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Original article

Randomized phase II study to determine the optimal dose of 3-week cycle nab-paclitaxel in patients with metastatic breast cancer

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy is commonly observed in patients treated with nanoparticle albumin–bound paclitaxel (nab-PTX). We conducted a multicenter randomized controlled study to evaluate the optimal dose of nab-PTX.

Methods: We compared three different doses of q3w nab-PTX (Standard: 260 mg/m^2 [SD260] vs Medium: 220 mg/m^2 [MD220] vs Low: 180 mg/m^2 [LD180]) in patients with HER2-negative metastatic breast cancer (MBC). Primary endpoint was progression-free survival (PFS). Grade 3/4 neuropathy rates in the three doses were estimated using the logistic regression model. The optimal dose was selected in two steps. Initially, if the hazard ratio (HR) for PFS was <0.75 or >1.33, the inferior dose was excluded, and we proceeded with the non-inferior dose. Then, if the estimated incidence rate of grade 3/4 neurotoxicity exceeded 10%, that dose was also excluded.

Results: One hundred forty-one patients were randomly assigned to SD260 (n = 47), MD220 (n = 46), and LD180 (n = 48) groups, and their median PFS was 6.66, 7.34, and 6.82 months, respectively. The HRs were 0.73 (95% confidence interval [CI]: 0.42–1.28) in MD220 vs SD260, 0.77 (95% CI 0.47–1.28) in LD180 vs SD260, and 0.96 (95% CI 0.56–1.66) in LD180 vs MD220. SD260 was inferior to MD220 and was excluded. The estimated incidence rate of grade 3/4 neurotoxicity was 29.5% in SD260, 14.0% in MD220, and 5.9% in LD180. The final selected dose was LD180.

Abbreviations: CI, confidence interval; CIPN, chemotherapy-induced peripheral neuropathy; CR, complete remission; DCR, disease control rate; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group performance; HR, hazard ratio; MBC, metastatic breast cancer; Nab-PTX, nanoparticle albumin–bound paclitaxel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PROs/HRQoL, patient-reported outcomes/health-related quality-of-life; QoL, quality-of-life; RDI, relative dose intensity; RECIST, response evaluation criteria in solid tumors; sb-PTX, comparing solvent-based paclitaxel; TNBC, triple-negative breast cancer; TTF, time-to-treatment failure.

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Conclusions: Intravenous administration of low-dose nab-PTX at 180 mg/m^2 q3w may be the optimal therapy with meaningful efficacy and favorable toxicity in patients with MBC.

1. Introduction

The primary goal of patient care in metastatic breast cancer (MBC) is palliation and maintaining good quality-of-life (QoL) throughout the disease course, along with prolonging survival. Chemotherapy remains the mainstay of patient care, and choosing an appropriate drug and optimizing the required dose are keys to achieving this goal.

Nab-paclitaxel (nab-PTX) is an albumin-stabilized nanoparticle formulation of paclitaxel and can be administered without ethanol or steroid premedication [1]. Currently, nab-PTX is approved for treating breast, gastric, lung, and pancreatic cancers, and intravenous administration at 260 mg/m^2 every 3 weeks (q3w) is the only indication for treating breast cancer with nab-PTX in Japan, US, and EU.

A Phase III study, CA012, comparing solvent-based paclitaxel (sb-PTX) (175 mg/m^2, q3w) with nab-PTX (260 mg/m^2, q3w) was conducted in patients with MBC [2]. The overall response rates (ORR) and progression-free survival (PFS) were significantly superior in the nab-PTX arm than in the sb-PTX arm. However, chemotherapy-induced peripheral neuropathy (CIPN) at grade 3 or higher occurred more frequently in the nab-PTX arm than in the sb-PTX arm (10.5% vs 2.2%, respectively).

Another Phase III trial, CALGB 40502, compared three regimens: weekly sb-PTX (90 mg/m^2), weekly nab-PTX at 150 mg/m^2, and ixabepilone (16 mg/m^2) with bevacizumab (10 mg/kg) every 2 weeks as first-line chemotherapy for MBC [3]. Compared with sb-PTX, nab-PTX did not improve PFS in the study, and CIPN was significantly higher in the nab-PTX arm than in the sb-PTX arm (25% vs 16%).

