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ORIGINAL ARTICLE

Phase I dose escalation study of weekly ixabepilone, an epothilone analog, in patients with advanced solid tumors who have failed standard therapy

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Abstract
Purpose To establish the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), safety and recommended Phase II dose of ixabepilone, administered weekly as an intravenous (IV) infusion to patients with solid tumors who have failed standard therapy.
Method This was an open-label, single-arm, Phase I, dose-escalation study.
Results The MTD of ixabepilone [30-min, weekly IV infusion on a 21-day schedule ($N = 33$)] was established at 25 mg/m^2. Grade 3 fatigue was the DLT in 2/4 patients treated at 30 mg/m^2. Ixabepilone was well tolerated at the MTD. Myelosuppression was rare, with no Grade 3/4 neutropenia. Due to the potential for cumulative neurotoxicity, the protocol was amended to a 1-h infusion, weekly for 3 weeks with a 1-week break. No DLT occurred at starting doses of 15, 20 and 25 mg/m^2 on this modified schedule ($N = 51$), although overall toxicity was less at 15 and 20 mg/m^2 than 25 mg/m^2. Five patients (2 on the 30-min/21-day schedule and 3 on the 60-min/28-day schedule) achieved durable objective partial responses across a variety of tumor types.
Conclusions Ixabepilone had an acceptable safety profile at the MTD of 25 mg/m^2 (as a 30-min weekly infusion on a continuous 21-day schedule) and at 20 mg/m^2 (as a 1-h weekly infusion on a modified 28-day schedule). The clinical activity and acceptable tolerability profile warrant further single- or combination-agent evaluation.

Keywords Ixabepilone · Dose-finding · Solid tumors · Weekly schedule

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Introduction

Resistance to chemotherapy is a significant problem that limits the effectiveness of current cancer treatments. Resistance may either be primary, or acquired after continued exposure to chemotherapeutic agents. It is, therefore, of great interest to identify new agents that can avoid key mechanisms of resistance. The epothilones and their analogs are a novel class of anti-neoplastic agents, derived from the myxobacterium *Sorangium cellulosum*. These macrolide antibiotics promote tumor cell death by causing cell cycle arrest at the G_2/M phase, inducing apoptosis [3], and have a tubulin-binding mode distinct from that of the taxanes. Ixabepilone is an epothilone B analog with high microtubule-stabilizing activity [9]. Ixabepilone demonstrates low susceptibility to the drug efflux proteins P-glycoprotein (P-gp) and multidrug-resistance-associated protein-1 (MRP1) [17], and to mechanisms involved in acquired and primary chemotherapy drug resistance to other microtubule-targeting agents, including tubulin mutations and βIII-tubulin isoform overexpression [8, 9]. In several clinical trials, ixabepilone has demonstrated feasibility and a manageable safety profile in patients with metastatic breast cancer and other tumors at multiple dosing and schedule options [2, 7, 13], including 6 mg/m^2 for 5 days every 3 weeks [1, 5, 12], 10 mg/m^2 for 3 days every 3 weeks [18], and 40 mg/m^2 every 3 weeks [15, 16].

This Phase I dose-escalation study was performed to establish the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), safety, and a recommended Phase II dose of ixabepilone, when administered weekly as an intravenous (IV) infusion to patients with tumors refractory to standard therapy, or for which there is no standard therapy. Secondary objectives included characterization of the bioavailability of oral ixabepilone as both a suspension and solution. The plasma pharmacokinetics and pharmacodynamics of both oral and IV ixabepilone were also evaluated. Any preliminary evidence of antitumor activity was carefully documented.

Patients and methods

Study design and treatment

In this open-label, single-arm, Phase I, dose-escalation study, ixabepilone was initially administered weekly as a 30-min IV infusion on a continuous 21-day cycle (hereafter referred to as the 30-min/21-day schedule). The starting dose was ixabepilone 1 mg/m^2, as it corresponded to 20% of the dose that was severely toxic to 10% of rats (STD_{10}) in the preclinical studies. Due to the occurrence of neurotoxicity in other trials of ixabepilone [15, 16], the infusion time was increased from 30 min to 1 h, and the schedule was modified to include a 1-week break in therapy. For the patients treated on this modified 28-day schedule (hereafter referred to as the 60-min/28-day schedule), one cycle was defined as 4 weeks and consisted of three weekly IV doses (on days 1, 8, and 15) followed by a 1-week rest period (i.e. the first administration of the next cycle was on day 29). Pre-medication was not required unless patients had experienced a hypersensitivity reaction (HR) with a prior ixabepilone dose, or if 2 patients experienced ≥ Grade 2 HRs. In the event of HR, the investigator and the sponsor selected an appropriate pre-medication regimen (consisting of H1/H2 blockers and/or dexamethasone) for subsequent cycles of therapy, based on the type and severity of the HR and premedication guidelines.

