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A Pediatric Phase 1 Trial and Pharmacokinetic Study of Ispinesib: A Children's Oncology Group Phase I Consortium Study

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Abstract

Purpose—To determine the maximum-tolerated dose, dose-limiting toxicities and pharmacokinetics of the kinesin spindle protein inhibitor ispinesib in pediatric patients with recurrent or refractory solid tumors.

Subjects and Methods—Ispinesib was administered as 1-hour intravenous infusion weekly × 3, every 28 days. Cohorts of 3-6 patients were enrolled at 5, 7, 9 and 12 mg/m^2/dose. Serial plasma samples for pharmacokinetic analyses were obtained after the first dose.

Results—Twenty-four (13 females) patients with a median (range) age of 10 years (1-19) were enrolled on the study. At the 12 mg/m^2 dose level dose-limiting neutropenia occurred in 2/6 patients and hyperbilirubinemia in 1/6 patients, while at the 9 mg/m^2 dose level 1/6 patients had dose-limiting neutropenia. There were no objective responses, but 3 patients (diagnoses of anaplastic astrocytoma, alveolar soft part sarcoma and ependymoblastoma) had stable disease for 4 to 7 courses. There was substantial inter-patient variation in drug disposition. The median (range) terminal elimination half-life was 16 hours (8-44) and the plasma drug clearance was 5 L/hr/m^2 (1-14).

Conclusions—The maximum tolerated and recommended phase II dose for ispinesib administered weekly × 3 every 28 days for children with solid tumors is 9 mg/m^2/dose. Plans for a phase II trial in select pediatric solid tumors are in development.

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Keywords

Ispinesib; pediatric cancer; solid tumors; Children Oncology Group; phase 1 trials

Introduction

Ispinesib (SB-715992) is a potent inhibitor (binding constant, Ki = 0.6 nM) of the kinesin spindle protein (KSP/HsEg5). KSP functions exclusively during mitosis, driving the spindle pole separation and establishing the mitotic spindle bipolarity.(1,2) This mitotic motor ATPase is essential for cell cycle progression and its inhibition arrests cells in mitosis.(3-5) KSP's over-expression, on the other hand, can induce a genomic instability leading to tumor formation.(6)

Ispinesib was discovered in the search for small molecule inhibitors of KSP. KSP inhibitors, including ispinesib, prevent the formation of a bipolar mitotic spindle,(7) eventually resulting in apoptotic cell death.(5) The drug has no effects outside mitosis, and thus it does not adversely affect non-dividing cells. As a result, peripheral neuropathy commonly seen with the anti-microtubule-directed vinca alkaloids and taxanes has not been associated with ispinesib.

At nanomolar concentrations, ispinesib was cytotoxic in the majority of tumor cell lines studied *in vitro* in the Pediatric Preclinical Testing Program, including acute lymphoblastic leukemia, Ewing sarcoma, rhabdomyosarcoma, rhabdoid tumor, neuroblastoma and glioblastoma cell lines.(8,26) The drug also demonstrated a high level of *in vivo* anti-tumor activity against Ewing sarcoma, Wilms tumor, glioblastoma, rhabdoid tumor and acute lymphoblastic leukemia xenografts.(8) Percent protein binding in humans ranges from 81.1% to 96.2% (mean, 90.5%).

Four dosing regimens have been explored in adult patients with solid tumors: once every 21 days found the maximum tolerated dose (MTD) to be 18 mg/m^2/dose (9), on a weekly × 3 every 28 days schedule the MTD was 7 mg/m^2/dose (10), on a day 1, 2 and 3 every 21 days schedule the MTD was 6 mg/m^2 (24), and on a day 1 and day 15 every 28 days schedule in patients with breast cancer the MTD was 12 mg/m^2 (25). Neutropenia was dose-limiting on the first three schedules; liver transaminase elevations were dose-limiting on the every 14 day schedule. The MTD of ispinesib administered on days 1, 2 and 3 every 21 days in adults with acute leukemia was 10 mg/m^2/dose, with dose-limiting neutropenia, hepatotoxicity (hyperbilirubinemia and elevated alanine aminotransferase) and mucositis being observed. Based on the high degree of ispinesib preclinical anti-tumor activity in pediatric tumor models,(7) the current study was performed to determine the MTD and recommended phase II dose of ispinesib, the incidence and severity of toxicities associated with ispinesib administration, and the pharmacokinetics of ispinesib in pediatric patients with recurrent or refractory solid tumors.

