Phase I Study of Eribulin Mesylate Administered Once Every 21 Days in Patients with Advanced Solid Tumors

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Abstract

Purpose: To evaluate the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetics of eribulin mesylate (E7389), a halichondrin B analogue, administered every 21 days in patients with advanced solid tumors.

Experimental Design: Eribulin mesylate was given as a 1-hour infusion every 21 days at doses of 0.25, 0.5, 1, 2, 2.8, and 4 mg/m^2. The MTD was identified using an accelerated titration design. The pharmacokinetics of eribulin were evaluated in the plasma and urine with the first dose.

Results: Twenty-one patients were enrolled. At 4 mg/m^2, three patients experienced a DLT of febrile neutropenia on day 7. The dose level was reduced to 2.8 mg/m^2 where two of three patients experienced dose-limiting febrile neutropenia. Six additional patients were enrolled at 2 mg/m^2 (seven patients in total received this dose) and one of these patients experienced a neutropenic DLT. The MTD of eribulin mesylate was therefore 2 mg/m^2. Nonhematologic toxicities included alopecia, fatigue, anorexia, and nausea. Pharmacokinetic analysis showed linear kinetics for eribulin over the dose range studied and a terminal half-life of 2 days. The plasma-concentration-time profile exhibited a rapid distribution phase followed by a slow elimination phase. Drug clearance was nonrenal. One patient with non–small cell lung cancer achieved an unconfirmed partial response and 12 patients had stable disease.

Conclusions: Eribulin mesylate administered as a 1-hour infusion every 21 days has a manageable toxicity profile at 2 mg/m^2, with further dose escalation limited by neutropenia.

Eribulin mesylate (E7389) is a nontaxane microtubule dynamics inhibitor that is a structurally simplified, synthetic analogue of the marine natural product halichondrin B, which was originally isolated from *Halichondria okadai* (1–4). Eribulin consists of the macrocyclic ketone analogue of the biologically active C1-C38 moiety of halichondrin B and, like the natural product, inhibits tumor cell proliferation by induction of G_2-M cell cycle arrest, disruption of microtubule polymerization, and initiation of apoptosis (2, 5–7). Eribulin inhibits microtubule dynamics through a novel mechanism distinct from those of other tubulin-targeted agents; it suppresses microtubule polymerization, exhibits no effect on microtubule depolymerization, and sequesters tubulin into nonfunctional aggregates (6, 8).

Preclinical studies show that eribulin is a potent inhibitor of proliferation in several cancer cell lines *in vitro*, including breast, colon, prostate, and melanoma (mean IC_{50} of 1.8 nmol/L; range 0.09-9.5 nmol/L), with potencies superior to those of vinblastine or paclitaxel in most cell lines examined (2). *In vivo*, eribulin has antitumor activity against a variety of human tumor xenografts, including melanoma, breast, ovarian, and colon cancer (2). In addition, eribulin inhibits *in vivo* tumor growth in taxane-resistant PTX10 and PTX22 human ovarian cancer cell lines, whose resistance is based on mutations in β-tubulin (9). These findings, combined with the novel effects on microtubule dynamics, suggest that eribulin has potential for a unique spectrum of clinical activity compared with other microtubule-targeting agents.

The aims of this phase I study were to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetics of eribulin when administered as a 1-h i.v. infusion once every 21 days to patients with advanced solid tumors. In preclinical studies, eribulin was evaluated as a slow i.v. bolus or a 1-hour i.v. infusion (10, 11). The tolerability of eribulin given as an i.v. infusion, as opposed to a slow i.v. bolus, was explored because other tubulin-targeting drugs are given over extended times (paclitaxel over 3 hours and docetaxel over 1 hour). Additionally, as other microtubule inhibitors are given at extended intervals, the schedule used in this study allows for potential combination with other agents that are given every 21 days.

