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ORIGINAL ARTICLE

Phase I clinical and pharmacokinetic study of 3-weekly, 3-h infusion of ixabepilone (BMS-247550), an epothilone B analog, in Japanese patients with refractory solid tumors

Toshio Shimizu · Noboru Yamamoto · Yasuhide Yamada · Yasuhito Fujisaka · Kazuhiko Yamada · Yutaka Fujiwara · Kyoko Takayama · Takuto Tokudome · Judith Klimovsky · Tomohide Tamura

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Abstract
Background Ixabepilone (BMS-247550) is the first in a new class of anti-neoplastic agents, the epothilone analogs, and is a highly active non-taxane anti-microtubule agent. This phase I study aimed to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), safety profile, pharmacokinetics, and antitumor activity of ixabepilone in Japanese patients.
Patients and methods Patients with solid tumors previously treated with up to four chemotherapy regimens received a 3-h intravenous infusion of ixabepilone every 3 weeks.
Results Fourteen patients received 43 cycles (median 3, range 1–8). The most common adverse events were neutropenia, mild-to-moderate fatigue, anemia, and peripheral neuropathy. DLTs occurred in one patient receiving 40 mg/m^2 (grade 4 neutropenia for 9 days) and in two patients receiving 50 mg/m^2 (grade 3 mucositis, ileus and febrile neutropenia; grade 4 neutropenia for 10 days). One paclitaxel- and docetaxel-pretreated patient with non-small cell lung cancer achieved a partial response lasting for 3 months; six additional patients (43%) achieved disease stabilization with tumor shrinkage of 3–35%. The plasma concentration–time profiles of ixabepilone during cycle 1 were similar across all doses evaluated.
Conclusions The MTD of ixabepilone is 50 mg/m^2 given over 3 h every 3 weeks. The recommended phase II dose is 40 mg/m^2, which is well tolerated and active. Data from Japanese patients are consistent with published phase I data from non-Japanese patients.

Keywords Anti-microtubule · BMS-247550 · Epothilone B analog · Ixabepilone · Pharmacokinetic · Phase I study

T. Shimizu · N. Yamamoto · Y. Yamada · Y. Fujisaka · K. Yamada · Y. Fujiwara · K. Takayama · T. Tamura (✉)
Division of Internal Medicine,
National Cancer Center Hospital,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: ttamura@ncc.go.jp

T. Tokudome
Bristol-Myers Squibb, Shinjyuku-ku,
Tokyo 163-1328, Japan

J. Klimovsky
Bristol-Myers Squibb, Pharmaceutical Research Institute,
Wallingford, CT 06492, USA

T. Shimizu
Department of Medical Oncology,
Kinki University Nara Hospital,
1248-1, Otoda-cho, Ikoma-city, Nara 630-0293, Japan
e-mail: tshimizu@nara.med.kindai.ac.jp

Introduction

Drugs that target microtubules are among the most commonly prescribed anticancer therapies. Several new anti-microtubule compounds are undergoing clinical evaluation, focusing on overcoming some of the problems associated with taxanes-based therapies, including difficulties with formulation, administration, and susceptibility to resistance conferred by the drug efflux *P*-glycoprotein (*P*-gp). Among these are the epothilones, a new class of anti-neoplastic agents originally isolated from the fermentation broth of the soil-derived myxobacterium, *Sorangium cellulosum* [4–6, 31]. Ixabepilone (BMS-247550; Bristol-Myers Squibb, Wallingford CT, USA; Fig. 1), a semisynthetic lactam analog, was developed as a metabolically more stable