Subjects and Methods

Subject Eligibility

Subjects > 12 months and ≤ 21 years of age with a histologically confirmed recurrent or refractory solid tumor, including CNS tumors and lymphoma, were eligible. Subjects with intrinsic brainstem gliomas were excluded from the requirement for histological verification. Other eligibility criteria included: the presence of measurable or evaluable disease; a Karnofsky or Lansky performance score of ≥ 60; recovery from the acute toxicities of prior therapies; no chemotherapy for > 3 weeks (6 weeks for nitrosourea); no growth factors or

biologic agents for > 7 days; no local radiation for ≥ 2 weeks; no bone marrow radiation for ≥ 6 weeks; no total body, craniospinal or pelvic (> 50% of the pelvis) radiation for ≥ 6 months; no stem cell transplant for ≥ 3 months; no active graft vs. host disease; adequate bone marrow function [absolute neutrophil count (ANC) ≥ 1,000/μL, platelet count ≥ 100 × 10^3/μL, and hemoglobin concentration ≥ 8.0 gm/dL]; adequate renal function (creatinine clearance ≥ 70 mL/min/1.73 m^2 or normal serum creatinine for age and gender); and adequate hepatic function (bilirubin ≤ 1.5 times upper limit of normal; alanine aminotransferase (ALT) ≤ 110 units/L (upper limit of normal, 45 units/L); and serum albumin ≥ 2.0 g/dL]. Study exclusion criteria included pregnancy, breast-feeding, and uncontrolled infection. In addition, use of enzyme-inducing anticonvulsants (e.g., phenytoin, phenobarbital, felbamate, primdone, oxcarbazepine or carbamazepine) or agents known to inhibit CYP3A4 (e.g., itraconazole, ketoconazole and voriconazole) were prohibited since ispinesib is metabolized by CYP3A4 (GlaxoSmithKline internal report). This trial was approved by local Institutional Review Boards, and all patients or their legal guardians signed a document of informed consent; when appropriate, assent was obtained according to individual institutional guidelines.

Drug Administration

Ispinesib was administered as an intravenous infusion over 1 hour on days 1, 8 and 15 of each 28 day course. Ispinesib was supplied by the Pharmaceutical Branch, National Cancer Institute (Bethesda, MD) in vials containing 4 mg, 5 mg or 10 mg in an isotonic 1 mg/mL solution. The calculated dose was added to 5% dextrose in water to attain a final concentration of ≤ 150 μg/mL. Concentrations > 48 but ≤ 150 μg/mL were administered in plastic or glass containers and those < 48 μg/mL in glass, PVC or non-DEHP containers with low-sorbing tubing.

Trial Design

The starting dose was 5 mg/m^2/dose, approximately 80% of the adult MTD, with planned escalations to 7, 9 and 12 mg/m^2/dose. Courses were repeated every 28 days if the patient had at least stable disease and met the inclusion criteria.

A patient was considered fully evaluable for toxicity if they experienced a DLT or received at least 85% of the total dose during course 1. A minimum of three patients were entered at each dose level, and the dose level was expanded to six patients if one patient experienced DLT during the first course of therapy. When DLT was observed in two patients of a cohort of three to six patients receiving the same dose of drug, the MTD was exceeded. If necessary, an additional three patients were added at the dose level immediately below the dose level at which the unacceptable level of toxicity was observed. The MTD of ispinesib was defined as the dose level immediately below the level at which at least two patients in a cohort of three to six experienced dose-limiting toxicity.

Toxicities were graded according to the NCI Common Toxicity Criteria (version 3.0). Dose-limiting non-hematologic toxicity was defined as any grade 3 or 4 adverse event attributable to the study drug with the specific exclusions of: 1) nausea or vomiting of < 3 days; 2) elevated transaminases that returned to levels that met the eligibility criteria within 7 days of study drug interruption and did not recur upon re-administration of the drug; and 3) fever or infection of < 5 days. Dose-limiting non-hematological toxicity included any grade 2 adverse event that persisted for ≥ 7 days and required treatment interruption, or any adverse event that required drug interruption for > 7 days or recurred upon drug re-administration. Hematologic dose-limiting toxicity was defined as grade 4 thrombocytopenia (platelet count < 25 × 10^3/μL) on 2 separate days, thrombocytopenia requiring platelet transfusion on 2

separate days in a 7-day period, and grade 4 neutropenia for > 7 days or occurring prior to day 15 dose.

Subjects who had hematologic DLT received the next lowest dose level for the subsequent courses. Subjects who had grade 4 neutropenia on day 8 or 15 did not receive the drug on these days and were considered to have DLT.

