

## Pediatric Phase I Trials in Oncology: An Analysis of Study Conduct Efficiency

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### A B S T R A C T

#### Purpose

To determine the efficacy and safety of pediatric phase I oncology trials in the era of dose-intensive chemotherapy and to analyze how efficiently these trials are conducted.

#### Methods

Phase I pediatric oncology trials published from 1990 to 2004 and their corresponding adult phase I trials were reviewed. Dose escalation schemes using fixed 30% dose increments were studied to theoretically determine whether trials could be completed utilizing fewer patients and dose levels.

#### Results

Sixty-nine pediatric phase I oncology trials enrolling 1,973 patients were identified. The pediatric maximum-tolerated dose (MTD) was strongly correlated with the adult MTD ( $r = 0.97$ ). For three-fourths of the trials, the pediatric and adult MTD differed by no more than 30%, and for more than 85% of the trials, the pediatric MTD was less than or equal to 1.6 times the adult MTD. The median number of dose levels studied was four (range, two to 13). The overall objective response rate was 9.6%, the likelihood of experiencing a dose-limiting toxicity was 24%, and toxic death rate was 0.5%.

#### Conclusion

Despite the strong correlation between the adult and pediatric MTDs, more than four dose levels were studied in 40% of trials. There appeared to be little value in exploring dose levels greater than 1.6 times the adult MTD. Limiting pediatric phase I trials to a maximum of four doses levels would significantly shorten the timeline for study conduct without compromising safety.

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### INTRODUCTION

Phase I studies in oncology are the critical first step in the clinical evaluation of novel anticancer agents. The primary objectives of such studies include describing and defining the toxicities of the drug, determining the maximum-tolerated dose (MTD) or recommended phase II dose, and studying the pharmacokinetics of the drug. Pediatric phase I studies are almost always performed following adult phase I trials.<sup>1</sup> Although this delays the timeline of pediatric drug development, it offers the distinct advantage of having data available from adult patients for

the design of the pediatric trial. The greatest impact of this is in defining the starting dose for the phase I trial. Whereas the starting dose for adult phase I trials are based on animal toxicology and are often at least an order of magnitude lower than the ultimate recommended dose,<sup>2,3</sup> pediatric trials historically begin at approximately 80% of the adult MTD,<sup>4</sup> greatly diminishing the likelihood that a pediatric patient would be enrolled at a biologically ineffective dose.

One would anticipate that with a prior knowledge of the adult MTD, pediatric phase I trials would meet their primary objectives in an efficient manner. However,

there are no published reports examining the efficiency of conducting pediatric phase I trials. Furthermore, the historical recommended starting dose of 80% was empirically derived during an era when children were less heavily pretreated and, in general, could tolerate higher doses of cytotoxic drugs than adult patients.<sup>5</sup>

We, therefore, reviewed the published experience with pediatric phase I trials from 1990 to 2004, a reporting period that encompasses an era when dose-intensive therapy was routinely administered as initial therapy in pediatric patients with high-risk tumors. Our objectives were not only to determine the safety and tolerability of pediatric phase I trials but also to examine how efficiently such trials are conducted. As a number of biologic agents are currently being developed, we also sought to get an initial indication of the pediatric phase I experience utilizing standard trial designs that were developed for the evaluation of cytotoxic drugs.

## METHODS

### Literature Review

Full length phase I pediatric clinical oncology trials published from 1990 to 2004 were identified by National Library of Medicine Gateway searches of English-language reports using the key words "pediatric," "phase," "cancer," and "trial." References of select articles were also reviewed for phase I studies. Lastly, the Children's Oncology Group database was used to identify completed and published phase I studies.

Studies included in the analysis were single-agent dose escalation trials; studies examining multiple agents were included only if a single drug was escalated. Phase I/II studies were included if there was a clear dose escalation scheme with a MTD and dose-limiting toxicities (DLTs) identified within the patient population. For the purposes of this study, we classified a drug as biologic if preclinical data suggested a primary mechanism of action that was immunologic, differentiating, or occurred via inhibition of a signal transduction pathway. Intrathecal agents, nondose escalation studies, pharmacokinetic only studies, and bone marrow transplant studies were excluded.

The following data were extracted from each publication: drug name, schedule, route of administration, concomitant cytotoxic or biologic drugs, concomitant hematopoietic growth factors, patient age (median and range), diagnoses, whether the study included patients with leukemia or solid tumors, starting dose, total number of patients entered, total number of patients assessable for toxicity, total number of patients assessable for response, number of dose levels studied, definition of DLT, DLTs, MTD, dose level at which the MTD occurred, less heavily pretreated MTD and dose level (if applicable), recommended phase II dose, steady-state plasma drug clearance, number of partial (PRs) and complete (CRs) responses, and number of deaths attributed to study drug.

### Pediatric Versus Adult Tolerability to Phase I Agents

Corresponding adult phase I studies were identified by searching the references of the pediatric publications. If no publication were identified, the National Library of Medicine database was searched and, if necessary, the National Cancer Institute's Cancer Therapy Evaluation Program was then queried. Adult

studies were included in the analysis if the route and schedule of administration were the same as the pediatric study. For studies that utilized a nonstandard definition of MTD, the data were reanalyzed using the standard definition of MTD defined as the dose level below that at which greater than or equal to two out of three to six patients experienced DLT.

