Phase I Trial and Pharmacokinetic Study of Ixabepilone Administered Daily for 5 Days in Children and Adolescents With Refractory Solid Tumors

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A B S T R A C T

Purpose

The objectives of this phase I trial were to determine the maximum-tolerated dose (MTD), toxicity profile, dose-limiting toxicities (DLTs), pharmacokinetics, and preliminary response rate for ixabepilone, a microtubule-stabilizing agent, administered intravenously daily for 5 days in children and adolescents.

Patients and Methods

Patients ≥ 2 and ≤ 18 years with relapsed or refractory solid tumors were enrolled onto sequential cohorts to the following five dose levels: 3.0 ($n = 3$), 4.5 ($n = 4$), 6.0 ($n = 3$), 8.0 ($n = 6$), and 10 ($n = 3$) mg/m²/d. Eligibility criteria, dose levels, definitions of DLT and MTD, and pharmacokinetic sampling times were designed to be as similar as possible to the adult phase I trial of ixabepilone on the same schedule.

Results

Nineteen children (median age, 10 years; range, 2 to 18 years) were enrolled, and 18 (12 with sarcomas) were assessable for toxicity. DLTs (grade 4 neutropenia for > 5 days and grade 3 fatigue) were observed in two of three patients receiving 10 mg/m²/d. The MTD of ixabepilone administered daily for 5 days every 21 days was 8 mg/m²/d. Myelosuppression, GI, and hepatic toxicities were common non-DLTs. Peripheral neuropathy was uncommon. Ixabepilone clearance was 475 ± 247 mL/min/m², volume of distribution at steady-state was 12.2 ± 5.4 L/kg, and half-life was 14 hours.

Conclusion

The recommended dose of ixabepilone for phase II trials in solid tumors is 8 mg/m²/d daily for 5 days every 21 days. This dose is 33% higher than the MTD in adults receiving the same dosing schedule. Pharmacokinetic parameters in children and adolescents were highly variable but similar to adults.

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INTRODUCTION

Ixabepilone (BMS-247550, NSC 710428) is a semi-synthetic analog of epothilone B, which is a natural product extracted from the myxobacterium *Sorangium cellulosum*.^{1,2} Ixabepilone binds tubulin and stabilizes microtubules, leading to microtubular bundling, formation of multipolar spindles, and mitotic arrest.³ Ixabepilone is primarily eliminated by extensive hepatic metabolism (CYP3A4/5). Although its mechanism of action is similar to that of the taxanes, ixabepilone exhibited a broader spectrum of antitumor activity in preclinical models of childhood tumors than paclitaxel,⁴ which proved to be clinically inactive in childhood cancers.

Dosing schedules of ixabepilone that have been studied in adults include a single intrave-

nous dose infused over 1 or 3 hours repeated every 21 days,⁵⁻⁷ weekly infusions,^{8,9} and once daily intravenous doses for 3 days¹⁰ or for 5 days,¹¹ repeated every 21 days. The maximum-tolerated dose (MTD) was 40 to 50 mg/m² on the single-dose schedule, 20 to 25 mg/m²/wk (60 to 75 mg/m²/course) on the weekly schedule, and 8 mg/m²/d (24 mg/m²/course) for the daily for 3 days schedule and 6 mg/m²/d (30 mg/m²/course) for the daily for 5 days schedule. Neutropenia was a consistent dose-limiting toxicity (DLT), and nonhematologic toxicities included fatigue, stomatitis, arthralgias, myalgias, diarrhea, and abdominal pain. Sensory peripheral neuropathy, which occurred in half of the patients, seemed to be dose related and cumulative on the single-dose schedule but less severe (primarily grade 1) on the daily dosing schedules.^{5,6,10-12}

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The pharmacokinetic profile of ixabepilone in adults^{5,6,11} was characterized by an initial rapid distributive phase with extensive tissue distribution (volume of distribution at steady-state of 1,200 to 1,500 L) followed by a prolonged terminal elimination phase with a half-life of 35 hours. Clearance in adults is 650 to 700 mL/min (approximately 375 mL/min/m²).

