

# Conduct of Phase I Trials in Children With Cancer

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**Purpose and Methods:** Future progress in the care of children with cancer requires appropriate evaluations of promising new agents for pediatric indications, beginning with well-conducted phase I trials. This report summarizes current guidelines for the conduct of pediatric phase I trials and represents a consensus between American and European investigators. The primary objective of pediatric phase I trials is to define safe and appropriate doses and schedules of new agents that can subsequently be used in phase II trials to test for activity against specific childhood malignancies. Prioritization of agents for evaluation in children is critical, since many more investigational agents are evaluated in adult patients than can be systematically evaluated in children. Considerations used in prioritizing agents include activity in xenograft models, novel mechanism of action, favorable drug-

resistance profile, and activity observed in adult trials of the agent.

**Results and Conclusion:** Distinctive characteristics of pediatric phase I trials, in comparison to adult phase I trials, include the necessity for multiinstitutional participation and their higher starting dose (typically 80% of the adult maximum-tolerated dose [MTD]), both of which reflect the relative unavailability of appropriate patients. The application of uniform eligibility criteria and standard definitions for MTD and dose-limiting toxicity (DLT) help to assure that pediatric phase I trials are safely conducted and reliably identify appropriate doses and schedules of agents for phase II evaluation. Where possible, pediatric phase I trials also define the pharmacokinetic behavior of new agents in children.

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ALTHOUGH THE MAJORITY OF CHILDREN with cancer are cured with current therapy, there are many for whom this therapy is unsatisfactory, either because of insufficient efficacy or because of intolerable short- and/or long-term complications. There remains a need to identify new anticancer agents for children that are more effective and less toxic.

Pediatric phase I trials are critical to the process of evaluating a new agent for potential benefit in children with cancer, since the adult phase I experience with the agent is not an adequate predictor of toxicity in children.<sup>1,2</sup> The tolerance of children to an agent may differ from that observed in adults for both pharmacokinetic (drug disposition) and pharmacodynamic (drug action) reasons. Physiologic differences between children and adults (eg, in renal

function, hepatic metabolism, and body composition) may result in different patterns of drug disposition.<sup>3,4</sup> Even with similar patterns of drug disposition, children may differ from adults in their susceptibility to the toxic effects of an agent, as exemplified by recent experience in children with all-trans retinoic acid. Children appeared especially susceptible to the CNS toxicities of this agent.<sup>5-8</sup>

The primary objective of pediatric phase I trials is to define a safe and appropriate dose and schedule for new agents that can subsequently be used in phase II trials to test for activity against specific childhood malignancies. It is important that a phase I trial determine an appropriate dose for phase II evaluation, since for most agents the highest tolerable dose should be used to evaluate antitumor activity. The use of a lower dose could lead to an underestimation of the true efficacy of an agent. Conversely, if the dose selected for phase II evaluation is too high, then individual patients are placed at undue risk for excessive toxicity.

Another objective of pediatric phase I trials is to characterize the nature and frequency of the toxicities that occur when children receive the agents under investigation. The unacceptably severe toxicities that limit use of higher doses are termed the dose-limiting toxicities (DLTs). Additional objectives are to define toxicity monitoring guidelines (eg, the type and frequency of laboratory studies) and to define the supportive care requirements needed to give an agent safely. Pediatric phase I trials also define the pharmacokinetic behavior of new agents in children. As discussed in a subsequent section, pharmacologic studies provide data that

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may facilitate selection of an optimal schedule of agent administration and may also permit comparison with the adult experience.

Although patients entered onto pediatric phase I trials are evaluated for tumor response, formal analysis of efficacy is limited in phase I trials because of sample size, the heterogeneity of tumors treated, the range of doses tested, and the extensive prior therapy of the study population. Nonetheless, 5% to 7.5% of children who enter phase I trials achieve either a partial or complete response.<sup>9-11</sup>

Ethical considerations are paramount in the conduct of phase I studies in children with cancer. Although these studies are conducted with the express intention to determine DLTs, maximal-tolerated doses (MTDs), and pharmacokinetics, children are given drugs on phase I studies with therapeutic intent. In this regard, it is important that pediatric phase I trials are initiated at doses near those used for phase II evaluations in adults, since this increases the likelihood for patient benefit. Nonetheless, participation must be within the context of fully informed consent given freely by parents and, where appropriate, by the child him/herself.

Formal pediatric phase I trials have been conducted in the United States for nearly two decades. Government regulations such as the United States Orphan Drug Act, and Food and Drug Administration (FDA) guidelines that encourage pediatric evaluations of new drugs have created an environment conducive to testing new anticancer drugs in children.<sup>12,13</sup> In Europe, pediatric phase I trials had been less commonly performed, partly due to a lack of regulation that recognized the need for evaluation of new agents in children. Hence, there was little incentive for pharmaceutical companies to provide new drugs for investigation in children. Additionally, it is only in recent years that individual national children's cancer groups in Europe have developed the structure and mechanisms to undertake multicenter and even multinational phase I studies.

Recently published and current phase I trials are listed in Table 1. This listing documents the substantial body of clinical experience in the conduct of pediatric phase I trials. The primary purpose of this report is to summarize the methodology for the conduct of pediatric phase I trials that has evolved from this experience and to describe new challenges that face pediatric investigators in planning and implementing future phase I trials. The clinical trials methodology that is described represents a consensus among European and American investigators that was initially reached at the International Society of Paediatric Oncology meeting in October 1993 and that was discussed again at the American Society of Clinical Oncology meeting in May 1997.