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Translational Relevance

Several tubulin-targeted agents are approved for the treatment of cancer. However, these agents are often associated with neuropathy and/or hypersensitivity reactions. Newer agents with improved safety profiles are needed. Eribulin mesylate (E7389) is a nontaxane microtubule dynamics inhibitor with a novel mechanism of action. Preclinical studies have shown that eribulin is a potent inhibitor of proliferation of several human cancer cell types *in vitro* and *in vivo*, including breast, colon, prostate, and melanoma. This phase I study evaluated the pharmacokinetics, maximum tolerated dose, toxicity profile, and antitumor activity of eribulin administered as a 1-hour infusion every 21 days. Eribulin showed a manageable tolerability profile with no instances of infusion-related reactions. Such characteristics are potentially advantageous over currently approved tubulin-targeted drugs. The results of phase III trials of eribulin in metastatic breast cancer are awaited. Eribulin represents a potential addition to the chemotherapy armamentarium for patients with cancer.

Patients and Methods

Eligibility criteria. Patients ages ≥18 y were eligible if they had a histologically or cytologically confirmed diagnosis of an advanced solid tumor, measurable disease, progression following standard therapy (or a tumor for which no standard therapy exists), received no more than two prior chemotherapy regimens for metastatic disease, a Karnofsky Performance Status of ≥70%, and a life expectancy of ≥3 months. Requirements for adequate organ function included an absolute neutrophil count of ≥1,500/μL, platelets ≥100,000/μL, creatinine ≤1.5 mg/dL, total bilirubin ≤1.5 mg/dL, and aspartate transaminase and alanine transaminase ≤2 times the upper limit of normal. Patients were excluded if they had received chemotherapy within 3 wk of eribulin treatment (6 wk for nitrosoureas) or significant comorbid conditions. Patients were not permitted to use medications metabolized by CYP3A4 or potent inhibitors or inducers of CYP3A4 (eribulin is a CYP3A4 substrate; ref. 12), or therapeutic doses of anticoagulants. Prophylactic use of antiemetics, antidiarrheals, and antiallergic measures, such as corticosteroids and antihistamines, were permitted. Prophylactic use of filgrastim, pegfilgrastim, and erythropoietin were permitted after the first treatment cycle. The protocol was approved by the institutional review board at each participating institution. All patients gave written informed consent before treatment.

Study design and treatment. This was a phase I, open-label, two-center study of eribulin mesylate administered as a 1-h infusion every 21 d. The starting dose level was 0.25 mg/m^2, and planned subsequent dose levels were 0.35, 0.5, 0.7, 1, 1.4, 2, 2.8, 4, 5.6, and 8 mg/m^2 (doses given are for the eribulin mesylate salt). The starting dose was chosen based on the findings of the first phase I study of eribulin (13) and was one dose level lower than the dose at which grade 3 toxicity occurred.

Dose escalation was conducted using a two-stage design based on design 3B of Simon et al. (14). In the accelerated stage, the dose was escalated among cohorts consisting of at most one patient per study site (provided that the second patient was enrolled no later than 1 wk after the first patient) in steps of two dose levels until either a patient experienced a single DLT or two patients experienced grade 2 toxicity (cumulative across all dose levels and cycles). Intrapatient dose escalation was permitted (with a maximum of one dose escalation per patient) once another patient was observed for at least 1 mo after treatment with the higher dose. The nonaccelerated stage commenced at one dose level above the highest dose administered in the accelerated stage and involved cohorts of at least three patients. Dose escalation was terminated when two or more patients experienced a DLT at a given dose level. Patients continued to receive eribulin until they no longer received clinical benefit, had progressive disease, or experienced unacceptable toxicity. The MTD was defined as the highest dose at which no more than one of six patients evaluable for toxicity experienced a DLT. At least six patients were to be treated at the MTD.

Eribulin was supplied by Eisai Medical Research, Inc., as an injectable solution in 1-mL vials containing 500 μg/mL of eribulin mesylate in ethanol/water. The drug solution was diluted with 4 mL of 0.9% sodium chloride to provide a 5-mL solution of 100 μg/mL and administered with a syringe pump as a 1-h infusion.

Clinical assessments. A medical history and demographic data were collected at screening (days -14 to 0). A physical examination and laboratory tests (including a complete blood count with differential, chemistry, and urinalysis) were done at screening and on days 1, 8, and 15 every cycle and at least 30 d after study completion. An electrocardiogram was obtained at baseline and at study completion. Imaging of involved cancer sites was done within 4 wk of enrollment and every 6 wk. Response was assessed using Response Evaluation Criteria in Solid Tumors (15).