Criteria for Assessment of Response

The NCI Response Evaluation Criteria in Solid Tumors (RECIST) were used for assessment of radiographic response.(11)

Pharmacokinetic Studies

In consenting patients, serial blood samples were collected during course one prior to the first dose of ispinesib, immediately after completion of infusion, and 15 min, 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 20-24 hr, and 44-48 hr following the infusion. All samples were collected in potassium-EDTA tubes and centrifuged at 2,500*g* for 10 min at 5°C. Plasma was frozen at -20°C until analysis. Ispinesib (molecular weight, 517.1) quantification in human plasma was performed using a high pressure liquid chromatography-mass spectrometry (LC/MS/MS) assay validated (Cedra Corporation) over a range of 0.1 to 100 ng/mL (~0.19 to 193 nM). Ispinesib was harvested from 0.2 mL human plasma by liquid-liquid extraction, using 2.1 mL (total volume) of 1:1 acetonitrile:dH_2O, 1.0 M sodium carbonate, and methyl tert-butyl ether containing 10 ng of an isotopically labeled internal standard, ispinesib-D4. Following centrifugation, the upper organic layer was removed and evaporated. The sample was then reconstituted in the mobile phase (acetonitrile:dH_2O:formic acid:ammonium hydroxide; 900:100:1.00:0.25) and an aliquot was analyzed using Sciex API 4000 HPLC-MS-MS equipped with a TurboIonSpray™ interface along with quality control samples (0.30, 20.0, and 80.0 ng/mL). The peak area of the mass-to-charge ratio (m/z) 517→247 of ispinesib product ion was measured against peak area of the m/z 521→251 of ispinesib-D4 internal standard product ion. Quantitation was performed using a weighted ($1/x^2$) linear least squares regression analysis generated from calibration standards prepared immediately prior to each run. Pharmacokinetic analysis was performed using WinNonlin® (Enterprise Edition version 4.0) non-compartmental methods.

Concentration-time data that were below the limit of quantification were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. Nominal protocol sample times were used for all pharmacokinetic and statistical analyses.

Results

From September 2006 to January 2008, 24 patients, 19 fully evaluable for toxicity, were enrolled on the study (Table I). The five toxicity inevaluable patients did not complete the first course of therapy secondary to early disease progression but did not develop dose limiting toxicity.

Table II summarizes the DLTs observed in the first course of therapy. At the 7 mg/m^2 dose level, one patient with hepatoblastoma experienced grade 3 elevated ALT that was initially attributed to the underlying tumor. Dose escalation proceeded, but upon further review the toxicity attribution was modified to be considered possibly related to ispinesib. At the 12 mg/m^2 dose level, 3 of 6 evaluable patients had DLT, two with grade 4 neutropenia and one with grade 3 hyperbilirubinemia. The grade 4 neutropenia occurred prior to day 15 in one patient and on day 15 in the other, precluding administration of the day 15 dose. The hyperbilirubinemia was observed in a patient with Wilms tumor and liver metastasis; a possible relationship to study drug could not be completely excluded. At the 9 mg/m^2 dose

level, 1 of 6 evaluable patients experienced dose-limiting neutropenia (grade 4 on day 15), defining this as the MTD.

Ispinesib was generally well tolerated although the median number of administered courses was only 1 (range 1-7). Grade 3 or 4 hematologic toxicities over all courses are shown in Table III. Non-hematological toxicities attributed to ispinesib that occurred in >10% of evaluable patients, with the exception of the DLTs noted above are shown in Table IV.

There were no objective tumor responses. Three of the 24 patients evaluable for response had stable disease and received 4 (12 mg/m^2 dose level, anaplastic astrocytoma), 5 (9 mg/m^2 dose level, alveolar soft part sarcoma) and 7 (7 mg/m^2 dose level, ependymoblastoma) complete courses of therapy. The patient with an anaplastic astrocytoma was removed from protocol therapy with stable disease for toxicity after the recurrence of dose-limiting neutropenia following an initial dose reduction.

Ispinesib pharmacokinetic parameters for the eleven patients who consented to participation in the pharmacokinetic studies are presented in Table V. There was a high degree of inter-patient variability observed across dose levels (Figure 1). Protocol deviations included 4 patients in whom pharmacokinetic samples were obtained from the same venous access site through which the drug was administered, creating the potential for an overestimate of plasma drug concentrations. For all patients studied, the median (range) terminal elimination half-life ($t1/2$) was 16 (8-44) hours, plasma drug clearance was 4.8 (1.2-13.5) L/hr/m^2, and the volume of distribution at steady state (Vss) was 84 (23-193) L/m^2.

