytotoxic drugs because their nonselective mechanisms of action are not dependent on the pathogenesis of the cancers for activity, unlike the new classes of molecularly targeted drugs.

Identifying new, more selective molecularly targeted drugs for childhood cancer is more challenging. Ideally, drug targets would be identified based on our rapidly expanding knowledge of the pathogenesis of childhood cancers at the molecular level and high-throughput screening would be used to discover inhibitors, which would then undergo preclinical and clinical development for the specific cancer type in children. However, due to the high research and development costs of bringing a new drug to market, it is not economically feasible for most pharmaceutical companies to develop new anticancer drugs only for a pediatric indication, given the low incidence of the various forms of childhood cancers.

The alternative approach would be to apply molecularly targeted drugs under development for common cancers in adults to childhood cancers, as has been done with cytotoxic agents. This approach requires some knowledge of the role of a drug's target(s) in the pathogenesis of various childhood cancers. Some molecularly targeted drugs inhibit multiple receptor tyrosine kinases and for some of these multitargeted anticancer drugs, the primary mechanism of action in a childhood cancer could be an off-target effect in cancers that occur in adults. For example, vandetanib was originally developed in adults as a VEGF and EGF receptor inhibitor but it also inhibits the *RET* gene product. Vandetanib has been studied in children [9] and approved in adults for the treatment of medullary thyroid cancer, which is caused by a mutation in the *RET* gene.

Extensive preclinical testing of new drugs in *in vitro* and *in vivo* models to assess antitumor activity is a standard component of the preclinical drug-development process, but has not proven to be reliably predictive of activity in clinical trials. The National Cancer Institute has funded a Pediatric Preclinical Testing Program (PPTP) to systematically assess the activity of new drugs in pediatric tumor cell lines *in vitro* and in xenograft models *in vivo* [10]. Although over 30 drugs have been tested, the PPTP has had a minimal impact on clinical development of new drugs in children. The models have yet to be prospectively validated as predictive of outcome in clinical trials and many of the agents tested by the PPTP will never reach Phase II testing in children because the clinical development of the drugs has been halted, usually because of a lack of activity in cancers in adults. In addition, the end points used to assess drug activity by the PPTP may not be optimal for testing molecularly targeted drugs. This indiscriminant cytotoxic era approach to screening for drug activity and the timing of testing of new drugs in pediatric tumor models, should be reassessed to ensure that the resources committed to the PPTP provide valuable and useful information to guide clinical drug development for childhood cancers. Recommitment of these resources to studying the expression and role of drug targets from common cancers in adults in the pathogenesis of childhood cancers would likely provide more useful information for prioritizing drugs for clinical development.

Patient population

Childhood cancers are rare diseases, and as cure rates rise, the number of children who have relapsed or treatment-refractory cancers and who are available

