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A Phase 1 and Pharmacokinetic Clinical Trial of Paclitaxel for the Treatment of Refractory Leukemia in Children: A Children's Oncology Group Study

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Background. This report summarizes a phase 1 study conducted by the Children's Cancer Group (CCG) to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), pharmacokinetics, and anti-leukemia activity of paclitaxel in children with advanced stage leukemias. ***Procedure.*** This study examined two dose escalation schedules of intravenous paclitaxel. Doses ranged from 250 to 500 mg/m^2 every 21 days in schedule A and 105 to 200 mg/m^2 weekly × 3 every 28 days in schedule B. Serial plasma samples for pharmacokinetic studies were obtained after the first paclitaxel dose. ***Results.*** Sixty-three patients (median 10 years) with refractory or relapsed leukemia (ALL) (n = 39), acute myeloid leukemia (AML) (n = 19), biphenotypic (n = 4), and JCML (n = 1)) were enrolled. The DLTs in schedule A were grade 4 hypertension and hyperbilirubinemia with an MTD of 430 mg/m^2 every 21 days. The DLTs in schedule B were coagulopathy, hyperkalemia, hyperbilirubinemia, elevated SGOT (n = 1, 125 mg/m^2), peripheral neuropathy (n = 1, 200 mg/m^2), and typhlitis (n = 1, 200 mg/m^2) with an MTD of 182 mg/m^2 weekly × 3 every 28 days. Among 54 evaluable patients, there was one complete response (CR), three partial responses (PR), and five patients with stable disease (SD). The mean terminal elimination half-life was 9.5 ± 3.4 hr and the mean plasma clearance was 23 ± 11 L/hr/m^2. ***Conclusions.*** Paclitaxel was tolerated at 430 mg/m^2 every 21 days and at 182 mg/m^2/dose weekly × 3 every 28 days in pediatric patients. The objective response rate across all dose levels and schedules was <10%. Pediatr Blood Cancer 2008;50:788–792.

Key words: ALL; AML; lymphoblastic; myelogenous; pediatric; taxol

INTRODUCTION

Although cure rates for children with newly diagnosed leukemia approach 85–90% for acute lymphocytic leukemia (ALL) and exceed 50% for acute myeloid leukemia (AML), the prognosis for children with relapsed leukemia remains poor and novel treatment approaches are needed for these patients. Paclitaxel, a diterpenoid that inhibits cancer cell growth by interfering with microtubule depolymerization, is approved for use in combination chemotherapy for advanced ovarian cancer, non-small cell lung cancer, and node-positive breast cancer (reviewed in [1,2]).

Previous studies have suggested that paclitaxel has activity against both ALL and AML in vitro [3,4]. Paclitaxel has been shown to potently inhibit growth proliferation of HL-60 and U937 AML cell lines and primary pediatric AML and ALL cells [4,5]. In addition, it appears to enhance the cytotoxic effects of cytarabine in vitro [5].

The most commonly utilized dosing schedules for paclitaxel in adults included a single 24-hr continuous infusion [6–8] given every 21 days and a 3-hr infusion administered weekly × 3 every 28 days [9]. The maximum tolerated dose (MTD) of 24-hr continuous infusion paclitaxel was 390 mg/m^2 while the MTD for the 3-hr weekly × 3 schedule was 100 mg/m^2/dose. The dose-limiting toxicity (DLT) was grade 3 mucositis or stomatitis.

Several schedules of paxlitaxel administration have been evaluated in children with solid tumors [7,10,11]. Hurwitz et al. administered single-dose paclitaxel every 21 days in doses ranging from 200 to 420 mg/m^2 [7]. The DLT was neurotoxicity and the recommended phase 2 dose was 350 mg/m^2. Hayashi et al. administered paclitaxel twice weekly for six doses every 28 days and recommended a paclitaxel dose of 65 mg/m^2/dose (390 mg/m^2/course) [10]. Sonnichsen et al. administered single-dose paclitaxel (200–420 mg/m^2) to 30 pediatric patients with refractory solid tumors and noted saturable distribution and elimination mechanisms, explaining a large variability in paclitaxel exposure based on dose [12]. A follow-up phase 1 study tested an alternative, single-dose paclitaxel schedule in seven pediatric patients with recurrent pediatric leukemia using a pharmacokintetically guided dosing strategy, targeting an AUC of 21–45 μM · hr (28–38 μg/ml · hr) [11]. The DLT in this study was mucositis [11]. The most effective dosing schedule for children with leukemia has not been determined. This report describes the results of phase 1 study of paclitaxel for pediatric patients with leukemia that evaluated single dose every 21 days (schedule A) and weekly × 3 every 28 days (schedule B) schedules of paclitaxel administration.

