Cancer Chemother Pharmacol (2012) 69:457–465
DOI 10.1007/s00280-011-1726-5

ORIGINAL ARTICLE

Phase I and pharmacokinetic study of nab-paclitaxel, nanoparticle albumin-bound paclitaxel, administered weekly to Japanese patients with solid tumors and metastatic breast cancer

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Received: 7 February 2011 / Accepted: 8 August 2011 / Published online: 19 August 2011

Abstract
Purpose We conducted phase I and tolerability studies to determine the maximum tolerated dose (MTD) and recommended dose of nab-paclitaxel when administered weekly with solid tumors and to evaluate the tolerability of weekly administration at a dose of 150 mg/m^2 with metastatic breast cancer (MBC) as a first-line therapy in Japanese patients.
Methods In this phase I study, patients with advanced solid tumors received nab-paclitaxel at dose levels of 80–125 mg/m^2 as 30-min infusions once a week for three weekly doses repeated every 4 weeks. In the tolerability study, patients received 150 mg/m^2 nab-paclitaxel. Blood samples at the first dose of nab-paclitaxel were collected for pharmacokinetic analysis.
Results Fifteen patients were treated for a median of five cycles in the phase I study. The MTD was 125 mg/m^2; the dose-limiting toxicity was neutropenia requiring skipping of the second or third weekly administration in the first cycle. In the tolerability study, six patients were treated for a median of six cycles; no intolerable toxicities were observed in the first cycle. Grade 3 sensory and motor neuropathy was observed in four and one patients, respectively. Ocular toxicities were observed in two patients (keratopathy and macular hole). Maximum paclitaxel concentration and area under the curve increased linearly with the dose.
Conclusions Weekly administration of nab-paclitaxel was well tolerated up to 100 mg/m^2 by heavily pretreated patients. For MBC patients, 150 mg/m^2 nab-paclitaxel as a first-line therapy was well tolerated. Dose reduction due to neuropathy allows multiple cycles of treatment.

Keywords Albumin-bound paclitaxel · Weekly administration · Phase I study · Ocular toxicity

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Introduction

Paclitaxel is a taxane with substantial antitumor activity that is widely used for breast, non-small-cell lung, and ovarian cancers. Because of its poor water solubility, conventional paclitaxel contains a combination of polyoxyethylated castor oil (Cremophor® EL) and ethanol as the vehicle [1]. This solvent induces hypersensitivity reactions and prolonged peripheral neuropathy [2, 3].

Nab-paclitaxel (Abraxane®; Abraxis BioScience Inc., California, USA) is a novel Cremophor EL-free, albumin-bound nanoparticle formulation of paclitaxel [4]. Preclinical studies in animals have demonstrated increased antitumor activity of nab-paclitaxel compared with equitoxic doses of paclitaxel. The use of a nanoparticle technology may also theoretically allow better delivery of drug to the tumor microenvironment, and it is clearly associated with more linear pharmacokinetics. Nab-paclitaxel allows safe infusion with no premedication and shorter infusion schedules [5]. In a phase III study, triweekly nab-paclitaxel showed a significantly higher response rate and longer progression-free survival (PFS) in patients with metastatic breast cancer (MBC) compared with standard triweekly paclitaxel [6]. Currently, a weekly schedule of paclitaxel is mainly used in adjuvant and metastatic disease for breast cancer [7, 8].

A phase I study of nab-paclitaxel administered weekly (three weekly doses, repeated every 4 weeks) for solid tumors demonstrated that the maximum tolerated doses (MTDs) for heavily and lightly pretreated patients were 100 and 150 mg/m^2, respectively [9]. In a randomized phase II study as first-line chemotherapy for MBC, 150 mg/m^2 weekly nab-paclitaxel demonstrated significantly longer PFS than the 100 mg/m^2 triweekly docetaxel [10].

The primary objectives of our present studies were as follows: (1) to determine the MTD and recommended dose (RD) of nab-paclitaxel when administered weekly in Japanese patients with solid tumors and (2) to evaluate the tolerability of weekly administration of nab-paclitaxel at a dose of 150 mg/m^2 in Japanese patients with MBC as a first-line therapy.

Patients and methods

Patient population

These studies were approved by the Institutional Review Board at the National Cancer Center and performed as a registration-directed trial in accordance with the Good Clinical Practice guideline, which is laid down by the revised Pharmaceutical Affairs Act in Japan.