An initial, accelerated dose-escalation phase was followed by a standard dose-escalation phase. During the accelerated phase, dose levels were 1, 2.5 mg/m^2, then 100% increments. Cohorts of ≥3 patients were treated at each dose level and observed for ≥3 weeks (one cycle) of IV treatment prior to opening the next dose level for enrollment. In the standard phase, dose escalation was altered according to a modified Fibonacci scheme. The first patient treated at each new dose level was followed for ≥3 weeks of IV treatment prior to enrolling/treating two more patients at that dose level. If none of the three patients experienced DLT, the next cohort started one dose level higher. If one patient experienced DLT, ≤3 additional patients were enrolled. At each new dose level, three patients were enrolled. The maximum administered dose (MAD) was to be the dose level at which at least 2/6 patients experienced DLT during the first course of treatment. Once MAD was defined, there was no further dose escalation, and a dose level below the MAD was considered the MTD. A maximum of 15 patients were treated at the MTD to confirm that it was a suitable recommended dose for future Phase II clinical trials of ixabepilone. During the accelerated and standard phases, intrapatient dose escalation was allowed after two courses. Patients continued on ixabepilone until disease progression or unacceptable toxicity.

When toxicity was observed (defined as the first instance of DLT or two instances of toxicity of CTC Grade ≥ 2), the accelerated dose escalation phase was terminated, and the standard phase was begun. DLT was defined as any of the following events which were attributed to IV ixabepilone and occurred during the first treatment cycle: Grade 4 neutropenia [absolute neutrophil count (ANC) <500 cells/mm^3] for ≥5 consecutive days or febrile neutropenia (fever ≥38.5°C and ANC <1,000 cells/mm^3); thrombocytopenia <25,000 platelets/mm^3 or bleeding episode requiring platelet transfusion; ≥Grade 3 nausea and/or vomiting, despite medical intervention and/or prophylaxis; any other ≥Grade 3 non-hematologic toxicity (except Grade 3 injection-site reaction); or a failure to readminister ixabepilone within 14 days of the last IV dose, due to delayed recovery from a treatment-related toxicity.

This study also assessed the absolute oral bioavailability of ixabepilone. Starting at the 20 mg/m^2 dose level, patients received an additional single oral dose of ixabepilone solution or suspension 6 days prior to the first cycle. The oral suspension was given as either a micronized or nonmicronized suspension at a fixed total dose of 50 mg. Any DLT observed following ixabepilone oral dosing was not considered in defining MTD for the IV regimen.

Eligibility

Male and female patients were aged ≥18 years, with a life expectancy of ≥3 months and a diagnosis of histologically or cytologically confirmed solid tumor for which standard therapy had failed or no known effective treatment existed. Inclusion criteria included: ≥4 weeks since the last use of chemotherapy (6 weeks for nitrosoureas and mitomycin-C), immunotherapy, hormonal therapy or radiotherapy (the latter involving ≤25% of the bone marrow-containing skeleton); adequate hematologic function (ANC ≥ 2,000 cells/mm^3; platelets > 100,000/mm^3); an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate hepatic [total bilirubin ≤ 1.5 mg/dL, alanine aminotransferase and aspartate aminotransferase ≤ 2.5 × upper limit

of normal (ULN)] and renal (serum creatinine $\leq 1.5 \times$ ULN) function. All patients provided written, informed consent.

Key exclusion criteria included: >2 prior chemotherapy regimens in the metastatic setting and/or >2 prior adjuvant/neoadjuvant chemotherapy regimens; pregnancy/breast-feeding/ineffective birth control; pre-existing peripheral neuropathy [>Grade 1 by Common Toxicity Criteria (CTC) version 2] due to any cause; active brain metastases; history of HIV infection; documented HR to prior paclitaxel or other therapy containing Cremophor® EL; and treatment with any investigational agents ≤4 weeks prior to study medication.