METHODS

Patient Eligibility

Patients ≤21 years of age at the time of original diagnosis with a histologically confirmed diagnosis of ALL, AML, or chronic myelogenous leukemia (CML) (>25% leukemia blast involvement), refractory to standard therapy, were eligible for this trial.

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The institutions and principal investigators of the Children's Oncology Group participated in the study (see Supplemental Table II).

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Additional eligibility requirements included an ECOG performance status of 0, 1, or 2; life expectancy $\geq$2 months; full recovery from the acute toxic effects of prior chemotherapy and radiotherapy, with at least 2 weeks since prior chemotherapy excluding steroids (4 weeks from prior nitrosourea therapy), and no prior treatment with paclitaxel; normal renal function; adequate liver function (total bilirubin $\leq$ 2 times the upper limit of normal (ULN), AST, and ALT $<$ 2.5 times ULN)); and adequate cardiac function (normal EKG and either shortening fraction $\geq$27% by echocardiogram or ejection fraction $\geq$50% by gated radionuclide study). All patients or their legal guardians provided written informed consent in accordance with institutional, FDA, and NCI policies.

Drug Administration

The starting dose of paclitaxel administered every 21 days over 24 hr (schedule A) was 250 mg/m^2/dose, 80% of the recommended adult starting dose [13]. Doses were escalated in 20% increments to a maximum 500 mg/m^2/dose. A single patient cohort received 250 mg/m^2/dose paclitaxel every 14 days (schedule A1) to confirm the safety of more frequent administration of taxol. The dose escalation schedule was then modified to administer paclitaxel weekly for three consecutive weeks every 28 days (schedule B). The starting dose for schedule B was 105 mg/m^2/dose (75% of the pediatric leukemia single-dose taxol MTD divided by three) and was increased over six dose levels to a final dose level of 200 mg/m^2/dose. Subsequent cycles of paclitaxel were administered in patients with stable disease or better if all grade 3 toxicities had resolved to $\leq$grade 2 within 2 weeks of the time that the next course was scheduled to begin. Doses were not held or omitted for hematologic toxicity.

A minimum of three patients were entered at each dose level and if one patient experienced DLT during the first cycle of therapy then the dose level was expanded to include up to six patients. The MTD was exceeded when DLT was observed in two patients of a cohort of three to six patients receiving the same dose of drug. The MTD of paclitaxel was defined as the dose level immediately below the level at which at least two patients experienced DLT. Patients were considered evaluable for DLT if they received at least one dose of paclitaxel. DLT was defined as a non-hematologic, non-resolving grade 3 paclitaxel-related adverse event or non-hematologic grade 4 paclitaxel-related adverse event that occurred during the first course. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria, v. 2.0.

Response

Patients were considered evaluable for response if they received at least one complete dose of paclitaxel, and had either at least one bone marrow evaluation during protocol therapy or had clinical evidence of progressive disease (PD) prior to stopping protocol therapy. A complete response (CR) was defined as a bone marrow with $<$5% leukemia cell infiltrate and no evidence of circulating blasts or extramedullary disease, recovery of absolute neutrophil count (ANC) to $>$1,000/ml and recovery of platelet count to $>$100,000/ml. Partial response (PR) was defined as a bone marrow with $\geq$5% and $<$25% leukemia cell infiltrate, and complete disappearance of circulating blasts with ANC and platelets recovery. PD was defined as an increase of at least 25% in the number of circulating blasts or bone marrow leukemia cell infiltrate, or the development of extramedullary leukemia. Stable disease (SD) was defined as any patient not meeting the criteria of CR, PR, or PD. Response was determined at the end of cycle 1.