### Efficiency of Study Conduct

The correlation between the adult and pediatric MTDs for cytotoxic and biologic agents was determined by regression analysis. As pediatric phase trials often escalate dose in increments of approximately 30%, the lower and upper bounds spanning three, four, or five theoretical dose levels that would capture at least 80% of the pediatric to adult MTD ratios was determined. The number of dose levels studied and the number of patients entered were tabulated.

### Safety

The types of DLTs observed on pediatric versus adult studies were recorded. The number of patients experiencing DLT and the number of patient deaths were tabulated. Toxic deaths were defined as a death of study participant in which the drug was possibly, probably, or definitely related to drug.

### Efficacy

Response data from each pediatric study were tabulated. For solid tumor studies, PRs were typically defined as a reduction of at least 50% in the sums of the products of the largest diameters of measurable lesions without the appearance of new lesions for 4 weeks. CRs were typically defined as the disappearance of all known disease for at least 4 weeks. PR for leukemic patients was defined as a bone marrow leukemic blast percentage of 5% to 25% for children with acute lymphoblastic leukemia and 5% to 40% for children with acute myelogenous leukemia and recovery of peripheral blood counts to an absolute neutrophil count of 1,000/ $\mu$ L and platelet count of at least 100,000/ $\mu$ L. A complete leukemic response was defined as less than 5% leukemic blasts in a normocellular or slightly hypocellular bone marrow with recovery of peripheral blood counts to at least an absolute neutrophil count of 1,000/ $\mu$ L and platelet count of at least 100,000/ $\mu$ L within 1 week of bone marrow response. Some individual study response definitions did not include time length requirements, and some did not define their criteria for response.

### Pharmacokinetics

The coefficient of variation (CV) in plasma drug clearance or apparent clearance was determined for each pediatric study using data derived from patients studied at either all dose levels or at the MTD. When clearance data were not reported, it was calculated, when possible, by dividing the dose by the area under the concentration-time curve. Plasma drug clearance in adult patients was compared with that observed in children by regression analysis.

## RESULTS

### Literature Review

Sixty-nine (53 cytotoxic and 16 biologic studies) pediatric phase I oncology trials evaluating 46 different anticancer agents published between January 1990 and December 2004 met eligibility criteria. Of these 69 trials, 55 were