Adverse events (AE) were evaluated and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0. Serious AEs were defined as any untoward medical occurrence that resulted in death, or was life-threatening, required hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital abnormality/birth defect. A DLT was defined during cycle 1 (and cycle 2 if the patient had

Table 1. Patient characteristics

Characteristic	No. patients (*N* = 21)
Median (range) age, y	62 (29-73)
Gender	
Male	13
Female	8
Race	
Caucasian	16
Hispanic	3
African American	2
KPS score at screening visit	
70	4
80	5
90	11
100	1
Tumor type	
NSCLC (1 unspecified)	6
Renal cell carcinoma	4
Gallbladder adenocarcinoma	2
Other*	9
No. chemotherapy regimens	
0	2
1	6
2	13
No. other prior cancer therapies †	
0	19
1	1
2	1

Abbreviation: KPS, Karnofsky performance status.
*Other tumors include pancreatic adenocarcinoma, bladder carcinoma, papillary carcinoma of the thyroid, colorectal carcinoma, esophageal adenocarcinoma, endometrial stromal sarcoma, intestinal adenocarcinoma, giant cell carcinoma, and oral cancer (one of each).
† Includes donor lymphocyte infusion and chemoembolization.

Table 2. DLTs at each dose level of eribulin mesylate

Dose (mg/m^2)	No. patients	No. patients with DLT	DLTs (*n*)
0.25	1	0	—
0.5	4	0	—
1	3	0	—
2	7*	1	Grade 4 febrile neutropenia with grade 2 oral candidiasis (1)
2.8	3	2	Grade 4 febrile neutropenia (2)
4	3	3	Grade 4 febrile neutropenia (3)

*One patient was not fully evaluable for determination of DLTs.

undergone intrapatient dose escalation) as grade 4 neutropenia not reversible to grade 3 or less within 5 d without the use of growth factors; febrile neutropenia; neutropenia associated with bacteremia or sepsis; grade 4 thrombocytopenia or grade 3 thrombocytopenia accompanied by clinically significant bleeding; or grade 3 or higher nonhematologic toxicity excluding untreated nausea, vomiting, or tumor flare/lysis.

Pharmacokinetic sampling and analysis. Blood plasma samples for pharmacokinetics were collected during cycle 1 predose and at 15, 30, 60, 65, 70, 90, and 105 min and 2, 4, 8, 12, 24, 48, 72, and 96 h after drug administration. Urine samples were collected predose and within 24, 48, and 72 h after the start of infusion on day 1 of cycle 1. Plasma and urine concentrations of eribulin were measured using a validated liquid chromatography tandem mass spectrometry method, described in detail elsewhere (16).

Briefly, analysis of eribulin in human plasma and urine (500 μL for each sample) was done using liquid chromatography/mass spectrometry/mass spectrometry on a triple quadrupole mass spectrometer under the positive ion mode. Liquid-liquid extraction with 90:5:5 ethyl acetate/methanol/ethanol (v/v/v) was used followed by reverse phase chromatography. Eribulin was monitored at precursor ion *m/z* 730.4 and product ion *m/z* 712.5. Quantitation was based on a 1/×2 weighted linear regression analysis of a