Study Drug

Paclitaxel was supplied in 5 ml ampules containing a concentrated sterile solution of 6 mg/ml in 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol from the Cancer Therapy Evaluation program (CTEP) (NCI, Bethesda, MD). Study drug was diluted to a final concentration of 0.3–1.2 mg/ml in either D_5W or normal saline. Paclitaxel was administered as a continuous, 24-hr intravenous infusion. Patients were premedicated with dexamethasone (20 mg/m^2 for two doses), diphenhydramine (1 mg/kg) and ranitidine (0.5 mg/kg) prior to paclitaxel administration.

Pharmacokinetics

Blood samples were collected from a peripheral vein remote from the chemotherapy infusion site into heparinized tubes at the following time points: pre-infusion, 2, 4, 8, and 16 hr during the infusion; end of infusion; and 15 min, 30 min, 1, 1.5, 2, 3, 4, 8, 16, and 24 hr after the end of the infusion. Plasma supernatants were frozen at -70°C until analysis. Paclitaxel plasma concentrations were measured using high-pressure liquid chromatography as previously described [14]. The UV absorbance signal peak height ratio (paclitaxel/*N*-cyclohexylbenzamide internal standard) was analyzed by linear least squares regression. The pharmacokinetics of paclitaxel were estimated using the program WinNonlin Version 1.5 (Pharsight Corporation, Mountainview, CA). Distribution (α) and elimination (β) rate constants and half-life values ($t_{1/2\alpha}$ and $t_{1/2\beta}$), $AUC_{0\text{-}\infty}$, steady-state volume of distribution (V_{ss}), and total plasma clearance (Cl) were determined by fitting the plasma concentration–time data (during infusion and post-infusion) to a two-compartment open model using non-linear least squares regression analysis. Linear regression analysis of variance was used to assess the linear effect of taxol dose with clearance according to the model:

$$y_i = \beta_0 + \beta_1(\text{dose level in mg/m}^2) + \varepsilon_i;\ \varepsilon_i \tilde{N}(0, \sigma^2)$$

RESULTS

Patient Treatment

A total of 63 patients (35 male), median age 10 years (range 0.8–23 years), were entered on study. The majority had relapsed ALL (n = 39) or AML (n = 19) (see Supplemental Table I). One patient died of an infection prior to treatment. Of the remaining patients, 22 were treated with single-dose paclitaxel every 21 days (schedule A), six were enrolled in the cohort that received paclitaxel every 14 days (schedule A1), and 34 received weekly paclitaxel for 3 weeks every 28 days (schedule B). Eight patients receiving single-dose paclitaxel received two treatment courses and three patients receiving weekly paclitaxel received more than one treatment course (Table I).

Toxicities

Forty-five patients were fully evaluable for toxicity. DLTs for schedule A (q 21 day) paclitaxel were grade 4 hypertension (n = 1, 430 mg/m^2) and grade 4 hyperbilirubinemia (n = 1, 500 mg/m^2) (Tables I and II). A second patient treated at the 500 mg/m^2 dose

TABLE I. Summary of Treatment With Paclitaxel

Dose group	Dose and frequency	Number of patients at dose level	Number of patients with 1st course DLT	Number of courses
1	250 mg/m^2 q 21 d	5	0	8
2	300 mg/m^2 q 21 d	3	0	4
3	360 mg/m^2 q 21 d	3	0	3
4	430 mg/m^2 q 21 d	7	1	9
5	500 mg/m^2 q 21 d	4	1[a]	6
6	250 mg/m^2 q 14 d × 2	6	0	4
7	105 mg/m^2 q 7 d × 3	4	0	4
8	125 mg/m^2 q 7 d × 3	7	1	10[b]
9	150 mg/m^2 q 7 d × 3	4	0	3
10	165 mg/m^2 q 7 d × 3	3	0	3
11	182 mg/m^2 q 7 d × 3	8	0	8
12	200 mg/m^2 q 7 d × 3	8	2	4

d, day; [a]One additional patient had a DLT in course 2; [b]one patient received three courses and one patient received four courses.