## SELECTION OF AGENTS FOR PHASE I EVALUATION IN CHILDREN

The most important consideration in the conduct of pediatric phase I trials is selection of appropriate agents for evaluation. Many more investigational agents are evaluated in adult patients than can be systematically evaluated in children. For example, the Cancer Therapy Evaluation Program of the National Cancer Institute currently sponsors clinical trials for more than 100 investigational agents. The relatively small number of pediatric patients eligible for phase I trials allows only a handful of these agents to be evaluated in children. Even if more agents could be evaluated in the pediatric phase I setting, it still would not be feasible to test more than several new agents every 1 to 2 years in phase II trials, since they require relatively large numbers of patients with a specific tumor diagnosis. Given the limitations in the number of pediatric phase I trials that can be accomplished, how might new agents be prioritized for pediatric evaluation?

Preclinical data from xenograft model systems of pediatric tumors can be especially valuable in identifying agents that warrant investigation in children.<sup>71</sup> Xenograft models have been developed for rhabdomyosarcoma,<sup>72-74</sup> acute lymphoblastic leukemia,<sup>75,76</sup> pediatric brain tumors,<sup>77-81</sup> neuroblastoma,<sup>82</sup> and osteosarcoma.<sup>83</sup> These models have been used to predict and study antitumor activity of various therapeutic agents, including alkylating agents,<sup>71,72,77</sup> topoisomerase-I inhibitors,<sup>73,74,79-82,84</sup> vinca alkaloids,<sup>85</sup> monoclonal antibody immunoconjugates,<sup>86,87</sup> and biologic agents.<sup>88</sup>

Agents with novel mechanisms of action deserve high priority for evaluation in pediatric patients. For example, paclitaxel and docetaxel act via stabilization of tubulin polymers, a mechanism of action not shared with agents currently used to treat children with cancer.<sup>89,90</sup> Similarly, topoisomerase-I inhibitors (eg, topotecan, irinotecan, and 9-aminocamptothecin) are not currently used as standard treatment for pediatric patients with cancer.

Novel formulations of already established agents that change the volume of distribution, accumulation in tumor tissue, and toxicity profile may be prioritized for evaluation in children. Anthracyclines encapsulated in liposomes exemplify this approach,<sup>91</sup> since in preclinical studies they appear to preferentially accumulate in tumor tissue<sup>92</sup> and cause less cardiotoxicity compared with nonencapsulated anthracyclines.<sup>93,94</sup> Phase I trials in adult patients have identified hand-foot syndrome and stomatitis as DLTs.<sup>95</sup>

Analogues of agents known to be active in pediatric malignancies should be prioritized for evaluation if they have favorable attributes (eg, decreased toxicity or decreased long-term sequelae) that clearly distinguish them from currently available agents of the same pharmacologic

Table 1. Examples of Recent (published since 1990) and Ongoing Pediatric Phase I Trials of Single Agents

