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Clinical Cancer Research

Cancer Therapy: Clinical

Phase II Trial of Ixabepilone Administered Daily for Five Days in Children and Young Adults with Refractory Solid Tumors: A Report from the Children's Oncology Group

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Abstract

Purpose: Ixabepilone is a microtubule-stabilizing agent with activity in adult solid tumors and in pediatric tumor xenograft models that are resistant to paclitaxel. The maximum tolerated dose on the daily-for-5-days i.v. schedule was 6 mg/m^2/dose in adults and 8 mg/m^2/dose in children, and the primary dose-limiting toxicity (DLT) was neutropenia. This study aimed to determine the response rate to ixabepilone in six solid tumor strata in children and young adults.

Experimental Design: We conducted a phase II trial of ixabepilone (8 mg/m^2/dose for 5 days every 21 days) using a two-stage design in taxane-naïve children and young adults with treatment-refractory, measurable rhabdomyosarcoma, Ewing sarcoma family tumors, osteosarcoma, synovial sarcoma, or malignant peripheral nerve sheath tumor, neuroblastoma, and Wilms tumor.

Results: Sixty-one eligible patients (36 male) were enrolled. Median (range) age was 13 years (range, 3-36). Fifty-nine patients were fully evaluable for toxicity and response. DLTs, most commonly myelosuppression, occurred in 11 patients (15% incidence in 3-18 years old and 33% in 19-36 years old; $P = 0.2$) during cycle 1. The median (range) number of cycles was 2 (range, 1-38). No partial or complete responses (response evaluation criteria in solid tumors) were observed. Seven patients received ≥3 cycles, and two had prolonged stable disease (Wilms' tumor, 38 cycles; synovial sarcoma, 8 cycles).

Conclusions: Ixabepilone at 8 mg/m^2/dose daily for 5 days was tolerable in children and adolescents, but did not show evidence of clinical activity in the childhood solid tumors studied. *Clin Cancer Res; 16(2); 750–4. ©2010 AACR.*

Ixabepilone (BMS-247550, NSC 710428, Ixempra) is a semisynthetic epothilone B analog with a mechanism of action (tubulin binding and microtubule stabilization) similar to that of the taxanes (1), but with activity in adult preclinical cancer models with *de novo* or acquired resistance to paclitaxel (2). In clinical trials in adults, ixabepilone was active against a broad range of refractory cancers resulting in Food and Drug Administration approval for the treatment of taxane or anthracycline refractory breast cancer (3) at a dose of 40 mg/m^2 i.v. infused over 3 hours every 21 days in combination with capecitabine, or as monotherapy for taxane, anthracycline, and capecitabine refractory breast cancer (4).

Although paclitaxel (5–7) and docetaxel (8–10) have minimal activity in pediatric phase I and II trials, the clinical development of ixabepilone for childhood cancers was stimulated by the broader spectrum of antitumor activity observed in pediatric preclinical models (11). Ixabepilone administered at the maximum tolerated dose (MTD) of 10 mg/kg on a schedule of every 4 days × 3 doses induced objective responses (≥50% volume regression) in xenograft models of rhabdomyosarcoma (3 of 3), neuroblastoma (3 of 5), Wilms' tumor (6 of 7), osteosarcoma (2 of 6), and brain tumor (multiple histologies; 4 of 8). Furthermore, responses superior to paclitaxel were observed in neuroblastoma, anaplastic astrocytoma, and anaplastic Wilms' tumor.

The pediatric phase I trial of ixabepilone assessed an i.v. schedule of daily for 5 days every 21 days, because it seemed to cause a lower incidence of sensory neuropathy in adults (12, 13) compared with every 21 days (14, 15) or

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Translational Relevance

Ixabepilone, a microtubule-stabilizing agent with a mechanism of action similar to taxanes, has a broad range of activity in adult refractory cancers. Based on a completed pediatric phase I trial and greater preclinical activity of ixabepilone compared with paclitaxel in a well-characterized panel of pediatric tumor xenograft models, we conducted a phase II trial of ixabepilone using the daily-for-5-days dosing schedule (8 mg/m^2/dose) in children and young adults with selected refractory solid tumors. No partial or complete responses were observed, and further clinical study of ixabepilone in patients with common refractory pediatric solid tumors is not planned. The activity of ixabepilone in preclinical pediatric xenograft models thus did not predict for activity of ixabepilone in children with refractory cancers. The lack of activity of microtubule-stabilizing agents in childhood compared with adult cancers may reflect biological differences, or the more heavily pretreated pediatric patient population.

the weekly dosing schedules (16). The MTD in children was 8 mg/m^2/dose, which exceeded the adult MTD of 6 mg/m^2/dose on the same dosing schedule using identical criteria for toxicity evaluation and definition of MTD (12, 17). Dose-limiting toxicities (DLT) were neutropenia and fatigue, and non-DLTs included myelosuppression, gastrointestinal, and hepatic toxicity. There was no dose-limiting neuropathy. The toxicity profile and pharmacokinetic parameters were similar in children and adults.