Objective responses to ixabepilone were observed in the phase I trials in patients with breast, ovarian, cervical, endometrial, lung, colon, and head and neck cancers and with lymphoma and melanoma. Efficacy for ixabepilone in breast cancer has been confirmed in phase II and III trials,¹³⁻¹⁸ and objective responses have also been observed in gastric,¹⁹ prostate,^{20,21} and non-small-cell lung cancers.²²

We performed a phase I trial of ixabepilone in children with relapsed or refractory solid tumors using the daily for 5 days dosing schedule as a result of the potentially lower incidence of severe sensory neuropathy with this schedule. In addition, this schedule was used in a phase I trial in adults performed at the National Cancer Institute (NCI),¹¹ which allowed us to follow the design (eligibility criteria, dose levels of ixabepilone, definitions of DLT and MTD, and pharmacokinetic sampling times) of the adult trial as closely as possible to ensure that the results in children could be meaningfully compared with those in adults.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients must have been ≥ 2 and ≤ 18 years of age with a histologically confirmed, measurable or assessable solid tumor that was refractory to standard treatment; must have recovered from the toxic effects of prior therapy; must have had a Karnofsky (children > 10 years) or Lansky (children ≤ 10 years) performance score ≥ 50 ; must not have had conventional chemotherapy within 28 days of study entry, investigational agents within 30 days of study entry, radiation therapy within 28 days of study entry, or colony-stimulating factors within 72 hours of study entry; and must have had an absolute neutrophil count $\geq 1,500/\mu\text{L}$, a platelet count $\geq 100,000/\mu\text{L}$, bilirubin $\leq 1.5\times$ the upper limit of normal, ALT and AST $\leq 2.5\times$ the upper limit of normal, and an age-adjusted normal serum creatinine or a creatinine clearance ≥ 60 mL/min/1.73 m².

Patients were excluded for myeloablative therapy requiring bone marrow or stem-cell rescue or extensive radiotherapy within the previous 6 months; active pregnancy or breastfeeding; concurrent use of other investigational agents or agents that induce or inhibit CYP3A4; pre-existing grade ≥ 2 sensory neuropathy; or a history of allergy to polyethoxylated castor oil (Cremophor EL; BASF Corp, Ludwigshafen, Germany). This trial was approved by the NCI Institutional Review Board, and all patients or their legal guardians signed a document of informed consent indicating their understanding of the investigational nature and the risks of this study.

Trial Design

This phase I trial was an open-label, single-institution, dose-escalation study to determine the MTD, toxicity profile, DLTs, pharmacokinetics, and preliminary response rate for ixabepilone in children and adolescents. Ixabepilone, which was provided by the NCI's Cancer Therapy Evaluation Program, was administered as a 1-hour intravenous infusion daily for the first 5 consecutive days of a 21-day cycle. Diphenhydramine and ranitidine were administered before each dose of ixabepilone. The starting dose of ixabepilone was 3 mg/m²/d with subsequent, sequential dose escalations to 4.5, 6, 8, and 10 mg/m²/d in cohorts of three to six patients. A single inpatient dose escalation by one dose level was allowed on subsequent cycles if the severity of toxicity on the prior cycle did not exceed grade 1 for nonhematologic toxicities or grade 2 for hematologic toxicities.

Monitoring for treatment-related toxicity included weekly physical examinations and performance status and a complete standardized neurologic

examination including a Purdue Pegboard test and the WEST-hand (Connecticut Bioinstruments Inc, Danbury, CT) Medical, Hood River, OR) esthesiometer test before each cycle, as previously described.²³ Serum chemistries were monitored weekly, and CBCs were monitored twice weekly. Clinical and laboratory adverse events were graded according to the NCI Common Toxicity Criteria version 2, except for motor and sensory neuropathy, which were graded using pediatric-specific scales.²³

Hematologic DLT was defined as grade 4 neutropenia ($< 500/\mu\text{L}$) of ≥ 5 days in duration, grade 4 thrombocytopenia ($< 10,000/\mu\text{L}$) occurring on 2 or more days of a treatment cycle, or failure to recover a neutrophil count to $\geq 1,500/\mu\text{L}$ or a platelet count to $\geq 75,000/\mu\text{L}$ by day 28 of the treatment cycle. Nonhematologic DLT was any grade 3 or 4 nonhematologic toxicity related to ixabepilone or failure to recover to grade ≤ 1 toxicity or to baseline toxicity level (if higher than grade 1) by day 28 of the treatment cycle. Exceptions were grade 3 elevations in ALT or AST that recovered to grade ≤ 1 by day 28 of the treatment cycle and grade 3 nausea or vomiting that was successfully controlled with antiemetics.