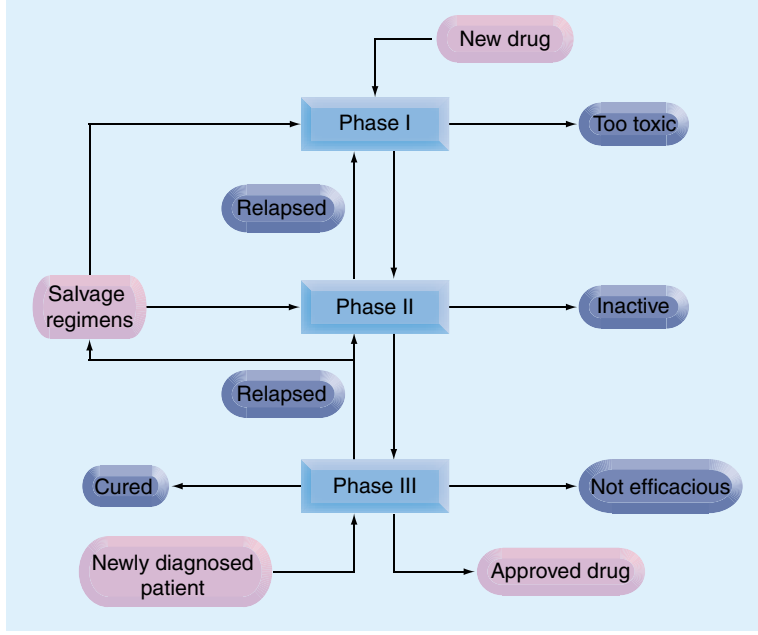

Figure 1. The clinical drug-development process for childhood cancers from the drug and patient perspective. Patients and drugs move through the phases of drug development in opposite directions. Development of a drug can be stopped at any of the phases if it is too toxic, inactive or not efficacious. However, this is generally not determined by the results of pediatric trials but by outcomes from separate trials in adults. Depending on the diagnosis, patients may receive conventional chemotherapy regimens after relapse and before enrollment onto investigational Phase I and II trials.

and eligible for enrollment on Phase I and II trials is declining. In addition, cancers with lower relapse-free survival rates are over-represented in the population of patients eligible for these trials [8,11]. The shrinking population of children with cancers that are refractory to standard treatments has yet to have an impact on our ability to perform Phase I trials in a timely fashion, in part because children may enroll sequentially on multiple Phase I trials.

The prior therapy of the patients enrolled on Phase I trials can influence the dose of the new agent determined by the Phase I trial [12,13]. As a general rule, childhood cancers with lower cure rates are treated with more intensive chemotherapy regimens. Patients who receive more dose-intensive frontline, conventional, cytotoxic chemotherapy and radiation prior to enrollment on a Phase I trial, may be less tolerant of the investigational agent and experience a dose-limiting toxicity on a lower dose level compared with a less heavily pretreated patient. Prior treatment with dose-intensive cytotoxic chemotherapy may be less likely to alter a patient's tolerance of molecularly targeted drugs because their mechanisms of action and toxicity profiles differ substantially from drugs used in frontline regimens [14]. Doses defined in Phase I single-agent trials performed in heavily pretreated patients may need to be adjusted when the new drug is studied in Phase III trials in combination regimens with previously untreated patients.

The enrichment of the relapsed population for patients with cancers that have higher relapse rates does limit our ability to evaluate the activity of new agents in tumors with high cure rates, such as Wilms' tumor. Although it seems intuitive that treatment-refractory cancers are in more urgent need of new treatments, developing less toxic drugs for cancers with high cure rates is equally important considering the potential long life-span of survivors of childhood cancers and the debilitating nature of some late effects of current treatments.

The ultimate goal of drug development in childhood cancers is the identification of drugs that will improve the cure rate of frontline therapy. The medical oncology approach to developing new drugs is often aimed at defining a role for new drugs in second- and third-line treatment regimens, where the goal of therapy is prolongation of life by months, rather than a cure. This approach does not apply to childhood cancers. Pediatric oncologists must 'prolong' a 4-year-old child's life by 70 years to be successful, and this can only be accomplished by curing the patient. Curing all patients obviates the need for second- and third-line treatment regimens. Therefore, the successful clinical development of a new agent for childhood cancers includes testing the agent in a frontline regimen in a Phase III trial and the rarity of childhood cancers is more limiting at this phase of drug development than in Phase I or II trials (Table 2).

Cancers in adults and children are classified based on the tissue of origin and histological appearance, which in turn determines the drug combination that is indicated for treatment. As we become more sophisticated in the use of newer molecularly targeted drugs, we will rely on the genetic and molecular profile of each patient's tumor to personalize treatment regimens. If this personalized approach to the selection of drugs extends into Phase I and II trials, it will have a significant impact on our approach to developing new drugs and our ability to accrue patients. Limiting eligibility on a Phase I trial to cancers with a specific molecular or genetic profile may enrich the population for those most likely to respond to the new agent but may also slow accrual to the trial if the profile is uncommon. This approach may also necessitate tumor biopsies to assess eligibility for the trial (see 'Ethical issues' section).

