【 ORIGINAL ARTICLE 】

A Multicenter Study of Docetaxel at a Dose of 100 mg/m² in Japanese Patients with Advanced or Recurrent Breast Cancer

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Abstract:

Objective This study examined the pharmacokinetics, safety and anti-tumor activity of docetaxel at a dose of 100 mg/m² in Japanese patients with advanced or recurrent breast cancer.

Methods Japanese patients with advanced or recurrent breast cancer received docetaxel at a dose of 100 mg/m² intravenously every three weeks. The pharmacokinetics were assessed during the first cycle. The patients were allowed to receive supportive care drugs based on the indications and dosages in Japan.

Results Six eligible patients aged 39-65 years old and 27 treatment cycles were analyzed. All patients experienced one or more adverse events (AEs). The common AEs were neutropenia, thrombocytopenia, alopecia, rash, diarrhea, neuropathy (sensory), fatigue, nausea, fever, hypoalbuminemia, alanine transaminase (ALT) increased, constipation, and taste alteration. Grade 3 or 4 AEs included neutropenia, leukopenia, anemia, lymphopenia, decreased appetite, γ-glutamyl transpeptidase (GTP) increased, aspartate transaminase (AST) increased, ALT increased, hypertension and cellulitis which were all reversible. There were no cases of febrile neutropenia, serious AEs or deaths. The median number of cycles was six. Dose reductions were not observed and most cycles were administered at their intended doses. No complete response and three partial responses were observed in four assessable patients with evaluable lesions. The maximum concentration and area under the blood concentration-time curve were 3,417.5 ng/mL and 4.35 μg·hr/mL (mean), respectively.

Conclusion Docetaxel at a dose of 100 mg/m² was tolerable with acceptable safety profiles and effective for Japanese patients with advanced or recurrent breast cancer with appropriate supportive therapies, and pharmacokinetic (PK) profiles which corresponded approximately with the findings of previous clinical studies.

Key words: docetaxel, 100 mg/m², phase I study, advanced or recurrent cancer, Japanese

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Introduction

Docetaxel is one of the most actively used chemotherapies in breast cancer treatment. In a phase III trial comparing three doses of docetaxel 60, 75 or 100 mg/m² as a second-line treatment of advanced breast cancer, a relationship between an increasing dose of docetaxel and increased tumor response was observed across the dose range of 60 to 100 mg/m² (response rate: 22.1%, 23.3% and 36.0%, respectively) (1). In two randomized phase III studies, docetaxel 100 mg/m² was significantly superior in overall survival and time to progression compared to other chemotherapy regimens (2, 3). Docetaxel was approved in 1996 for locally advanced or metastatic breast cancer (MBC), with a dose of 60 to 100 mg/m². In contrast, the approved dose of docetaxel in Japan is up to 75 mg/m² in breast cancer due to a lack of evidence for Japanese patients. A Japanese phase I study demonstrated the pharmacokinetics, tolerability, and safety of 10-90 mg/m² docetaxel in Japanese patients, but it did not evaluate 100 mg/m² docetaxel (4).

The incidences of most hematologic and non-hematologic toxicities of docetaxel were also related to increasing the dose (1). In the previous Japanese phase II trial with 4 cycles of fluorouracil, epirubicin and cyclophosphamide followed by 4 cycles of docetaxel 100 mg/m² for breast cancer in the neoadjuvant setting, forty-two percent (19 patients) needed dose reduction or discontinuation during docetaxel treatment (5). It was thought that the cause of docetaxel of dose reduction or discontinuation may have been insufficient supportive care. Because no pharmacokinetic (PK) or safety data for 100 mg/m² docetaxel are available for Japanese patients with breast cancer with appropriate supportive care, we conducted a clinical trial to evaluate the pharmacokinetics, safety and preliminary efficacy of 100 mg/m² docetaxel in Japanese patients with advanced or relapsed breast cancer.