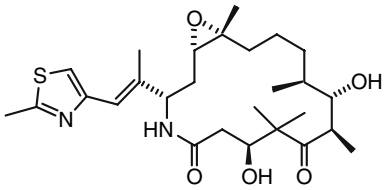

Fig. 1 The chemical structure, molecular formula, and molecular weight of ixabepilone. Molecular formula = $C_{27}H_{42}N_2O_5S$. Molecular weight = 506.7

derivative of epothilone B. It has demonstrated in vivo antitumor activity in a wide range of cancer xenografts, including paclitaxel-resistant tumor models [19]. Like taxanes, epothilones bind tubulin, stabilize microtubules, and block cells in mitosis at the G_2/M transition, resulting in cell death [7]. However, in vitro studies have shown that ixabepilone is 2.5-fold more potent than taxanes in inducing microtubule polymerization [24], is cytotoxic at low nanomolar concentrations, and is synergistic with a number of antitumor agents [9, 18, 20]. In vivo, ixabepilone demonstrates high anti-angiogenic activity and is more effective than paclitaxel in killing endothelial cells, which are involved in angiogenesis and express multidrug resistance-1 (MDR-1) and *P*-gp genes.

One of the key differences between ixabepilone and taxanes is the low susceptibility of ixabepilone to tumor resistance mechanisms [17, 24]. Overexpression of MDR-1 and multidrug resistance-associated protein (MRP) genes is a major cause of both intrinsic and acquired resistance to many chemotherapies, including taxanes and anthracyclines, and represents a major challenge in cancer therapy [8]. Since ixabepilone is a poor substrate for MRP1, *P*-gp, and other cell transporters involved in chemotherapy drug resistance, concentrations of this novel anti-neoplastic agent are maintained at their target, resulting in activity of ixabepilone in multidrug-resistant cell lines [24]. These mechanisms are supported by preclinical data: ixabepilone has shown impressive, broad-spectrum activity against paclitaxel-resistant human colon (HCT116/VM46), ovarian (Pat-7 and A2780Tax), and breast (Pat-21) cancer models, suggesting that ixabepilone may provide a new treatment option for taxane-resistant cancers [16, 19].

Phase I evaluation of a Cremophor-based formulation of ixabepilone has included a number of different schedules: a 3-weekly schedule, a weekly schedule, administration on days 1–5 every 21 days, and administration on days 1–3 every 21 days [1, 11, 23, 35]. Antitumor responses were observed in all previous phase I trials, including patients with melanoma, ovarian cancer, non-small cell lung cancer (NSCLC), and breast cancer. In trials evaluating ixabepilone administered intravenously over 1 h every 21 days, peripheral neuropathy was dose limiting. Data from preclinical and phase I studies of ixabepilone and other epothilones, together with the experience of paclitaxel, suggested that 3-h infusion may be better tolerated than 1-h infusion in terms of peripheral sensory neuropathy [10, 15, 27, 30]. In addition, it was considered possible that C_{max} may correlate with acute neuropathy, as observed for other drugs, such as oxaliplatin [21, 28, 32]. Therefore, ixabepilone was administered as a 3-h intravenous infusion every 3 weeks in this phase I trial.

The aims of this study were to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs), identify the recommended phase II dose, and evaluate the safety profile, antitumor activity, and pharmacokinetics of ixabepilone administered as a 3-h intravenous infusion every 3 weeks to patients with refractory advanced solid tumors.

Patients and methods

Eligible patients were: Japanese, aged 20–75 years and had solid tumors refractory to conventional treatment or for which no standard treatment is available; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; had adequate hematopoietic reserves (absolute neutrophil count [ANC] $\geq$2,000 per μl, platelet count $\geq$100,000 per μl, hemoglobin $\geq$9.0 g/dl); total bilirubin and serum creatinine $\leq$1.5 × upper limit of institutional normal (ULN); AST and ALT $\leq$2.5 × ULN; no chemotherapy or radiation within the previous 4 weeks; no nitrosoureas or mitomycin within the previous 6 weeks; and had given consent to be hospitalized during the first course. Patients were ineligible if: they had symptomatic brain metastasis; other non-malignant systemic disease; active, uncontrolled infection; pre-existing grade 3 or 4 [National Cancer Institute Common Toxicity Criteria (NCI CTC)] neurotoxicity from previous therapy; HIV or hepatitis B or C virus; if they were pregnant or nursing; or if they required steroid therapy. All patients provided written informed consent before entering the study.