Pediatric Phase I Trials in Oncology

Table 1. Cytotoxics

Drug	Schedule	Adult DLT	Pediatric DLT	Adult MTD	Pediatric MTD	Refs
Solid tumor						
<sup>131</sup> I-metaiodobenzylguanidine	IV 1.5-2h × 1	M	M, ENDO	9 mCi/kg	12 mCi/kg	26, 15
Fluorouracil	IV 15min/d × 5d q 21d	M, MUC	M, STOM	300 mg/m <sup>2</sup> /d	450 mg/m <sup>2</sup> /d	27, 28
Fluorouracil	24h CI × 5d q 21-28d	MUC	MUC	900 mg/m <sup>2</sup> /d	1100 mg/m <sup>2</sup> /d	29, 30
9-aminocamptothecin	72h CI q 21d	M	M	45 mcg/m <sup>2</sup> /h	52 mcg/m <sup>2</sup> /h	31, 32
Acivicin	IV 15-30min/d × 5d q 21-28d	CNS, M	CNS, M	15 mg/m <sup>2</sup> /d	26 mg/m <sup>2</sup> /d	33, 10
Bryostatins-1	Peds: IV 1h/d 1d/wk × 3wk q 28d Adult: IV 1h/wk q 14d	C	C	50 mcg/m <sup>2</sup> /dose	44 mcg/m <sup>2</sup> /dose	34, 35
Diaziquone	IV 4h/wk × 4wk	M, STOM	M	50 mg/m <sup>2</sup>	72 mg/m <sup>2</sup>	36, 37
Docetaxel	IV 1h × 1 q 21d	M	C, M	85 mg/m <sup>2</sup>	65 mg/m <sup>2</sup>	38, 39
Etoposide	po tid (adult qd) × 21d q 28d	M	GI	50 mg/m <sup>2</sup> /d	60 mg/m <sup>2</sup> /d	40, 41
Fazarabine	IV 1h/d × 5d q 21-28d	M	M	40 mg/m <sup>2</sup> /d	65 mg/m <sup>2</sup> /d	36, 8
Flavone acetic acid	IV 24h CI q 21d	C	None	14,000 mg/m <sup>2</sup>	17,500 mg/m <sup>2</sup>	36, 42
Fludarabine phosphate	24h CI × 5d	M	M	125 mg/m <sup>2</sup>	107 mg/m <sup>2</sup>	43, 44
Gencitabine	IV 30min weekly × 3wk q 28d	M	M	790 mg/m <sup>2</sup> /wk	1200 mg/m <sup>2</sup> /wk	45, 46
Ifosfamide	Peds: IV 15min/d q other day × 3 q 21d Adult: IV 2h/d × 3 consecutive d q 21d	Phase 2	M	2500 mg/m <sup>2</sup> /d	3000 mg/m <sup>2</sup> /d	47, 48
Ifosfamide	Peds: IV 15min/d (adult 2h) × 3d q 21d	Phase 2	M	2500 mg/m <sup>2</sup> /d	2133 mg/m <sup>2</sup> /d	47, 49
Indicine-N-oxide	IV 15min/d × 1 q 21-28d	M	M	7.25 g/m <sup>2</sup>	7.5 g/m <sup>2</sup>	50, 51, 52
Irinotecan	IV 2h/d (adult 30 min) × 3d q 21d	GI, M	GI, M	100 mg/m <sup>2</sup> /d	170 mg/m <sup>2</sup> /d	53, 9
Irinotecan	IV 2h (adult 30 min) × 1 q 21d	M	GI, M	600 mg/m <sup>2</sup>	600 mg/m <sup>2</sup>	54, 55
Nolatrexed dihydrochloride	24h CI × 5d q 21-28d	M, MUC	M, MUC	800 mg/m <sup>2</sup> /d	640 mg/m <sup>2</sup> /d	56, 57
Paclitaxel	24h CI q 21d	PNS	CNS, PNS	350 mg/m <sup>2</sup>	250 mg/m <sup>2</sup>	58, 59
Pegylated liposomal doxorubicin	IV 4h (adult 1h) × 1 q 28d	D, MUC	MUC	60 mg/m <sup>2</sup>	60 mg/m <sup>2</sup>	60, 61
Piritrexim	po q12h (adult qd) × 5d q 21 d	D, M, MUC	M, MUC	400 mg/m <sup>2</sup> /d	140 mg/m <sup>2</sup> /d	62, 7
Piritrexim	po q8h (adult qd) × 5d/wk × 3wk q 28d	M	M, MUC	25 mg/dose	20 mg/m <sup>2</sup> /dose	63, 64
Pyrazoloacridine	IV 1h × 1 q 21d	CNS, M	M	600 mg/m <sup>2</sup>	640 mg/m <sup>2</sup>	65, 66
Rebeccamycin analog	IV 1h × 1 q 21d	M	M	572 mg/m <sup>2</sup>	585 mg/m <sup>2</sup>	67, 68, 69
Temozolomide	po daily × 5d	M	M	200 mg/m <sup>2</sup> /d	180 mg/m <sup>2</sup> /d	70, 71
Temozolomide	po daily × 5d	M	M	200 mg/m <sup>2</sup> /d	200 mg/m <sup>2</sup> /d	70, 72
Topotecan	24h CI × 1 q 21d	M	M	8.4 mg/m <sup>2</sup> /d	5.5 mg/m <sup>2</sup> /d	73, 6
Topotecan	24h CI × 3d q 21d	M	M	1.05 mg/m <sup>2</sup> /d	1 mg/m <sup>2</sup> /d	74, 75
Topotecan	IV 30min/d × 5d q 21d	M	M	1.5 mg/m <sup>2</sup> /d	2 mg/m <sup>2</sup> /d	76, 77, 78
Topotecan	po daily × 10d q 28d	GI, M	GI, M, STOM	1.4 mg/m <sup>2</sup> /d	1.8 mg/m <sup>2</sup> /d	79, 80
Trimetrexate	IV 30min/d × 5d	M	D, H, M, MUC	7.6 mg/m <sup>2</sup> /d	9.2 mg/m <sup>2</sup> /d	81, 82
I 131-Metaiodobenzylguanidine*	Peds: IV 30 min × 1		M		2.5 Gy	83
Cyclophosphamide†	IV 1h/d 2d/wk (adult 1d) q 14d	M	M	4.5 mg/m <sup>2</sup>		84, 85
Docetaxel‡	Peds: IV 1h × 1 q 21d		C, D		185 mg/m <sup>2</sup>	86
Irinotecan*	Peds: IV 1h/d × 5d q 21d		GI, M		195 mg/m <sup>2</sup> /cycle	87
Paclitaxel*	Peds: IV 3h/d, 2d/wk × 3 wk q 28d		M		300 mg/m <sup>2</sup> /cycle	88
Sulofenur§	po bid (adult qd) 5d/wk × 3 wks	M, MHG	MHG	810 mg/m <sup>2</sup> /d		89, 90
Thioguanine	Peds: 24-36h CI		M	300 mg/m <sup>2</sup>	480 mg/m <sup>2</sup>	91
Leukemia						
Carboplatin	24h CI × 5d	M	H, R	300 mg/m <sup>2</sup> /d	216 mg/m <sup>2</sup> /d	92, 93
Gemcitabine	IV 6h 1d/wk × 3wk q 28d	D, MUC	H	4800 mg/m <sup>2</sup> /wk	3600 mg/m <sup>2</sup> /wk	94, 95
Topotecan	24h CI × 5d q 21-28d	MUC	MUC	3.8 ng/mL	4 ng/mL	96, 97, 98
Topotecan	IV 30min/d × 8.5d (adult 5d) q 21d	C, H, M	GI, INF, MUC	22.5 mg/m <sup>2</sup>	21.6 mg/m <sup>2</sup>	99, 100
2-Chlorodeoxyadenosine¶	24h CI × 5d q 10d (adult 5-14d)	M	M		8.9 mg/m <sup>2</sup> /d	101, 102
Fluorouracil#	Peds: IV 15min/d × 5d q 21d		M, STOM		650 mg/m <sup>2</sup> /d	28
Diaziquone#	Peds: IV 4h/wk × 4wk q 36d		M		120 mg/m <sup>2</sup>	37
Indicine-N-oxide#	Peds: IV 15min/d × 1 q 21d		M		6 g/m <sup>2</sup>	52