Materials and Methods

Eligibility criteria

The key inclusion criteria were: aged ≥20 years; histologically confirmed unresectable locally advanced or MBC that were measurable or nonmeasurable by Response Evaluation Criteria in Solid Tumors (RECIST) V1.1; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; hemoglobin level ≥8 g/dL; neutrophil count ≥1,500/μL; platelets ≥100,000/μL; aspartate aminotransferase/alanine transaminase levels ≤2.0-fold the institutional upper limit of normal (ULN); total bilirubin level ≤1.5 mg/dL; alkaline phosphatase level ≤2.5-fold the institutional ULN; creatinine level ≤1.0 mg/dL; more than 2 weeks since surgery; more than 4 weeks since chemotherapy or hormone therapy, or more than 2 weeks since radiation therapy; life expectancy of ≥3 months; a negative human epidermal growth factor 2 (HER2) status or a positive HER2 status, but unsuitable for anti-HER2 therapy; recovery of all toxicities from previous treatments to lower than grade 1 according to the Common Terminology Criteria for Adverse Events, v 4.0 (CTCAE v4); and written informed consent. The key exclusion criteria were: a history of hypersensitivity to docetaxel, alcohol, dexamethasone, or polysorbate 80; unstable or untreated central nervous system metastasis; history of other malignancy within 5 years; severe complications such as mental disease or mental manifestations, infection, disorder of heart; peripheral neuropathy greater than grade 2 according to the CTCAE v4.0; history of docetaxel treatment for advanced or recurrent breast cancer; not hospitalized for at least 15 days from start of the first course. Docetaxel was provided as an investigational drug by Sandoz. Because the investigational drug formulations in this study contained ethanol, the patients with history of alcohol allergy were excluded in this study.

Study design and endpoint

This was a non-randomized, open-label, phase I clinical study in Japanese patients with advanced or MBC. The primary endpoint was the safety of 100 mg/m² docetaxel in advanced or recurrent breast cancer patients. The secondary outcome measures include pharmacokinetic data and preliminary efficacy.

Ethical implementation

This study was conducted in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice Guidelines, and the protocol was approved by the institutional review board at each participating institution. Written informed consent was obtained from all individual participants included in the study. This study was registered with University hospital Medical Information Network. The clinical trial number is UMIN000015820.

Treatment

Docetaxel was provided as an investigational drug by Sandoz,Tokyo, Japan. Docetaxel at a dose of 100 mg/m², diluted in 250 mL physiological saline or a 5% glucose solution was administered as a one-hour intravenous infusion every three weeks until disease progression, unacceptable toxicity, the discontinuation period is longer than 14 days, or discontinuation at the request of the patient or investigator. A neutrophil count ≥1,500/μL, platelet count ≥10×10⁴/μL, creatinine level ≤1.0 mg/dL, aspartate aminotransferase/alanine transaminase levels ≤2-fold the institutional ULN, total bilirubin level ≤1.5 mg/dL, and non-hematological toxicities ≤ grade 1 were required on the day of treatment. If grade 4 febrile neutropenia, or grades 3 or 4 severe non-hematological toxicities were observed despite supportive therapies described below, the next cycle of treatment was postponed until recovery to grade 1 or baseline, and subsequent doses were reduced. Up to three dose reductions were allowed per patient from starting dose of 100 mg/m² to 75 mg/m², then to 60 mg/m², and finally to 50 mg/m². Patients

were withdrawn for grade 4 febrile neutropenia and grade 3 or 4 non hematologic toxicity despite of reduction to 50 mg/m^2. All patients were given 16 mg dexamethasone as pre-medication starting 24 hours before docetaxel infusions for 3 days. However, dexamethasone, an inducer of the CYP3A activity (6, 7), may affect the PK parameters of docetaxel and accordingly, all patients were given dexamethasone on days 3 to 5 in the first cycle only.

The following drugs and treatments that may affect the pharmacokinetics, safety and efficacy evaluation of this drug are prohibited from being used concomitantly from the time of obtaining consent to the final administration date of the study drug or the decision date of discontinuation: (1) other chemotherapy, hormone therapy, immunotherapy and surgical therapy for malignant tumors, (2) radiation therapy, (3) radiopharmaceuticals, (4) Azole antifungal agents, and (5) other unapproved drugs and all investigational drugs.