Based on data from the pediatric phase I trial and the greater preclinical activity compared with paclitaxel in a well-characterized panel of pediatric tumor xenograft models (18), we conducted a phase II trial of ixabepilone using the daily-for-5-days dosing schedule to define the response rate in children and young adults with selected recurrent or refractory solid tumors.

Materials and Methods

Patient eligibility. Patients must have been ≥12 mo old and ≤35 y of age at original diagnosis (except for patients with neuroblastoma or Wilms' tumor who must have been ≤21 y of age when originally diagnosed) and must have had a Karnofsky (patients >10 y) or Lansky (children ≤10 y) performance score ≥50. Patients were required to have had a measurable, refractory, or recurrent solid tumor with no known curative treatment options and histologic confirmation of the solid tumor strata under evaluation. All patients must have recovered from the toxic effects of prior therapy. Intervals from prior therapy to enrollment included 2 wk for conventional chemotherapy, 7 d for biological agents, 4 mo for allogeneic and 2 mo for autologous stem cell transplant, 14 d for radiation therapy, or 1 wk since colony stimulating factor administration. Organ function requirements included an absolute neutrophil count ≥1,500/mcL, a platelet count ≥75,000/mcL, bilirubin ≤1.5 times the upper limit of normal, alanine aminotransferase/aspartate aminotransferase ≤2.5 times the upper limit of normal, and an age-adjusted normal serum creatinine or a creatinine clearance ≥70 mL/min/1.73 m^2.

Patients were excluded for concurrent use of other investigational agents, strong inhibitors of CYP3A4 including grapefruit juice, St. John's Wort, enzyme-inducing anticonvulsants, and prior taxane use. A history of allergy to cremaphor EL, pre-existing grade ≥2 sensory neuropathy, and active pregnancy or breastfeeding were also exclusion criteria. There was no limit for the number of prior treatment regimens.

This trial was approved by local institutional review boards. All patients or their legal guardians signed a document of informed consent, and assent was obtained, as appropriate, according to individual institutional guidelines.

Trial design. This was an open-label phase II Children's Oncology Group trial to estimate the response rate to ixabepilone in six solid tumor strata. Ixabepilone was provided by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) and administered as a 1-h i.v. infusion at the pediatric solid tumor MTD of 8 mg/m^2/dose (maximum, 16 mg/dose) daily for the first 5 consecutive days of each 21-d cycle. Diphenhydramine (1 mg/kg, maximum 50 mg) and ranitidine (1 mg/kg, maximum 50 mg) were administered i.v. or orally prior to each dose of ixabepilone. Monitoring for treatment-related toxicity included history, physical examination, and performance status prior to each cycle; serum chemistries prior to each cycle and mid-cycle; and complete blood counts weekly or twice weekly with neutropenia or thrombocytopenia.

Tumor burden was measured radiographically using response evaluation criteria in solid tumors (19) prior to treatment and then after every other treatment cycle. Clinical and laboratory adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3. DLTs requiring a dose reduction of ixabepilone to 6 mg/m^2/dose (maximum, 12 mg/dose) for subsequent cycles included grade ≥3 nonhematologic toxicities (except for grade 3 nausea and vomiting controlled by antiemetics and grade 3 serum transaminase elevation that returns to baseline by cycle day 28) and grade 4 thrombocytopenia. If grade 4 neutropenia (<500/mcL) occurred on two consecutive measurements ≥3 d apart or neutropenia caused a treatment delay beyond cycle day 28, the ixabepilone dose was not modified for next cycle, but a granulocyte stimulating factor, such as filgrastim, was added to the regimen. If severe or protracted neutropenia recurred after addition of granulocyte stimulating factor, the ixabepilone dose was reduced to 6 mg/m^2/dose for subsequent cycles. A second dose reduction to 4.5 mg/m^2/d if the patient subsequently experienced DLT was also allowed.

A two-stage design was used to evaluate ixabepilone in six disease strata: embryonal or alveolar rhabdomyosarcoma, osteosarcoma, Ewing sarcoma/peripheral neuroectodermal tumor, synovial sarcoma or malignant peripheral nerve

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sheath tumor, Wilms' tumor, and neuroblastoma. At the first stage for each stratum 10 patients were to be enrolled. If no patient experienced an objective response, ixabepilone was to be considered inactive in that stratum, and enrollment to that stratum was terminated. If ≥1 patient achieved a partial response or complete response, 10 additional patients would be enrolled to that stratum. Ixabepilone would be considered to be active if ≥3 of 20 patients in the expanded stratum experienced a partial response or complete response. With this design, ixabepilone would be identified as inactive if the true response rate was 5% with a probability of 0.93, and would be identified as active if the true response rate was 30% with a probability of 0.95.