Discussion

In this trial, 24 pediatric patients received 1-hour intravenous infusion of ispinesib as monotherapy at 5, 7, 9 or 12 mg/m^2/dose weekly × 3, every 28 days. The MTD was 9 mg/m^2/dose, ~30% higher than the recommended adult phase II dose of 7 mg/m^2/dose. Overall, ispinesib appeared to be well tolerated. The primary dose-limiting adverse events were neutropenia and hepatotoxicity. The neutropenia was rapidly reversible; it was dose-limiting because it precluded administration of all three doses of ispinesib during the first course. A recent adult phase I trial with another KSP inhibitor, SB-743921 (given on days 1 and 15, every 28 days), showed 50% increase in MTD with prophylactic filgrastim (unpublished data). Thus, it may be possible to increase ispinesib dose on the weekly schedule by addition of filgrastim.

The observation of dose-limiting hepatotoxicity in two patients on this trial was confounded by the presence of involvement of the liver by tumor. No objective responses were observed, although 3 patients were noted to have stable disease, receiving 3 to 7 courses of therapy.

Similar to adult trials, (9,12-14) we observed a high degree of interpatient variability in the drug disposition (Table V,Figure 1). The estimated median (range) terminal $t_{1/2}$ of 16 hours (8-44 hours) in children appeared to be independent of dose (5-12 mg/m^2). This high degree of interpatient variation is similar to that observed in adult trials, with reports of terminal half-lives ranging from 17 to 56 hours with doses of 1-21 mg/m^2,(9) 20 to 53 hours with doses of 1-21 mg/m^2,(15) and 13 to 96 hours with doses of 1-8 mg/m^2.(14) Thus the lower median terminal half-life observed in children should be interpreted with caution, as the small number of subjects studied and limited duration of sampling in both adult and pediatric subjects cannot allow us to conclude that true differences exist in drug disposition. The number of patients studied and the limited number developing DLT did not allow for study of PK-PD relationships.

Phase II trials of ispiniseb, all using a dose of 18 mg/m^2 on the once every 21 day schedule, have been performed in adult patients with breast, ovarian, non-small cell lung cancer, squamous cell carcinoma of the head and neck, melanoma, renal cell carcinoma, prostate cancer, colorectal cancer, and hepatocellular carcinoma.(13,16-23) Four of 45 (9%) previously treated patients with metastatic breast cancer had partial responses, and one of 19 patients (5%) with platinum/taxane refractory ovarian cancer had a radiographic partial response. No significant activity has been observed to date for other adult tumor indications.

In conclusion, ispinesib administered as 1-hour intravenous infusion at 9 mg/m^2/dose weekly × 3, every 28 days is well tolerated in pediatric patients. Plans for a phase II trial in select pediatric solid tumors are in development.

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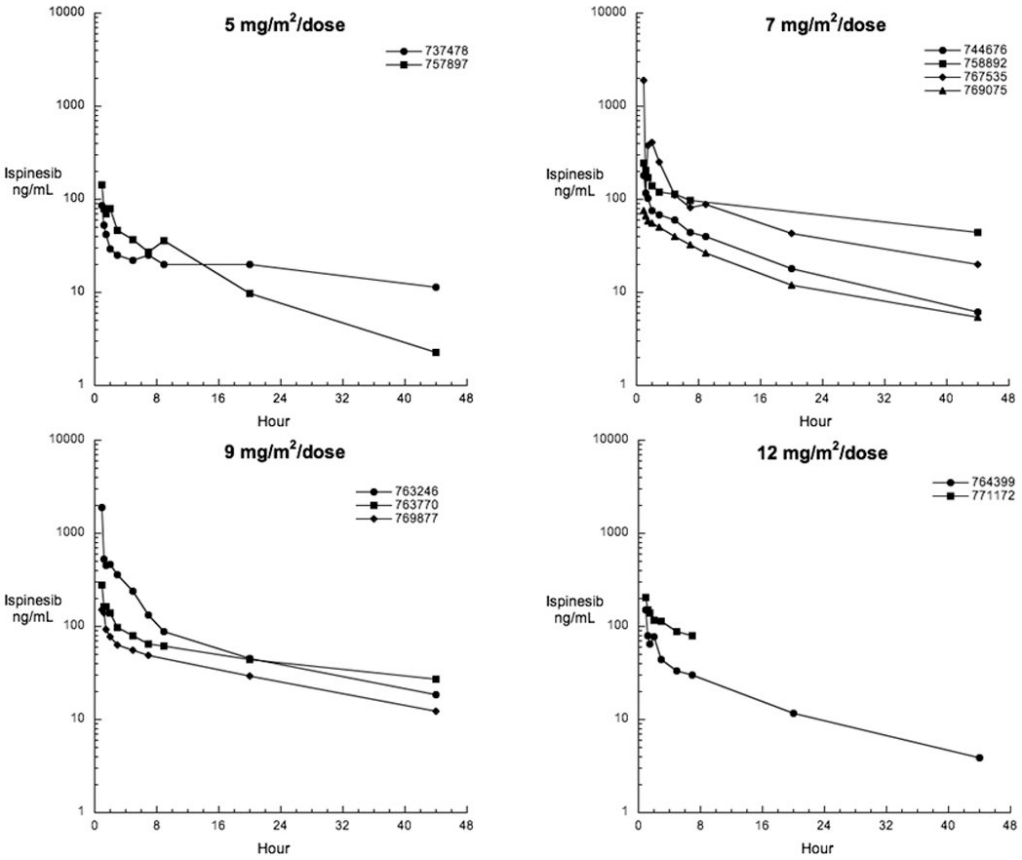