level experienced grade 4 stomatitis and diarrhea early in the second treatment course and no further dose escalations were done using this dosing schedule. DLTs with schedule B (weekly paclitaxel × 3, every 21 days) administration included one patient who experienced grade 4 coagulopathy, hyperkalemia, hyperbilirubinemia, and elevated SGOT (125 mg/m^2/dose), grade 4 peripheral neuropathy (n = 1, 200 mg/m^2/dose), grade 4 stomatitis, and grade 4 typhlitis (n = 1, 200 mg/m^2/dose). The MTD of weekly paclitaxel for 3 weeks every 28 days was 182 mg/m^2/dose (Table I). A summary of all reported grade 3 and 4 non-hematologic toxicities is shown in Table II. The most frequent paclitaxel-related events were stomatitis/mucositis (three patients), hypertension (two patients), hyperbilirubinemia (two patients), and elevated transaminases (two patients).

TABLE II. Summary of All Grade 3 or 4 Non-Hematologic Toxicities

	Number of events in 62 patients	
Description	Related to study drug	Unrelated to study drug
Hypertension	2[a]	2
Hypotension	0	2
Hyperbilirubinemia	2[b,c]	4
Stomatitis/mucositis	3[d]	0
Infection	0	6
Coagulopathy	1[c]	0
Hyperkalemia	1[c]	0
Elevated transaminases	2[c]	2
Peripheral neuropathy	1[e]	0
Typhlitis	1[d]	1
Rash	1	0
Pancreatitis	0	1
Hemorrhagic cystitis	0	1
Hyperglycemia	0	5
Hypercalcemia	0	1
Diarrhea	0	1
Nausea/vomiting	0	1
Pulmonary infiltrates	0	2

[a]DLT in one patient receiving 430 mg/m^2 taxol (dose level 4); [b]DLT in one patient receiving 500 mg/m^2 taxol (dose level 5); [c]DLTs in one patient with severe tumor lysis syndrome receiving 125 mg/m^2 weekly taxol (dose level 8); [d]DLTs in one patient receiving 200 mg/m^2 weekly taxol (dose level 12); [e]DLT in one patient receiving 200 mg/m^2 weekly taxol (dose level 12).

Response

Using an intention to treat analysis, 54 of the 62 treated patients were evaluable for response (18/23 using schedule A, 30/34 using schedule B) (Table III). Eight patients were not evaluable for response due to early death related to PD (n = 5), early withdrawal due to toxicity (n = 2), or lack of an assessable bone marrow aspirate in the absence of PD following the first treatment cycle (n = 1). One CR was observed in a 15-year-old male with pre-B ALL treated with weekly paclitaxel (schedule B) using 125 mg/m^2/dose. PR were also observed in two patients with pre-B ALL treated with weekly paclitaxel using 125 and 182 mg/m^2/dose (schedule B), and one patient who received 300 mg/m^2/dose every 3 weeks (schedule A). Four evaluable patients had SD and 46 had PD.

Pharmacokinetics

Single-dose paclitaxel pharmacokinetics were characterized in 17 patients and summary data are provided in Table IV. Paclitaxel plasma concentrations were best fit to a two-compartment model (Fig. 1). Mean volume of distribution at steady state was 139 L/m^2. The overall mean distribution half-life ($t_{1/2}\alpha$) and mean elimination half-life ($t_{1/2}\beta$) for 16 of the 17 patients were 0.8 ± 0.6 and 9.5 ± 3.6 hr, respectively. Data for one patient with substantially prolonged elimination half-life were not included in these estimates. Mean plasma clearance was 23 ± 12 L/hr/m^2. There was a pattern of decreasing clearance rate with increasing dose (slope = −0.04; 95% confidence interval: −0.13–0.34, $R^2 = 0.11$) but this was not statistically significant ($P = 0.18$) (Fig. 2).