Agent	Solid Tumor/ Leukemia	Schedule	Group or Institution
Acivicin <sup>14</sup>	Solid tumor	30 min IV inf., daily × 5	POG
AG337 (Thymitaq) <sup>15</sup>	Solid tumor and leukemia	CI × 120 h	UKCCSG
Aminopterin <sup>16</sup>	Leukemia	PO q 12 h × 2 repeated weekly	Dallas
Carboplatin <sup>17</sup>	Leukemia	CI × 120 h	CCG
Compound 506U <sup>18</sup>	Leukemia	1-h IV inf., daily × 5	Duke & others
Etoposide <sup>19</sup>	Solid tumor	PO q 8 h × 21 days	SJCRH
2-Chlorodeoxyadenosine <sup>20</sup>	Leukemia	CI × 120 h	SJCRH
Crisnatol mesylate <sup>21</sup>	Brain tumor	CI × 72 h	CHLA
Fludarabine <sup>22</sup>	Solid tumor and leukemia	CI × 120 h	CCG & PB/NCI
5-FU <sup>23</sup>	Solid tumor	CI × 120 h	POG
5-FU + LV <sup>24</sup>	Solid tumor and leukemia	5-FU: IV inf. daily × 5 LV: daily × 6	CCG
G-CSF <sup>25</sup>	Solid tumor	SC daily × 10	SJCRH
GM-CSF <sup>26</sup>	Solid tumor	2-h IV inf., daily × 14	SJCRH
Ifosfamide <sup>27</sup>	Solid tumor	IV inf., daily × 3	SJCRH
Ifosfamide <sup>28</sup>	Solid tumor	IV inf., every other day × 3	SJCRH
Indicine N-oxide <sup>29,30</sup>	Solid tumor and leukemia	15-min IV inf., daily × 5	CCG
Interferon-β <sup>31</sup>	Solid tumor	30-min IV inf., 3× per week (MWF)	Multiple
Interferon-γ <sup>32</sup>	Leukemia	SC × 14 days	SJCRH
Interleukin-1α <sup>33</sup>	Solid tumor	SC × 4 days	SJCRH
Interleukin-2 <sup>34</sup>	Solid tumor and leukemia	IV bolus, MWF × 3 wk	POG
Interleukin-2 <sup>35</sup>	Solid tumor and leukemia	CI × 120 h	PB/NCI & CCG
Interleukin-2 <sup>36</sup>	Leukemia (after ABMT)	CI × 96 h × 3 wk	Minnesota
Interleukin-6 (+ ICE chemotherapy) <sup>37</sup>	Solid tumor	SC daily	CCG
Irinotecan <sup>38</sup>	Solid tumor	2-h IV inf.	SFOP
MIBG [ <sup>125</sup> I] <sup>39,40</sup>	Neuroblastoma	IV inf.	CCG
MIBG [ <sup>131</sup> I] <sup>41,42</sup>	Neuroblastoma	IV inf.	CCG
MIBG [ <sup>131</sup> I] <sup>43</sup>	Solid tumor	IV inf.	UKCCSG
Monoclonal antibody 14G2A + interleukin-2 <sup>44</sup>	Neuroblastoma	2-h IV inf. × 5 days (IL-2: CI × 96 h)	CCG
Vinorelbine <sup>45</sup>	Solid tumor and leukemia	IV q wk × 5 wk	CCG
Phenylacetate <sup>46</sup>	Solid tumor	CI × 28 days	PB/NCI
Piritrexim <sup>47</sup>	Solid tumor	PO q 12 h × 5 days	PB/NCI
Piritrexim <sup>48</sup>	Solid tumor	PO q 8 h × 5 days repeated weekly × 3	PB/NCI
PiXY-321 (+ ICE chemotherapy) <sup>49</sup>	Solid tumor	SC daily × 14 days	CCG
PiXY-321 (+ ICE chemotherapy) <sup>50</sup>	Solid tumor	SC daily × 14 days	SJCRH
PSC-833 (+ etoposide) <sup>51</sup>	Solid tumor	PO q 6 h × 3 days repeated weekly × 3	SFOP & UKCCSG
Retinoic acid (all-trans) <sup>5</sup>	Solid tumor and leukemia	PO daily × 28 days	PB/NCI & CCG
Sulofenu <sup>52</sup>	Solid tumor	PO q 12 h × 5 days repeated weekly × 3	SJCRH
Paclitaxel <sup>53</sup>	Solid tumor	CI × 24 h	POG
Paclitaxel <sup>54,55</sup>	Leukemia	CI × 24 h	CCG
Paclitaxel <sup>56</sup>	Solid tumor	IV inf. (0.75 mg/m <sup>2</sup> /h) q 4 days × 3 days	New York & others
Paclitaxel <sup>57</sup>	Solid tumor	3-h IV inf.	SFOP
Docetaxel <sup>58,59</sup>	Solid tumor	1-h IV inf.	PB/NCI & CCG
Temozolamide <sup>60</sup>	Solid tumor	PO daily × 5 days	UKCCSG
Temozolamide <sup>61</sup>	Solid tumor	PO daily × 5 days	CCG
Thioguanine <sup>62</sup>	Solid tumor	CI × 24 h	PB/NCI
Thiotepa + GM-CSF <sup>63</sup>	Solid tumor	Thiotepa: IV bolus × 1; GM-CSF: daily SC	PB/NCI
Thiotepa <sup>64</sup>	Solid tumor	CI × 72-168 h	UKCCSG
Topotecan <sup>65</sup>	Solid tumor	CI × 24 h	PB/NCI & CCG
Topotecan <sup>66</sup>	Solid tumor	CI × 72 h	SJCRH
Topotecan <sup>67</sup>	Solid tumor	30-min IV inf., daily × 5	POG
Topotecan <sup>68</sup>	Leukemia	CI × 120 h	SJCRH
Trimetrexate <sup>69</sup>	Solid tumor	30-min IV inf., daily × 5	POG
Tumor necrosis factor <sup>70</sup>	Solid tumor	30-min IV inf., daily × 5	POG

Abbreviations: 5-FU, fluorouracil; LV, leucovorin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICE, ifosfamide and carboplatin and etoposide; ABMT, autologous bone marrow transplantation; IV, intravenous; inf., infusion; CI, continuous infusion; h, hours; min, minutes; SC, subcutaneous; wk, week; PO, oral; q, every; POG, Pediatric Oncology Group; CCG, Children's Cancer Group; UKCCSG, United Kingdom Children's Cancer Study Group; SJCRH, St. Jude Children's Research Hospital; PB/NCI, Pediatric Branch of the National Cancer Institute; SFOP, French Society of Pediatric Oncology; MIBG, meta-iodobenzylguanidine.

class. For example, the anthrapyrazoles (eg, Dup-937 and Dup-941)<sup>96</sup> and the benzothioapyranindazoles (eg, CI-958)<sup>97</sup> have shown antitumor activity in preclinical and clinical studies that appears similar to that observed for the structurally related anthracyclines, but the cardiotoxicity of these agents in rodent and canine model systems is significantly less than that observed for anthracyclines. In a similar manner, agents that reduce the acute and chronic toxicities of standard therapeutic drugs (eg, dexrazoxane for the anthracyclines and amifostine for alkylating agents and ionizing radiation) may be prioritized with the goal of developing equally effective treatment regimens that are less toxic.<sup>98,99</sup>

Preclinical evaluation may also suggest a favorable resistance profile for a new agent. Many tumor-cell lines with resistance to specific cytotoxic agents have been developed, and an agent may be of special interest because of its activity against these resistant cell lines. For example, MGI 114 (a novel semisynthetic antitumor agent derived from the sesquiterpene mushroom toxin illudin S) is active against xenograft models refractory to existing agents and is active against multidrug-resistant tumor cells that express P-glycoprotein.<sup>81,100,101</sup>