Pharmacokinetic assessments

Blood samples for assessment of ixabepilone pharmacokinetic parameters were collected pre-dose and at regular intervals for up to 72 h after administration (00:15, 00:30, 00:45, 01:00, 01:30, 02:00, 03:00, 04:00, 06:00, 08:00, 24:00, 48:00, 72:00 h:min). Plasma was stored at −20°C for pharmacokinetic assessment by a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method described previously [6]. The following pharmacokinetic values were determined for ixabepilone IV infusion and oral dosing: maximum plasma concentration (C_{max}); area under the plasma concentration versus time curve (AUC) and plasma terminal half-life ($t_{1/2}$).

Pharmacodynamic assessments

Blood samples for assessment of pharmacodynamic parameters were collected pre-dose. Post-dose samples were collected at 00:30, 06:00, and 24:00 (h:min) after oral administration and after start of the 30-min infusion, and at 01:00, 02:58, 24:00, and 48:00 (h:min) after the start of the 1-h infusion. The peripheral blood mononuclear cell (PBMC) pellets were stored at −70 to −80°C until pharmacodynamic analysis. The PBMC preparations were lysed, and the amount of tubulin in the unpolymerized versus the polymerized form was determined by Western blot analysis.

Safety assessments

Toxicity was evaluated continuously, and laboratory tests (hematology and serum chemistry) were performed weekly. Patients were included in the safety analysis if they had received ≥1 oral or IV dose of ixabepilone. Safety was assessed through medical review of adverse events (AEs), physical examination and clinical laboratory data. Adverse events were assessed on the basis of the worst grade on study according to CTC Version 2.0. Treatment was delayed by 1 week for patients with ANC <1,500 cells/mm^3, platelet count <100,000 cells/mm^3, ALT and AST >2.5 × ULN, or serum creatinine >1.5 × ULN. Any treatment-related toxicity had to be resolved to baseline or Grade 1 (except alopecia) prior to retreatment.

Efficacy assessments

Tumor evaluations were performed every 6 weeks for patients treated on the 30-min/21-day schedule and every 8 weeks for patients treated on the 60-min/28-day schedule. All patients who received ≥1 IV or oral dose of ixabepilone had their response classified by the investigator and medical monitor, according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Statistical methods

Safety and efficacy data were analyzed for all treated patients (patients who received ≥1 IV or oral dose of ixabepilone). Descriptive statistics were employed in the analysis of all safety and laboratory observations. Pharmacokinetic analyses included all patients for whom adequate concentration versus time data were available. Pharmacodynamic data were analyzed in all patients with percent polymerized tubulin data available at baseline and at least one post-dose timepoint. Pharmacokinetic and pharmacodynamic data were summarized separately for patients who received 30-minute IV infusions versus patients receiving 1-h infusions, and those receiving oral solution or suspension doses. All pharmacokinetic and pharmacodynamic data were analyzed using SAS/STAT® Version 8.2 software, and summary statistics tabulated by dose, route of administration and duration of infusion.

Ethical considerations

The study protocol was approved by local ethics committees and the study was conducted in accordance with the US Food and Drug Administration, the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Results

Patients

Eighty-seven patients were enrolled at two study centers: one in Belgium and one in the USA. Of these, 86 patients were treated: 34 on the 30-min/21-day schedule and 52 on the 60-min/28-day schedule. The median age of the study population was 55 years. Nearly all patients (88%) had received prior chemotherapy, and 56% of patients on the 30-min/21-day schedule and 46% on the 60-min/28-day schedule had received ≥2 prior chemotherapy regimens (Table 1). The numbers of patients included in each dose

Table 1 Baseline demographics and characteristics of patients with advanced solid tumors treated with ixabepilone

Characteristic	Number of patients (%)	
	Ixabepilone	
	30-min/21-day schedule	60-min/28-day schedule
	N = 34	*N* = 52
Age (years)		
Median	55	55
Range	30–73	33–79
<65	27 (79)	44 (85)
≥65	7 (21)	8 (15)
Ethnicity		
Caucasian	33 (97)	50 (96)
Black	1 (3)	–
Asian/Pacific Islanders	–	1 (2)
Hispanic/Latino	–	1 (2)
ECOG performance status		
0	5 (15)	10 (19)
1	25 (74)	34 (65)
2	4 (12)	6 (12)
Not reported	–	2 (4)
Prior chemotherapy	30 (88)	46 (88)
Prior hormonal/ immunotherapy	10 (29)	16 (31)
Prior radiotherapy	20 (59)	25 (48)
Prior surgery	34 (100)	51 (98)
Number of prior chemotherapy regimens		
0	4 (12)	6 (12)
1	11 (32)	22 (42)
2	10 (29)	20 (39)
3	8 (24)	1 (2)
4	1 (3)	3 (6)

cohort on the ixabepilone 30-min/21-day and 60-min/28-day dosing schedules are summarized in Table 2.