DISCUSSION

We investigated the safety and tolerability of paclitaxel in 62 children with relapsed leukemia. This study represents the largest

TABLE III. Summary of Responses to Paclitaxel*

Dose level	Dose and frequency	Number of patients treated	Responses				
			CR	PR	SD	PD	NE
1	250 mg/m^2 q 21 d	5				4	1
2	300 mg/m^2 q 21 d	3		1		2	
3	360 mg/m^2 q 21 d	3				3	
4	430 mg/m^2 q 21 d	7			2	4	1
5*	500 mg/m^2 q 21 d	4				2	2
6	250 mg/m^2 q 14 d × 2	6				6	
7	105 mg/m^2 q 7 d × 3	4				4	
8	125 mg/m^2 q 7 d × 3	7	1	1	1	3	1
9	150 mg/m^2 q 7 d × 3	4				2	2
10	165 mg/m^2 q 7 d × 3	3				3	
11	182 mg/m^2 q 7 d × 3	8		1		7	
12	200 mg/m^2 q 7 d × 3	8			1	6	1
All doses		62	1	3	4	46	8

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; d, day; *one patient assigned to dose level 5 did not receive treatment.

pediatric study of paclitaxel in children. The recommended phase 2 paclitaxel dose using a single dose of paclitaxel every 21 days (schedule A) is 430 mg/m^2, which is higher than the dose tolerated in adults with solid tumors (170–250 mg/m^2) [1,14], adults with leukemia (250–315 mg/m^2) [13], and pediatric patients with solid tumors (350 mg/m^2) [7]. This phase 2-recommended dose is based on the first course DLTs of hypertension and hyperbilirubinemia in one heavily pretreated post-transplant patient and the second course DLT of stomatitis in another patient at the 500 mg/m^2 dose level. Toxicities were not substantially different than those reported in adults. Although taxol is uncommonly associated with liver toxicity, it has been previously reported [15].

The recommended phase 2 paclitaxel dose for schedule B (weekly × 3 weeks, every 28 days) was 182 mg/m^2/dose (546 mg/m^2 per course), which is also higher than the weekly paclitaxel dose tolerated in adults (80–100 mg/m^2/dose, 300 mg/m^2/course) [9] or in children with solid tumors (65 mg/m^2/dose; 390 mg/m^2/course) [10]. The DLTs using a weekly dosing schedule were grade 4 peripheral neuropathy and grade 4 typhlitis (200 mg/m^2 weekly), which have been previously reported as DLTs in both adults and children [7,16].

The pharmacokinetic behavior of paclitaxel in children enrolled in this trial was similar to that previously described in adults and children. The average clearance (23 L/hr/m^2) and volume of distribution (139 ± 108 L/m^2) values in this study were similar to that reported in adults and children [7,17]. Distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$) in this study were slightly longer than those reported in adults ($t_{1/2\alpha}$ = 48 min (0.8 hr) vs. 4–30 min; $t_{1/2\beta}$ = 9.5 vs. 1.5–8.4 hr [17]). Although lower than expected from adult data [17], the peak plasma concentrations (C_{max}) in our study (0.38–1.3 μg/ml) were similar to that previously reported in children [7,12].

Two previous pediatric studies have reported saturable paclitaxel pharmacokinetics, contributing to substantial interpatient variability in clearance values [11,12]. To adjust for the resulting variability in paclitaxel C_{max} and clearance at high paclitaxel doses, Woo et al. implemented a dose-individualized strategy (termed maximum tolerated systemic exposure, MTSE) based on target AUC values in six children with refractory leukemia [11]. Paclitaxel clearance in that study ranged from 113 to 311 ml/min/m^2 (6.8–18.7 L/hr/m^2), which was similar to the authors' previous experience with paclitaxel in children with solid tumors [12]. The average clearance for children with refractory leukemia in this study (23 L/hr/m^2) was moderately higher than that reported by Woo et al., but the 95% confidence interval for the mean clearance for patients enrolled in this study includes 6.8 L/hr/m^2 indicating the results of the current investigation are consistent with these previously published results.