A final factor that is used to prioritize an agent for evaluation in children is the degree of activity (and toxicity) that is observed in trials in adult patients. Preliminary evidence of antitumor activity of the taxanes and the topoisomerase-I inhibitors towards adult malignancies has provided additional impetus for expedient evaluation of these classes of agents in children. However, the disappointing activity observed to date for paclitaxel against solid tumors that occur in children illustrates the limitations of using antitumor activity observed in adult patients to predict antitumor activity in the pediatric setting.<sup>102</sup>

## DESIGN AND CONDUCT OF PEDIATRIC PHASE I STUDIES

### *Eligibility Criteria*

The application of eligibility criteria for phase I trials is to ensure that patients have an adequate physiologic status, so that the organ-specific toxicities observed in phase I trials can be attributed to the agents being studied, rather than to underlying organ dysfunction. The adequacy of kidney and liver function is especially important, since inadequate hepatic or renal function may impair drug clearance, which may lead to excessive toxicity and to the determination of an inappropriately low MTD. For example, patients with diminished glomerular filtration rate are at higher risk of severe myelosuppression following carboplatin treatment compared with patients with normal renal function.<sup>103</sup> Patients with solid tumors should have adequate marrow function to permit evaluation of hematopoietic toxicity. Additionally,

patients should have recovered from the toxicities of previous therapy and should not be receiving concurrent anticancer therapy. Table 2 lists specific eligibility criteria that are commonly applied in pediatric phase I trials.

### *Multi-institutional Setting*

Because of the small number of pediatric patients eligible for phase I trials, most are accomplished by multi-institutional collaborations. In the United States, the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) phase I consortia each include 15 to 30 institutions that enter patients onto phase I studies, with data from these institutions reported to each consortium's central coordinating center. The coordinating center and study chair are responsible for ensuring that the phase I trial is conducted as prescribed by the protocol, and for ensuring compliance with all regulatory reporting requirements for the investigational agents under evaluation. Individual institutions are responsible for timely and accurate submission of data and for the submission of patient samples for pharmacokinetic studies. On-site audits of the phase I institutions are conducted at regular intervals.

### *Starting Dose and Subsequent Dose Levels*

Adult phase I trials generally begin at a dose equivalent to 10% of the dose found to be lethal to 10% of mice (or the most sensitive rodent species) in toxicology studies.<sup>104</sup> Such a dose is used to minimize the risk of severe toxicity in the first humans who receive the new agent. Although initial dose escalations are large (in the absence of toxicity), it is not uncommon for adult phase I studies to evaluate 10 to 20 dose levels before DLT is reached. A variety of dose-escalation strategies have been proposed and evaluated with the goal to minimize the number of dose levels required to reach the MTD (eg, pharmacologically guided dose escalation).<sup>105</sup> However, even with the use of these alternative strategies, phase I trials often require the evaluation of many dose levels.

There are insufficient numbers of pediatric patients to permit dose escalation in pediatric phase I trials along the entire dose-toxicity curve, and therefore alternative strategies have been devised. The common practice in pediatric phase I trials is to use a starting dose that is 80% of the MTD determined in adult patients who have received significant prior therapy, and then to escalate the dose in 30% increments in successive cohorts of patients with no inpatient dose escalation generally permitted. Using this starting dose strategy, pediatric phase I trials commonly require evaluation of fewer than five dose levels.<sup>10</sup> This strategy presumes that children will have a similar or higher threshold for toxicity in comparison to adults and minimizes the number

Table 2. Suggested Guidelines for Patient Eligibility Criteria for Pediatric Phase I Trials