The MTD was determined from DLTs occurring during the first treatment cycle. The MTD was defined as the dose level immediately below the dose level at which two or more patients in a cohort of up to six patients experienced a DLT. Three patients ≤ 12 years old and three patients more than 12 years old were enrolled at the MTD. In patients with measurable disease, response was assessed by Response Evaluation Criteria in Solid Tumors.

Pharmacokinetics

Detailed pharmacokinetic sampling (before infusion; 0.5 hours into the infusion; at the end of infusion; and 0.25, 0.5, 0.75, 1, 2, 3, 5, 7, 10, and 23 hours after infusion) was performed after the first dose on cycle 1. Trough (before infusion) and peak (end of infusion) samples were obtained for doses 2 through 5, and 24- and 48-hour samples were drawn after the fifth dose. Sample processing and storage, the liquid chromatography/mass spectrometry/mass spectrometry method (lower limit of quantification of 2 ng/mL, intra-assay precision within 9%, and interassay precision within 12% relative standard distribution) used to quantify ixabepilone in the plasma samples, and the pharmacokinetic analyses performed on the plasma ixabepilone concentrations were identical to those previously described for the phase I trial of the daily for 5 days schedule in adults to allow for a direct comparison of pediatric and adult data.¹¹

RESULTS

Patient Characteristics

The characteristics of the 19 children and adolescents who were enrolled onto the study are listed in Table 1. Eighteen patients received all five daily doses of ixabepilone on cycle 1 and were assessable for toxicity. A 13-year-old girl (patient 5), who was enrolled onto the second dose level (4.5 mg/m²/d) and received five doses, was not assessable for toxicity because she was removed from study before the end of the first cycle to receive palliative radiation for tumor-related pain. This patient did not experience ixabepilone-related DLT. Pharmacokinetic samples were available from this patient, and these results are reported.

Toxicity and MTD

Toxicities that occurred during the first cycle of treatment and that were judged to be possibly, probably, or definitely related to ixabepilone in the 18 assessable patients are listed in Table 2 by dose level and NCI Common Toxicity Criteria grade. Myelosuppression increased in incidence and severity with increasing dose. The three patients receiving a dose of 10 mg/m²/d experienced grade 4 neutropenia, which was dose limiting (≥ 5 days in duration) in one patient. Thrombocytopenia was less severe than neutropenia. GI toxicity (anorexia, nausea, and vomiting), fatigue, and elevated hepatic transaminases were also prominent but generally mild and tolerable. Two of

Table 1. Baseline Patient Characteristics

Characteristic	No. of Patients (N = 19)
No. of assessable patients	18
Age, years	
Median	10.5
Range	2-18
Sex	
Male	10
Female	8
Performance score (Lansky or Karnofsky)	
Median	90
Range	70-100
Tumor type	
Rhabdomyosarcoma	3
Other soft tissue sarcoma	4
Osteosarcoma	3
Ewing sarcoma	2
Hepatoblastoma	2
Wilms' tumor	2
Neuroblastoma	1
Other	1
No. of prior chemotherapy regimens	
Median	3
Range	1-10
Patients who had prior radiation therapy	10

three patients receiving a dose of 10 mg/m²/d experienced a DLT; one had grade 4 neutropenia for more than 5 days, and the other had grade 3 fatigue.

The 8 mg/m²/d dose level was subsequently expanded to six patients, and one of the additional three patients was hospitalized for generalized grade 3 neuropathic pain and grade 3 anorexia with dehydration and subsequently developed grade 3 stomatitis, grade 4 neutropenia, and low-grade fever. This patient subsequently received six additional cycles at a reduced dose of 6 mg/m²/d and tolerated this lower dose. None of the other five patients at the 8 mg/m²/d dose level experienced a DLT, and therefore, 8 mg/m²/d on a daily for 5 days schedule is the MTD of ixabepilone in children and adolescents.