Phase I study for solid tumors

Eligible patients included men and non-pregnant women with adequate birth control with biopsy-proven diagnoses of solid tumors for which standard therapy had failed and who had not received any chemotherapy and any radiotherapy for at least 3 weeks before enrollment. The other requirements were as follows: age between 20 and 75 years; ECOG performance status (PS) 0–2; life expectancy ≥60 days; adequate bone marrow function (white blood cell count ≤ 12 000/mm^3, absolute neutrophil count (ANC) ≥ 2 000/mm^3, hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 100 000/mm^3); adequate liver function (total bilirubin ≤ 1.5 mg/dL and liver transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] < 100 IU/L); adequate renal function (serum creatinine ≤ 1.5 mg/dL); serum albumin ≥3.0 g/dL; and written informed consent. Patients with prior history of taxane administration were allowed. The exclusion criteria were as follows: (1) any surgery within 4 weeks before enrollment; (2) history of radiotherapy with >30% of hematopoietic bone marrow; (3) pre-existing neuropathy ≥grade 2; pleural effusion or ascites requiring drainage; (4) brain metastases with any symptoms or required treatment; (5) chronic steroid treatment; (6) serious pre-existing medical conditions such as infections, pulmonary fibrosis, diabetes, or heart disease; and (7) hepatitis B or C virus or human immunodeficiency virus infection.

Table 1 Dose levels

Level	Dose (mg/m^2)	No. of patients treated	No. of cycles
1	80	3	4, 1, 6
2	100	6	5, 2, 6, 6, 8, 6
3	125	6	5, 7, 1, 2, 2, 3
4[a]	150	6	4, 4, 6, 6, 6, 19

[a] Among patients in the tolerability study of weekly nab-paclitaxel at a dose of 150 mg/m^2 for metastatic breast cancer

Tolerability study at a dose of 150 mg/m^2 for MBC

Patients with histologically or cytologically confirmed MBC were eligible if they had not received chemotherapy for metastatic disease. Previous endocrine therapy for MBC or adjuvant chemotherapy was allowed. Patients who had received taxane-based neoadjuvant or adjuvant therapy were required to have had a disease-free interval of at least 6 months after completion of taxane therapy. Those with human epidermal growth factor receptor-2 (HER2)-negative disease were eligible. Other inclusion and exclusion criteria were the same as those followed for the phase I study for solid tumors.

Study design and treatment

Nab-paclitaxel was provided as an investigational drug by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan).

Phase I study for solid tumors

Nab-paclitaxel was administered weekly for 3 weeks, followed by 1 week of rest (one treatment cycle). Doses were 80, 100, and 125 mg/m^2 administered as intravenous infusions over 30 min without premedication to prevent hypersensitivity reactions (Table 1). A treatment cycle was repeated every 28 days. Dose reductions were allowed to the next lower dose level in the second course if a patient experienced a dose-limiting toxicity (DLT) or grade 2 neuropathy in the first cycle. Dose escalations were not permitted among patients within a specified dose level. The rationale for the dose range of this study was determined from the phase I study among heavily pretreated patients [9].

Before the second and third weekly administration within each cycle, ANC and platelet counts were required to be ≥1,000/mm^3 and ≥75,000/mm^3, respectively. If ANC and platelet counts did not fulfill the required criteria, the relevant weekly administration was skipped. Moreover,

before the administration of the following cycle, patients were required to have ANC $\geq$1,500/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$8.0 g/dL, total bilirubin $\leq$1.5 mg/dL, liver transaminases <100 IU/L, serum creatinine $\leq$1.5 mg/dL, and $\leq$grade 2 neurotoxicity. If any toxicity did not improve within 3 weeks, the treatment was withdrawn.

Doses were escalated according to the standard "3 + 3" rule. Three patients were treated at a starting dose of 80 mg/m^2. If no DLT occurred in the first three patients, then three patients were enrolled into the next dose level. If a DLT occurred, three additional patients were then enrolled at the same dose level. If a DLT occurred in only one of six patients at a dose level, three new patients were then enrolled into the next dose level. The MTD was defined as the dose level at which two out of three to six patients showed DLTs. The RD was defined as the dose level that was one level below the MTD, and a total of six patients were treated at the RD to evaluate the safety profile.

DLTs were defined as any of the following drug-related events occurring in the first cycle: (1) grade 4 thrombocytopenia; (2) grade 3 thrombocytopenia with required platelet transfusion; (3) grade 4 neutropenia for $\geq$4 days; (4) grade 3 or 4 febrile neutropenia; (5) grade 3 or 4 non-hematologic toxicity, excluding nausea and vomiting; and (6) skipping of the second or third weekly administration.