Category	Eligibility Criteria
Age	≤ 21 years of age at time of study entry.
Histologic verification	Histologically or cytologically documented diagnosis of cancer (not required for brain stem tumors).
Refractoriness to conventional therapy	Refractory to conventional therapeutic modalities or have a tumor for which there is no known effective therapy.
Life expectancy	At least 8 weeks.
Performance status	Adequate performance status (POG performance status of ≥ 50%; or CCG 0, 1, or 2 pediatric performance status [status 2 is "slight decrease in activity, out of bed for 12 hours per day"]).
Nutritional status	Adequate nutritional status (defined by ≥ 3rd percentile weight for height) and serum albumin ≥ 3.0 g/dL.
Recovery from prior cytotoxic therapy	Full recovery from the toxic effects of prior therapy, with at least 3 weeks since last chemotherapy (6 weeks since nitrosourea therapy).
Recovery from prior growth factor therapy	No hematopoietic growth factors for at least 1 week before protocol entry.
Prior radiotherapy	The initial cohorts of patients may include patients with prior extensive XRT, who meet the criteria given below. If hematopoietic DLT is observed in the initial cohorts of patients, then escalation may be attempted from this dose level in less heavily pretreated patients (excluding patients with extensive prior XRT). (a) 6 weeks must have elapsed since XRT to any significant marrow containing compartment. (b) 6 months must have elapsed since craniospinal radiation (> 24 Gy), total abdominal + pelvic + lung XRT, mantle + Y ports, or TBI.
Prior BMT	The initial cohorts of patients may include patients with prior BMT, who otherwise meet the protocol's eligibility criteria and who meet the specific criteria for BMT patients given below. If hematopoietic DLT is observed in the initial cohorts of patients, then escalation may be attempted from this dose level in less heavily pre-treated patients (excluding patients with prior BMT). Patients with prior BMT must have recovery of all organ systems, with a minimum of 3 months since transplant. A minimum of 6 months is required after TBI preparative regimens. There must be no active GVHD, and patients should not be receiving therapy for GVHD.
Hematopoietic function	ANC ≥ 1.0-1.5 × 10 <sup>9</sup> /L, platelets ≥ 100-150 × 10 <sup>9</sup> /L, and Hg > 9-10 g/dL (transfusions allowed). These criteria are not applicable in leukemia phase I trials.
Renal function	Must have a serum creatinine below the upper limit of normal for age (eg, 1 yr ≤ 0.6 mg/dL; 2-3 yr ≤ 0.7 mg/dL; 4-7 yr ≤ 0.8 mg/dL; 8-10 yr ≤ 0.9 mg/dL; 11-12 yr ≤ 1.0 mg/dL; 13-17 yr ≤ 1.2 mg/dL; 18-19 yr ≤ 1.3 mg/dL). If the serum creatinine is above the upper limit of normal for age, then the creatinine clearance (or radioisotope GFR) must be ≥ 70 mL/min/1.73 m <sup>2</sup> .
Hepatic function	Bilirubin < 1.5 mg/dL. ALT < 5 × institutional upper limit of normal.
Pulmonary function	When applicable, must have adequate pulmonary function, documented by no evidence of dyspnea at rest, no exercise intolerance, and pulse oximetry >94% (if there is clinical indication for oximetry).
Cardiac function	When applicable, shortening fraction of ≥ 27% by ECHO or ejection fraction of > 50% ECHO or gated radionuclide study.
Seizure disorders	Patients with seizure disorders requiring anticonvulsant therapy should be considered for exclusion, because of possible alterations in drug metabolism induced by concurrent anticonvulsant therapy.
Pregnancy	Females of childbearing age (eg, any menstruating female) generally require a negative pregnancy test or other evidence of not being pregnant, if exclusion of pregnant patients is justified.
HIV status	Eligibility criteria regarding HIV (+) patients should be justified: eg, symptomatic patients with active opportunistic infections or requiring therapy for HIV-associated conditions might be excluded, while HIV (+) patients who have adequate organ function and otherwise meet the protocol's eligibility criteria might be included.
Infections	No culture-positive active infections (bacterial, viral or fungal).
Informed consent	Must be approved by institutional review board and signed by parent or guardian and when appropriate by the patient him/herself (either assent or consent as indicated).

Abbreviations: XRT, radiation therapy; TBI, total-body irradiation; GVHD, graft-versus-host disease; ANC, absolute neutrophil count; Hg, hemoglobin; GFR, glomerular filtration rate; ECHO, echocardiogram; HIV, human immunodeficiency virus.

of children required for phase I trials.<sup>1</sup> The occurrence of unanticipated, severe toxicity at the starting dose level is also minimized, since there is extensive adult experience to document the relative safety of this dose level.

An additional advantage of beginning pediatric trials at 80% of the adult MTD is that all patients entered onto a phase I study receive a dose of the agent that has biologic activity. This is not true for adult trials, in which the first

patients entered may receive such low doses of the agent that a biologic effect cannot be detected. The chance of a patient achieving a beneficial response is obviously enhanced when biologically active doses of the agent are administered.

#### Definition of DLT

A critical aspect in the design of a phase I trial is the careful definition of those toxicities that are considered

unacceptable and that therefore limit dose escalation. The severity of toxicities is graded according to the National Cancer Institute Common Toxicity Criteria.<sup>106</sup> Unacceptable nonhematopoietic toxicities generally include those of grade 3 (severe) or grade 4 (life-threatening) severity. It is common to accept as tolerable certain specific grade 3 toxicities (eg, grade 3 nausea and vomiting, grade 3 hepatic toxicity that is rapidly reversible, and grade 3 fever).

Hematopoietic DLT is defined by both the severity of myelosuppression and by its duration. Grade 4 granulocytopenia ( $< 0.5 \times 10^9/L$ ) or thrombocytopenia ( $< 25 \times 10^9/L$ ) that persists for more than 5 to 7 days is commonly considered dose-limiting.

Special consideration must be given to defining DLTs for phase I trials to evaluate schedules that call for prolonged administration of an agent (eg, daily administration for multiple weeks). In this setting, persisting grade 1 and 2 toxicities may be intolerable to patients, and definitions of DLT should be appropriately modified to account for this.<sup>107</sup> Additionally, the definition of hematopoietic DLT also requires modification, since continuing drug treatment for 5 to 7 days after grade 4 granulocytopenia is observed can expose patients to unacceptably prolonged neutropenia.

For pediatric phase I leukemia trials, the definition of nonhematopoietic DLT is the same as that used for solid tumor trials. However, hematopoietic DLT is defined by an unacceptably prolonged duration of marrow aplasia (eg, a neutrophil count  $< 0.5 \times 10^9/L$  and a platelet count  $< 50 \times 10^9/L$  at 5 weeks after treatment if bone marrow examination shows no evidence of leukemic or malignant infiltrate); nadir granulocyte and platelet counts are not relevant due to the underlying hematopoietic disorder.

While only the first course of therapy is used to define DLT, data from patients who receive multiple courses can provide preliminary evidence for cumulative toxicity. In this regard, patients are generally able to continue on study for multiple treatment courses in the absence of progressive disease, provided that their physician feels they are receiving overall objective benefit from treatment (eg, pain relief, prolonged disease stabilization, or response).

#### *Definition of MTD*

The MTD is defined as the dose level immediately below the level at which two patients in a cohort of two to six patients experience DLT. Six patients are evaluated at the MTD, and no more than one of these patients can experience a DLT. The MTD, as defined in this manner, is the dose that would be applicable in a phase II trial for patients with similar histories of prior therapy.