Screening and study assessments

Medical history, physical examinations, and routine laboratory evaluations were performed before treatment initiation and weekly thereafter. Chest and other relevant X-rays were performed during screening and after alternate cycles. Adverse events were monitored and recorded throughout the study and graded according to NCI CTC, version 3.0. Tumor response of measurable target lesions was assessed according to response evaluation criteria in solid tumors (RECIST).

Treatment administration

Ixabepilone was supplied by Bristol-Myers Squibb (Wallingford, CT, USA), and was diluted in an ethanol USP + cremophor-EL mixture (1:1 by volume) to achieve a final concentration of approximately 2 mg/ml (ixabepilone vials contain 530 mg of cremophor-EL and 2 mg of ixabepilone/ml). Ixabepilone was administered intravenously over 3 h every 21 days with hypersensitivity prophylaxis (diphenhydramine 50 mg and famotidine 20 mg orally 1 h before ixabepilone administration). Anti-emetic premedication was not mandatory in the protocol. Granulocyte colony-stimulating factor (G-CSF) was used for febrile neutropenia, sepsis with neutropenia, or recurrent grade 4 neutropenia.

DLTs and MTD

The ixabepilone starting dose was 15 mg/m^2, escalating to 30, 40, and 50 mg/m^2 in subsequent cohorts of at least three patients. The following adverse events during cycle 1 were defined as DLTs: grade 4 neutropenia (ANC <500 per μl) for >5 days; febrile neutropenia (fever of >38.5°C with ANC <1,000 per μl); thrombocytopenia (platelet count <25,000 per μl); grade ≥3 nausea and/or vomiting despite maximal anti-emetic therapy; any other grade ≥3 non-hematologic toxicity considered related to ixabepilone; ≥14-day delay in starting cycle 2. If any patient experienced a DLT during the first cycle, three additional patients were treated at that dose level. Patients experiencing a DLT could continue ixabepilone therapy at the preceding dose level. Retreatment in subsequent courses was initiated only after hematologic recovery (ANC ≥1,500 per μl, platelet count ≥100,000 per μl) and resolution of all other toxicities to grade ≤1 or baseline intensity.

MTD was defined as the dose level at which two or more patients experienced a DLT in the first cycle. The recommended dose was defined as the dose level immediately below the MTD.

Plasma sampling and assay

Blood samples were obtained before the start of drug infusion and at 1.5, 3 (before the end of infusion), 3.5, 4, 5, 6, 8, 24, 48, 72 h after the start of infusion. Plasma samples were stored at −70°C until assayed.

A liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method for quantification of ixabepilone in 0.2 ml of human ethylenediaminetetraacetic acid (EDTA) plasma was developed at Bristol–Myers Squibb (New Brunswick, NJ). The lower quantitation limit was 2.0 ng/ml. After the addition of an internal standard to 0.2 ml of each calibration standard, quality control sample, and study sample, and precipitation with acetone, the supernatant was extracted with 1-chlorobutane. After centrifugation, the lower aqueous layer was frozen and the organic layer was transferred to a clean tube and evaporated to dryness. The residue was reconstituted and injected into the LC/MS/MS system. Chromatographic separation was achieved, isocratically, on a model ODS-AQ column (4.6 × 50 mm; YMC, Wilmington, NC) with detection by negative electrospray tandem mass spectrometry (Micromass, Beverly, NJ). The standard curve, which ranged from 2 to 500 ng/ml for all analyses, was fitted to a $1/x$ weighted quadratic regression model.