Seven patients received more than one cycle of ixabepilone (median, five cycles; range, two to 13 cycles; total, 44 cycles), including three patients who received two, three, and seven cycles at the MTD. Two patients experienced a DLT on cycle 2, one at 6 mg/m²/d (grade 4 neutropenia for ≥ 5 days) and one at 8 mg/m²/d (grade 3 diarrhea). The latter patient subsequently received and tolerated an additional five cycles at 6 mg/m²/d. Two patients had their dose escalated on cycle 2 from 3 to 4.5 mg/m²/d in one patient and from 4.5 to 6 mg/m²/d in the other patient. The higher dose on cycle 2 was tolerated by both patients. The toxicity profile of ixabepilone on cycle 2 and later cycles was identical to that on cycle 1. Neutropenia (grade 3 or 4 in five patients) was the most significant toxicity. A single episode of grade 3 thrombocytopenia was observed in one patient. The nonhematologic toxicities were mild, except for the grade 3 diarrhea and an episode of grade 3 vomiting.

Peripheral neuropathy occurred in five of 18 patients on cycle 1 and was mild (grade 1 in four of five patients). The severity (grade) did not seem to be dose related. There was no statistical difference in the median Purdue Pegboard score or gram forces detected using the

WEST-hand esthesiometer at baseline compared with end of cycle 1, off-study evaluation, or worst score at any evaluation during protocol therapy. Myalgia was also an uncommon toxicity on this schedule. There was no evidence of cumulative peripheral neuropathy in the seven patients who received more than one cycle. Two of these patients had grade 1 peripheral neuropathy on a subsequent cycle.

Two patients experienced a grade 2 hypersensitivity reaction on cycles 1 and 3. Both patients were able to continue receiving ixabepilone, one of them with the addition of dexamethasone to the premedication regimen.

Pharmacokinetics

Pharmacokinetic sampling was performed in 16 of 19 enrolled patients, and the pharmacokinetic parameters derived using model-independent methods are listed in Table 3. A representative plasma concentration-time curve from a patient who received the MTD is shown in Figure 1. The plasma concentration-time profile of ixabepilone in children and adolescents was similar to that in adults and was characterized by an initial rapid distributive phase followed by an elimination phase with a mean half-life after the first dose of 14 hours. This estimate of the half-life is similar to the 17-hour half-life in adults who were treated on the same schedule,¹¹ but the limited sampling duration (24 hours) may result in underestimation of the half-life. Eight patients had plasma samples obtained 24 and 48 hours after the fifth dose, and half-life estimates from these two points exceeded 24 hours in seven of the eight patients.

The end of infusion plasma concentration at the 8 mg/m²/d dose level was 105 ± 18 ng/mL, and by 24 hours, the plasma concentration had fallen to 4.6 ± 3.3 ng/mL. Figure 2 shows the mean end of infusion and trough plasma concentrations over the 5-day treatment course in a subset of patients with complete sample sets at the 4.5-, 6-, and 8-mg/m²/d dose levels. As in adults, there was minimal accumulation of ixabepilone over the 5-day treatment course. Trough concentrations 24 hours after the fifth dose were less than two-fold higher than trough concentrations after the first dose.

The distribution and clearance of ixabepilone in children and adolescents were highly variable (Table 3), and no relationship between dose and area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) was observed. The mean $AUC_{0-\infty}$ in adults ($n = 16$) who received the adult MTD of 6 mg/m²/d on the daily for 5 days schedule was 254 ng · h/mL, and at the same dose, the $AUC_{0-\infty}$ in three children was 168 ng · h/mL. At the pediatric MTD of 8 mg/m²/d, the $AUC_{0-\infty}$ in the pediatric ($n = 5$) and adult ($n = 8$) populations were 335 and 325 ng · h/mL, respectively.

On this study, clearance was more rapid in males (median, 561 mL/min/m²) than females (median, 328 mL/min/m²), but this difference was not statistically significant ($P = .20$). Clearance was not age dependent within the pediatric population, and the mean clearance in children and adolescents (475 mL/min/m²) was similar to the clearance in adults (416 mL/min/m²).¹¹ The volume of distribution at steady-state in children (12.2 L/kg) was large, similar to adults (11.8 L/kg), and consistent with extensive tissue binding of the drug. There was no relationship between the $AUC_{0-\infty}$ after the first dose and percent decrease in the neutrophil count from baseline to nadir during cycle 1.