In practice, the MTD is defined in a phase I trial by adding cohorts of three patients at each dose level, and using the following rules to determine whether dose escalation should occur:

- (a) If zero of three patients experience DLT, then escalate to the next higher dose level.
- (b) If one of three patients experience DLT, then add three more patients at that dose level:
  - (i) If zero of these three patients experience DLT (ie, only one of six patients at the dose level), then escalate to the next higher dose level.
  - (ii) If one of these three patients experience DLT, then the MTD has been exceeded; three more patients are then added at the previous dose level (if only three patients had been treated previously at the prior level).

Accrual to trials must be temporarily suspended at each dose level after three patients (or six patients) have been entered, so that the patient cohort can be observed for the required length of time after treatment (usually 21 to 28 days). This allows all toxicity observed at the dose level to be fully evaluated so that a decision about further dose escalation can be made.

Any strategy that uses limited numbers of patients provides only an estimate of the MTD. Using the definitions of MTD and the rules for dose escalation provided, the likelihood of declaring a dose level too toxic is small ( $\approx 10\%$ ) when the true DLT rate is 0.05, while the likelihood of accepting as tolerable a dose level with a true DLT rate greater than 0.35 is low ( $\approx 10\%$ ).<sup>108</sup> Thus, the methodology for establishing the MTD has the greatest likelihood of defining a dose as the MTD if the true DLT rate of that dose is between 0.10 and 0.25.

#### *Use of Hematopoietic Growth Factors*

If myelotoxicity is identified as the DLT in a phase I trial, further dose escalation may be attempted by using hematopoietic growth factors (eg, granulocyte or granulocyte-macrophage colony-stimulating factor). A cohort of patients receiving the hematopoietic growth factor is treated at the dose level at which unacceptable myelosuppression was observed. Escalation then proceeds until the MTD of the agent with the growth factor is defined (using the rules outlined earlier for MTD determination). Using this strategy, escalation of one or more additional dose levels may be achieved.<sup>59</sup>

#### *Standard Criteria for Antitumor Response*

Data concerning antitumor efficacy are only a secondary goal of any phase I trial. Nonetheless, it is important that

responses be described in a uniform manner using objective, reproducible criteria.<sup>109,110</sup> As novel agents and therapeutic modalities are introduced into clinical trials, it may be necessary to revise the definition of what is considered a positive response. Antiangiogenesis agents, growth factor antagonists, and therapies based on gene transfection may require different efficacy end points from the standard criteria for antitumor response.

### Phase I Trials of Combinations of Agents

All chemotherapy regimens used with curative intent in pediatric oncology today involve combinations of agents. The assessment of appropriate combinations of a new agent with currently available agents is an important component of pediatric drug development. Thus, there is a role for phase I studies that define tolerable doses and anticipated toxicities for new agents when given as a combination. A number of phase I studies using combinations of agents have been conducted, or are currently ongoing, as listed in Table 3. Starting doses for phase I trials of combinations of agents can be based on doses tolerable in adults, when these data are available. When there is no prior experience in adult patients, then starting doses generally begin at least one dose level below the MTD of each agent. However, a more conservative approach may be appropriate when there is preclinical evidence for significant interactions between the agents under evaluation. For example, when topotecan is combined with standard doses of either cisplatin,<sup>111</sup> carboplatin,<sup>112</sup> or cyclophosphamide,<sup>113,114</sup> the tolerable dose of

topotecan is less than 50% of its MTD as a single agent. Dose escalation in combination studies is usually at 30% increments: the trial design may include escalation of only one agent or may prescribe escalation of both agents (in which case only one agent is generally escalated at each step).

### Regulatory Reporting Requirements

Clinical trials that use investigational agents require careful monitoring and compulsory reporting of data to sponsoring bodies and regulatory agencies. The protocol document should carefully specify the reporting requirements of the individual institutions and of the coordinating center, with special attention to the prompt reporting of adverse drug reactions.

## CLINICAL PHARMACOLOGY IN PEDIATRIC ONCOLOGY DRUG DEVELOPMENT

Almost all pediatric phase I trials seek to define the pharmacokinetic behavior in children of the agent under investigation. Pharmacokinetic data may be clinically useful in a number of ways, several of which are noted here.

- (a) The interpatient variability in systemic exposure is important to define in a phase I study. Pharmacokinetic data may identify subgroups of patients with altered drug disposition who may be especially susceptible to toxicity from the agent under study. Documentation of delayed clearance in patients with diminished renal or hepatic function may lead to appropriate