Tolerability study at a dose of 150 mg/m^2 for MBC

Nab-paclitaxel at a dose of 150 mg/m^2 was administered weekly for 3 weeks, followed by 1 week of rest. Before the second and third weekly administration within each cycle, ANC and platelet counts were required to be $\geq$500/mm^3 and $\geq$75,000/mm^3, respectively, with $\leq$grade 2 neurotoxicity. If a patient did not fulfill the required criteria, the relevant weekly administration was skipped. The required criteria for administration of the subsequent cycle were same as those in the phase I study for solid tumors. If any toxicity did not improve within 3 weeks, treatment of nab-paclitaxel was withdrawn. Intolerable toxicities were defined as any of the following drug-related events occurring during the first cycle: (1) grade 4 thrombocytopenia; (2) grade 3 thrombocytopenia that required platelet transfusion; (3) grade 3 or 4 febrile neutropenia; (4) grade 3 or 4 non-hematologic toxicity excluding nausea and vomiting; and (5) skipping the second or third weekly administration. If four or more patients out of six did not show intolerable toxicities, the weekly administration of 150 mg/m^2 was considered tolerable. Dose reductions were allowed to the next lower dose level in the second cycle if a patient experienced an intolerable toxicity or grade 2 neuropathy in the previous cycle. Treatment was repeated until disease progression or unacceptable toxicity.

Assessments

All adverse events were categorized according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0. Blood cell counts and blood chemistry were completed before each administration of nab-paclitaxel to assess renal and hepatic functions. An objective response for an evaluable patient was assessed every 4–8 weeks according to Response Evaluation Criteria in Solid Tumors version 1.0 [11].

Pharmacokinetic studies

Whole blood samples (6 mL of heparinized tube and 1 mL of K_3EDTA-containing tube in the phase I study for solid tumors, 3 mL of heparinized tube in the tolerability study for MBC) were collected during administration of the first dose of nab-paclitaxel in the arm contralateral to the drug infusion arm. Samples were drawn at the following 12 time points: 0 (pre), 15, 30 (immediately before the termination of infusion), 45 min, and 1, 1.5, 2, 4, 10, 24, 48 and 72 h from the beginning of infusion in the phase I study for solid tumors. In the tolerability study for MBC, samples were drawn at the following 9 time points: 0 (pre), 30 min (immediately before the termination of infusion), and 1, 2, 4, 10, 24, 48, and 72 h from the beginning of infusion. Heparinized samples were immediately centrifuged at 1,900*g* for 15 min, and aliquots of resultant plasma were stored with whole blood at −20°C until analysis. Paclitaxel concentration was quantitated using liquid chromatography and tandem mass spectrometry in the Alta Analytical Laboratory (California, USA). The lower limit of quantification for paclitaxel in the plasma and whole blood was 1.00 and 5.00 ng/mL, respectively.

Each patient's whole blood and plasma concentration profiles of paclitaxel were used to estimate the elimination half-life ($t_{1/2}$), area under the concentration–time curve through the last measurable time point (AUC_{0-t}), AUC through infinity (AUC_{inf}), total body clearance (CL), and apparent volume of distribution (V_z) by a non-compartment analysis using the WinNonlin software (version 4.1, Pharsight Corp., California, USA). The maximum concentration (C_{max}) of paclitaxel was determined from the actual measured value. The AUC was calculated by the trapezoidal method. The AUC_{inf} was obtained by summation of the AUC_{0-t} and the extrapolated area estimated by taking the ratio between the last measurable concentration and the apparent elimination rate constant. Regression analysis of each of individual C_{max}, AUC_{0-t}, and AUC_{inf} versus the dose was performed to evaluate the pharmacokinetic linearity. The SAS software (version 8.2, SAS Institute, Inc., North Carolina, USA) was used for statistical analysis.

Table 2 Patient characteristics in the phase I study

Characteristics	No. of patients
Male:female	6:10
Age (years)	
Median (range)	57 (27–73)
ECOG performance status	
0	12
1	4
Tumor type	
Adrenal cortex	1
Bladder/urethra	2
Breast	3
Ovary/peritoneum	4
Prostate	1
Unknown primary	3
Soft tissue sarcoma	2
Prior treatment	
Surgery	12
Radiotherapy	5
Chemotherapy	15
No. of prior chemotherapy regimens	1
0	1
1	3
2	3
≥3	9
Paclitaxel	9
Docetaxel	6

Results

Phase I study for solid tumors

Between May 2006 and June 2007, 16 patients were enrolled into this phase I study, and 15 of the 16 patients received at least one dose of nab-paclitaxel (Table 1). One patient with ovarian cancer at dose level 2 did not receive nab-paclitaxel due to elevation in the serum creatinine before drug administration. Patient characteristics are shown in Table 2. Patients received a median of five cycles of nab-paclitaxel (range, 1–8 cycles; 3–23 doses), and 10 patients received at least three cycles.