Pharmacokinetic analysis

The plasma concentration–time data for ixabepilone in cycle 1 were analyzed by a non-compartmental method in Kinetica version 4.2 (InnaPhase Corporation, Philadelphia, PA). The following pharmacokinetic parameters of ixabepilone were determined: maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), terminal elimination half-life ($t_{1/2}$), total body clearance (CL_{tot}) and volume of distribution at steady-state (V_{ss}). $AUC_{0-\infty}$ was determined by summing the areas from time zero to the time of last measured concentration, calculated using a log-trapezoidal method, and the extrapolated area. The extrapolated area was determined by dividing the final concentration by the slope (k) of the terminal log-linear phase. The absolute value of k was also used to estimate the apparent terminal elimination half-time, $t_{1/2} = \ln 2/k$. CL_{tot} was determined by dividing dose by $AUC_{0-\infty}$. V_{ss} was calculated by multiplying CL_{tot} by MRT determined as the area under the moment curve to infinity divided by $AUC_{0-\infty}$.

Results

Patient characteristics

Between March 2004 and February 2005, 14 patients were enrolled at the National Cancer Center Hospital, Tokyo, Japan. Patient characteristics are shown in Table 1. Most patients were heavily pretreated; the median number of prior regimens was two. Five of the seven taxane-pretreated patients had received paclitaxel or docetaxel less than 6 months before receiving ixabepilone.

DLTs and MTD

Table 2 shows patient distribution by dose level. At the 40 mg/m^2 dose level, one of three patients experienced

Table 1 Patient characteristics

Characteristics	No. of patients (n = 14)
Gender (male/female)	11/3
Age (years)	
Median	55
Range	36–72
ECOG performance status	
0	2
1	12
Tumor type	
NSCLC	7
Mesothelioma	2
Thymic cancer	1
Ovarian cancer	1
Colorectal cancer	1
Cholangiocellular carcinoma	1
Liposarcoma	1
Previous treatment	
Chemotherapy	13
No. of prior regimens	
1	2
2	6
3	1
4	4
Prior taxane therapy	7
Prior chemoradiation	3
Surgery only	1

ECOG Eastern co-operative oncology group, *NSCLC* non-small cell lung cancer

Table 2 Dose-escalation scheme

Dose level (mg/m^2)	No. of patients	No. of cycles
15	3	4
30	3	19
40	6	16
50	2	4
Total	14	43

grade 4 neutropenia lasting for 9 days. Therefore, three additional patients were treated at this dose level, none of whom experienced a DLT. The only other significant toxicity among the six patients treated at this dose level was grade 3 dehydration during the second cycle in a patient with heavily pretreated NSCLC. At the 50 mg/m^2 dose level, the first two patients experienced DLTs (grade 3 mucositis, ileus and febrile neutropenia in a patient with thymic cancer; grade 4 neutropenia lasting for 10 days in a patient with mesothelioma). Consequently enrollment was stopped and this dose level was identified as the MTD. The recommended dose level for phase II evaluation was determined as 40 mg/m^2.

Safety

A total of 43 cycles were administered to 14 patients, with a median of three cycles per patient (range, 1–8). Five patients (36%) received at least four cycles and three patients (21%) received at least six cycles. One patient with NSCLC received eight cycles at 30 mg/m^2 and another patient with NSCLC received seven cycles at 40 mg/m^2 without any grade 3 or 4 toxicity. The incidence of hematologic toxicities by dose level is shown in Table 3. There were no grade 3 or 4 episodes of thrombocytopenia and anemia was mostly mild or moderate. The onset of neutropenia was generally 10–14 days after treatment. The most common non-hematologic adverse events were fatigue, neurotoxicity, gastrointestinal discomfort, mucositis, and myalgia/arthralgia (Table 4). Fatigue typically occurred during the first week of each treatment cycle and usually resolved before the next treatment cycle. Peripheral neurotoxicity with ixabepilone was characterized by paresthesia in a symmetric, glove-and-stocking distribution. Ten patients (71%) experienced arthralgia, myalgia, or both in 17 courses (40%) across all dose levels. Gastrointestinal discomfort, commonly reported as distention and nausea with or without vomiting, was generally manageable with anti-emetics. All cases of mucositis were mild or moderate except for the DLT. Six patients developed asymptomatic superficial phlebitis during infusion of ixabepilone, which resolved after completion of infusion in all cases. No patient experienced hypersensitivity reactions following ixabepilone administration.