**Table 3. Examples of Phase I Studies of Combinations of Agents**

Agent (Reference)	Solid Tumor/Leukemia	Schedule	Group or Institution
Amifostine + melphalan <sup>115</sup>	Solid tumor	Amifostine IV 15-min inf., then melphalan IV 5-min inf.	PB/NCI
Fludarabine + Ara-C <sup>116</sup>	Leukemia	Fludarabine-araAMP CI × 48 h; then Ara-C-CI × 72 h	CCG
Fludarabine + Ara-C + Idarubicin <sup>117</sup>	Leukemia	Fludarabine-araAMP CI × 48 h; then Ara-C CI × 72 h Idarubicin 30-min IV inf. at h 0, 24, and 48	CCG
Ifosfamide + etoposide + G-CSF <sup>118</sup>	Solid tumor	Etoposide 1-h IV inf.; then ifosfamide 1-5-h IV inf.	POG
ICE <sup>119,120</sup>	Solid tumor	Carboplatin 1-h IV inf. Day 1; then etoposide 1-h IV inf. and ifosfamide 15-min IV inf. on days 2-4	SJCRH
ICE <sup>121</sup>	Solid tumor	Etoposide 1-h IV inf. and ifosfamide 1-h IV inf. × 3 days; then carboplatin 1-h IV inf. day 3.	POG
Interferon-α + ATRA	Solid tumor and leukemia	Interferon-α SC days 1-5 for 4 wk ATRA PO days 2-4 for 4 wk.	PB/NCI & CCG
6-MP + Ara-C	Leukemia	6-MP CI × 24 h; then Ara-C CI × 72 h	CCG
Paclitaxel + carboplatin	Solid tumor	Taxol 6-h IV inf.; then carboplatin 1-h IV inf. on day 2	POG
Paclitaxel + ifosfamide	Solid tumor	Taxol 6-h IV inf.; then ifosfamide 1-h IV inf. daily × 3	POG
Topotecan + cyclophosphamide <sup>113</sup>	Solid tumor	30-min IV inf. (both agents) daily × 5	POG
Tiazofurin + 6-TG	Leukemia	Tiazofurin 1-h IV inf. and 6-TG 1-h IV inf. × 5 days	POG
Topotecan + cisplatin	Solid tumor	Cisplatin 6-h IV inf.; then topotecan CI × 72 h	CCG
Topotecan + carboplatin <sup>112</sup>	Solid tumor	Carboplatin 1-h IV inf.; then topotecan CI × 72 h	SJCRH
TNF + Act-D <sup>122</sup>	Solid tumor	TNF: IV daily × 5 Act-D: IV daily × 5	CCG

Abbreviations: Ara-C, cytarabine; ATRA, all-trans retinoic acid; 6-MP, mercaptopurine; 6-TG, thioguanine; TNF, tumor necrosis factor; Act-D, dactinomycin; ICE, ifosfamide, carboplatin, and etoposide; Idarubicin, idarubicin.

- dose modifications based on organ function. For example, it is becoming increasingly common to base carboplatin dose on quantitative assessment of renal function.<sup>120,123,124</sup>
- (b) Pharmacokinetic studies can define the relationship between dose and systemic exposure, as measured by the area under the curve (AUC), and are required to define the relationship between specific toxicities observed and systemic exposure to the agent.
  - (c) Pharmacokinetic data (eg, half-life and peak serum levels) can also provide information to assist in the rational selection of schedules of administration for phase II trials. Pharmacokinetic data may be used to define optimal schedules and routes of administration, particularly when target serum levels can be estimated from preclinical studies. For agents with cell-cycle specificity, the optimal schedule may be one that provides the greatest duration of exposure above a threshold level.<sup>125</sup> For agents without cell-cycle specificity, a schedule associated with the highest systemic exposure may prove most efficacious.
  - (d) Pharmacokinetic studies can also identify agents with saturable clearance mechanisms (eg, paclitaxel and all-*trans* retinoic acid),<sup>126,127</sup> a setting in which disproportionately large increases in toxicity can result from minor increases in dose.
  - (e) For selected agents, pharmacokinetic studies may be used to define the dosing of individual patients, using the maximum-tolerated systemic exposure (MTSE) concept.<sup>128</sup> Using the MTSE strategy, phase I trials escalate based on systemic exposure (rather than dose) until the maximum systemic exposure level associated with acceptable levels of toxicity is defined (ie, the MTSE). Subsequently, patients treated in phase II trials receive a dose of the agent that is individualized so that their systemic exposure approximates the MTSE as defined in the phase I trial. The MTSE approach presumes the availability of accurate and precise analytical methods for determining levels of the agent (and/or its active metabolites), and the application of modeling and adaptive control strategies for dosage adjustments during a treatment course.
  - (f) The comprehensive pharmacokinetic studies performed in the phase I setting may also permit establishment of limited sampling strategies that facilitate defining pharmacokinetic-pharmacodynamic relationships in larger populations of children during phase II studies.

Pharmacokinetic data obtained in pediatric phase I trials allow comparisons of systemic exposure and toxicity between adult and pediatric patients receiving comparable amounts of the agent. These comparisons are especially important when the adult and pediatric studies have determined significantly different MTDs. In this situation, similar pharmacokinetic data imply a difference in susceptibility to toxicity between the adult and pediatric populations treated. This differential sensitivity might result from age-related differences in the response of normal tissue/organs to the agent being studied. Alternatively, this phenomenon may be related to differences in the intensity of prior therapy or to differential toxicities from prior therapy between the adult and pediatric populations.

Phase I studies may also provide an opportunity to examine the intracellular metabolism of agents. This approach has been applied extensively to the use of cytarabine (ara-C) in leukemic patients. The goal of these studies has been to increase the intracellular accumulation of ara-CTP, which is the predominant active metabolite of ara-C. This has been accomplished by either modifying the ara-C dose (or schedule of administration)<sup>129,130</sup> or by giving ara-C with biochemical modulators (eg, fludarabine and mercaptopurine).<sup>116,130-132</sup> Examples of current pediatric phase I studies in which intracellular pharmacokinetics play a central role are the POG study of tiazofurin given with thioguanine and the CCG study of ara-C given with mercaptopurine.

Another important function of pharmacokinetic studies in pediatric phase I trials is to provide data required by the United States FDA to support pediatric indications for oncologic agents.<sup>13,133</sup> Policy changes have been implemented by the FDA to facilitate approval of drugs for use in children when the drugs are already approved for use in adults. Pharmacokinetic data from the pediatric population are generally required by the FDA to support the recommended pediatric dosage, which is incorporated into the "Pediatric Use" subsection of the drug's package insert.