Safety

Determination of maximum tolerated intravenous dose

During the study, 43 patients (20 on the 30-min/21 day schedule and 23 on the 60-min/28-day schedule) each received a single oral dose of ixabepilone on day-6. The trial was prospectively designed such that the administration of one oral dose on day-6 was not likely to affect overall toxicity associated with the IV regimen. DLTs observed following oral dosing were not considered in defining MTD for the IV regimen. Two patients received oral ixabepilone only, without an IV dose, and were excluded from the DLT analysis.

Table 2 Ixabepilone dose cohorts

Dose cohort	Number (%) of treated patients	Number of cycles administered
N = 86		
30-min/21-day schedule[a]		
Oral solution only	1 (1.2)[b]	1
1 mg/m^2	4 (4.7)	8
2.5 mg/m^2	4 (4.7)	16
5 mg/m^2	3 (3.5)	4
10 mg/m^2	3 (3.5)	9
20 mg/m^2 + oral solution	3 (3.5)	17
25 mg/m^2 + oral solution	12 (14.0)	49
30 mg/m^2 + oral solution	4 (4.7)	11
60-min/28-day schedule[c]		
Oral suspension only[d]	1 (1.2)[b]	1
15 mg/m^2	9 (10.5)	22
20 mg/m^2	10 (11.6)	30
20 mg/m^2 + oral solution	2 (2.3)	9
20 mg/m^2 + oral suspension[d]	3 (3.5)	10
25 mg/m^2	10 (11.6)	22
25 mg/m^2 + oral solution	4 (4.7)	15
25 mg/m^2 + oral suspension[d]	13 (15.1)	51

[a] Ixabepilone administered as a 30-min infusion on days 1, 8 and 15 every 3 weeks (1 cycle = 3 weeks)

[b] One patient received a single oral dose (solution or suspension) of ixabepilone only

[c] Ixabepilone administered as a 1-h infusion on days 1, 8 and 15 every 4 weeks followed by a 1-week break (1 cycle = 4 weeks)

[d] Fixed total dose of 50 mg

At the 30 mg/m^2 dose, Grade 3 fatigue was the DLT in 2/4 patients during the first cycle. Both patients also had Grade 1/2 anemia at baseline that did not worsen during the first treatment cycle. The MTD, therefore, was established as 25 mg/m^2 IV. This dose cohort was expanded to a total of 12 patients without further occurrence of DLT during the first cycle. None of the patients treated at doses ≤25 mg/m^2 experienced DLT.

Although neurotoxicity was not considered to be a DLT event in cycle one, the increase in the severity of sensory neuropathy with repeated exposure prompted the initiation of the modified 60-min/28-day schedule, which consisted of 3 weekly 1-h IV doses (on days 1, 8 and 15) followed by a 1-week rest period. The starting dose on this amended schedule was initially 25 mg/m^2 ± oral dose (the MTD identified on the 30-min/21-day schedule), but was reduced to 20 or 15 mg/m^2 (±oral dose), because of cumulative neurotoxicity observed in patients enrolled at 25 mg/m^2. No DLT was observed in the 51 patients treated with any of the three starting doses during Cycle 1 of the modified 60-min/28-day schedule.

Adverse events with intravenous ixabepilone

Adverse events were generally mild to moderate (Grade 1/2), irrespective of their assumed relationship to IV ixabepilone treatment. Overall, ixabepilone had an acceptable safety profile at the MTD of 25 mg/m^2 on the 30-min/21-day schedule and at 20 and 15 mg/m^2 on the 60-min/28-day schedule. With all three regimens, severe non-hematologic and hematologic toxicities were rare, HRs were largely mitigated by premedication and there were no dose interruptions or discontinuations due to hypersensitivity. Common toxicities associated with other cytotoxic agents (e.g., nausea, vomiting, stomatitis, mucositis and diarrhea) were generally of mild to moderate severity, and all patient deaths were attributed to disease progression. Myelosuppression of any type was uncommon on both schedules.