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum-tolerated dose; IV, intravenously; M, myelosuppression; ENDO, endocrine; MUC, mucositis; STOM, stomatitis; CI, continuous infusion; CNS, central nervous system; C, constitutional symptoms; GI, gastrointestinal; PNS, peripheral nervous system; D, dermatologic; H, hepatic; MHG, methemoglobinemia; R, renal; INF, infections.

\*No corresponding adult study using the same administration schedule.

†Pediatric study was phase I/II with main endpoint dose intensity and response.

‡No corresponding adult study using granulocyte colony-stimulating factor.

§Pediatric study had no MTD because each dose level was associated with unacceptable methemoglobinemia.

||No good corresponding adult study as study escalated dose and infusion duration.

¶Adult study pharmacokinetics study only.

#No corresponding adult leukemia study on same administration schedule; (patients with solid tumors are reported).

Table 2. Biologics

Drug	Schedule	Adult DLT	Pediatric DLT	Adult MTD	Pediatric MTD	Refs
Solid tumor						
9- <i>cis</i> -retinoic acid	Peds: po tid × 28d Adult: po bid × 28d	CNS, GI	CNS	91.5 mg/m <sup>2</sup> /d	85 mg/m <sup>2</sup> /d	103, 104, 24
All- <i>trans</i> -retinoic acid	po q12h (adult qd)	CV	CNS	215 mg/m <sup>2</sup> /d	60 mg/m <sup>2</sup> /d	11, 105
Fenretinide	po daily	D, OC	OC	200 mg/d	4000 mg/m <sup>2</sup> /d	106, 12
Interferon beta*	Peds: IV 30min/d MWF × 6 wks Adult: IV push 2d/wk × 5+ wk	None	CNS, H, M	500 mU/m <sup>2</sup> /wk	500 mU/m <sup>2</sup> /wk	107, 108
Interleukin-2†	24h CI × 5d (adult 7d) × 3wk	C, CV, DPS	CV, H, M, PULM, R	7×10 <sup>6</sup> U/m <sup>2</sup> /wk	15×10 <sup>6</sup> U/m <sup>2</sup> /wk	109, 14
Recombinant TNF‡	IV 30min/d × 5d q 14-21d	C, CV	H	150 mcg/m <sup>2</sup>	300 mcg/m <sup>2</sup>	110, 13
13- <i>cis</i> -retinoic acid§	Peds: po bid × 14d q 28d		D, GI, M, METAB,		160 mg/m <sup>2</sup> /d	111
Interleukin-2§	Peds: IV 1.73h/d × 9d q 31.5d		None		18×10 <sup>6</sup> U/m <sup>2</sup>	112
SU101§	Peds: 96h CI q 21d Adult: 24h CI weekly × 4wk	None	CNS	440 mg/m <sup>2</sup> /d	390 mg/m <sup>2</sup> /d	113, 114
Leukemia						
Anti-B4-blocked ricin	24h CI × 7d	H, M	CLS	50 mcg/kg/d	40 mcg/kg/d	115, 116
Interferon gamma	Peds: subcutaneous injection daily Adult: IM daily	C, M	C, CV, R	0.5 mg/m <sup>2</sup> /d	0.5 mg/m <sup>2</sup> /d	117, 118

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum-tolerated dose; GI, gastrointestinal; CV, cardiovascular; D, dermatologic; OC, ocular; MWF, Monday-Wednesday-Friday; IV, intravenously; H, hepatic; M, myelosuppression; CI, continuous infusion; C, constitutional symptoms; DPS, decreased performance status; PULM, pulmonary; R, renal; TNF, tumor necrosis factor; METAB, metabolic; CLS, capillary leak syndrome; IM, intramuscular; SQ, subcutaneous.  
\*MTD defined with inpatient dose escalation scheme.  
†DLT definitions differ substantively.  
‡Pediatric patients were prehydrated to prevent hypotension.  
§Excluded: no corresponding adult study of the same administration schedule.  
||Corresponding adult study is IM versus SQ.

single-agent studies and 14 were multiagent studies. Nine studies were in patients with leukemia only (two biologic, seven cytotoxic), and 14 studies (five biologic, nine cytotoxic) were performed in patients with either solid tumors or leukemia (Tables 1 and 2). These 69 studies enrolled 1,973 patients (52% males) with a median of 25 patients per study. Of the 1,973 patients enrolled, 1,779 patients (90.2%) were fully assessable for toxicity, and 1,809 patients (91.7%) were assessable for response. The overall median age of children enrolled onto these phase I studies was 10.9 years. Neuroblastoma was the most common diagnosis (Fig 1).