Table 2. Patient numbers and timelines for the development of a new agent for Ewing sarcoma from Phase I through Phase III trials.

Phase	Estimated accrual rate (patients/year)	Trial duration	Drugs tested per year
I	300	12–24 months	10
II	40	12 months	2
III	140	6–8 years	0.15

Phase I trials to identify the dose are not disease specific and are conducted in children with all types of refractory solid tumors, and there are many competing Phase I trials open at any time. Phase II and III trials are disease specific. Based on the success rate of current treatment (70% event-free survival [EFS] for localized disease and 10% EFS for metastatic disease), 85 patients with Ewing sarcoma per year will relapse, and at best a half may be available and eligible for a Phase II trial. There may be several competing Phase II trials ongoing concurrently. A total of 20 patients would be required to demonstrate a drug is active in Phase II. The accrual to the Phase III trial in the table is based on the accrual rate to a recent Children's Oncology Study. Approximately 400–500 patients would be required to detect a 15% improvement in EFS with a new treatment in a randomized trial. There is typically a single Phase III trial ongoing for newly diagnosed patients with localized disease. Survival end points on Phase III require 3–5 years of patient follow-up.

Box 1. The role of pharmacokinetic studies in the clinical development and use of new anticancer drugs in adults and children.

- Description of drug disposition and degree of interpatient variability
  - Bioavailability
  - Distribution
  - Metabolism
  - Excretion
- Comparison of different populations
  - Children vs adults
  - Age strata within the pediatric population (infants vs children vs adolescents)
- Effect of hepatic or renal dysfunction on drug disposition†
- Dose dependence of drug disposition
- Drug interactions
- Correlation of pharmacokinetic parameters with patient characteristics to develop rational adaptive dosing methods
- Correlation of drug concentration with toxic and therapeutic drug effects for therapeutic drug monitoring

†Although adequate excretory organ function is required for eligibility on pediatric Phase I trials, the definition of 'adequate' often allows for organ function tests to be outside the normal range (e.g., bilirubin less than 1.5-times the upper limit of normal).

Ethical issues

Children are afforded additional protections as research subjects in the US Federal Regulations. Research studies that pose greater minimal risk to subjects should also offer the "prospect of direct benefit to the individual subjects." The risks to the subject must be balanced by the potential benefit and the benefit-to-risk ratio should be as favorable as potential alternative approaches. Investigational anticancer drugs clearly pose significant risks to the subjects enrolled on Phase I and II trials. These risks are quantified from the incidence and severity of ensuing drug toxicities, which are the primary end points of Phase I trials. A total of 24% of children enrolled on Phase I trials of anticancer drugs will experience a dose-limiting toxicity and the toxic death rate is 0.5% [8]. This degree of toxicity is not substantially different from the alternative of conventional cytotoxic chemotherapy in the relapsed setting. Benefit has been quantified by assessing the objective response rate, which is defined as a decrease in the diameter of tumors by at least 30%. The objective response rate across Phase I trials approaches 10% [8], but other potential benefits such as relief of symptoms or prolongation of survival are not as easily quantified.

Although assessing response or efficacy (i.e., benefit) is not the primary objective of a Phase I trial, Institutional Review Boards (IRBs) at most pediatric centers accept that these trials offer the potential for benefit and that the benefit-to-risk ratio justifies approval of Phase I trials of new investigational anticancer drugs in children with treatment-refractory cancers. The primary objective of Phase II trials is to quantify benefit (response) at a dose defined as having an acceptable level of toxicity on prior Phase I trials. IRB approval of Phase II trials has been less controversial.