30-min/21-day schedule At the MTD of 25 mg/m^2 on the 30-min/21-day schedule, no patients developed Grade 3/4 neutropenia. Sensory neuropathy was mostly Grade 1/2 [occurring in 7 (58%) patients], with Grade 3 neuropathy observed in only 1/12 (8%) patients. In those patients with neuropathy, its severity typically increased cumulatively with repeated exposure. Dose-limiting fatigue was noted at 30 mg/m^2, and was of Grade 3 severity in 3/12 (25%) patients at the MTD. Two patients on this schedule experienced severe HRs in the absence of premedication with H1 and H2 blockers. The first, receiving 1 mg/m^2, had a Grade 3 bronchospasm that led to interruption of the first IV dose, which was not completed. Despite premedication with antihistamine, a similar reaction occurred after administration of the second dose, and the patient discontinued treatment. The second, receiving 5 mg/m^2, experienced Grade 4 anaphylaxis during the third weekly dose on Cycle 1. After premedication with antihistamine and dexamethasone, this patient completed Cycle 1 and all three doses of Cycle 2 with no further HRs. Following these two HRs, all patients subsequently enrolled received premedication with oral H1 and H2 blockers, as specified in the study protocol and no further HRs were observed. Grade 3/4 treatment-related AEs in patients on the ixabepilone 30-min/21-day schedule are summarized in Table 3. Treatment delays occurred in 12 patients (36%) on the 21-day cycle. Most treatment delays lasted ≤8 days. No delays met the criteria for DLTs.

60-min/28-day schedule Due to relatively high rates of sensory neuropathy observed in this schedule at the 25 mg/m^2 dose (Table 3), the starting dose on the 60-min/28-day schedule was reduced to 20 or 15 mg/m^2. Overall, toxicity was generally less at 20 mg/m^2 than at 25 mg/m^2, with the most notable being Grade 3/4 sensory neuropathy (7 vs 19%, respectively); the only Grade 4 case occurred at the 25 mg/m^2 dose level. As with the 30-min/21-day dosing schedule, the severity of neuropathy increased cumulatively with repeated exposure. Grade 1/2 sensory neuropathy was seen in 27 (53%) of patients on this schedule. Grade 3

Table 3 Number (%) of patient with grade 3/4 adverse events, ixabepilone 30 min/21, and 60-min/28-day schedules, all treated patients

Dose cohort (mg/m^2)	No. of patients	Sensory neuropathy	Fatigue	Myalgia	Arthralgia	Diarrhea	Vomiting	Nausea	Stomatitis	Mucositis	Neutropenia
30-min/21-day schedule											
1	4	–	–	–	–	–	–	–	–	–	–
2.5	4	–	1 (25)	–	–	–	–	–	–	–	–
5	3	–	–	–	–	–	–	–	–	–	–
10	3	–	–	–	–	–	–	–	–	–	–
20 + SOL	3	1 (33)	–	2 (67)	1 (33)	–	–	–	–	–	–
25 + SOL	12	1 (8)	3 (25)	2 (17)	2 (17)	1 (8)	–	–	–	–	–
30 + SOL	4	1 (25)	3 (75)	–	–	–	–	–	–	–	2 (50)
All dose cohorts	33	3 (9)	7 (21)	4 (12)	3 (9)	1 (3)	–	–	–	–	2 (6)
60-min/28-day schedule											
15	9	1 (11)	1 (11)	–	–	–	–	–	–	–	2 (22)
20	10	1 (10)	4 (40)	–	–	–	–	–	–	–	2 (20)
20 + SOL	2	–	–	–	–	–	1 (50)	–	1 (50)	–	–
20 + SUSP	3	–	–	–	–	–	–	–	–	–	–
25	10	1 (10)		–	–	–	–	–	–	–	–
25 + SOL	4	1 (25)	1 (25)	–	–	–	–	–	–	–	1 (25)
25 + SUSP	13	3 (23)		–	–	1 (8)	1 (8)	1 (8)	–	–	1 (8)
All dose cohorts	51	7 (14)	6 (12)	–	–	1 (2)	2 (4)	1 (2)	1 (2)	–	6 (12)

SOL solution, *SUSP* suspension

neutropenia was seen in 2/15 (13%) patients at the 20 mg/m^2 dose level, but no patients experienced Grade 4 neutropenia. Ixabepilone was also well tolerated at the 15 mg/m^2 dose on this schedule, with 2/9 (22%) patients experiencing severe adverse events (1 with sensory neuropathy and 1 with fatigue, both Grade 3). Treatment-related fatigue was generally mild-to-moderate at all doses, although Grade 3 fatigue occurred in ten (20%) patients.