### Pediatric Versus Adult Tolerability to Phase I Agents

Of the 55 single-agent trials, 11 (eight cytotoxic) were excluded from the pediatric and adult comparison aspect of the study. Reasons for exclusion included: no corresponding adult study using the same schedule ( $n = 7$ ), use of hematopoietic growth factors ( $n = 1$ ), no defined pediatric MTD ( $n = 2$ ), and only examining dose-intensity ( $n = 1$ ).

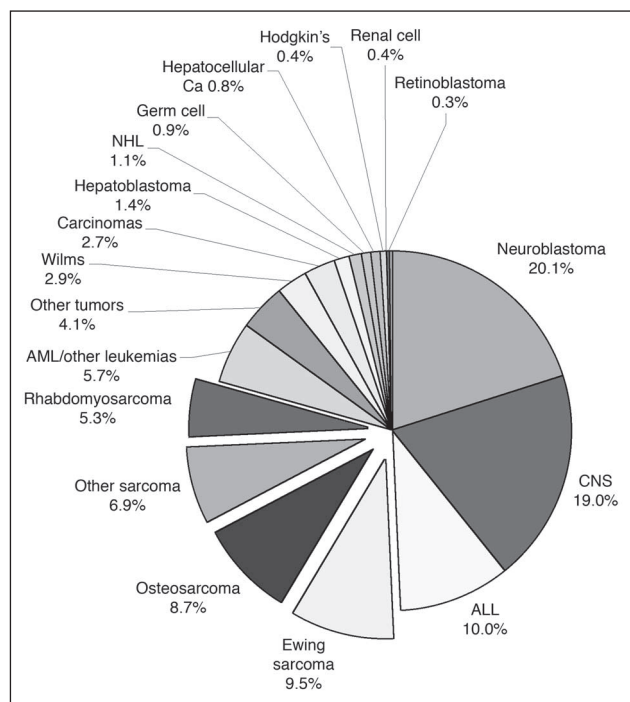
The 44 single-agent trials available for comparison were divided according to cytotoxic versus biologic compounds studied. The MTDs of both adult and pediatric corresponding studies are shown in Tables 1, 2, and 3. Thirty-six single-agent cytotoxic studies (Fig 2A) and eight biologic studies (Fig 2B) were compared. For three-fourths of the trials, the pediatric and adult MTDs differed by no more than 30%, and for more than 85% of the

trials, the pediatric MTD was less than or equal to 1.6 times the adult MTD.

### Efficiency of Study Conduct

The pediatric MTD was strongly correlated with the adult MTD ( $r = 0.97$ ). Defining boundaries one potential dose level below (0.7-fold) and two potential dose levels above (1.6-fold) the adult MTD allowed for determination of studies that fell outside of a theoretical four-dose level range (Fig 3). For cytotoxic agents, two studies had a MTD ratio less than 0.7 (topotecan given as a 24-hour infusion<sup>6</sup> and piritrexim<sup>7</sup>), and three studies had a MTD ratio greater than 1.6 (fazarabine,<sup>8</sup> irinotecan,<sup>9</sup> and acivicin<sup>10</sup>). For biologic agents, one study (all-*trans* retinoic acid<sup>11</sup>) had a pediatric to adult MTD ratio less than 0.7, and three (fenretinide,<sup>12</sup> recombinant tumor necrosis factor,<sup>13</sup> and interleukin-2<sup>14</sup>) had MTD ratios greater than 1.6.

The number of patients enrolled and the number of dose levels per study are shown in Figures 4A and 4B. Sixty-seven studies delineated the number of patients enrolled at each dose level. Two hundred ten out of the 317 dose levels studied (66%) enrolled more than three patients. The average number of dose levels studied was 4.6 (median, four; range, two to 13), the average number of patients enrolled per dose level was 5.1 (median, five; range, two to 23), and the average number of pediatric patients enrolled onto a study was 29 (median, 25; range, 11 to 81).



**Fig 1.** The distribution of patients (n = 1,807) enrolled onto pediatric phase I trials. Diagnoses with five or more patients are shown. The other tumor category includes patients listed as "other" within each report as well as those patients with a disease that accrued fewer than five patients onto all phase I trials reported. NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia.

## Safety

There were sufficiently detailed DLT data available from 1,066 patients (47 studies) to estimate that the likelihood of a patient developing a DLT once enrolled onto a study was 24%. There were 10 toxic deaths (0.5% toxic death rate) across all studies. Further analysis of deaths attributed to drug show a mean of 0.14 deaths per study (median, zero; range, zero to three). All but two of the toxic deaths were at dose levels above the MTD, and of the remaining two, one was at the highest dose given in a study that did not reach an MTD and the other was at the MTD. Toxic deaths included one patient who died from intractable seizures and aspiration pneumonia, two from respiratory distress and hepatobiliary dysfunction, one from progressive midbrain dysfunction in which drug causality could not be ruled out, one from hepatic necrosis and encephalopathy, two from profound aplasia, and three patients with fulminant hepatic failure.

## Efficacy

Objective responses were recorded in 67 trials. Forty out of the 67 studies representing 26 different drugs had at least one objective response. In total, there were 50 CRs and 123 PRs in the 1,809 patients assessable for response, for an overall objective response rate of 9.6%. The average number of responses observed on a study was 2.6 (median, one;

range, zero to 15). When analyzed separately, the response rate for single-agent phase I studies was 6.8% and for multiagent phase I studies 20.1%. The dose levels at which responses were observed, however, were not routinely reported, and thus, no correlation could be made between response observed and dose level treated.