*Supportive therapies:*The concomitant use of the following drugs and therapies are permitted. (1) 5-HT3 antagonist and steroids for prophylaxis or symptomatic treatment of nausea and/or vomiting. (2) Symptomatic treatment for edema (e.g., Furosemide). (3) granulocyte-colony stimulating factor (G-CSF) administration is permitted when the investigator considers it necessary. In two phase III studies, the incidences of febrile neutropenia in patients with breast cancer receiving docetaxel at a dose of 100 mg/m^2 were 14.1 and 16.8% (3, 4). The European Organisation for Re-search and Treatment of Cancer (EORTC) and National Comprehensive Cancer Network (NCCN) guidelines recommended the prophylaxis with a G-CSF even in regimens with a febrile neutropenia incidence of 10 to <20% if the patient presents risk factors for febrile neutropenia (8, 9). Pegfilgrastim and daily G-CSF were allowed as prophylactic and therapeutic use for docetaxel-induced myelosuppression. Although pegfilgrastim has been approved and used at a fixed dose of 6.0 mg per chemotherapy cycle in many countries, the approved dose of pegfilgrastim in Japan is 3.6 mg.

Study evaluations

Radiologic tumor assessments were performed at baseline and every two treatment cycles. Tumor markers such as carcinoembryonic antigen (CEA), CA15-3, NCC-ST-439 were performed every month. Complete blood counts, hematological test chemical analysis, urinalysis were performed every week during treatment. Chest X-rays were performed at baseline and at every treatment cycle. Responses were classified according to RECIST version 1.1. Adverse events (AEs) were graded according to CTCAE version 4.0.

Pharmacokinetics

Blood samples for the pharmacokinetic analysis were obtained on days 1 to 3 of the first cycle. Two milliliters of blood were collected in heparinized tubes before drug administration, at the end of docetaxel infusion, and 0.25, 0.5, 1, 3, 5, 9, 24, and 48 hours after dosing. After centrifugation, the plasma specimens were stored at -60℃ until used

for the assays. The plasma docetaxel concentration was determined using a validated liquid chromatography-tandem mass spectrometry (lower limit of quantification, 10.0 ng/mL) at FALCO Biosystems (Kyoto, Japan). PK parameters were calculated using Phoenix WinNonlin software (version 7.0, Certara, Princeton, USA), applying a non-compartmental approach. The SAS software program (version 9.3, SAS Institute, Cary, USA) was used for the statistical analysis.

Pharmacokinetic data, maximum concentration (C_{max}), maximum drug concentration time, area under the blood concentration-time curve (AUC), elimination rate constant (kel), drug half-life (T1/2), maximum drug concentration time (Tmax), plasma clearance (CL/F), and volume of distribution /bioavailability(Vd/F) were calculated according to the blood drug concentration of each individual.

Statistical considerations

We assessed the safety, the primary endpoint, by evaluating AEs according to CTCAE v4.0. The 3+3 cohort design is the most popular method in phase I oncology trials. Because the cohort size is up to six in this design, we planned to enroll six patients in this trial. We evaluated the patients who were given 100 mg/m^2 docetaxel at least once from a group targeted for safety analysis. We estimated the incidence of AEs as two-sided 95% confidence intervals based on a binominal distribution. Efficacy was evaluated according to the objective response. The response to treatment was assessed by independent review committee according to RECIST version1.1 criteria.

Results

Patient characteristics

Seven patients were enrolled from two centers in Japan between July 2015 and February 2017. One of the patients was ineligible because of a failure to meet the criteria for prior therapy within 28 days of study entry. Six patients who received 100 mg/m^2 docetaxel in at least one cycle were assessable for safety and pharmacokinetics. Chemotherapy lines were 1st line in four patients, 2nd-line in one patient, and 3rd-line in one patient with advanced or recurrence breast cancer. The patient characteristics are shown in Table 1.