Antitumor activity

Among the 11 patients evaluable for response, evidence of antitumor activity was observed in seven (50%) (Table 5). One patient with paclitaxel- and docetaxel-pretreated NSCLC receiving 40 mg/m^2 ixabepilone achieved a partial response (shrinkage in mediastinal lymph node metastases). The response lasted for 3 months. Another patient with docetaxel-refractory advanced NSCLC who received eight cycles at the 30 mg/m^2 dose had a minor response in a chest wall lesion and pleural effusion reduction lasting for 6 months. Five patients achieved stable disease, with tumor shrinkage ranging from 3 to 35%. Among the six patients treated at the recommended dose level, one (17%) achieved a partial response and two (34%) showed disease stabilization.

Table 3 Hematologic toxicities (all cycles)

Dose level (mg/m^2)	No. of patients (no. of cycles)	No. of patients (no. of cycles) with toxicity								
		Neutropenia					Anemia		Thrombocytopenia	
		Grade 3	Grade 4 lasting ≤5 days	Grade 4 lasting >5 days	Grade 4 with fever	DLT	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
15	3 (4)	0	0	0	0	0	3 (4)	–	1 (1)	–
30	3 (19)	0	0	0	0	0	3 (19)	–	1 (1)	–
40	6 (16)	2 (2)	1 (2)	1 (1)	0	1[a]	5 (14)	1 (1)	1 (1)	–
50	2 (4)	0	1 (2)[b]	1 (1)	1 (1)	2[c]	2 (4)	–	1 (1)	–
Total (% of patients)	14 (43)	14	7	14	7	3	93	7	29	0

[a] Grade 4 neutropenia for 9 consecutive days

[b] This patient was also counted as Grade 4 neutropenia with fever

[c] Febrile neutropenia, grade 3 mucositis and ileus in one patient; grade 4 neutropenia for 10 consecutive days in one patient

Table 4 Non-hematologic toxicities (all cycles)

Dose level	No. of patients (cycles)	No. of patients (no. of cycles) with toxicity									
		Fatigue/generalized weakness		Neurotoxicity		Myalgia/arthralgia		Gastrointestinal discomfort[a]		Mucositis	
		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
15	3 (4)	–	–	–	–	–	–	–	–	–	–
30	3 (19)	3 (10)	–	3 (18)	–	3 (7)	–	1 (1)	–	1 (1)	–
40	6 (16)	6 (11)	–	6 (12)	–	5 (6)	–	4 (4)	–	4 (4)	–
50	2 (4)	2 (4)	–	1 (3)	–	2 (4)	–	1 (2)	1 (1)[b]	1 (2)	1 (1)[b]
Total (% patients)		79	0	71	0	71	0	43	7	43	7

[a] Complaints of distension, queasiness with or without diaphoresis, anorexia with or without nausea, vomiting, constipation or altered bowel movements characterized as "not normal", abdominal cramping, or symptoms of gastrointestinal reflux (burning or distension)

[b] Dose-limiting toxicity

Table 5 Antitumor activity

Response	Number of patients (%)
Partial response	1 (7)[b]
Stable disease	6 (43)[c]
Progressive disease	4 (29)
Not evaluable[a]	3 (21)

[a] Not evaluable: not assessed for response

[b] Dose level 40 mg/m^2

[c] Three patients at 30 mg/m^2, two patients at 40 mg/m^2, one patient at 50 mg/m^2

Pharmacokinetics

Plasma samples were obtained from 14 patients during the first cycle of treatment. Pharmacokinetic parameters, except for C_{max} and T_{max}, were not obtained from one patient during the first course at the lowest dose due to insufficient plasma concentration data. The plasma concentration–time profiles of ixabepilone during cycle 1 were similar across all doses, although total plasma concentrations increased in a dose-dependent manner with a significant increase at 50 mg/m^2 (Fig. 2). After 3-h infusion of ixabepilone, plasma concentrations decreased in a bi-exponential manner at each dose level with less than 4% of the C_{max} 72 h after administration.