DLT and RD

No DLTs were observed during the first cycle of treatment among the first three patients at 80 and 100 mg/m^2. One of the first three patients at 125 mg/m^2 needed to skip the third weekly administration because of grade 3 neutropenia. Further, one of the additional three patients needed to skip the second weekly administration because of grade 3 neutropenia. Therefore, two of the six patients receiving 125 mg/m^2 experienced DLTs; the MTD was accordingly identified as 125 mg/m^2. One of the additional three patients at 100 mg/m^2 needed to skip the third weekly administration because of grade 3 neutropenia. Further, one of the six patients at 100 mg/m^2 experienced DLT; therefore, 100 mg/m^2 was determined as the RD. Efficacy evaluation revealed no objective response among 14 patients.

Hematologic toxicity

Grade 3 or 4 neutropenia was observed in three of 11 cycles (27%) at 80 mg/m^2, eight of 33 cycles (24%) at 100 mg/m^2, and 11 of 20 cycles (55%) at 125 mg/m^2, respectively (Table 3). In the first cycle, one patient at 80 mg/m^2, two patients at 100 mg/m^2, and three patients at 125 mg/m^2 experienced grade 3 neutropenia. The median duration between the start of drug administration and the nadir of ANC for the first cycle was 21 days (7–29). Grade 2 or higher neutropenia improved by ≥one grade within 7 days (3–28). One patient at 125 mg/m^2 experienced grade 3 febrile neutropenia in the second cycle. Grade 1 or 2 anemia was observed in two patients at 80 mg/m^2 (two in the first cycle) and six at 100 mg/m^2 (three in the first cycle). At 125 mg/m^2, grade 1 and grade 3 anemia were observed in one and three patients, respectively (in the first cycle, grade 1, 2, and 3 anemia were observed in one, one, and two patients, respectively). One patient with hemorrhagic ascites and ovarian cancer experienced grade 4 anemia during the first cycle at 80 mg/m^2 and received blood transfusion. Two patients at 125 mg/m^2 showed grade 1 thrombocytopenia in the first cycle. One patient at 100 mg/m^2 and three patients at 125 mg/m^2 required dose modification because of neutropenia.

Non-hematologic toxicities

Non-hematologic toxicities were generally mild (Table 4). Grade 1 or 2 nausea, diarrhea, fatigue, and myalgia were observed in 53, 60, 73, and 47% of the 15 patients, respectively. Ten of 15 patients experienced grade 1 or 2 rash on upper arms, lower legs or body trunk, which were relieved by the suspension of nab-paclitaxel or treatment of anti-allergic drugs (four episodes of 11 cycles at 80 mg/m^2, five of 33 cycles at 100 mg/m^2, and six of 20 cycles at 125 mg/m^2).

Nine and two of 15 patients showed grade 1 and 2 peripheral sensory neuropathy, respectively. Three patients at 125 mg/m^2 showed grade 1 peripheral sensory neuropathy in the first cycle. One patient at 125 mg/m^2 who showed peripheral sensory neuropathy in the second cycle developed grade 2 in the fourth cycle and required dose modification. One patient at 125 mg/m^2 experienced grade 1

Table 3 Neutropenia by dose levels

	80 mg/m^2 $N = 3$	100 mg/m^2 $N = 6$	125 mg/m^2 $N = 6$	150 mg/m^2 $N = 6$[a]
Total cycles	11	33	20	45
	No. of patients	No. of patients	No. of patients	No. of patients
Neutropenia				
Grade 0	2	3	3	12
Grade 1	4	8	0	8
Grade 2	2	14	6	16
Grade 3	3	8	10	9
Grade 4	0	0	1	0
Nadir of ANC (/mm^3)				
Mean	1,789	1,021	1,055	834
SD	1,153	410	1,003	175
Median	1,534	913	745	796
Range	784–3,048	595–1,736	348–3,060	630–1,132