Treatment exposure

The median number of cycles was six (Table 2). The total number of administration cycles was 27. The incidence of treatment delays was low and most cycles were administered on schedule, and most delays were for nonmedical reasons. Dose reductions did not occur and most cycles were administered at their intended dose (median relative dose-intensity 100%). All six patients received 3.6 mg pegfilgrastim at the first cycle. Pegfilgrastim was administered as a prophylactic use in 21 cycles and daily G-CSF was administered as a

Table 1.   Demographics and Baseline Characteristics.

	n=6
Age, years, median (range)	55 (39-65)
Race	
Japanese	6 (100%)
Sex	
Male	0 (0%)
Female	6 (100%)
ECOG performance status, n (%)	
0	4 (67%)
1	2 (33%)
ER and PgR status, n(%)	
ER and/ or PgR positive	4 (67%)
ER and PgR negative	2 (33%)
HER2 status, n(%)	
Positive	0 (0%)
Negative	6 (100%)
Number of organs involved, n(%)	
0	4 (67%)
1	2 (33%)
Most common metastatic sites, n(%)	
Bone	3 (50%)
Liver	0 (0%)
Lung	0 (0%)
Lymph nodes	3 (50%)
Others	2 (33%)
Previous anticancer therapy for MBC, n(%)	
0	4 (67%)
1	1 (17%)
2	1 (17%)
Prior chemotherapy	
Taxanes	3 (50%)
Anthracyclines	4 (67%)
Fluoropyrimidine	3 (50%)
Prior endocrine therapy, n(%)	
Yes	4 (67%)
No	2 (33%)
Prior radiation therapy, n(%)	
Yes	3 (50%)
No	3 (50%)

ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal receptor 2; MBC: metastatic breast cancer

Table 2.   Docetaxel Administration.

	n=6
Number of cycles, median, (range)	6 (1-6)
Cumulative dose, mg/m², median, (range)	600 (100-600)
Dose reductions, cycle, n(%)	0 (0%)
Dose delays, cycle, n(%)	2 (7%)
Median relative dose-intensitiy(%)	100%

topenia (n=6), alopecia (n=5), diarrhea, neuropathy (sensory), rash (n=4), fatigue, nausea, fever, hypoalbuminemia, alanine transaminase (ALT) increased, constipation, taste alternation (n=3), decreased appetite, insomnia, conjunctivitis, uric blood, γ-glutamyl transpeptidase (GTP) increased, aspartate transaminase (AST) increased, thrombocytosis, anemia, edema, myalgia, uric sugar and leukopenia (n=2). Drug-related interstitial lung disease was not observed after three months since the last administration of docetaxel. Grade 3 or 4 non-hematological AEs included decreased appetite, γ-GTP increased, AST increased, ALT increased, hypertension, and cellulitis (n=1) and these AEs were reversible. Although fifty-percent (3 patients) experienced Grade 4 neutropenia, no febrile neutropenia was observed.

Efficacy

The best overall response was determined in four assessable patients with evaluable target lesions by independent review committee. No complete response was observed. The best tumor responses were a partial response in three patients and stable disease in one patient.

Pharmacokinetics

Blood samples for the pharmacokinetic analysis were available from all six patients who received docetaxel at a dose of 100 mg/m² at least once in the first cycle. The plasma concentration-time curves are shown in Figure. Pharmacokinetic parameters for docetaxel in plasma are shown in Table 4. C_{max} was 3,417.5±666.0 ng/mL and AUC was 4.35±1.94 μg·hr/mL(mean±SD.).

Discussion

This study assessed the pharmacokinetics, safety and preliminary efficacy of 100 mg/m² docetaxel in Japanese patients with advanced or relapsed breast cancer, which had not been previously clarified in Japanese patients.

We considered the similarity of the dose-AUC relationship between Japanese and Caucasian populations by a meta-analysis approach based on the published trial results. A linear regression model, in which AUC was set as the dependent variable and the dose (60, 75 and 100 mg/m²) as the independent variable, was applied for Caucasian (1). The ratio of (mean AUC) / (model prediction value) in each dose was in the range of 0.97 to 1.02 and very close to 1, which thus indicated a good model prediction. For Japanese, the dose of our trial was 100 mg/m² and another used four doses of 50,

therapeutic use in five cycles at the discretion of the treating physician. Five patients were withdrawn at the request of the patient, and one patient was withdrawn because of disease progression. One patient did not have hypersensitivity, but was intolerant to ethanol containing docetaxel. She withdrew consent at the first cycle on day 16.