One patient on the 60-min/28-day schedule (receiving 25 mg/m^2) experienced a Grade 3 hypersensitivity reaction (HR) characterized by hot flash, abdominal cramps, and sweating flushing during the second weekly dose of Cycle 1. Following premedication with H1/H2 blockers and dexamethasone, the patient received the scheduled dose 2 days later, and remained on study. No further HRs were reported. Grade 3/4 treatment-related AEs in patients on the ixabepilone 60-min/28-day schedule are summarized in Table 3. Sixteen patients (31%) on the 28-day cycle had treatment delays lasting for ≤8 days; none met the criteria for DLTs.

Adverse events with oral ixabepilone

Overall, oral administration of ixabepilone was well tolerated. Patients who received oral ixabepilone experienced few treatment-related AEs/laboratory abnormalities, and no hypersensitivity reactions were reported during the oral dose period. Two patients were discontinued after receiving oral ixabepilone and prior to receiving their first IV dose for reasons other than toxicity [one because of a concurrent disease (herpetic esophagitis) and one for progressive disease].

Efficacy of intravenous ixabepilone

Five patients (2 on the 30-min/21-day schedule at the MTD of 25 mg/m^2 and 3 on the 60-min/28-day schedule at 20 or 25 mg/m^2) achieved durable objective partial responses across a variety of tumor types. All of the responders had failed multiple prior therapies, including three patients who had previously been treated with a taxane (Table 4).

Pharmacokinetics and oral bioavailability of ixabepilone

The mean plasma concentration–time profiles of ixabepilone following 30-min and 1-h IV infusion and oral administration are presented in Fig. 1. Overall, the geometric mean C_{max} and AUC_{∞} for ixabepilone appeared to increase approximately proportionally to dose following IV administration. However, due to the small sample size in the dose groups other than 25 mg/m^2, this interpretation should be viewed with caution. The estimated geometric mean for the absolute bioavailability (F) of oral solution was 41.3%

Table 4 Responses to ixabepilone

Patient gender/age/race	Tumor type	Prior systemic therapies	Ixabepilone regimen	Total cycles	Best response[a]	Duration of overall response (days)[b]	Reason off-study
F/52/Caucasian	Breast	Cyclophosphamide/epirubicin, tamoxifen, exemestane	20 mg/m^2 (Q28 days)	5	Partial	110[c]	Grade 2 fatigue/Grade 2 paresthesia
F/68/Caucasian	Breast	Doxorubicin, tamoxifen, anastrozole, exemestane	20 mg/m^2 (Q28 days)	4	Partial	112[c]	Grade 2 neuropathy
M/48/Caucasian	Colon	Carboplatin/paclitaxel, fluorouracil/leucovorin, irinotecan	25 mg/m^2 + SOL (Q21 days)	4	Partial	212	Patient decision
F/61/Caucasian	Ovary	Carboplatin/paclitaxel, tamoxifen	25 mg/m^2 + SOL (Q21 days)	9	Partial	212[c]	Completed treatment
F/43/Caucasian	Head and neck	Cisplatin/fluorouracil, carboplatin/docetaxel	25 mg/m^2 + SUSP (Q28 days)	7	Partial	191	Disease progression

SOL solution, *SUSP* suspension

[a] As determined by the investigator

[b] Days from first day of treatment until progressive disease or death

[c] Patients who did not progress or die were censored on the date of their last tumor assessment