According to the post-marketing surveillance of nab-PTX use in Japanese breast cancer patients, one-third of patients required dose reductions after receiving an initial dose [4]. Although the recommended dosage of nab-paclitaxel by the Pharmaceuticals and Medical Devices Agency, the US Food and Drug Administration, and European Medicines Agency is 260 mg/m^2 intravenously over 30 min every 3 weeks, for MBC, 27.3% of patients starting at this dose required subsequent reductions. Grade 2/3 CIPN was frequently observed (42.5% and 10.8%, respectively). Therefore, further studies are required to find the optimal dose of q3w nab-PTX in Japanese patients.

Nab-PTX promptly collapses in the blood to yield albumin-bound PTX and is efficiently delivered to tumor cells [5]. Nab-PTX is more efficient than sb-PTX even at similar doses. Several studies have demonstrated the safety and efficacy of nab-PTX q3w at reduced doses [6–8]. In a single arm Phase II trial, CA002-0LD, nab-PTX was administered at 175 mg/m^2 q3w. The resulting ORR was 39.5% and no grade 3/4 CIPN was observed [6]. Thus, the effectiveness of lower-dose nab-PTX may be similar to that of standard-dose nab-PTX. Here, we conducted a randomized Phase II study to optimize the nab-PTX dose comparing three different doses of nab-PTX (180 mg/m^2 vs 220 mg/m^2 vs 260 mg/m^2) q3w, in patients with MBC.

2. Materials and methods

2.1. Patients

Patients between 20 and 75 years of age with pathologically confirmed stage IV breast adenocarcinoma, an Eastern Cooperative Oncology Group performance status (ECOG) of 0 or 1, and up to one chemotherapy regimen for MBC were eligible for the study. If sensory neuropathy was present, it was restricted to grade 1 for inclusion. Neoadjuvant or adjuvant chemotherapy followed by one line of chemotherapy for MBC was allowed if 6 or more months had elapsed from the end of neo- or adjuvant chemotherapy to the diagnosis of recurrence. Patients were excluded if they were receiving concurrent immunotherapy or hormonal therapy for breast cancer or had parenchymal brain metastases (unless stable), a history of class II to IV congestive heart failure, or other malignancy within the last 5 years that could affect the diagnosis or assessment of breast cancer.

2.2. Study design

The study was approved by an appropriate institutional review board and all patients provided informed consent for participation. The CSPOR Data Centre confirmed patient eligibility, and treatment was assigned using a minimization method with the allocation factors for eligible patients. The allocation factors were as follows: institution, hormone sensitivity, prior chemotherapy, taxane, and disease-free interval (DFI) from surgery.

2.3. Study end points

The primary endpoint was PFS, which was defined as the time from the date of randomization to that of disease progression or death, whichever occurred first. Secondary endpoints included time-to-treatment failure (TTF), overall survival (OS), ORR, disease control rate (DCR), adverse events, and patient-reported outcomes/health-related quality-of-life (PROs/HRQoL). QoL was assessed in this trial and the results has been submitted separately to another journal.

2.4. Tumor assessments

Tumor responses were assessed every 6 weeks for the first 18 weeks and every 9 weeks thereafter (regardless of treatment schedule). Patients with measurable disease were evaluated for complete remission (CR), partial response (PR), stable disease, or progressive disease per the Response evaluation criteria in solid tumors (RECIST) guidelines.

For safety or tolerability evaluations, investigator-assessed incidence of adverse events was reported. Laboratory abnormalities and incidence of dose modifications or interruptions, with premature discontinuation of the study drug, were recorded. All toxicities were graded according to the National Cancer Institute

Common Terminology Criteria for Adverse Events (version 4.0).

2.5. Statistical methods

The purpose of the main analysis was to select the optimal dose that conferred reasonable PFS and tolerable neurotoxicity profile, from the three tested dose levels [9]. We defined the optimal dose as that where the PFS was not inferior to PFS of SD260, and where the grade 3 neurotoxicity rate was less than 10%. The selection consisted of two steps. First, pairwise comparison of PFS was conducted using three Cox regressions, each of which included two dose groups of the three tested doses. If the HR was outside the range of 0.75 and 1.33, the inferior dose group was excluded and we proceeded with the non-inferior doses. Second, we chose the greatest dose level from the dose groups whose estimated incidence probability of grade 3/4 neurotoxicity was less than 10%. The neurotoxicity probabilities in the three dose groups were estimated by the single logistic regression including the doses as a continuous variable, because the dose-dependent increase in neurotoxicity was regarded as a reasonable assumption. Regardless of the result of the first dose-selection step, the logistic regression included all dose groups to precisely estimate the dose-toxicity curve. If the estimated neurotoxicity incidence exceeded 10% at any non-inferior dose levels, we chose the lowest dose level. This design, called the selection design [9], selects the optimal dose worthy of further investigation in a subsequent phase III trial based on the HR estimates of the PFS and the estimates of neurotoxicity incidence probability of the three arms; not based on their confidence intervals. In this respect, this selection design is different from the ordinary non-inferiority and superiority trials, and the definition of non-inferiority on PFS is also different as described above.