Summary statistics for the pharmacokinetic parameters by dose are shown in Table 6. When administered as a 3-h infusion at doses of 15–50 mg/m^2, C_{max} (range 62.12–583.53 ng/ml) and $AUC_{0-\infty}$ (range 567.37–6324.18 ng h/ml) increased in a greater than dose-proportional manner. CL_{tot} (range 12–49 l/h) and V_{ss} (range 365–1,910 l) decreased according to the dose increments with a significant decrease at 50 mg/m^2.

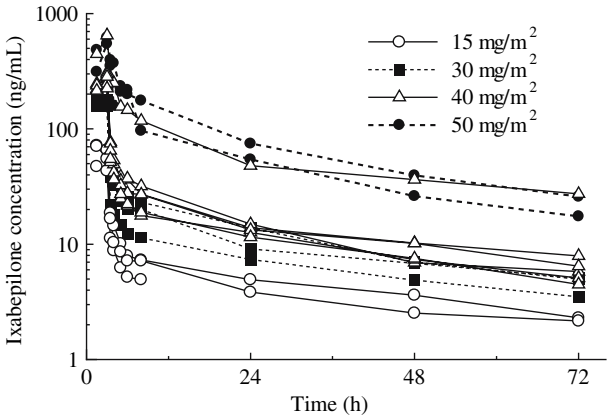

Fig. 2 The plasma concentration–time profiles of ixabepilone following 3-h intravenous administration, cycle 1

Discussion

In this phase I study of ixabepilone given over 3 h every 3 weeks to Japanese patients, the MTD was determined to be 50 mg/m^2, the recommended phase II dose selected was 40 mg/m^2. DLTs were neutropenia, febrile neutropenia, mucositis and ileus. Evidence of antitumor activity was seen in taxane-pretreated patients, including a partial response in a patient previously treated with both docetaxel and paclitaxel receiving a dose of 40 mg/m^2, suggesting that ixabepilone may be active in taxane-resistant or -refractory settings. Five patients with NSCLC received four or more cycles, of who three received at least six cycles and achieved disease stabilization with tumor shrinkage. In addition, an objective tumor response was observed.

Treatment was well tolerated for up to eight cycles. The main toxicities of ixabepilone were myelosuppression and cumulative peripheral neuropathy. There were no grade 3 or 4 cases of neurotoxicity, suggesting that administration by 3-h rather than 1-h infusion reduced the severity of neurotoxicity. The safety profile, DLTs and recommended phase II dose in the present study are consistent with those reported from previous phase I studies in which ixabepilone was administered as a 1-h infusion every 3 weeks to non-Japanese patients [13, 23]. In one study, grade 4 neutropenia and neutropenic sepsis were dose limiting at 56 mg/m^2; grade 3 and 4 vomiting and fatigue were also reported at this dose level and the recommended phase II dose was 40 mg/m^2 [13]. A second study investigating 1-h infusion every 3 weeks identified the same recommended phase II dose [23]. DLTs were neutropenia and abdominal pain/nausea. Additional toxicities reported with 3-weekly regimens include grade 3–4 emesis, fatigue, grade 1–2 myalgia, arthralgia, rash, mucositis, and hand–foot syndrome [13, 14].