Correlative studies are playing an increasingly important role in the clinical development of new anticancer drugs in adults and children. However, these strictly research studies do not offer the prospect for direct benefit to the subjects enrolled on Phase I and II trials. These procedures can be approved by an IRB if they will yield generalizable knowledge and pose no more than a minor increase over minimal risk to the subject. The research procedures must also be reasonably commensurate with those that subjects may experience as part of their routine medical care. Children with cancer experience a variety of procedures as part of the diagnosis, staging and treatment of their disease, and correlative studies are often similar to routine medical procedures (e.g., drawing a blood sample).

The critical role of pharmacokinetic (PK) studies in clinical drug development in adults and children is outlined in Box 1. Drawing additional blood samples for PK studies is usually considered a minor increase over minimal risk. Although studying the PK of new anticancer drugs is an important objective of pediatric Phase I trials, participation in this component of the study is often considered to be optional to the patient and family because they only serve a research purpose. Considering that only three to six patients are enrolled on a dose level in a Phase I trial, poor compliance with PK studies can significantly impair our understanding of the drug's disposition in children.

Some recent pediatric Phase I trials have required that subjects agree to participate in PK studies as an eligibility criterion. The justification is that the

PK component of the trial is a primary objective. As we move away from using toxicity as the primary determinant of an anticancer drug's dose (see 'Dose' section), PK end points may become the primary end point to define the optimal dose. Required participation in PK studies has been accepted by the IRBs of the institutions experienced in performing pediatric Phase I trials. Given the increasing importance of PK studies and the low level of risk involved in performing the sampling, PK studies should be required on all pediatric Phase I trials.

Directly measuring the effect of a molecularly targeted drug on signaling pathways in tumors, provides a potential alternative method of defining the optimal (therapeutic) dose of a drug. However, performing invasive serial tumor biopsies to obtain research specimens, poses more than a minor increase over minimal risk and offers no direct benefit to the subject. Leukemia with circulating blasts and tumors present in the bone marrow are the exception, as these can be safely serially sampled. However, the biology of tumor cells metastatic to bone marrow may not be reflective of tumor cells in the primary tumor. For investigational drug trials performed in pediatric subjects with solid tumors, drug effects are often measured in a surrogate tissue, such as peripheral blood mononuclear cells, but this may not be predictive of the effect of the drug in tumor cells. Noninvasive methods for assessing drug effect in childhood cancers must be developed and validated. Alternatives could include functional imaging techniques, serum biomarkers or circulating tumor cells [15].

Drug availability

A combination of incentives (e.g., the additional 6 months of marketing exclusivity in the USA if pediatric studies are completed) and requirements from regulatory agencies in the USA and Europe, have led to an increase in early phase clinical trials of new agents in children with cancer and new labeling information for children [16–19]. The timing of when new drugs are made available for pediatric studies, relative to the status of clinical development in adults, is variable and often sponsor specific. Pediatric Phase I trials can start once an MTD and drug safety profile are defined in adults, but if Phase II or III trials in adults fail to demonstrate activity or efficacy, the drug may not be available to complete pediatric Phase II and III trials. Delaying pediatric trials until a new drug is approved and on the market will ensure that the drug is available to complete pediatric Phase I and II trials. However, accrual to these trials could be compromised by the commercial access to the drug. Given that clinical development of a new agent for a pediatric indication will take considerably longer than for an indication in a common form of cancer in adults, pediatric trials should start as soon as possible after Phase I trials in adults are complete, despite the risk that the drug's path toward approval in adults may not be guaranteed.

Most molecularly targeted anticancer drugs are formulated as tablets or capsules for oral administration and available tablet sizes are based on the recommended fixed dose in adults. Pediatric liquid formulations are often not available for pediatric Phase I trials. Without a liquid formulation, children enrolled on pediatric trials must be able to swallow capsules and this will restrict enrollment of infants

Table 3. Dosing table for a pediatric Phase I trial with dose levels in mg/m² and the actual dose for each range of body surface area.