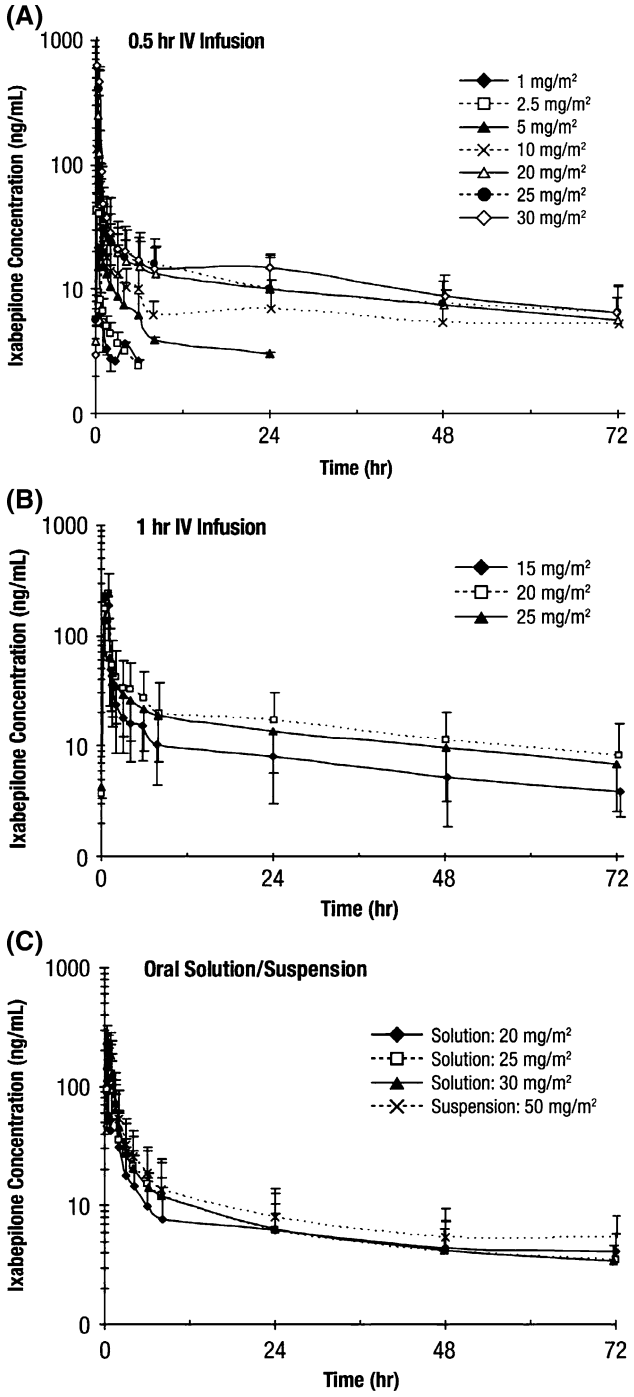

Fig. 1 Mean plasma concentration-time profiles of ixabepilone following (**a**) 30-min and (**b**) 1-h IV infusion and (**c**) oral administration

[coefficient of variance (CV) = 43%] across the three studied doses versus 36.6% (CV = 46%) for the oral suspension. The variability of exposure to ixabepilone following oral administration appeared to be greater than that following IV administration. Although the $t_{1/2}$ appeared to be lower in the 5 mg/m^2 30-min IV infusion group compared with all other groups, this was because the plasma concentrations of ixabepilone in these patients were only quantifiable through 24 h. Calculation of pharmacokinetic parameters for ixabepilone without a full concentration-time profile up to 72 h tended to underestimate $t_{1/2}$, as well as AUC.

Pharmacodynamics of ixabepilone

The percent polymerized tubulin values in PBMCs increased from baseline within an hour of ixabepilone administration for most doses across IV and oral administration methods. For example, increases in tubulin polymerization relative to baseline were 19% for the 25 mg/m^2 IV 30-min cohort after 0.5 h, 24% for the 25 mg/m^2 IV 1-h cohort after 1 h, 11% for the 25 mg oral solution cohort after 0.5 h and 10% for the 50 mg oral suspension cohort after 0.5 h. In several cases, values remained above baseline up to 24 h later.

Discussion

Resistance to multiple chemotherapies is a major problem in a wide range of tumor types; hence, development of agents less susceptible to mechanisms that enable tumor progression could provide clinical benefit in many disease settings. Ixabepilone, was, therefore, a promising candidate for evaluation in patients with tumors that had failed prior therapy, due to its reduced susceptibility to several key mechanisms of tumor drug resistance [8, 9, 17]. Treatment with ixabepilone has demonstrated feasibility and a favorable safety profile in metastatic breast cancer and other tumor types, at different dosing and schedule options [1, 5–7, 11, 15, 18], such as the 40 mg/m^2 every 3 weeks schedule, now approved by the Food and Drug Administration as monotherapy for the treatment of patients with metastatic breast cancer resistant or refractory to anthracyclines, taxanes, and capecitabine, or in combination with capecitabine in patients with resistance to anthracyclines and taxanes. Other ixabepilone schedules that have been evaluated in clinical trials include 6 mg/m^2 for 5 days every 3 weeks [1, 12], 10 mg/m^2 for 3 days every 3 weeks [18], and 20 mg/m^2 weekly × 3 every 4 weeks [4].

There is considerable interest in an alternative weekly administration of ixabepilone, particularly as prior results in breast cancer show greater clinical benefit with weekly paclitaxel than the 3-weekly schedule [14]. In agreement with the study reported here, other weekly schedules of ixabepilone including 2.5–30 mg/m^2 IV over 1 h weekly in a 4-week cycle (without a built-in rest period) [7] and 20 mg/m^2 IV over 1 h weekly × 3 every 28 days [4, 10] have demonstrated feasibility and a favorable safety profile in patients with breast and prostate cancer, and other advanced solid malignancies. However, until results of

comparative studies are available, no conclusions can be made regarding the relative benefit of the weekly schedule. Several randomized phase two studies are planned or ongoing which will better address the relative merits of the weekly schedule versus the FDA approved regimen of 40 mg/m^2 every 21 days.