Toxicity

No serious AEs or deaths were observed in any patients during this study. However, at least one drug-related AE was reported in each of the six patients. Fifty-percent (3 patients) had at least one ≥ grade 3 non-hematological AE. Types and incidences of AEs are listed in Table 3. Frequently occurring AEs (≥2 patients) included neutropenia and thrombocy-

Table 3. Patients with Adverse Events and Laboratory Abnormalities (≥ 2 Patients with All Grade Adverse Events and ≥1 Patient with Grade 3 or 4 Adverse Events).

|		All grade	Grade 3	Grade4
Hematological adverse events	Neutropenia	6 (100%)	2 (33%)	3 (50%)
	Thrombocytopenia	6 (100%)	0 (0%)	0 (0%)
	Thrombocytosis	2 (33%)	0 (0%)	0 (0%)
	Anemia	2 (33%)	1 (17%)	0 (0%)
	Leukopenia	2 (33%)	1 (17%)	1 (17%)
	Lymphopenia	1 (17%)	1 (17%)	0 (0%)
Non-hematological adverse events	Alopecia	5 (83%)	-	-
	Rash	4 (67%)	0 (0%)	0 (0%)
	Diarrhea	4 (67%)	0 (0%)	0 (0%)
	Neuropathy(sensory)	4 (67%)	0 (0%)	0 (0%)
	Fatigue	3 (50%)	0 (0%)	0 (0%)
	Nausea	3 (50%)	0 (0%)	0 (0%)
	Fever	3 (50%)	0 (0%)	0 (0%)
	Hypoalbuminemia	3 (50%)	0 (0%)	0 (0%)
	ALT increased	3 (50%)	1 (17%)	0 (0%)
	Constipation	3 (50%)	0 (0%)	0 (0%)
	Taste alternation	3 (50%)	0 (0%)	0 (0%)
	Decreased appetite	2 (33%)	1 (17%)	0 (0%)
	Insomnia	2 (33%)	0 (0%)	0 (0%)
	Conjunctivitis	2 (33%)	0 (0%)	0 (0%)
	Uric blood	2 (33%)	0 (0%)	0 (0%)
	γ-GTP increased	2 (33%)	1 (17%)	0 (0%)
	AST increased	2 (33%)	1 (17%)	0 (0%)
	Edema	2 (33%)	0 (0%)	0 (0%)
	Myalgia	2 (33%)	0 (0%)	0 (0%)
	Uric sugar	2 (33%)	0 (0%)	0 (0%)
	Hypertension	1 (17%)	1 (17%)	0 (0%)
	Cellulitis	1 (17%)	1 (17%)	0 (0%)

ALT: alanine transaminase, γ-GTP: γ-glutamyl transpeptidase, AST: aspartate transaminase

60, 70 and 90 mg/m^2 (4). We calculated the AUC prediction value based on the above Caucasian regression model. The ratio of (Japanese mean AUC) / (model prediction value) was in the range of 0.88 to 1.15 for each dose, and in particular, it was 0.88 in case of 100 mg/m^2 (Table 5). The prediction error was at most 15% and rather not large. The AUC sample distribution at 100 mg/m^2 dosing in Caucasian was mean: 5.00 μg·hr/mL and SD was 2.80 μg·hr/mL. In comparison, in our study the mean was: 4.35 μg·hr/mL and range: 2.52-7.72 μg·hr/mL. In other words, our AUC sample distribution was within the range of the Caucasian sample distribution. Therefore, this suggests a similar linear dose-AUC relationship for Japanese and Caucasians.

In previous Western studies, hematologic toxicity and non-hematologic toxicities such as alopecia, hypersensitivity, asthenia, fever in the absence of infection, infection, neuromotor toxicity, neurosensory toxicity, pain, pulmonary toxicity, nail disorders, peripheral edema, skin toxicity and stomatitis were related to an increased dose (1). The types of drug-related AEs observed in our study were largely consistent with the known or expected toxicity profiles of docetaxel, and the majority of events were grade 1 or 2, with a few grade 3 or 4 events, and AEs were generally manageable.