Evaluable patients were assessed for the incidence of DLT during each cycle. The probability of DLT during the first cycle was compared across groups defined by age in years at enrollment by using the exact conditional test of equality of proportions (20).

Results

Patient characteristics. From May 5, 2006 to April 17, 2007, 64 patients were enrolled, 61 of whom were eligible. Two patients were ineligible because organ function requirements for enrollment were not met, and one patient had signed an expired informed consent document. Two of the ineligible patients received ixabepilone, completed one treatment cycle, and did not experience DLT. The characteristics of the 61 eligible patients are listed in Table 1. Of the 61 eligible patients, 1 did not receive ixabepilone due to rapid disease progression, and 1 received only a small portion of the first dose of ixabepilone due to a grade 2 hypersensitivity reaction, after which the parents refused further treatment. These two patients were replaced, resulting in 11 eligible patients in the osteosarcoma and neurobalstoma strata. Of 59 patients, 27 (46%) presented with one or more measurable pulmonary lesions. Other common disease sites were pelvis (n = 6), abdomen (n = 6), and mediastinum (n = 5).

Toxicity. Toxicities and responses are reported for the remaining 59 response-evaluable patients, which included 47 patients who were 3 to 18 years old and 12 patients who were 19 to 36 years old.

Eleven (19%) of 59 patients experienced a DLT during cycle 1, and 5 of these 11 patients developed more than one DLT (Table 2). Myelosuppression (neutropenia > thrombocytopenia) was the most common DLT occurring in 4 of 12 (33%) patients in the 19- to 36-year-old age group and 7 of 47 (15%) of patients in the 3- to 18-year-old age group. The frequency of neutropenia in the two age groups was not statistically significant (P = 0.2, exact conditional test). Only one 5-year-old patient developed dose-limiting grade 3 sensory neuropathy, which resolved, and the patient subsequently tolerated ixabepilone at a reduced dose. Six patients experienced DLT during subsequent cycles, three of whom had more than one DLT. Four of these six patients had previously had a DLT in cycle 1. DLTs that were judged to be related to ixabepilone and that occurred on subsequent cycles were neutropenia, thrombocytopenia, anorexia, pain, sensory neuropathy, febrile neutropenia, elevated lipase, hyperglycemia, and hypertension. Thirteen patients died within one month of terminating protocol therapy. All deaths were related to disease progression.

Non-DLTs that were related to ixabepilone and that occurred in ≥5% of treatment cycles included fever (without neutropenia), fatigue, nausea and vomiting, serum transaminase elevation, hyperglycemia, hypomagnesemia, hyponatremia, anemia, neutropenia, lymphopenia, and thrombocytopenia. Myelosuppression was the most common non-DLT and the vast majority of non-DLTs were grade 1. Non–dose-limiting sensory neuropathy occurred in only one patient and was grade 1.

Tumor response. Fifty-nine patients were evaluable for response, 10 patients in each disease stratum with exception of the Ewing sarcoma stratum, which included 9 eligible patients evaluable for response. The cooperative group opted to halt enrollment to the Ewing sarcoma strata based on lack of response in other strata. The median number of treatment cycles was 2 (range, 1-38). No partial or complete responses were observed across the six disease strata. Accrual was halted after the first stage in all disease strata because the target response rate was not met.

Table 1. Baseline characteristics of 61 eligible patients

Characteristic	
Gender, male: female	36:25
Median (range) age at study enrollment in years	
All patients (n = 61)	13 (3-36)
Alveolar or embryonal RMS (n = 10)	13 (4-25)
Ewing sarcoma or PNET (n = 9)	16 (10-36)
Osteosarcoma (n = 11)	16 (8-20)
Synovial sarcoma or MPNST (n = 10)	18 (7-24)
Neuroblastoma (n = 11)	6 (3-12)
Wilms' tumor (n = 10)	6 (3-15)
ECOG performance score, n (%)	
0	43 (70.5)
1	11 (18.0)
2	7 (11.5)
Race, n (%)	
White	46 (75.4)
Black	10 (16.4)
Asian	3 (4.8)
Other/Unknown	2 (3.2)
Median (range) number of prior chemotherapy regimens	
All diagnoses	2 (1-7)
Neuroblastoma	3 (1-6)
Wilms' tumor	3.5 (1-7)
Number who had prior radiation (%)	34 (56%)

Abbreviations: PNET, primitive neuroendocrine tumor; MPNST, malignant peripheral nerve sheath tumor; ECOG, Eastern Oncology Cooperative Group.