## Pharmacokinetics

Twenty-one studies reported the necessary pharmacokinetic data to allow for calculation of CV in drug clearance (Table 3). The median CV in drug clearance was 42% (range, 11% to 69%). Plasma drug clearance in children was highly correlated with that observed in adults ( $r = 0.97$ ), with a median ratio of pediatric to adult clearance (or apparent clearance) of 0.95. Despite the strong correlation, there was a wide range of ratios observed across studies (0.06 to 2.2).

## DISCUSSION

With the exception of childhood leukemias, the proportion of diagnoses of children enrolling on pediatric phase I trials generally reflects the number of patients who experience a relapse of their disease (Fig 1). Patients with neuroblastoma, brain tumors, or sarcomas represented approximately two-thirds of patients enrolled on phase I trials. Multiple factors may contribute to the under-representation of children with leukemia on phase I trials, including the availability of varied salvage regimens, including stem-cell transplants, the rapidity of disease progression in recurrent leukemia, and phase I trial design limitations.

In an era when children with newly-diagnosed, high-risk malignancies are routinely treated with dose intensive regimens, the conduct of phase I trials in relapsed or refractory patients continues to be safe and relatively well-tolerated. Approximately one in four children enrolled onto a phase I trial experienced a DLT. Because the design of phase I trials in most circumstances necessitates the determination of a MTD, this degree of toxicity is anticipated and is significantly less than the 80% frequency of grade 3 or greater toxicity observed on many front-line multiagent regimens.<sup>16</sup> Importantly, treatment-related mortality was less than 0.5%.

The likelihood of achieving an objective response when participating in a pediatric phase I trial was 9.6%. This is similar to the 7.9% objective response rate reported in pediatric phase I trials conducted in earlier eras<sup>17</sup> but higher than the 3% to 6% objective response rate observed on phase I trials conducted in adult patients.<sup>18-22</sup> Not surprisingly, and similar to phase I trials in adults,<sup>21</sup> the response rate was higher in trials that combined an investigational drug with drugs with known anticancer activity (20.1%) versus an investigational drug alone (6.8%). It should be emphasized that the definition of direct patient benefit may

Table 3. Plasma Drug Clearance

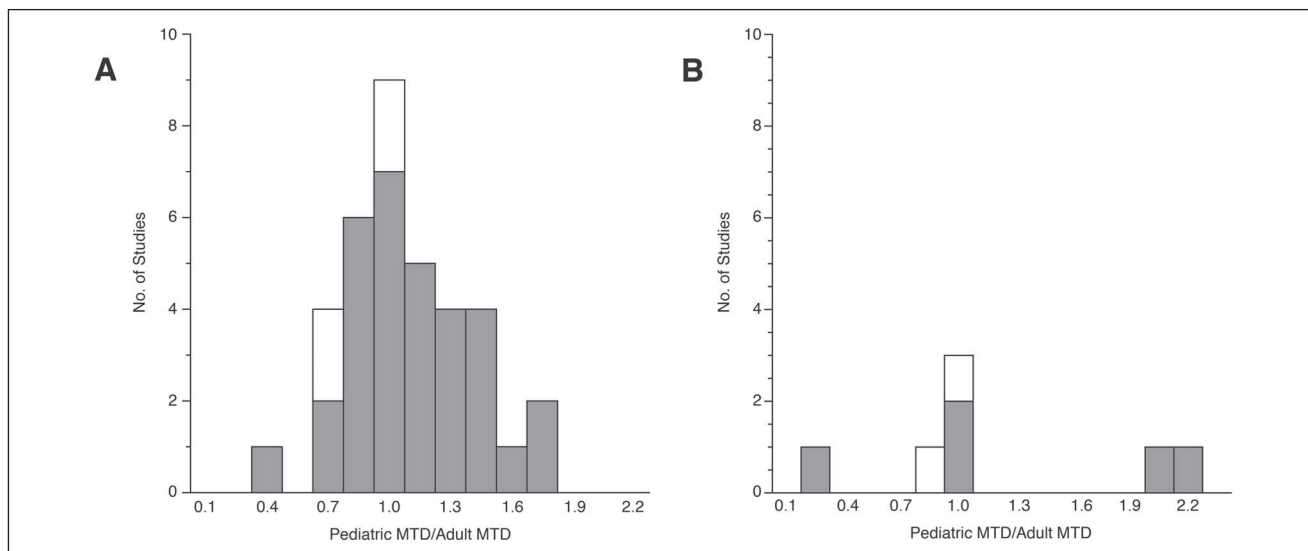
Drug	CV Pediatric Drug Clearance	Drug Clearance in Children (L/h/m <sup>2</sup> )		Drug Clearance in Adults (L/h/m <sup>2</sup> )		Ratio of Pediatric to Adult Drug Clearance	References
		Mean	SD	Mean	SD		
9- <i>cis</i> -retinoic acid (Adamson et al)	0.60	128.6*	128.6*	114.4*	150.4*	1.1	24,103
All-trans retinoic acid (Smith et al)	0.42	667*	400*	764*	230*	0.9	11,105
Doxil (Marina et al)	0.38					0.5	61,119
Median		0.03		0.06			
Range		0.02–0.05		0.03–0.24			
Fenretinide (Garaventa et al)	0.49	43.6*		56.6		0.8	12,120
Flavone acetic acid (Pratt et al)	0.18	2.0	0.4	3.1	2.4	0.7	42,121
Fludarabine (Avramis et al)	0.66	0.61	0.11			0.06	44,122
Median				9.6			
Range				4.1–15			
Gemcitabine Reid et al	0.5					1.2	45,46,95
Median		165		137			
Range		66–402		26–553			
Steinherz et al	0.56						
Irinotecan (Vassal et al)	0.46	20.7	9.5	15	1	1.4	54,55
Nolatrexed	0.28					1.3	56,57
Median		4.1		3.1			
Range		2.3–5.9		2.3–3.2			
Piritrexim Adamson et al (1990)	0.12	11.3	39.4 <sup>a</sup>	9.7	19.4	1.2	7,64
Adamson et al (1992)	0.69						
Rebeccamycin analog (Langevin et al)	0.11	8.0	1.0	7.57	4.2	1.1	68,69
SU101 (SU0020; Adamson et al)	0.47	0.008	0.004	0.017	0.011	0.5	113,114
Temozolomide (Eslin et al)	0.35	5.9	1.4	6.1	0.6	1.0	72,123
Thioguanine (Kitchen et al)	0.56	47.9	16.1	135	21.2	0.35	91,124
Topotecan lactone Tubergen et al	0.39	16.7	6.5			0.49	6,73,75,100
Median				34.2			
Range				15–59			
Pratt et al	0.32						
Blaney et al	0.23						
Furman et al	0.46						
Topotecan lactone (oral; Daw et al)	0.4	145	404	66.6	185.2	2.2	79,80