Table 3. AEs related to eribulin occurring in two or more patients

AE	Eribulin mesylate initial dose level (mg/m^2)											
	0.25 (*n* = 1)		0.5 (*n* = 4)		1 (*n* = 3)		2 (*n* = 7)		2.8 (*n* = 3)		4 (*n* = 3)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Blood and lymphatic system disorders												
Anemia	0	0	1 (25)	0	1 (33)	0	1 (14)	0	1 (33)	0	1 (33)	0
Febrile neutropenia	0	0	0	0	0	0	0	1 (14)	0	2 (67)	0	3 (100)
Neutropenia	0	0	0	0	0	1 (33)*	1 (14)	4 (57)	0	1 (33)	0	1 (33)
Leukopenia	0	0	0	0	0	1 (33)*	1 (14)	0	0	1 (33)*	1 (5)	3 (14)
Thrombocytopenia	0	0	0	0	1 (33)	0	0	0	0	0	1 (33)	0
Gastrointestinal disorders												
Constipation	0	0	0	0	0	0	1 (14)	0	0	0	1 (33)	0
Dry mouth	0	0	0	0	1 (33)	0	1 (14)	0	0	0	0	0
Nausea	0	0	2 (50)	0	0	0	0	0	0	0	2 (67)	0
Vomiting	0	0	0	0	0	0	0	0	0	0	2 (67)	0
Metabolism and nutrition disorders												
Anorexia	0	0	1 (25)	0	0	0	2 (29)	0	0	0	0	0
Decreased appetite	0	0	1 (25)	0	1 (33)	0	0	0	1 (33)	0	0	0
General disorders and administration site conditions												
Fatigue	0	0	2 (50)	0	0	0	2 (29)	0	2 (67)	0	1 (33)	0
Pyrexia	0	0	0	0	0	0	1 (14)	0	0	0	1 (33)	0
Laboratory investigations												
Alanine amino-transferase increases	0	0	3 (75)	0	0	0	0	0	0	0	0	0
Alkaline phosphatase increases	0	0	2 (50)	0	0	0	0	0	0	0	0	0
Weight decreases	0	0	1 (25)	0	1 (33)	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders												
Cough	0	0	0	0	0	0	1 (14)	0	0	0	1 (33)	0
Skin and subcutaneous tissue disorders												
Alopecia	0	0	0	0	0	0	3 (43)	0	1 (33)	0	3 (100)	0
Pruritic rash	0	0	0	0	0	0	1 (14)	0	1 (33)	0	0	0
Vascular disorders												
Hypotension	0	0	1 (25)	0	0	0	0	0	0	0	1 (33)	0

*No grade 4 events.

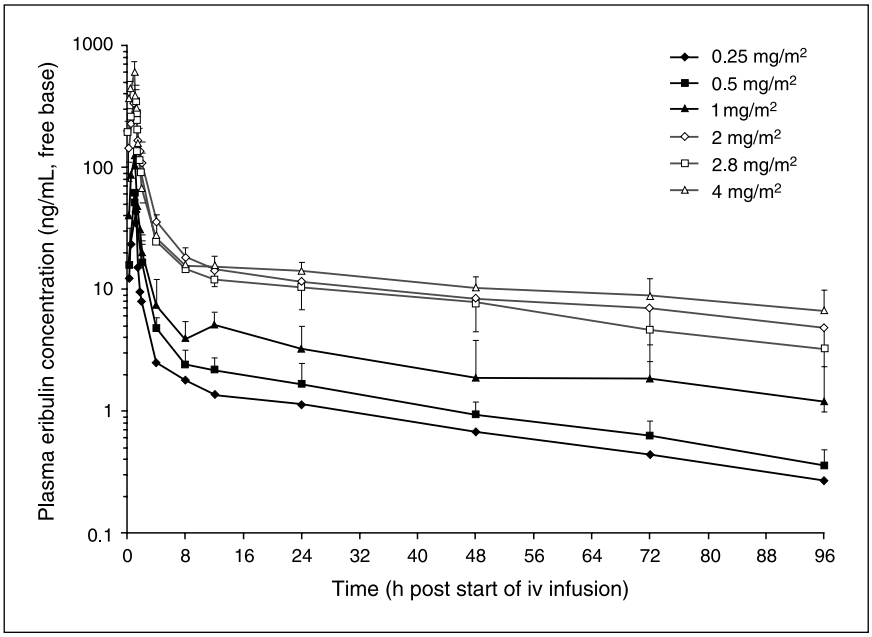

Fig. 1. Mean (±SD) plasma concentration of eribulin mesylate versus time in patients treated with a 1-h infusion on day 1 of a 21-d cycle.

calibration curve of peak area ratios of eribulin to internal standard versus eribulin concentrations.

The quantifiable range of the assay was from 0.177 (plasma) or 0.442 (urine) to 88.5 ng/mL of the eribulin-free base. Pharmacokinetic parameters were calculated by a noncompartmental approach using WinNonlin software version 4.1 (Pharsight Corporation).