During the dose-escalation phase of this trial in patients with advanced solid tumors who had failed standard therapy, ixabepilone was administered as a weekly 30-min IV infusion at doses of 1, 2.5, 5, 10, 20, 25, and 30 mg/m^2 on a 21-day schedule. The MTD was established at 25 mg/m^2 on this dosing schedule. Overall, administration of ixabepilone was well tolerated when administered weekly on this 30-min/21-day schedule; myelosuppression of any type was rare and none of the patients treated at the MTD developed Grade 3/4 neutropenia. Although cumulative neurotoxicity was not a DLT (defined as toxicities occurring during cycle 1) in this Phase I trial, in view of data from other clinical trials [15, 16] the 30-min/21-day administration schedule was modified to a weekly, 60-min IV infusion including a 1-week break, with the aim of reducing the incidence of neurotoxicity. Two Phase II trials have shown that switching from ixabepilone 50 mg/m^2 Q3 W infused over 1 h to 50 mg/m^2 over 3 h Q3 W led to a reduction in the peripheral sensory neuropathy observed [15, 16]. Grade 3/4 peripheral sensory neuropathy was noted in 42% of patients receiving ixabepilone 50 mg/m^2 over 1 h, compared with 22% of those who received an infusion of ixabepilone 50 mg/m^2 over 3 h in the trial by Roché et al. In the study by Thomas et al., grade 3/4 peripheral sensory neuropathy occurred in 38 and 12% of patients in the 50 mg/m^2 over 1 h and 40 mg/m^2 over 3 h groups, respectively [16].

When patients were treated with the modified 60-min/28-day schedule at 25 mg/m^2 (the MTD identified on the 30-min/21-day schedule), the rate of Grade 3/4 sensory neuropathy was 14%. The starting dose of ixabepilone was reduced to 20 or 15 mg/m^2 on the 60-min/28-day schedule; neurotoxicity was reduced on the 60-min/28-day schedule following these dose adjustments.

Durable partial responses to ixabepilone were achieved in this study in a range of tumor types. Responders had received ixabepilone on the 30-min/21-day schedule at the MTD (25 mg/m^2) or on the 60-min/28-day schedule at 20 or 25 mg/m^2. All five responders had failed multiple prior therapies, including taxanes (3 patients). Consistently, in other Phase I single-agent trials with ixabepilone administered at different doses and schedules, antitumor activity has been demonstrated in a broad range of tumor types, including pretreated tumors or those regarded as difficult to treat [2, 5, 7, 11, 13]. The efficacy of ixabepilone in tumor types considered difficult to treat may be explained by the high anti-microtubule activity of ixabepilone and its reduced susceptibility to common mechanisms of chemotherapy resistance that limit the activity of other microtubule inhibitors such as the taxanes [8, 9, 17].

Taken together, the safety and preliminary efficacy results of this study suggest that both the 25 mg/m^2 30-min/21 day schedule and the 20 mg/m^2 60 min/28-day schedule are suitable for further exploration in Phase II clinical trials, although it should be noted that patients treated with the latter remained on-study longer than patients treated with the former, receiving a median of three versus two cycles, respectively.

This was the first clinical trial to evaluate the oral bioavailability of ixabepilone. The trial was prospectively designed such that the oral dose of 50 mg administered on day-6 was not likely to affect overall toxicity associated with IV ixabepilone. The absorbed oral dose was about half the MTD. The variability of ixabepilone exposure resulting from the administration of ixabepilone oral solution and suspension was found to be greater than that for IV administration. Further investigations into the use of oral ixabepilone will be required, and are currently ongoing.

In conclusion, this Phase I study demonstrated that ixabepilone had an acceptable safety profile at the MTD of 25 mg/m^2 administered as a 30-min weekly infusion on a continuous 21-day schedule, and at 20 mg/m^2 administered as a 1-h weekly infusion on a modified 28-day schedule, suggesting that these regimens are suitable for Phase II studies. Durable objective responses were reported for patients with a variety of tumor types and in several patients who had previously failed taxane therapy. These data support the continued clinical development of ixabepilone administered on a weekly IV regimen.

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Appendix

List of trial investigators

Primary investigators are in italics.

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