According to the selection design, the required sample size was calculated based on the probability that the true optimal dose is correctly chosen by the above two-step procedure. The study was planned to ensure the selection of an MD220 with a probability of 70%, when the one-year PFSs of all three doses were 30% and the grade 3 neurotoxicity rates of SD260, MD220, and LD180 were 15%, 8%, and 0.1%, respectively. This required 40 patients per group with expected registration periods of two years and follow-up periods of two years. Eventually, we chose 42 patients per group. Other simulations are provided in the Supplementary Table S1.

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000012429), on November 1, 2014. The details are available at the following web address: http://www.umin.ac.jp/ctr/.

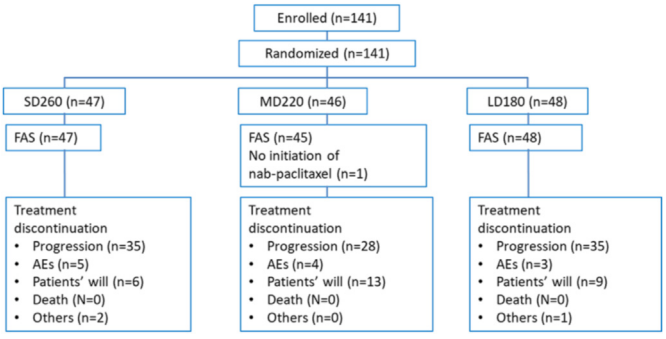

Fig. 1. Consort diagram. One hundred forty-one patients were enrolled in the study and randomized into one of three groups: SD260 or MD220 or LD180, where the subjects were treated with 260 mg/m^2 or 220 mg/m^2 or 180 mg/m^2 of nab-PTX, respectively, every 3 weeks until either disease progression or unacceptable toxicity.

3. Results

3.1. Enrolment

Between February 2015 and February 2017, 141 patients were enrolled and randomly assigned to different dose groups. One patient did not start treatment in the MD220 arm (Fig. 1). Overall, 47 patients were treated with SD260 of nab-PTX; 46, with MD220; and 48, with LD180. At the time of reporting, all patients had stopped the study therapy. The median follow-up time was 25 months.

Patient characteristics were well-balanced between the study arms except with performance status 1a, which was a little higher in LD (Table 1). Median age was 57 years. Seventy-four percent of patients had visceral metastases and an ECOG of zero; 78% had hormone receptor-positive disease; and 22% triple-negative BC (TNBC) tumors. Among treated patients, 55% had a DFI from the diagnosis of primary tumor to diagnosis of metastatic disease of more than 2 years, 26% received chemotherapy for MBC, and 38% received prior taxanes.

3.2. Dose selection

Median PFS was 6.66 (95% CI 4.82–8.82), 7.34 (95% CI 4.59–8.92), and 6.82 months (95% CI 4.43–9.15) in the SD260, MD220, and LD180 groups, respectively (Fig. 2). The HRs were 0.73

Table 1
Characteristics of patients.

	SD260 (n = 47)	MD220 (n = 45)	LD180 (n = 48)	P-value
Median age, years (range)	59.0 (36–75)	61.0 (34–74)	58.5 (35–74)	0.82
PS (ECOG)				0.22
0	38 (80.9%)	34 (75.6%)	31 (64.6%)	
1	9 (19.1%)	10 (22.2%)	17 (35.4%)	
ER-positive	38 (80.9%)	34 (75.6%)	37 (77.1%)	0.88
PgR-positive	29 (61.7%)	22 (48.9%)	27 (56.3%)	0.53
Disease-free interval				0.93
De novo	13 (27.7%)	12 (26.7%)	11 (22.9%)	
≥2 years	27 (57.4%)	24 (53.3%)	27 (56.3%)	
<2 years	13 (27.7%)	9 (20.0%)	10 (20.8%)	
Chemotherapy for MBC				0.96
Yes	12 (25.5%)	11 (24.4%)	13 (27.1%)	
No	35 (74.5%)	34 (75.6%)	35 (72.9%)	
Prior taxane therapy				0.88
Yes	19 (40.4%)	17 (37.8%)	17 (35.4%)	
No	28 (59.6%)	28 (62.2%)	31 (64.6%)	