It was reported that docetaxel induced grade 3/4 neutropenia and febrile neutropenia more frequently in Asian studies compared to non-Asian studies (10). Although pegfilgrastim has been approved and used in a fixed dose of 6.0 mg per chemotherapy cycle in many countries, the approved dose of pegfilgrastim in Japan is 3.6 mg. A phase III placebo-controlled, double blind, randomized trial of pegfilgrastim 6.0 mg in patients with breast cancer who received docetaxel 100 mg/m^2 in Europe and North America demonstrated that it significantly reduces the incidence of febrile neutropenia and neutropenia-related hospitalizations and intra venous anti-infective use (11). In a randomized phase III study of pegfilgrastim 3.6 mg in Japanese patients with breast cancer who received docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every three weeks, pegfilgrastim markedly reduced the incident of febrile neutropenia and neutropenia-related hospitalizations and intra venous anti-infective use (12). Our study showed that pegfilgrastim 3.6 mg may prevent docetaxel at a dose of 100 mg/m^2 induced neutropenia in Japanese patients with breast cancer. Interstitial lung disease (ILD) is more common in Japanese patients with non-small cell lung cancer (NSCLC) during chemother-
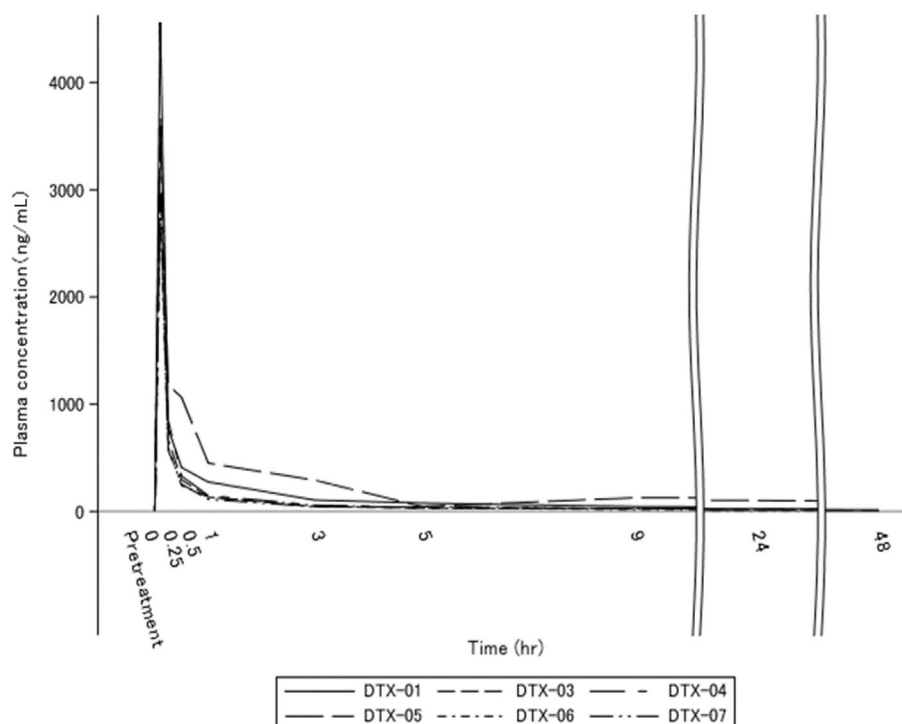
Figure.   Plasma concentration-time curves.

Table 4.   Pharmacokinetic Parameters.

	Mean	Standard deviation	Median	Maximum	Minimum
Elimination rate constant (kel) (/hr)	0.0629	0.0535	0.0470	0.1671	0.0227
Drug half-life (T1/2), (hr)	16.8	9.8	14.7	30.6	4.1
Maximum drug concentration time (T_{max}), (hr)	1	0	1	1	1
Maximum concentration (C_{max}), (ng/mL)	3,417.5	666.0	3,276.3	4,562.9	2,815.8
Volume of distribution /bioavailability(Vd/F), (mL/m^2)	214,127.1	128,430.4	195,821.1	441,146.2	68,601.5
Clearance /bioavailability (CL/F), (mL/hr/m^2)	26,320.4	9,673.9	27,522.8	39,656.8	13,013.2
AUC, (μg·hr/mL)	4.35	1.94	3.62	7.72	2.52

AUC: Area under the blood concentration-time curve

Table 5.   Meta-analysis of AUC (μg·hr/ mL).