Dose level (mg/m²)	Percentage change (%)	Drug dose (BSA: m²; dose: mg)							
20	-25	BSA	≤0.75	0.76–1.25	1.26–1.75	≥1.76			
		Dose	10	20	30	40			
25	Starting dose	BSA	≤0.6	0.61–1.0	1.01–1.40	1.41–1.8	>1.8		
		Dose	10	20	30	40	50		
32	28	BSA	≤0.47	0.48–0.78	0.79–1.09	1.1–1.40	1.41–1.71	≥1.72	
		Dose	10	20	30	40	50	60	
40	25	BSA	≤0.38	0.39–0.62	0.63–0.86	0.87–1.12	1.13–1.38	1.39–1.62	≥1.63
		Dose	10	20	30	40	50	60	70

This example assumes that the smallest available tablet size is 10 mg and the maximum tolerated dose in adults was 50 mg (28 mg/m²). For a child of 0.62 m² BSA the prescribed dose would be 20 mg regardless of the assigned dose level 25, 32 or 40 mg/m².
BSA: Body surface area.

and younger children. If available tablet sizes are large, relative to the dose increment between dose levels, the actual dose in mg on two sequential dose levels may be identical for children within certain body surface area (BSA) ranges (Table 3). Pediatric investigators should start discussions about the development of a palatable pediatric liquid formulation, prior to writing the pediatric Phase I trial. An additional advantage to an oral liquid formulation, is that it allows for more accurate, continuous dosing in small children at a given mg/m^2 dose level, compared with tablets or capsules.

Dose

Selecting the appropriate dose of a new drug in Phase I testing is obviously critical to a drug's success. Identifying the MTD remains the standard end point for Phase I trials of conventional cytotoxic chemotherapy agents, as well as the new classes of molecularly targeted drugs. Toxicity-based dosing is a pragmatic solution for ensuring a maximal therapeutic effect with cytotoxic drugs that have a low therapeutic index, but the disadvantage is that the MTD also ensures the drug will have toxicity. The MTD is usually only 25–30% lower than a dose that caused unacceptable toxicity and we accept dose-limiting toxicity in up to a third of patients treated at the MTD.

A therapeutic end point for determining the dose has been impractical for cytotoxic anticancer drugs, because most patients treated on a Phase I single-agent trial will not have a measurable tumor response, even if the agent later proves to be efficacious in patients with newly diagnosed cancers, when administered in the adjuvant (minimal disease) setting. In addition, Phase I dose-finding trials accrue patients with a variety of different cancer types and it is unlikely that the sensitivity to a given drug will be uniform across all types of cancer. Cytotoxic drugs, such as alkylating agents, have *in vitro* dose–response curves in tumor cell lines that are log-linear (a twofold increase in drug concentration will result in a tenfold increase in tumor cell kill). This observation has led to the mantra of more is better when it comes to the dose and the most one can administer safely to a patient is the MTD.

More selective molecularly targeted drugs have the potential to be less toxic, but if we continue to use the MTD as the recommended dose of these agents, this potential will never be realized. Most molecularly targeted drugs are classical noncompetitive receptor inhibitors and their dose–response curves will asymptotically approach a maximum effect, which occurs when receptor binding sites are saturated. Once the dose that produces the maximum effect is reached, further increases in the dose only have the potential to increase the toxic effects of the drug. Shifting the focus of Phase I trials to identifying the dose that saturates receptor binding sites and produces the maximum therapeutic effect could avoid unnecessary toxicity. This will require a greater emphasis on pharmacological principles in the design, selection of end points and analysis of the results of Phase I trials. Examples of recently conducted pediatric Phase I trials that used alternative end points to determine the dose are described below.