Results

Patient characteristics. Between August 2003 and April 2005, a total of 21 patients were enrolled, and all received one or more cycles of eribulin. All patients were eligible for toxicity and response assessment. Patient characteristics are shown in Table 1. The most common tumor types were non–small cell lung cancer (NSCLC) and renal cell carcinoma. A total of 85 treatment cycles were administered, with a median number of two cycles (range 1-17). Of the 19 patients who received prior chemotherapy, four patients (21%) had received paclitaxel and two patients (11%) had received docetaxel for metastatic disease. Reasons for discontinuation included progressive disease (16), toxicity (2), physician discretion (2), and withdrawal of consent (1).

Dose-limiting toxicities and maximum tolerated dose. The dose of eribulin mesylate was escalated from 0.25 mg/m^2 to 0.5, 1, and 2 mg/m^2 in the accelerated dose-escalation stage of the trial and to 4 mg/m^2 in the nonaccelerated stage. Eribulin mesylate was tolerated until the 4 mg/m^2 dose level, where three patients experienced febrile neutropenia on day 7 (Table 2). The dose was reduced to 2.8 mg/m^2, where two of three patients experienced febrile neutropenia. Six additional patients were enrolled at the 2 mg/m^2 dose (seven patients in total) and one of these patients experienced grade 4 febrile

Table 4. Pharmacokinetic parameters for eribulin mesylate administered on day 1 of a 21-d cycle (noncompartmental model)

		Pharmacokinetic parameters					
Dose* (mg/m^2)	*n*	C_{max} (μg/mL)		$AUC_{0-\infty}$ (h · μg/mL)		$t_{1/2}$(h)	
		Mean (SD)	%CV	Mean (SD)	%CV	Mean (SD)	%CV
0.25 (0.221)*	1	0.044		0.138		35.2	
0.5 (0.442)*	4	0.063 (0.02)	29	0.210 (0.05)	26	34.4 (6.78)	20
1 (0.884)*	3	0.127 (0.04)	31	0.486 (0.33)	68	45.9 (21.92)	48
2 (1.767)*	7	0.369 (0.04)	10	1.842 (0.85)	46	48.8 (22.07)	45
2.8 (2.474)*	3	0.340 (0.13)	39	1.412 (0.63)	44	42.3 (6.75)	16
4 (3.535)*	3	0.528 (0.18)	34	2.334 (0.91)	39	66.0 (21.50)	33
All doses	21	n/a	n/a	n/a	n/a	46.5 (18.68)	40

Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve; C_{max}, maximal plasma concentration; CV, coefficient of variation; n/a, not applicable; $t_{1/2}$, elimination half-life; V_{ss}, volume of distribution at steady state.
*Doses given are for the eribulin mesylate salt; doses in parentheses are the freebase dose equivalents.
† Normalized for each 1 mg/m^2 of freebase equivalent dose.

neutropenia, which was a DLT. Of note, another patient treated at the 2 mg/m^2 dose level had a decline in leukocyte count from a pretreatment level of 6,300/μL to 2,000/μL on day 8, and, in response, granulocyte-colony stimulating factor (filgrastim) was administered. The neutrophil count was unavailable, which precluded determination of whether this event was a DLT, so the patient was considered not evaluable. There were no nonhematologic DLTs observed during this trial. The MTD for eribulin mesylate administered as a 1-hour infusion every 21 days was defined as 2 mg/m^2.

Adverse events. The most frequently reported AEs (all grades) considered possibly or probably related to the study drug were neutropenia (38%), fatigue (33%), and alopecia (33%). A total of 10 patients experienced 22 serious AEs (all causalities). Seven patients reported nine serious AEs that were considered to be treatment related: hyponatremia (one patient; grade 3); febrile neutropenia (five patients; all grade 4); and grade 4 febrile neutropenia, grade 2 pyrexia, and grade 3 infection in one patient. One patient died of progressive disease during the study.