ANC absolute neutrophil count, *SD* standard deviation

[a] Among patients in the tolerability study of weekly nab-paclitaxel at a dose of 150 mg/m^2 for metastatic breast cancer

Table 4 Non-hematologic toxicities by dose levels (toxicities in the first cycle)

All cycles (toxicities in the first cycle)	80 mg/m^2 $N = 3$				100 mg/m^2 $N = 6$				125 mg/m^2 $N = 6$				150 mg/m^2 $N = 6$[b]			
Adverse event/grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Nausea	3 (2)				2 (1)	1			2 (1)				4 (4)			
Vomiting	1	1 (1)			1 (1)	1			1 (1)				1 (1)	1		
Myalgia					3 (2)				4 (1)				3 (4)	2 (1)		
Diarrhea	2 (1)				2 (3)	2 (1)			2 (2)	1 (1)			4 (1)	2 (2)		
Stomatitis									2 (1)				3 (1)			
Peripheral sensory neuropathy	1 (1)				4 (3)	1			4 (3)	1			(5)	2	4	
Peripheral motor neuropathy									1				3		1	
Rash	1	1 (1)			4 (2)				4 (4)				4 (2)	2 (1)		
Nail changes					4				3				2	3	1	
Edema	1 (1)				3								4		1	
Fatigue	1	1			3 (2)	2			3 (1)	1 (1)			2 (2)	2 (1)		
Elevation of liver transaminase[a]			1		2 (2)	1			4 (3)	1 (1)			4 (1)			

[a] Elevation of aspartate aminotransferase and/or alanine aminotransferase

[b] Among patients in the tolerability study of weekly nab-paclitaxel at a dose of 150 mg/m^2 for metastatic breast cancer

peripheral sensory and motor neuropathy in the third cycle. One patient at 80 mg/m^2 and three at 100 mg/m^2 experienced grade 1 peripheral sensory neuropathy in the first cycle. The median duration between the start of administration and the onset of peripheral sensory neuropathy was 28 days (range, 2–162), and these symptoms resolved at a median of 11.0 days (range, 4–42). Hypersensitivity reactions were not observed in this phase I study.

One patient at 80 mg/m^2 with cervical lymph node metastases, which was diagnosed as unknown primary, showed grade 2 dysphagia in the sixth cycle; further treatment was stopped following the patient's refusal. Treatment was discontinued in 14 of the 15 patients because of disease progression.

Tolerability study at a dose of 150 mg/m^2 for MBC

Between March 2008 and August 2009, six patients were enrolled into this tolerability study. Patients' characteristics were as follows: median age, 59 years (range, 47–71); PS (0: five patients, 1: one patient); hormone receptor-positive disease, six patients; prior anthracycline therapy, four patients; and prior radiotherapy, two patients. All patients had undergone surgical resection and received endocrine

therapy for adjuvant therapy and metastatic disease. One patient had received docetaxel in a neoadjuvant setting.

Compliance with treatment

Six patients received a median of six cycles (range, 4–19 cycles; 12–56 doses); no intolerable toxicities were observed in the first cycle. The average dose of nab-paclitaxel and the proportion of the actual dose to the planned dose (mg/m^2/week) were 82.8 ± 10.6 mg/m^2/week and 73.6 ± 9.4%, respectively. All six patients experienced at least one dose delay due to adverse events (five: sensory neuropathy; one: nausea). The reasons for discontinuation of nab-paclitaxel were as follows: one, disease progression; two, adverse events (grade 3 peripheral edema and grade 2 peripheral sensory neuropathy, respectively); and three, patient's refusal. Four of five patients undergoing efficacy evaluation showed a partial response.