TABLE IV. Pharmacokinetics of Paclitaxel in Pediatric Leukemia

Dose level (mg/m^2)[a]	AUC (μg/ml · hr)	C_{max} (μg/ml)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	CL (L/hr/m^2)	V_{ss} (L/m^2)
250 (n = 4)	10.0 ± 4.1	0.38 ± 0.13	0.6 ± 0.2	8.8 ± 5.2	28 ± 11	146 ± 28
300 (n = 3)	16.4 ± 9.6	0.65 ± 0.4	0.8 ± 0.7	10.6 ± 4.4	26 ± 22	202 ± 214
360 (n = 2)	23.6 ± 15.3	0.93 ± 0.68	0.4 ± 0.1	8.1 ± 2.8	19 ± 13	96 ± 111
400 (n = 1)	18.6	0.74	0.7	9.9	23	101
430 (n = 5)	22.4 ± 7.4	0.87 ± 0.28	1.2 ± 0.7	10.5 ± 3.4	21 ± 9.5	141 ± 100
500 (n = 2)	36.0 ± 12	1.3 ± 0.7	1.1 ± 0.9	118 ± 157[b]	15 ± 6	1171 ± 1617[b]
Mean ± SD			0.8 ± 0.6	9.5 ± 3.6	23 ± 12	139 ± 108

[a]Mean ± SD for n patients; [b]included one outlier ($t_{1/2}$ = 230 hr; V_{ss} = 2315 L/m^2) that was excluded from calculation of the composite mean.

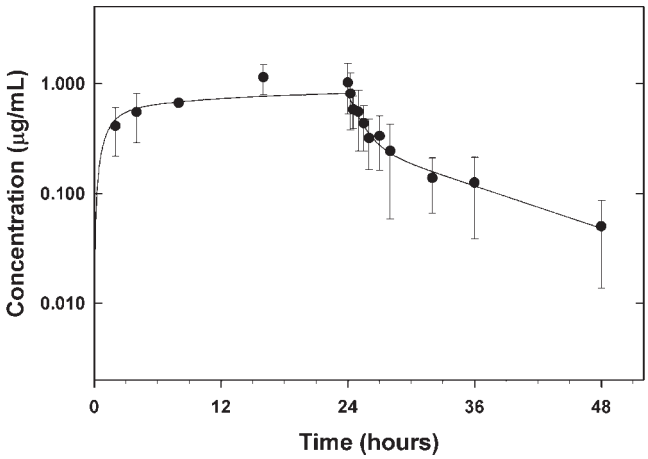

Fig. 1. Paclitaxel plasma concentrations versus time in pediatric patients. Paclitaxel (430 mg/m^2) was administered by 24-hr infusion. Symbols and error bars represent the mean ± SD for data from five patients. The solid line illustrates a fit of the data to a two-compartment open model.

In this study, we observed one CR and three PR in 62 treated patients. In an adult phase 1 and 2 trials of paclitaxel in leukemia, there was only one transient response [6,13]. Weekly paclitaxel dosing in adults with leukemia was also found to be ineffective [9]. In one prior pediatric study in leukemia, all seven children treated had disease progression after one or two cycles [11]. Although this trial was not an efficacy study, the paucity of objective responses coupled with the cumulative results of other studies suggest that paclitaxel is ineffective as a single agent in the treatment of recurrent or refractory leukemia using these dosing schedules. No further development of this agent in leukemia is planned within the Children's Oncology Group.