The neutropenia associated with eribulin exhibited a nadir 7 to 15 days after the first treatment with recovery to normal by the end of the 21-day cycle. The mean, median, and range for the nadir in absolute neutrophil count during cycle 1 were 1,390/μL, 780/μL, and 100/μL to 3,580/μL, respectively, among the six patients who received the 2 mg/m^2 dose and had data during this time. There were two cases of grade 1 thrombocytopenia at the 1 and 1.4 mg/m^2 dose levels. Grade 1 anemia occurred at doses $\geq$0.5 mg/m^2 in 24% of patients. Seven patients received filgrastim or pegfilgrastim therapy, six patients received erythropoietin therapy, and, of these, two patients received therapy with both types of growth factor. There were no other serious hematologic events.

The majority of nonhematologic AEs were grades 1 and 2 across the entire dose range (Table 3). The most common nonhematologic toxicities attributed to eribulin were fatigue (33%; all grade 1 or 2), alopecia (33%; all grade 1 or 2), and nausea (19%; all grade 1). There was a single occurrence of grade 1 peripheral neuropathy, which occurred in a patient treated at the 4 mg/m^2 dose level.

Pharmacokinetics. Plasma samples for analysis of eribulin pharmacokinetics were obtained from all 21 patients. Individual plasma eribulin concentrations were measurable up to 96 h following the infusion. The pharmacokinetic profile of eribulin was characterized by an extensive volume of distribution, a slow-to-moderate clearance, and a slow elimination (Fig. 1), with only a small fraction of the drug ($\sim$7%) excreted unchanged in the urine. Eribulin exhibited a plasma terminal half-life of $\sim$2 days. Plasma area under the concentration-time curve ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) increased approximately linearly over the dose range studied (Table 4); the dose-normalized C_{max} and $AUC_{0-\infty}$ values were consistent across dose levels with the exception of the 2 mg/m^2 dose level, where higher values were observed.

Antitumor activity. Among the 21 assessable patients, there were no complete responses. However, one patient (4 mg/m^2) with NSCLC who had no prior taxane therapy received four cycles of eribulin and achieved an unconfirmed partial response. Twelve patients experienced stable disease (3 NSCLC, 2 renal cell carcinoma, 2 gallbladder adenocarcinoma, 1 pancreatic adenocarcinoma, 1 intestinal adenocarcinoma, 1 esophageal adenocarcinoma, 1 oral cancer, 1 endometrial stromal sarcoma). The median duration of stable disease was 86 days (range 47-386 days). Of the 12 patients who experienced disease stabilization, four had received prior taxane therapy.

Discussion

In this phase I study of eribulin mesylate given as a 1-hour infusion every 21 days, the MTD of eribulin was 2 mg/m^2. Febrile neutropenia was the principal DLT and has also been observed with eribulin given as a bolus over 1 to 2 minutes weekly on days 1, 8, and 15 of a 28-day cycle (13). This finding is consistent with preclinical observations of reversible bone marrow toxicity that was also dose limiting in rats and dogs (11). Fatigue, alopecia, and nausea were the most common nonhematologic toxicities and this side effect profile is comparable with that which has been reported previously with the other two schedules. Notably, neuropathy, an AE expected of a tubulin-targeting agent (17, 18), was not a predominant toxicity on this study, as only one patient experienced grade 1 neuropathy at a dose higher than the MTD. It should be noted, however, that the median number of treatment cycles in this study was 2, and a higher incidence of neuropathy might be expected over a longer treatment period. In addition, because only seven patients were treated, there is a possibility that other grade 3 or 4 toxicities might be observed in a larger patient population.

Pharmacokinetic analysis showed that the plasma disposition of eribulin was biexponential. Plasma concentrations

Table 4. Pharmacokinetic parameters for eribulin mesylate administered on day 1 of a 21-d cycle (noncompartmental model) (Cont'd)