Table 2. Patients With Ixabepilone-Related Toxicity During Cycle 1 by Dose Level and NCI-CTC Toxicity Grade

Toxicity	No. of Patients With Toxicity at Dose Level																			
	3 mg/m ² /d (n = 3)				4.5 mg/m ² /d (n = 3)				6 mg/m ² /d (n = 3)				8 mg/m ² /d (n = 6)				10 mg/m ² /d (n = 3)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Allergy/immunology																				
Allergic reaction																		1		
Blood/bone marrow																				
Hemoglobin		1	1			1				2			2	1	2				2	
Neutrophils							2			1		1			4	1*				3
Platelets									1			1		1	1*		3			
Cardiovascular																				
Hypertension													1				1			
Constitutional																				
Fatigue		1											3					1	1	
Fever without neutropenia					1												1			
Dermatology																				
Alopecia					1								3	2						
Flushing																	1			
Pruritus																	1			
GI																				
Anorexia	1								1						1*		2			
Constipation										1								1		
Dehydration														1	1*					
Diarrhea																	1			
Nausea							1					1	1	1	1*		2			
Stomatitis															1*		1			
Vomiting						1					1		2		1		2			
Hemorrhage																				
Epistaxis													1							
Hepatic																				
Increased alkaline phosphatase													1					1		
Increased bilirubin									1				1	1						
Hypoalbuminemia																	1			
Increased AST					1				1	1			3				1			
Increased ALT									1				2							
Infection																				
Fever/neutropenia															1*					
Metabolic/laboratory																				
Hyperkalemia													1							
Hypertriglyceridemia													1							
Neurology																				
Dizziness															1*					
Irritability (≤ 3 years)														1						
Sensory neuropathy					1				1				1		1*		1			
Pain																				
Abdominal													1				2			
Bone																				
Myalgia	1														1*			1		
Other													1							

Abbreviation: NCI-CTC, National Cancer Institute Common Toxicity Criteria.

*Toxicities occurring in the same patient.

Tumor Response

There were no complete or partial responses in the 18 patients who were assessable for response. Four patients had stable disease for more than three cycles, including one patient with neuroblastoma (five cycles), one patient with Ewing sarcoma (seven cycles), and two patients with other soft tissue sarcomas (12 and 13 cycles).

DISCUSSION

Children and adolescents tolerated ixabepilone at doses of up to 8 mg/m²/d administered on a daily for 5 consecutive days schedule repeated every 21 days. The DLTs in two of three patients at the

Table 3. Pharmacokinetic Parameters for Ixabepilone From 16 Children and Adolescents

Patient	Dose Level (mg/m ² /d)	Dose (mg)	AUC _{0-∞} (ng · h/mL)	Clearance (mL/min/m ²)	Vd _{ss} (L/kg)	Half-Life (h)
1	3.0	2.3	182	272	13.3	20.2
2	3.0	2.4	262	188	5.3	10.1
3	3.0	6.6	210	238	6.0	15.8
4	4.5	4.4	89.1	848	6.5	4.7
5	4.5	7.1	261	291	7.8	14.9
6	4.5	7.0	285	264	15.1	30.8
7	4.5	3.2	151	506	22.8	18.0
8	6.0	6.3	272	364	9.0	12.4
9	6.0	4.2	100	998	18.8	8.4
10	6.0	10.0	133	737	7.4	7.5
11	8.0	4.0	362	368	17.3	15.7
12	8.0	14.0	326	403	10.3	17.2
17	8.0	18.0	476	281	12.6	13.8
18	8.0	9.4	216	616	18.3	13.9
19	8.0	10.4	293	451	8.1	8.3
14	10.0	11.9	223	767	17.0	12.2

Abbreviations: AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; Vd_{ss}, volume of distribution at steady-state.

10-mg/m²/d dose level were neutropenia and fatigue. One of the six patients receiving 8 mg/m²/d experienced a variety of grade 3 DLTs (GI, neuropathy, myalgia, fever, and neutropenia). Neutropenia was the most consistent dose-related toxicity observed on the study, and neutropenia was more severe than thrombocytopenia, as we previously observed with docetaxel in children.^{24,25} Hepatic and GI toxicities were common but mild (grade 1) in most patients and not clearly dose related. Neuropathy, myalgia, and arthralgia were not prominent and not cumulative in the few patients who received multiple treatment cycles.