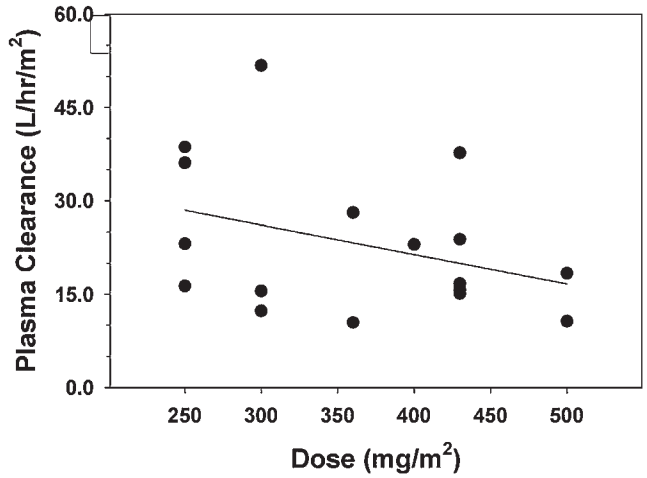

Fig. 2. Paclitaxel clearance versus dose in pediatric patients. Single-dose paclitaxel was administered to 17 pediatric patients with leukemia at six dose levels (250 mg/m^2 (n = 4); 300 mg/m^2 (n = 3); 360 mg/m^2 (n = 2); 400 mg/m^2 (n = 1); 430 mg/m^2 (n = 5); and 500 mg/m^2 (n = 2)) and clearance was determined as described (Methods).

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REFERENCES

1. Crown J, O'Leary M. The taxanes: An update. Lancet 2000;355: 1176–1178.
2. Mekhail TM, Markman M. Paclitaxel in cancer therapy. Expert Opin Pharmacother 2002;3:755–766.
3. Bhalla K, Ibrado AM, Tourkina E, et al. Taxol induces internucleosomal DNA fragmentation associated with programmed cell death in human myeloid leukemia cells. Leukemia 1993;7:563–568.
4. Consolini R, Pui CH, Behm FG, et al. In vitro cytotoxicity of docetaxel in childhood acute leukemias. J Clin Oncol 1998;16: 907–913.
5. Curtis JE, Minkin S, Minden MD, et al. A role for paclitaxel in the combination chemotherapy of acute myeloblastic leukaemia: Preclinical cell culture studies. Br J Haematol 1996;95:354–363.
6. Colburn DE, Thomas DA, Giles FJ. Phase II study of single agent paclitaxel in adult patients with relapsed acute lymphocytic leukemia. Invest New Drugs 2003;21:109–111.
7. Hurwitz CA, Relling MV, Weitman SD, et al. Phase I trial of paclitaxel in children with refractory solid tumors: A pediatric oncology group study. J Clin Oncol 1993;11:2324–2329.
8. Rowinsky EK. Update on the antitumor activity of paclitaxel in clinical trials. Ann Pharmacother 1994;28:S18–S22.
9. Munker R, Kantarjian H, O'Brien S, et al. Phase I study of taxol in refractory acute myelogenous leukemias using a weekly schedule. Acta Haematol 1998;99:106–108.
10. Hayashi RJ, Blaney S, Sullivan J, et al. Phase 1 study of paclitaxel administered twice weekly to children with refractory solid tumors: A pediatric oncology group study. J Pediatr Hematol Oncol 2003;25:539–542.
11. Woo MH, Relling MV, Sonnichsen DS, et al. Phase I targeted systemic exposure study of paclitaxel in children with refractory acute leukemias. Clin Cancer Res 1999;5:543–549.
12. Sonnichsen DS, Hurwitz CA, Pratt CB, et al. Saturable pharmacokinetics and paclitaxel pharmacodynamics in children with solid tumors. J Clin Oncol 1994;12:532–538.
13. Rowinsky EK, Burke PJ, Karp JE, et al. Phase I and pharmacodynamic study of taxol in refractory acute leukemias. Cancer Res 1989;49:4640–4647.
14. Wiernik PH, Schwartz EL, Einzig A, et al. Phase I trial of taxol given as a 24-hour infusion every 21 days: Responses observed in metastatic melanoma. J Clin Oncol 1987;5:1232–1239.
15. Seiter K, Feldman EJ, Traganos F, et al. Evaluation of in vivo induction of apoptosis in patients with acute leukemia treated on a phase I study of paclitaxel. Leukemia 1995;9:1961–1966.
16. Kris MG, O'Connell JP, Gralla RJ, et al. Phase I trial of taxol given as a 3-hour infusion every 21 days. Cancer Treat Rep 1986;70:605–607.
17. Sonnichsen DS, Relling MV. Clinical pharmacokinetics of paclitaxel. Clin Pharmacokinet 1994;27:256–269.