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Table 2. Dose-limiting ixabepilone-related toxicities during cycle 1 by CTCAE v.3 toxicity grade and divided by age group (3-18 y, 19-36 y, and all patients)

	Age in years (*n*)				
	3-18 (47)		19-36 (12)		All Patients (59)
	CTCAE V.3 toxicity grade				
CTCAE toxicity category and term	**3**	**4**	**3**	**4**	**3 and 4**
Blood/Bone marrow					
Neutropenia		2*		3*	5*
Thrombocytopenia				2	2
Pain					
Myalgia	1	1			2
Other	1				1
Neurology					
Sensory neuropathy	1				1
Aphasia	1				1
Constitutional					
Fatigue			1		1
Fever	1				1
Gastrointestinal					
Anorexia	1				1
Dehydration			1		1
Metabolic					
Hyponatremia	1				1
Hemorrhage					
CNS		1			1

NOTE: Five patients experienced more than one DLT.
Abbreviation: CNS, central nervous system.
*Neutropenia was dose-limiting if grade 4 suppression occurred on two consecutive measurements at least 3 d apart.

Seven patients received ≥3 cycles of ixabepilone: two patients with rhabdomyosarcoma (3 cycles each); one patient each with Ewing sarcoma (4 cycles), neuroblastoma (4 cycles), osteosarcoma (6 cycles), and synovial sarcoma (8 cycles); and one 6-year-old patient with Wilms tumor, who received 38 treatment cycles. This patient had received six prior myelosuppressive regimens, and was enrolled with innumerable pulmonary nodules, which were not biopsied due to history of recurrent spontaneous pneumothoraces. The patient had dose reductions after cycle 4 for fever, neutropenia, and sensory neuropathy, and after cycle 15 for lipase elevation, and was removed from the trial with stable disease.

Discussion

This phase II trial confirmed the tolerability of the MTD (8 mg/m^2/dose) of ixabepilone from the pediatric phase I trial (17) on a daily-for-5-days schedule in children and adolescents. The DLT rate in the 12 patients >18 years was 33%, which would have exceeded the acceptable rate in the phase I trial, consistent with the lower MTD (6 mg/m^2/dose) in adults on this dosing schedule. The toxicity profile in children and adults was similar to that in the previously reported clinical trials (12, 17, 21). Myelosuppression was the predominant toxicity, and peripheral neuropathy was minimal on this dosing schedule. Cumulative toxicity could not be evaluated, because of the small number of patients who received >2 treatment cycles.

Ixabepilone was inactive in the six solid tumor strata evaluated. Incongruity in the result of this study and the pediatric xenograft model data may be due to a number of factors. The dosing schedule used in the pediatric xenograft models (11), in which tumor regressions were observed, differed from the dosing schedule used in this phase II trial, raising the question if responses might have been observed on the schedule of every 4 days × 3 doses evaluated in the pediatric xenograft model. However, the MTDs and activity observed on the three dosing schedules in adults (40 mg/m^2 as a single dose, 30 mg/m^2 divided into 5 daily doses, and 60 to 75 mg/m^2 divided into 3 weekly doses) do not indicate that the drug's effects are schedule dependent. Moreover, we studied a dose and schedule that had greater dose intensity than that utilized in adult trials, rendering it unlikely that efficacy would be observed on alternative short-duration schedules.

The relationship of schedule of ixabepilone (daily-for-5-days dosing versus every 21 days dosing) to response was

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explored in a randomized phase II trial of ixabepilone in non–small cell lung cancer (NSCLC). Although the toxicity profile differed with more serious and frequent toxicities (mucositis, neutropenia) occurring in the q21 day schedule, the response rates were similar in both groups (reviewed in ref. 22). Finally, as the pediatric xenograft testing was initiated after the pediatric phase I study established a MTD of ixabepilone using the daily-for-5-days schedule (11), it would not have been easily feasible to evaluate a different dosing schedule in the pediatric phase II trial.

We specifically did not utilize less well-established criteria for clinical efficacy, such as prolonged stable disease, as a primary end point, as the myelosuppression resulting from ixabepilone would not justify diminishing the dose intensity of more active agents currently utilized in the treatment of childhood solid tumors.

The vinca alkaloids, which bind to tubulin and block microtubule formation and were clinically developed several decades ago, are active against a broad spectrum of childhood cancers. However, despite their activity against a broad variety of cancers in adults, the taxanes (7, 10) and now apparently the epothilones, have minimal activity in childhood cancers. This disparity between the activity of microtubule-stabilizing agents in adult and childhood cancers may reflect biological differences in the cancers occurring in the two age groups. Alternatively, the lack of antitumor activity observed in this phase II trial may reflect the more heavily pretreated patient population. Although further development of ixabepilone in children with solid tumors is not planned, a cohort of children with advanced, refractory leukemia continues on study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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