#### FUTURE STRATEGIES IN PEDIATRIC DRUG DEVELOPMENT

A general challenge to the oncology community is to identify new effective therapies and to integrate them with current therapy. For some new treatment strategies such as gene therapy, antisense oligonucleotide therapy, and biologic-based therapies (eg, cytokines, monoclonal antibodies), the conventional phase I trial design may require modification. However, there will remain the need for initial studies in pediatric populations that document safety and define toxicities associated with novel therapies. A specific challenge for

pediatric oncologists will be to assure that the initial clinical trials of these agents in children are sufficient to establish adequate and safe doses and delivery methods, and to define the toxicities and the relevant biologic effects associated with these doses and delivery methods.

One potential problem recently identified is the determination of MTDs in pediatric phase I trials that are lower than those defined in adult patients.<sup>141</sup> For example, four recent pediatric phase I trials have determined MTDs significantly below the doses being evaluated in adult patients (Table 4). It should be noted that prior to the mid 1980s, pediatric phase I trials usually defined pediatric MTDs that were equal to or greater than adult MTDs for the same agent.<sup>1</sup> The recently observed differences in MTD between adult and pediatric phase I trials may relate to differences in the intensity of prior therapy between adult and pediatric patients entered onto phase I trials.<sup>141</sup> The association between prior therapy and reduced tolerance to myelotoxic agents has been recognized among adult patients who entered phase I trials for a number of years,<sup>142</sup> and is also observed in pediatric patients.<sup>119,120</sup> However, it should be noted that the trend for lower MTDs in recent pediatric trials (compared with adult trials) is not universal and that the pediatric phase I trial of paclitaxel established a significantly higher MTD than the comparable adult phase I trials.<sup>53,55</sup>

If current pediatric phase I trials in heavily pretreated patients define MTDs that tend to be lower than those determined in adult patients with minimum prior therapy, then application of the pediatric MTD to less heavily pretreated pediatric patients may be problematic. This approach would not satisfy the underlying principle that the maximal dose of an agent be used in phase II trials to increase the likelihood of benefit to the patient, as well as the likelihood of observing antitumor activity for the agent.

The strategy used by medical oncologists to circumvent the problem of patient populations with significant prior therapy (ie, to enter patients with minimal or no prior therapy onto phase I trials) cannot be easily applied by pediatric oncologists. Almost all children with cancer who are eligible for phase I trials will have received significant prior therapy, since treatment is usually given with curative intent (even after an initial relapse). However, it may be possible to enter patients with limited prior therapy onto pediatric phase I trials, once an MTD is defined in a more

heavily pretreated population. If this strategy is selected, the patient population should be carefully defined to include only patients with poor prognosis for whom there is no known effective salvage therapy. This requirement may be relaxed for very promising agents that have demonstrated significant antitumor activity in the initial cohort of patients. This approach was successfully applied in a pediatric phase I trial of docetaxel. For children with extensive prior therapy, an MTD of 65 mg/m<sup>2</sup> was identified, while children with less prior therapy were able to tolerate doses up to 125 mg/m<sup>2</sup>.<sup>58,59</sup>

Recognition of the possibility that the MTD defined in a pediatric phase I trial may be lower than the dose that would be tolerated in less heavily pretreated patients implies that the early stages of certain phase II studies might evaluate the appropriateness of the dose being used in the patient population being studied. Should the recommended phase II dose appear to be without significant toxicity (ie, below the MTD for the population being treated), then early consideration can be given to systematic evaluation of a higher dose during the conduct of the phase II study. However, the difficulty in collecting detailed toxicity data with rapid turnaround times in phase II studies involving many institutions limits the ability to perform planned dose escalation studies in this setting.

A final challenge for pediatric investigators is to ensure that new agents continue to be available for evaluation in children at appropriate stages of the agents' development. Since the relatively small number of children with cancer limits their importance to pharmaceutical sponsors as a commercial market, pediatric investigators must continuously advocate for the access of their patients to new agents. Agents that have completed phase I trials in adults and that have shown activity against pediatric tumors in xenograft systems or have shown promising antitumor activity against adult tumors should be available for evaluation in children. Pediatric investigators will continue to play a critical role in this process by working diligently to identify those agents that appear most promising for pediatric indications and then working closely with pharmaceutical sponsors and regulatory agencies to ensure that appropriate doses and schedules are identified in phase I trials, and that therapeutic effectiveness is determined in phase II trials in children.

Table 4. MTDs on Pediatric and Adult Phase I Trials

Agent	Schedule	Adult MTD	Pediatric MTD	DLT
Fazarabine <sup>134,135</sup>	24-h infusion	54.5 mg/m <sup>2</sup> /h	15 mg/m <sup>2</sup> /h	Hematopoietic
Piritrexim <sup>47,136</sup>	Twice-daily × 5 days	480 mg/m <sup>2</sup> /d	140 mg/m <sup>2</sup> /d	Hematopoietic, mucositis, nausea/emesis
Topotecan <sup>65,137,138</sup>	24-h infusion	10 mg/m <sup>2</sup> per 24 h	5.5 mg/m <sup>2</sup> per 24 h	Hematopoietic
Docetaxel <sup>58,139,140</sup>	1-h infusion	100 mg/m <sup>2</sup>	65 mg/m <sup>2</sup>	Hematopoietic

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