Dose (mg/m^2)	50	60	70	75	80	90	100
AUC from linear regression model of Caucasian (A)	2.08	2.65	3.23	3.52	3.80	4.38	4.96
Caucasian mean AUC (B)		2.71		3.41			5.00
Ratio (B/A)		1.02		0.97			1.01
Japanese mean AUC (C)	2.08	2.44	3.7			4.37	4.35
Ratio (C/A)	1.00	0.92	1.15			1.00	0.88

apy than elsewhere (13-16). In a previous Western study, docetaxel-induced pulmonary toxicity was related to increased dose in breast cancer (3).

Although we performed chest X-rays at every treatment cycle, radiologic tumor assessments had to include chest CT, and medical examination or telephone survey after 3 months since the last docetaxel administration to detect ILD, no ILD was observed in this study.

Edema is well recognized as a cumulative AE of docetaxel. It can result in treatment delay or discontinuation if serious (17). Corticosteroids are generally administered to reduce incidence and delay the onset of edema (18). The administration of dexamethasone starting 24 hours before docetaxel infusions for 3 days as premedication in our study was set by referencing previous studies (3, 4). The incidence of edema was 33% in our study, compared to 45% in a pre-

vious study (3), which did not show an increasing trend. It should be noted that the dose and timing of dexamethasone in our study are different from the recommendations of the Japanese guidelines (19). Previous studies have shown that dose-dense chemotherapy could be a risk factor for pneumocystis jirovecii pneumonia (PJP) development (20-22). In the dose-dense chemotherapy regimen, these agents are administered on an every-two weeks schedule, while in the standard regimen, they are administered on an every-three-weeks schedule. Previous studies have indicated patients who developed PJP received a median steroid dose of 16.4 mg prednisone equivalents per day for 65 days (9.1 weeks) prior to PJP diagnosis. A previous case report documented that a Japanese patient who developed PJP received a median steroid dose of 11 mg prednisone equivalents per day for 65 days from the start of dose-dense chemotherapy to the diagnosis of PJP (23). In our study, the median steroid dose and the median duration of docetaxel were 15.2 mg prednisone equivalents per day and 120 days, respectively. High-dose dexamethasone may therefore be a risk of PCP, so further research is required to obtain more definitive evidence.

In a phase III trial, the median number of treatment cycles and median relative dose-intensity were six cycles and 97% for 100 mg/m^2 (3), which were similar to our study. Appropriate supportive care in this study may have contributed to management of AEs, resulting in an improved tolerability of docetaxel in Japanese patients.

We acknowledge the limitations associated with the small sample size in our study. While the anti-tumor response and safety profiles may not be concluded, our preliminary results support the potential use of docetaxel 100 mg/m^2 in Japanese patients with breast cancer. Further investigation is warranted to confirm these results.

Docetaxel at a dose of 100 mg/m^2 plays an important role in therapy for HER2 positive or negative breast cancer, and its efficacy has been proven in both the neoadjuvant (24-27) and the adjuvant setting (28, 29). Sixty-six percent of patients (4 patients) in our study received non-steroidal anti-inflammatory drugs (NSAIDs) and/or opioid due to cancer-related symptoms such as lymphangitis induced respiratory symptoms and cancer pain. Although our patients tended to be more fragile than patients with breast cancer in the neoadjuvant or the adjuvant setting, most patients in our study were able to receive docetaxel without dose reduction. It is expected that docetaxel at a dose of 100 mg/m^2 is effective in Japanese patients with breast cancer in the neoadjuvant or the adjuvant setting.

Depending on the goals of therapy and the individual characteristics of the patient, we need to continue to work towards determining the optimal dose of docetaxel.

In conclusion, docetaxel at a dose of 100 mg/m^2 showed a promising efficacy with manageable toxicities under careful observation and with appropriate supportive care in Japanese patients with advanced or recurrent breast cancer.

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