Toxicities

Grade 3 neutropenia was observed in nine of 45 cycles (Table 3). Four of six patients showed grade 3 neutropenia in the first cycle. Grade 4 neutropenia or febrile neutropenia was not observed in any of the cycles. The mean nadir of ANC was 834 ± 175/mm^3. The median duration between the start of drug administration and the nadir of ANC for the first cycle was 15 days (range, 15–22). Grade 2 or higher neutropenia improved by ≥one grade within 7 days (range, 6–21). Two and four patients experienced grade 1 and 2 anemia, respectively. No thrombocytopenia was observed in any of the cycles. Grade 1 or 2 edemas and rashes were observed in all six patients, and one of them developed grade 3 edema in the fourth cycle (Table 4). One patient showed a grade 1 hypersensitivity reaction in the second cycle. Five of six patients showed grade 1 peripheral sensory neuropathy in the first cycle. In the subsequent cycles, two patients showed grade 2 peripheral sensory neuropathy and four developed grade 3 (one patient in the second cycle, two in the third cycle, and one in the fourth cycle). Five patients who showed peripheral sensory neuropathy required dose reductions (three patients: three times in six cycles, one patient: three times in four cycles, and one patient: two times in 19 cycles), and four patients also developed peripheral motor neuropathy (three patients: grade 1 in the fourth, third, and third cycle and one: grade 3 in the second cycle). These motor neuropathies manifested as weakness in both legs and improved to grade 1 or 0 within 1 to 2 weeks after interruption. Three patients showed grade 2 nail changes (onychitis), of which one developed grade 3 (nail loss) in the fifth cycle. Two patients showed ocular toxicities. One patient developed blurred vision in the sixth cycle and was diagnosed as superficial keratopathy. The grade 2 keratopathy resolved to grade 1 with ocular instillation, and this patient continued to undergo treatment with nab-paclitaxel up to 19 cycles with dose modifications due to sensory neuropathy (150 mg/m^2: four cycles, 125 mg/m^2: one, and 100 mg/m^2: 14). The other patient (57 years old, female) complained of a visual disturbance after the sixth cycle and was diagnosed with bilateral grade 3 macular hole (a small break of the level the macula). Her symptom has been relieved with vitreous surgery.

Pharmacokinetics

Blood samples for pharmacokinetic analysis were available from all of 21 patients in the first cycle. The C_{max} of paclitaxel was observed at the end of nab-paclitaxel infusion; paclitaxel in plasma subsequently decreased in a multiphasic manner (Fig. 1). The C_{max} and AUC_{inf} of paclitaxel increased according to the increasing dosage. The mean plasma half-life ranged from 23 to 26 h. Half-life and clearance were relatively similar across different dose levels. The pharmacokinetic parameters and concentration–time profile, which were obtained at doses of 80, 100, and 125 mg/m^2 in the phase I study for solid tumors, were similar between whole blood and plasma. The regression analysis suggested the dose proportionality of nab-paclitaxel within the dose range from 80 to 150 mg/m^2 (R^2 of $C_{max} = 0.5389$, $P = 0.0002$ and R^2 of $AUC_{inf} = 0.3650$, $P = 0.0037$). The %decrease in ANC in the first cycle was not correlated with AUC_{inf} and C_{max} of paclitaxel in plasma. Further, the %decrease in ANC in the first cycle was not related to the dose, the C_{max}, the AUC_{inf}, or the duration of a certain plasma concentration of paclitaxel (≥0.05 or ≥0.1 μM) (Table 5).

Discussion

In this phase I study of nab-paclitaxel with 30-min intravenous infusions weekly for 3 weeks repeated every 4 weeks among Japanese patients with prior chemotherapy, the RD was determined as 100 mg/m^2 based on DLT. In the previous study of weekly nab-paclitaxel, two of three patients at 125 mg/m^2 with heavy pretreatment experienced DLT of grade 4 neutropenia [9]. In our present phase I study, skipping the second or third weekly administration in the first cycle was one of the definitions for tolerability of weekly administration; two of the six patients at 125 mg/m^2 needed to skip the second or third weekly administration in the first cycle because of grade 3 neutropenia. Consequently, this RD was the same dose as that for the heavily pretreated patients in the previous study [9]. Among heavily pretreated patients, both hematologic and non-hematologic