This pediatric phase I trial was designed to allow for direct comparison of results in children and adults receiving ixabepilone on the daily for 5 days schedule. The phase I trial in adults performed at the NCI used an accelerated dose-escalation design with initial dose-escalation increments of 100% (1.5, 3, and 6 mg/m²/d).^{11,26} The accel-

erated escalation was halted at the third dose level because toxicity data from concurrent phase I trials indicated that the third dose level was close to the MTD. The starting dose for our pediatric trial was selected as one dose level below the MTD (3 mg/m²/d), and the dose levels of 6 and 8 mg/m²/d were also included. We added an intermediate dose level (4.5 mg/m²/d) between the starting dose and the adult MTD and a 10 mg/m²/d dose level. The traditional method of determining dose levels for a pediatric phase I trial using 80% of the adult MTD as a starting dose and escalating in 33% increments would have yielded dose levels of 4.8, 6.5, 8.5, and 11.3 mg/m²/d.

Neutropenia was the primary DLT in adults at 8 mg/m²/d and was also dose limiting at 10 mg/m²/d on our trial, which used the same definition of dose-limiting neutropenia. An attempt was made in the adult study to re-escalate to the 8 mg/m²/d dose level by adding filgrastim to shorten the duration of neutropenia, but two of six patients experienced dose-limiting neutropenia. Children and adolescents tolerated a 33% higher dose of ixabepilone on the daily for 5 days schedule than adults.

Pharmacokinetic sampling times, the ixabepilone assay method, and the derivation of pharmacokinetic parameters were identical for the adult and pediatric trials. The pharmacokinetic parameters were similar in children and adults (Table 4), but there seemed to be more variability in the pediatric population. The coefficients of variation for ixabepilone clearance in adults and children were 31% and 52%, respectively. Although the mean clearance of ixabepilone in children was 18% higher than in adults, more rapid elimination does not seem to fully account for the 33% higher tolerable dose in children.

The half-life in children estimated from the 24- and 48-hour plasma concentrations after the fifth dose exceeded 24 hours, consistent with the half-life of more than 30 hours reported in adults on the less frequent administration schedules.^{5,6} Despite the long terminal half-life, there was minimal accumulation of drug over the 5-day treatment course. Trough concentrations at the 8 mg/m²/d dose level increased from 4.5 ng/mL on day 2 to 7.9 ng/mL on day 6, but there was no impact on end of infusion (peak) concentrations, which were 114 ng/mL on day 1 and 94 ng/mL on day 5.

Fig 1. Plasma concentration-time profile for a representative patient at the maximum-tolerated dose (8 mg/m²/d).

Fig 2. (A) Mean peak (end of infusion) plasma concentrations and (B) mean trough plasma concentrations of ixabepilone over the course of the 5-day treatment course at three dose levels (4.5, 6, and 8 mg/m²/d) in patients for whom samples were available and measurable. The day 7 trough concentration represents the plasma concentration 48 hours after the fifth dose of ixabepilone.

The activity of ixabepilone at the 8 mg/m²/d dose on the daily for 5 days schedule in childhood solid tumors is being assessed in a phase II trial within the Children's Oncology Group based on the safety and

Table 4. Comparison of Pharmacokinetic Parameters in Children and Adults¹¹ Receiving Ixabepilone on the Daily for 5 Days Schedule

Pharmacokinetic Parameter	Adults (n = 22)	Children (n = 16)
AUC_{0-∞} at 6 mg/m²/d, ng · h/mL		
Mean	272	168
SD	72	91
No. of patients	14	3
AUC_{0-∞} at 8 mg/m²/d, ng · h/mL		
Mean	338	335
SD	108	96
No. of patients	8	5
Clearance, mL/min/m²		
Mean	402	475
SD	125	247
Vd_{ss}, L/kg		
Mean	11.8	12.2
SD	6.3	5.4
Half-life, h		
Mean	16.8	14.0
SD	6.0	6.1

Abbreviations: AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; SD, standard deviation; Vd_{ss}, volume of distribution at steady-state.

tolerability data from this trial and preclinical activity in xenograft models of rhabdomyosarcoma, neuroblastoma, and Wilms' tumor.⁴ We are also studying the tolerability of the 8 mg/m²/d dose daily for 5 days in children with relapsed leukemia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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