Results of a phase II study evaluating the every 3 weeks 3-h infusion regimen in patients with pancreatic cancer have recently been published. Ixabepilone showed encouraging activity and the most common toxicities were myelosuppression, neuropathy, and nausea and vomiting [34]. Phase II studies evaluating alternative schedules (1-h infusion of 50 mg/m^2 every 3 weeks; 6 mg/m^2, days 1–5, every 3 weeks) have demonstrated activity in patients with taxane-pretreated metastatic gastric cancer and taxane-pretreated advanced breast cancer, respectively [3, 22]. Preliminary data from other phase I and II studies indicate that ixabepilone shows anti-tumor activity in NSCLC, ovarian cancer, prostate cancer, melanoma, and colorectal cancer [1, 11, 12, 14, 23, 29, 33, 35]. These data suggest that ixabepilone has activity even in tumor types not typically recognized as taxane sensitive.

A recent study showed that the plasma concentration of ixabepilone and severity of neutropenia correlate with the level of microtubule bundle formation (MBF) in peripheral blood mononuclear cells (PBMCs) [25]. In a previous study assessing 1-h infusion of ixabepilone every 3 weeks, the pharmacokinetics of ixabepilone were characterized by rapid tissue distribution and extensive tissue binding, as evidenced by a large V_{ss} value [26]. Based on the half-life values, no accumulation of exposure was anticipated when ixabepilone was administered over 3 h every 3 weeks. The

Table 6 Pharmacokinetic parameters of ixabepilone 3-h infusion

Dose level (mg/m^2)	No. of patients	$AUC_{0-\infty}$ (ng h/ml)		C_{max} (ng/ml)		$t_{1/2}$ (h)		CL_{tot} (l/h)		V_{ss} (l)	
		Geometric mean	CV %	Geometric mean	CV %	Mean	SD	Mean	SD	Mean	SD
15	3	567.37[a]	12[a]	62.12	22	35.99[a]	3.39[a]	48.87[a]	6.74[a]	1,909.57[a]	153.34[a]
30	3	1,353.01	18	195.29	23	42.97	15.10	42.70	10.75	1759.07	676.18
40	6	2,301.31	83	313.04	47	43.00	14.45	31.68	12.85	1,171.20	343.89
50	2	6,324.18	27	583.53	8	28.57	3.90	11.87	2.59	364.97	44.06

$AUC_{0-\infty}$ Area under the concentration-versus-time curve from time zero to infinity, C_{max} peak plasma concentration, CL_{tot} total body clearance, V_{ss} volume of distribution at steady state

[a] $n = 2$

distribution of $t_{1/2}$ values in the present study was similar across dose groups and no dose effect was observed.

Due to the small number of patients in each treatment group, especially the 50 mg/m^2 dose cohort ($n = 2$), no firm conclusions regarding pharmacokinetic linearity could be drawn. However, in this study, pharmacokinetics were approximately linear up to the dose level of 40 mg/m^2 and ixabepilone had AUC values that increased in a greater than dose-proportional manner at 50 mg/m^2. In the previous non-Japanese phase I study, [2] ixabepilone showed almost the same exposure between 40 mg/m^2 ($N = 14$) and 50 mg/m^2 ($N = 8$) dose levels with relatively high coefficient of variation values (56% at 40 mg/m^2 and 47% at 50 mg/m^2), suggesting that ixabepilone has essentially large inter-individual variability.

Ixabepilone is metabolized by CYP3A4. Since there are generally no ethnic differences in CYP3A4, this suggests that the effect of pharmacogenetics on drug pharmacokinetics is irrelevant. We believe that the differences with the 50 mg/m^2 dose are due to the limited number of patients and inter-individual variability.

We conclude that ixabepione at the recommended phase II dose (40 mg/m^2 as a 3-h infusion every 3 weeks) is well tolerated and active in Japanese patients. Moreover, 3-h infusion every 3 weeks appears to reduce the incidence of neurotoxicity compared with a 1-h infusion schedule. Further evaluation of the recommended regimen, particularly in patients with NSCLC, is warranted.

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