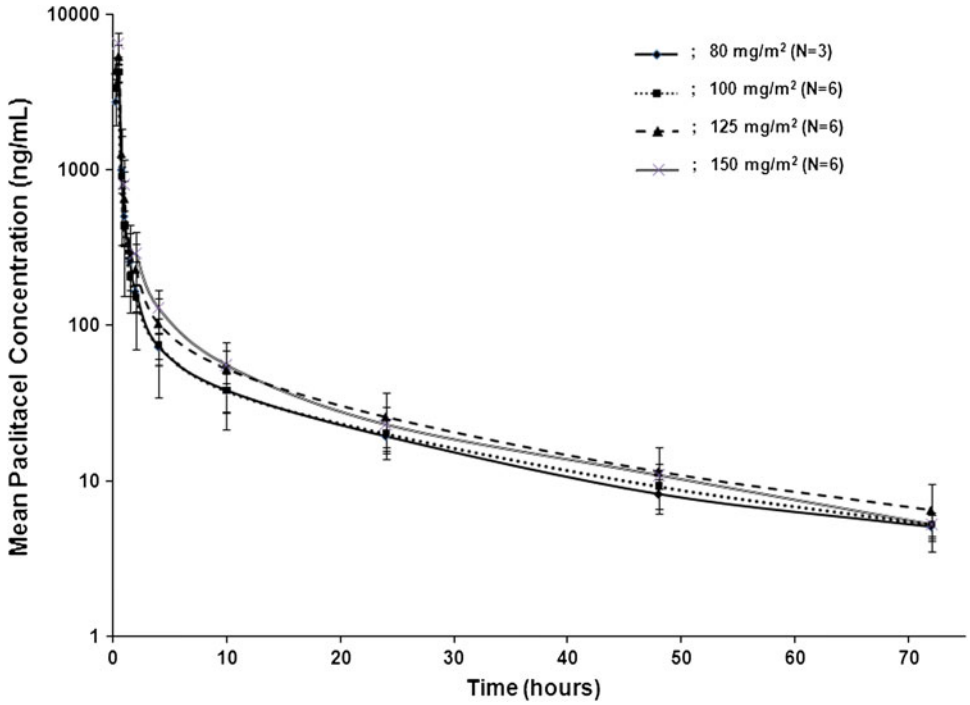

Fig. 1 Mean plasma paclitaxel concentration–time profiles. *Error bar* standard deviation

Table 5 Whole blood and plasma pharmacokinetic parameters of paclitaxel for the first cycle

Dose (mg/m^2)	C_{max} (ng/mL)		AUC_{inf} (ng h/mL)		$t_{1/2}$ (h)		CL (L/h/m^2)		Vz (L/m^2)	
	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
Whole blood										
80, $n = 3$	3,753	32.0	4,703	36.5	22.7	10.6	18.4	30.9	609	34.6
100, $n = 6$	4,567	12.3	4,944	18.2	23.4	25.0	20.8	19.6	688	21.2
125, $n = 6$	5,948	18.4	6,513	28.6	23.2	16.0	20.7	31.9	683	29.8
Plasma										
80, $n = 3$	4,217	14.1	4,006	32.4	25.2	9.1	21.3	28.0	781	32.5
100, $n = 6$	4,253	12.2	4,141	13.0	26.1	28.1	24.5	12.8	916	27.1
125, $n = 6$	5,397	18.7	5,483	31.4	24.6	17.5	24.8	32.6	893	42.8
150, $n = 6$[a]	6,512	18.0	6,316	23.1	23.2	15.1	24.6	19.3	839	32.3

CV coefficient of variation, C_{max} maximum concentration, AUC_{inf} area under the concentration–time curve up to infinity hour, $t_{1/2}$ terminal elimination half-life, *SD* standard deviation, *CL* clearance, V_Z volume of distribution based on terminal phase

[a] Among patients in the tolerability study of weekly nab-paclitaxel at a dose of 150 mg/m^2 for metastatic breast cancer

toxicities were generally mild, and 10 of 15 patients (67%) could receive at least three cycles of treatment.

The efficacy of 150 mg/m^2 weekly nab-paclitaxel as a first-line chemotherapy for MBC has been presented in the phase II study [10], which was the RD for lightly pretreated patients in the previous study [9]. Therefore, we decided to pursue a tolerability study of weekly administration at a dose of 150 mg/m^2 for MBC in a first-line setting. In this tolerability study, the ANC count was required to be ≥500/mm^3 before the second and third weekly administration to preserve dose intensity. Four of six patients developed grade 3 neutropenia in the first cycle; however, grade 4 neutropenia and febrile neutropenia were not observed. The 150 mg/m^2 dose level was well tolerated; however, four patients developed grade 3 peripheral sensory neuropathy, while five required dose reductions 14 times in all 45 cycles because of sensory neuropathy. In the previous phase II study, 74 patients received a median of 10 cycles of 150 mg/m^2 weekly nab-paclitaxel; 47% of them required at least one dose reduction (two-thirds: hematologic toxicities and one-third: grade 3 or 4 non-hematologic toxicities) [10]. If patients at 150 mg/m^2 of weekly nab-paclitaxel continue the treatment for multiple cycles, dose reduction may be required due to neuropathy.