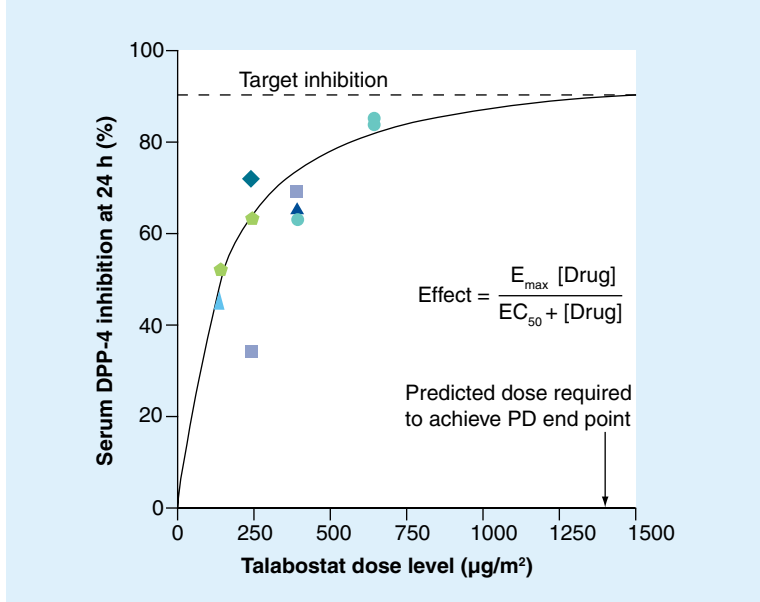

Figure 2. Dose–response curve for the DPP inhibitor talabostat using a surrogate end point (inhibition of serum DPP-4) to measure drug effect.
A maximum effect model (equation) was fit to the data and used to project the dose required to inhibit serum DPP-4 activity by 90%. Intrapatient dose escalation was allowed on subsequent treatment cycles and some patients were studied on more than one dose level. Each shape represents a different patient (n = 6).
DPP: Dipeptidyl peptidase.
Data taken from [20].

Talabostat is a dipeptidyl peptidase (DPP) inhibitor that was at one point under development as an anticancer drug because it inhibits fibroblast activation factor, which is involved in tumor stromal remodeling. Talabostat also inhibits circulating DPP-4 at similar drug concentrations. A pediatric Phase I dose-finding trial was designed and conducted with >90% inhibition of serum DPP-4 as the primary end point (Figure 2) [20]. A maximum effect model was fit to the dose–response data, allowing us to project the dose required to achieve 90% inhibition of the surrogate target, in the absence of dose-limiting toxicity. Unlike the standard 3 + 3 Phase I trial design, this