NOTE. The CV in plasma drug clearance (or apparent clearance) for pediatric studies is reported in the second column. Clearance values were obtained either directly from the published report or were derived from area under the concentration-time curve (AUC) data at the maximum tolerated dose.  
<sup>a</sup>Clearance derived from AUC data (AUC<sub>0-24</sub>) at the maximum tolerated dose.

extend beyond objective response, in the form of disease stabilization or symptom relief, and thus, the proportion of patients who derived direct benefit from participation on a phase I trial should not be equated to the observed response rate. However, data on symptom relief and disease stabilization have not historically been captured during the conduct of phase I trials, and thus, estimates of the fraction of

patients who derive direct benefit, although greater than the response rate, cannot be made.

In general, the definition of nonhematologic DLTs was identical in adult and pediatric trials (data not shown). For the hematologic toxicity, however, often either a greater degree or a longer duration of myelosuppression was required in pediatric studies than in adult studies to qualify as



**Fig 2.** Histogram of the pediatric: adult maximum-tolerated dose (MTD) ratios for cytotoxic (A) and biologic (B) drugs. The shaded portions are studies performed in patients with solid tumors, and the open portions are studies performed in patients with leukemia. Fenretinide had an exceptionally high MTD ratio<sup>20</sup> and was not included in 2B.

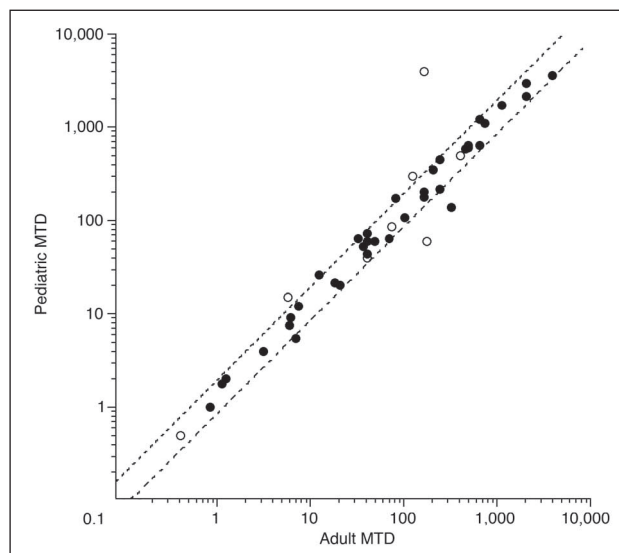
a DLT. This may, in part, account for the higher MTDs occasionally observed in pediatric studies in which myelosuppression was dose-limiting.