Pharmacokinetic parameters							
V_{ss}(L/m^2)		C_{max}/dose† (μg/mL)		$AUC_{0-\infty}$/dose† (h · μg/mL)		CL (L/h/m^2)	
Mean (SD)	%CV	Mean (SD)	%CV	Mean (SD)	%CV	Mean (SD)	%CV
53.3		0.197		0.624		1.60	
67.6 (25.24)	37	0.142 (0.04)	29	0.474 (0.12)	26	2.22 (0.57)	26
86.7 (11.55)	13	0.144 (0.04)	31	0.550 (0.38)	68	2.42 (1.38)	57
47.8 (10.14)	21	0.209 (0.02)	10	1.042 (0.48)	46	1.16 (0.54)	47
87.4 (49.32)	56	0.138 (0.05)	39	0.571 (0.25)	44	2.12 (1.25)	59
114.2 (16.36)	14	0.149 (0.05)	34	0.660 (0.26)	39	1.70 (0.75)	44
72.5 (31.17)	43	0.168 (0.05)	28	0.722 (0.40)	55	1.78 (0.89)	50

declined slowly with a $t_{1/2}$ of ~2 days. C_{max} and AUC increased proportionally in a dose-dependent manner. The pharmacokinetic profile of eribulin was comparable at similar doses across the three phase I studies, which used different dosing schedules or infusion times (13, 19). The urinary excretion data showed that eribulin is minimally excreted by the kidney. Less than 10% of eribulin was detected unchanged in the urine, which was also similar to the weekly schedule. There is an ongoing study evaluating the metabolism of eribulin in the setting of hepatic dysfunction as renal clearance does not seem to have a major role (NCT00706095).

Eribulin has been studied as a slow i.v. bolus or a 1-hour i.v. infusion in other phase I trials. In the first phase I study, eribulin mesylate was administered as an i.v. bolus over 1 to 2 minutes on days 1, 8, and 15 of a 28-day cycle in 38 patients (13). The MTD was 1.4 mg/m^2, with neutropenia as the DLT observed at 2 mg/m^2. In the other phase I trial, eribulin was given as a 1-hour i.v. infusion on days 1, 8, and 15 of a 28-day cycle (20). Neutropenia was also reported as the most common DLT with a MTD of 1 mg/m^2. These results are consistent with the study reported here. A shorter infusion would achieve higher peak plasma concentrations compared with the 1-hour infusion, and the higher C_{max} would help to achieve levels associated with apoptosis preclinically (100 nmol/L; ref. 5).

The weekly schedule as a bolus was chosen for further development of eribulin in phase II and III trials. In two phase II trials, patients with metastatic disease were initially treated with eribulin mesylate at 1.4 mg/m^2/wk on days 1, 8, and 15 of a 28-day cycle, which was the MTD from the phase I study (21, 22). In these phase II studies, many patients experienced dose interruption or omission due to neutropenia on day 15 (21, 22). This necessitated a change in the treatment schedule to days 1 and 8 of a 21-day cycle (21, 22). A recent study in Japan formally evaluated eribulin given on days 1 and 8 of a 21-day cycle (23). This study affirmed that neutropenia was the main toxicity associated with treatment and that the recommended phase II dose with this schedule is 1.4 mg/m^2 (23). The development of eribulin includes phase Ib and phase II studies to evaluate eribulin in combination with other anticancer agents. For these studies, the 2 mg/m^2 dose given on day 1 of a 21-day cycle determined in the present study will be evaluated.

Eribulin causes neutropenia and fatigue, which are toxicities also common to taxanes (24). However, neuropathy did not seem to predominate and there were no instances of infusion-related reactions. Eribulin, which is prepared in an aqueous solution, has a short infusion time and does not require steroid or antihistamine premedications. These are distinct advantages compared with currently approved microtubule-targeting agents.

Although efficacy was not a specified end point of this study, one unconfirmed partial response was observed in a patient with NSCLC and 12 patients with a variety of tumor types experienced stable disease. Four of these 12 patients had received prior treatment with a taxane, which suggests that eribulin may have activity in taxane-resistant patients.

In conclusion, eribulin mesylate as a 1-h infusion every 21 days has a manageable tolerability profile and has anti-proliferative activity in several tumor types. Several phase II trials of eribulin mesylate as monotherapy are ongoing or completed (21, 22, 25). The results of phase III trials in metastatic breast cancer are awaited. Combination studies of eribulin with other cytotoxic drugs are currently being explored.

Disclosure of Potential Conflicts of Interest

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