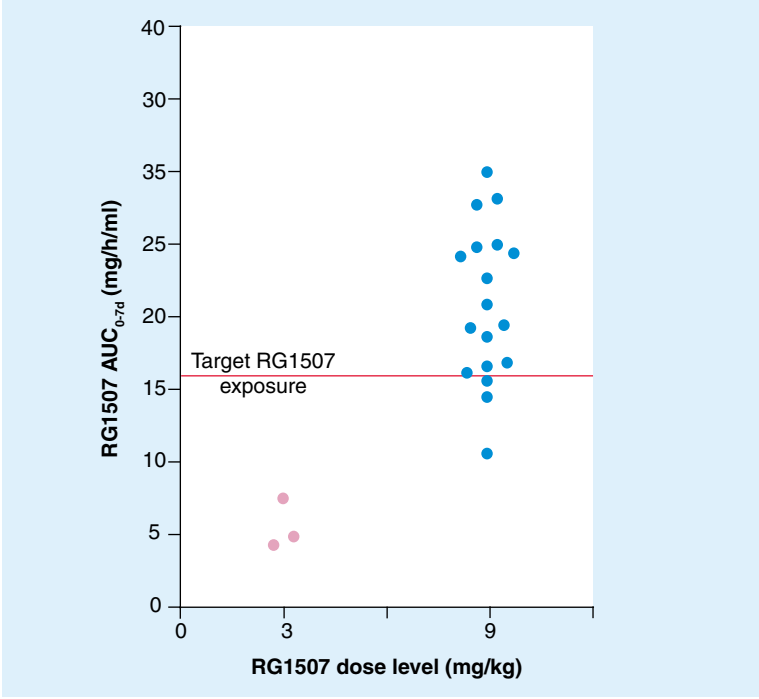

Figure 3. The area under the curve for RG1507 over the 7-day dosing interval at the two dose levels studied in children. Each point represents the AUC_{0-7d} from an individual subject. The mean AUC_{0-7d} at the 9-mg/kg dose level exceeded the target, which was 80% of the AUC_{0-7d} in adults at the recommended adult dose of 9 mg/kg.
AUC_{0-7d}: Area under the curve from day 0 to 7.
Data taken from [21].

modeling approach uses the data from all dose levels to determine the optimal dose.

In our recent pediatric Phase I trial of RG1507, which is a monoclonal antibody directed against the IGF-1 receptor, a PK end point was used to define the optimal dose in children [21]. In the adult Phase I trial of RG1507, a MTD was not defined because toxicities were minimal. Therefore, MTD would not have been a logical or scientifically valid end point for the subsequent pediatric Phase I trial. The pediatric Phase I trial was designed to identify the dose that, in the absence of dose-limiting toxicity, achieved a target mean area under the plasma concentration–time curve (AUC) that was at least 80% of the mean AUC in adults at the recommended adult dose. Two dose levels were studied and the results are shown in Figure 3. This trial design was feasible because the interpatient variability of RG1507 was low.

Both trial designs described above included contingencies to alter the dose escalation scheme and end point if dose-limiting toxicity was observed before the alternative end point was reached. These trials demonstrate the feasibility of using new designs and end points for pediatric dose-finding studies, especially for noncytotoxic agents.

Determining the optimal pediatric dose by analyzing the dose–response relationship requires a broad dose range to be studied. Current Phase I trial designs use 80% of the MTD of the drug in adults as the starting dose and escalate the dose in 30% increments and typically no more than four dose levels are studied. If the adult MTD of a drug is 100 mg/m^2, then the dose levels for a pediatric Phase I trial would likely be 80, 100, 130 and 170 mg/m^2, which represents only a twofold dose range if all dose levels were tolerable.

The use of 80% of the adult MTD as a starting dose is based on a meta-analysis of Phase I trials performed in the 1970s and 1980s comparing MTDs of 14 cytotoxic anticancer drugs in children and adults who were treated on the same dosing schedule [7]. In this early era of drug development, children tended to tolerate higher doses than adults when the dose was normalized to BSA. On average, the MTD in children was 1.3-fold higher than the MTD in adults. Extrapolating this 80% rule to noncytotoxic, molecularly targeted drugs has not been demonstrated to be safe.

The selection of a starting dose for pediatric Phase I trials must balance patient safety with ensuring that the dose has the potential to provide therapeutic benefit. An alternative to the 80% rule would be to use a lower starting dose, which will be safer, and allow intrapatient dose escalation on subsequent treatment cycles if the starting dose was well tolerated. Intrapatient dose escalation would enhance the likelihood of a therapeutic effect of the drug in individual subjects. In addition, studying each patient at multiple dose levels provides valuable dose–response data that can complement the interpatient dose–response analysis. Although a confounding effect of cumulative toxicity is used as an argument against intrapatient dose escalation on Phase I trials, this can be avoided by using only the data from the first treatment cycle to determine the recommended dose. For standard cytotoxic drugs (e.g., doxorubicin and cisplatin) that have cumulative toxic effects (e.g., cardiotoxicity or ototoxicity), these cumulative toxicities do not alter the starting dose of these agents. Instead, we modify later doses or limit the lifetime dose to minimize the cumulative toxic effects.