Figure 1.
Plasma concentration time curves for individual patients receiving ispinesib at the indicated dose levels.

Table I

Patient characteristics (*n* = 24)

Characteristic	
Male/female	11/13
Age (years)	
Median	10
Range	1-19
Race	
White	19 (79%)
African-American	4 (17%)
Unknown	1 (4%)
Ethnicity	
Non-Hispanic	17 (71%)
Hispanic	4 (17%)
Unknown	3 (12%)
Diagnoses	
Non-CNS tumors	
Soft tissue sarcoma	2
Rhabdomyosarcoma	2
Osteosarcoma	1
Wilms tumor	2
Hepatoblastoma	3
Lymphoepithelial carcinoma	1
Adenocarcinoma	1
Neuroendocrine hepatic carcinoma	1
Pancreatoblastoma	1
CNS tumors	
Malignant glioma	5
Astrocytoma	1
Ependymoma	3
Atypical teratoid/rhabdoid tumor	1
Prior therapies	
Chemotherapy regimens	
Median	1
Range	0-6
Radiation	15

Table II
DLTs in the first course at each dose level

Dose Level (mg/m^2/dose)	No. of patients entered	No. of evaluable patients	No. of patients with DLT	DLT (*n*)
5	4	3	0	None
7	5	4	1	Elevated ALT, AST (1)*
9	9	6	1	Neutropenia (1)
12	6	6	3	Neutropenia (2) Hyperbilirubinemia (1)

* The elevated ALT and AST were retrospectively attributed to ispinesib by the treating physician.

Table III

No. of courses with grade 3 or 4 hematological toxicities (independent of frequency or attribution) observed in the patients evaluable for hematological toxicities

Toxicity Type	Course 1 (19 courses)		Courses 2-7 (15 courses)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	1	0	0	0
Lymphopenia	2	1	2	0
Neutropenia	5	3*	1	1*
Thrombocytopenia	1	0	0	0

*Dose-limiting

Table IV

No. of courses with non-hematologic, non-dose-limiting toxicities related to protocol therapy that occurred in > 10% of evaluable patients

	Course 1 (19 courses)		Courses 2-7 (15 courses)
Toxicity	**Grades 1 and 2**	**Grade 3**	**Grades 1 and 2**
Fatigue	3	0	1
Constipation	2	0	0
Diarrhea	2	0	0
Nausea	4	0	1
Vomiting	3	0	1
Hypoalbuminemia	3	0	0
ALT	3	1	0
AST	2	1	0
Hyperbilirubinemia	1	1	0
Alkaline phosphatase	2	0	0
Electrolyte abnormality	4	0	0

Table V

Ispinesib plasma pharmacokinetic parameters by dose level

Dose level mg/m^2/dose	Patient	Cmax (ng/mL)	AUC_{last} (hr*ng/mL)	AUC_{INF} (hr*ng/mL)	$t_{1/2}$ (hr)	Clearance (L/hr/m^2)	Vss (L/m^2)	
5	737478**	86	945	1662	44	3.0	177	*
	757897	145	908	938	9	5.3	61	
7	744676	181	1319	1449	14	4.8	84	*
	758892**	244	3716	5733	32	1.2	51	
	767535	1900	4090	4596	18	1.5	24	*
	769075	75	851	970	15	7.2	145	
9	763246	1880	4814	5243	16	1.7	23	*
	763770	281	2506	3811	33	2.4	102	
	769877	149	1526	1865	19	4.8	118	
12	764399	149	819	890	13	13.5	193	
	771172**	204	732	1690	8	7.1	83	

* Protocol deviation with samples obtained from same venous access site as drug administration; concentrations obtained may be overestimates;

* AUC extrapolated values for these patients were >30% (fewer data points were available for these patients).