The types of toxicities experienced by children enrolled onto phase I trials were, with few exceptions, the same as those experienced by adult patients (Tables 1 and 2). Not surprisingly, we also found a strong correlation between the MTD observed in adult patients and the MTD defined in pediatric patients (Fig 3). The correlation was stronger for cytotoxic drugs ( $r = 0.97$ ) than for biologic agents ( $r = 0.3$ ). However, one cannot conclude that differences in MTD, when observed, were the result of true differences in tolerability. For certain drugs, such as the retinoids,<sup>11,23,24</sup> a difference in tolerability between adult and pediatric patients indeed appears to underlie the differences in MTD. Of the six drugs in which the pediatric MTD exceeded the adult MTD by a factor greater than 1.6, two (fazarabine,<sup>8</sup> irinotecan<sup>6</sup>) had a ratio of only 1.7, and for the three biologic agents (fenretinide,<sup>12</sup> rTNF,<sup>13</sup> and IL-2<sup>14</sup>), a difference in the definition of DLT was the major factor underlying the discordant MTDs. Of note, following completion of the fenretinide phase I pediatric trial, subsequent studies of fenretinide found that higher doses could also be tolerated in adult patients.<sup>25</sup>

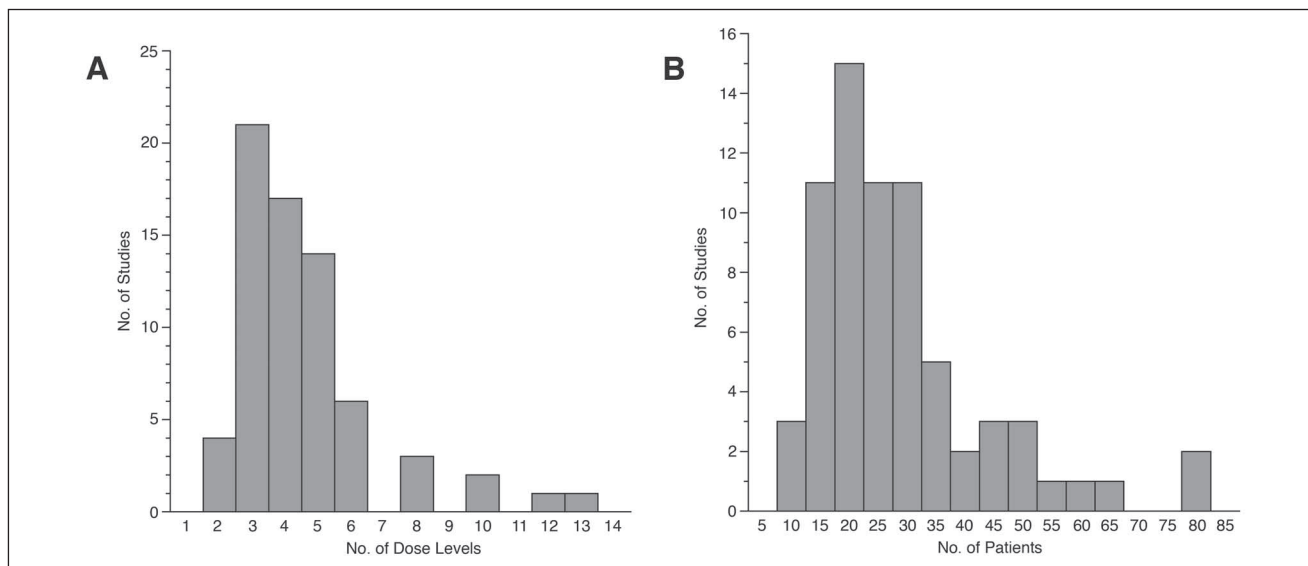
Despite the strong correlation between the adult and pediatric MTD, 40% of studies enrolled patients onto more than four dose levels (Fig 4A), and 46% of studies required more than 25 assessable patients to reach their conclusion (Fig 4B). One would anticipate that for studies requiring more than four dose levels, the pediatric MTD would greatly exceed the adult MTD. However, we did not find this to be the case, as the pediatric MTD was less than

two-fold the adult MTD for all of the cytotoxic drugs and all but two of the biologic drugs studied.

The primary reasons that such a high fraction of studies were not efficient in reaching their conclusion appears to be two-fold. First, the likelihood that the pediatric MTD would exceed the adult MTD by more than 1.6-fold is small (Figs 1A and 1B), making exploration of levels beyond this of little value. Secondly, many studies, either by initial design or by later modification, explored dose levels that differed



**Fig 3.** Scatter plot of pediatric maximum-tolerated doses (MTDs) versus adult MTDs. Closed circles are studies of cytotoxic drugs, and open circles are studies of biologic drugs. The dotted lines represent a theoretical range of four dose levels from 0.7 to 1.6 times the adult MTD.



**Fig 4.** The number of dose levels studied (A) and the number of patients enrolled (B) in each pediatric trial.

from a previously studied dose level by increments significantly smaller than 30%.

On the basis of this analysis, we propose that changes in study design could increase the efficiency in which pediatric phase I trials are conducted. Unless it is anticipated that pediatric oncologists, patients, and families would be willing to have children tolerate significantly worse toxicities than those experienced on the corresponding adult phase I trial, there appears little value in exploring dose levels more than 1.6 times the adult MTD. Caveats to this recommendation are two-fold: if drug disposition (pharmacokinetics) differs significantly from adults, or if the toxicity profile in children is found to differ significantly from adults, higher (or potentially lower) dose levels might need to be explored.

Secondly, attempts to fine-tune the recommendation for phase II dosing by examining increments of less than 30% should, in general, not be made during the conduct of the phase I study. Limiting pediatric phase I trials to the study of no more than four doses levels (0.7, 1.0, 1.3, and 1.6 times the adult MTD), would significantly shorten the timeline for the conduct of these studies and would be unlikely to result in a conclusion that differs substantively from trials that examine a greater number of dose levels.

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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