The utility of dosing drugs based on BSA in adults has recently been questioned, because the degree of interpatient variability in drug exposure is similar for a fixed dose (mg) compared with a dose normalized to BSA (mg/m^2). This is especially true for orally administered drugs that cannot be dosed continuously like

intravenous drugs. As a result, most adult Phase I trials of oral molecularly targeted anticancer drugs employ fixed dosing, but administering the same fixed dose across a pediatric population is not feasible given the broad range in body size and excretory organ function in the pediatric population. Converting a fixed mg dose in adults to a comparable mg/m^2 dose in children requires a conversion factor, and the average adult BSA of 1.8 m^2 is usually used for this conversion (e.g., an adult fixed dose of 200 mg is equivalent to a pediatric dose of 110 mg/m^2). The need for this conversion factor adds another variable to selecting a starting dose for a pediatric Phase I trial.

Conclusion

New anticancer drugs must be developed separately in children because of potential differences in drug disposition, tissue/organ sensitivity to the toxic effects of the drug, and the pathogenesis and tissue of origin of the cancers occurring in children compared with adults. Although a parallel drug-development process in children that used a similar approach to that used in adults was successful for cytotoxic anticancer drugs, new classes of more selective molecularly targeted drugs will require:

- A process for prioritizing which agents to study in children based on target expression in childhood cancers;
- New clinical trial end points and designs to define the optimal dose based on therapeutic effect, rather than toxicity, as well as more sensitive measures to detect antitumor activity;
- A commitment from pharmaceutical companies to develop pediatric liquid formulations for orally administered drugs prior to the start of pediatric Phase I trials;
- Pediatric drug development plans that include studying new agents in frontline treatment regimens for children with newly diagnosed cancers.

Executive summary

Background

- New anticancer drugs are developed separately in children because of potential differences in drug disposition, tissue/organ sensitivity to the drug's toxic effects and pathogenesis and tissue of origin of childhood cancers compared with cancers in adults.
- A new approach to clinical drug development, including innovative clinical trial end points and designs, is required for studying anticancer drugs in children.

Drug discovery & selection

- The focus of new drug development for childhood cancers has shifted to molecularly targeted drugs, which selectively inhibit cell-signaling pathways responsible for the malignant phenotype.
- Studying the expression and role of drug targets from common adult cancers in the pathogenesis of childhood cancers would provide information needed for prioritizing drugs for clinical development in children.

Patient population

- As cure rates for childhood cancers rise, fewer patients are available and eligible for Phase I and II trials and the population is skewed towards diseases with lower relapse-free survivals.
- Basing eligibility for Phase I trials of molecularly targeted anticancer drugs on the genetic or molecular profile of the patient's cancer may slow accrual to the trial.
- The successful clinical development of a new agent for childhood cancers includes testing the agent in a frontline regimen in a Phase III clinical trial. The rarity of childhood cancers is more limiting at this phase of drug development than in Phase I or II trials.

Ethical issues

- Children are afforded additional protections as research subjects, and research studies that pose a risk to subjects must also offer the prospect of direct benefit to subject. This limits the type of correlative studies that can be performed as part of a Phase I trial.
- Alternative, noninvasive methods for assessing drug effect in childhood cancers must be developed. Alternatives could include functional imaging techniques, serum biomarkers or circulating tumor cells.

Drug availability & dose

- Pediatric trials should start as soon as possible after Phase I trials in adults are complete, despite the risk that the drug's path toward approval in adults may not be guaranteed.
- Pediatric investigators should start discussions about the development of a palatable pediatric liquid formulation prior to writing the pediatric Phase I trial.
- Alternative end points to toxicity that can be used to define the optimal pediatric dose of anticancer drugs must be developed for Phase I trials of molecularly targeted drugs in children.

Future perspective

A more rational and efficient approach to pediatric anticancer drug development must be established by devising and validating new clinical trial end points and designs, founded in pharmacological principles, in order to realize the potential of molecularly-targeted drugs to be a less toxic approach to control tumor growth, invasion and metastatic spread in childhood cancers.

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