Adverse events in our present studies comprised well-recognized events of Cremophor EL-based paclitaxel. One of 21 patients showed a grade 1 hypersensitivity reaction in this weekly administration without corticosteroid premedication in a short-duration infusion. The major hematologic toxicity was neutropenia lasting for a short duration. Stomatitis, peripheral neuropathy, nail changes, and peripheral edema appeared to be dose-related. In our present studies, peripheral sensory neuropathy had resolved within 2 weeks. In the study of triweekly 260 mg/m^2 nab-paclitaxel, grade 3 sensory neuropathy improved with interruption of treatment to grade 2 or 1 in a median of 22 days [6]. In our present studies, one of six patients at 125 mg/m^2 and four of six patients at 150 mg/m^2 showed peripheral motor neuropathy associated with sensory neuropathy. Three of six patients at 260 mg/m^2 and two of three at 300 mg/m^2 showed grade 1 or 2 motor neuropathy in the previous study of triweekly nab-paclitaxel [12]. Neutropenia and neuropathy induced by nab-paclitaxel resolved in relatively short durations; therefore, 3-week administration followed by 1 week of rest is a suitable schedule for the weekly administration. Ocular toxicities were observed in two of six patients at 150 mg/m^2 (grade 3 bilateral macular hole and grade 2 superficial keratopathy in the sixth cycle). In association with retinal lesion, cystoid macular edema, which is a condition of abnormal thickening of the retina associated with the accumulation of excess fluid, has been previously reported in patients treated with nab-paclitaxel [13, 14]. Because macular hole becomes common with age and myopia [15], it is difficult to prove a causal relationship between this adverse event and nab-paclitaxel. A previous phase I study of triweekly nab-paclitaxel reported ocular toxicity (superficial keratopathy) to be one of the DLTs [16]. In the phase II study of triweekly nab-paclitaxel at a dose of 300 mg/m^2 for MBC, 63 patients received a median of 6 cycles, with 24% experiencing dry eyes or blurred vision [17]. Photophobia and blurred vision during 3-h infusion of paclitaxel at higher doses have been reported [18]. From the findings of our present studies and the previous study [16], we consider that patients treated with 150 mg/m^2 weekly nab-paclitaxel for multiple cycles should be monitored for ophthalmologic abnormalities.

In the Japanese patients in our present studies and previous study, the paclitaxel pharmacokinetic profiles of nab-paclitaxel showed multiphasic elimination and were similar to those in Western patients reported in the previous studies [9, 12, 19]. In our present studies, the relationship between the dosage of nab-paclitaxel and AUC of paclitaxel was linear over 80–150 mg/m^2, and no dose-dependent changes in whole blood and plasma clearance were observed. The volume of distribution of plasma paclitaxel with nab-paclitaxel was relatively larger than that of Cremophor EL-based paclitaxel. Comparative studies of nab-paclitaxel (260 mg/m^2, 30-min infusion) and Cremophor EL-based paclitaxel (175 mg/m^2, 3-h infusion) have shown that paclitaxel clearance and volume of distribution were significantly higher for nab-paclitaxel than for Cremophor EL-based paclitaxel [19, 20]. In the preclinical mouse xenograft models, intratumoral concentrations of paclitaxel were higher following the administration of nab-paclitaxel compared with equal doses of Cremophor EL-based paclitaxel [5]. This accumulation of paclitaxel may be supported by increased binding to endothelial cells, increased endothelial transcytosis for nab-paclitaxel in the absence of Cremophor EL. These findings appeared to allow for greater drug distribution (volume of distribution) and to influence the higher tumor response as compared with Cremophor EL-based paclitaxel. A relationship between the time above a certain threshold concentration and %decrease in ANC was reported in a previous study of triweekly Cremophor EL-based paclitaxel [21]. In a phase I study of triweekly nab-paclitaxel, the C_{max} and AUC_{inf} were correlated with the %decrease in ANC and grade 3 non-hematologic toxicity [16]. In contrast, the %decrease in ANC was not correlated with AUC_{inf}, C_{max}, or the durations of plasma concentration of paclitaxel in our present studies. The reason for this finding may be the lower dose administered for the single treatment in the weekly schedule and the small sample size.

In conclusion, the weekly administration of nab-paclitaxel was well tolerated up to 100 mg/m^2 for heavily pretreated Japanese patients. For patients without cytotoxic therapy for metastatic disease, a dose level of 150 mg/m^2 was well tolerated; however, grade 3 sensory neuropathy and ocular toxicities were noted. Paclitaxel pharmacokinetic profiles of nab-paclitaxel were similar to those in Western patients. Monitoring for neurotoxicity and ophthalmologic abnormalities is necessary with nab-paclitaxel administration at the indicated dose levels; moreover, in multiple cycles, dose reduction may be required to resolve neuropathy at a dose level of 150 mg/m^2.

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