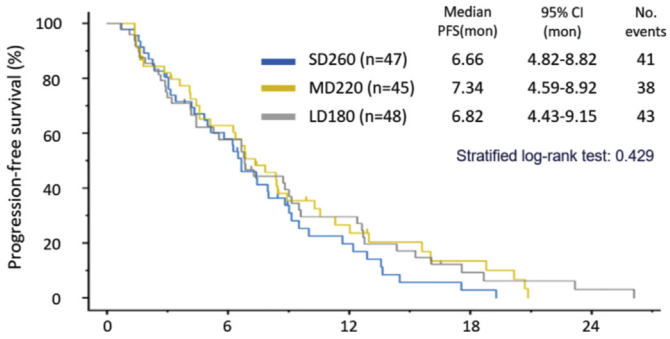

Fig. 2. Progression-free survival by treatment groups. Curves were drawn using Kaplan-Meier estimation by the assigned groups. Events were defined as disease progression or death by any causes.

(95% confidence interval [CI]: 0.42–1.28) in MD220 vs SD260, 0.77 (95% CI 0.47–1.28) in LD180 vs SD260, and 0.96 (95% CI 0.56–1.66) in LD180 vs MD220. SD260 was inferior to MD220 and was excluded (Table 2). In the second stage, the frequencies estimated by logistic regression for CIPN G3/4 were 14.0% and 5.9% for MD220 and LD180, respectively (Table 2), and MD220 exceeding 10% were excluded. Resultantly, LD180 was selected as the most optimal dose.

3.3. Efficacy

ORRs were 48.7%, 44.1%, and 37.8% in SD260, MD220, and LD180, respectively. The OS events occurred at 77/140 (55%) at the time of analysis, and the median OS was 2.1, 2.8, and 2.5 years for SD260, MD220, and LD180, respectively There were no significant differences between treatment groups. The TTFs were similar between these groups (5.31, 5.11, and 5.28 months, respectively).

3.4. Toxicity

The common adverse events were sensory neuropathy, fatigue, arthralgia, myalgia, and leukopenia (Table 3). Grade3/4 sensory neuropathy and myalgia were more commonly observed in patients who received SD260 and MD220 than in those who received LD180 (Table 3: 31.9, 8.9 vs 8.3% and 12.8, 6.7 vs 0%, respectively, Supplementary Figure S1). Notably, sensory neuropathy of grade 2 or higher was more common, and rapidly occurred in the SD260 group than in the MD220 or LD180 groups (Fig. 3).

Grade 3/4 neutropenia events were more common in SD260 or MD220 than in LD180 groups (Table 3: 25.4, 37.7 vs 14.7%, respectively). The dose reduction rate during treatment was significantly higher in SD260 group than in the other groups (Table 4).

3.5. Relative dose intensity (RDI)

The RDI in each group to the planned SD260 regimen were 0.87, 0.77, and 0.63 in SD260, MD220, and LD180, respectively (Table 5).

4. Discussion

This is the first randomized control study that has compared the reduced doses of nab-PTX with the standard dose (260 mg/m^2) q3w, in patients with MBC, and evaluated the non-inferiority (with the intention of selecting the optimal dose) of the reduced initial doses to the standard dose, in terms of PFS and the adverse events, including CIPN. We found that LD180 was not inferior to SD260 or MD220 and selected this dose because it had less than 10% of the

Table 2
Selection of the optimal dose.

Cox regression	Hazard ratio (HR) of PFS		Selection[a]
	Estimate	95% CI	
MD220 vs SD260	0.73	(0.42, 1.28)	Drop SD260 due to HR < 0.75
LD180 vs SD260	0.77	(0.47, 1.28)	Equivalent
LD180 vs MD220	0.96	(0.56, 1.66)	Equivalent
Logistic regression	**Incidence (%) of CIPN = /> Gr3**		**Selection[b]**
	Estimate	95% CI	
SD260	29.5	(18.7, 43.2)	Not candidate for 2nd selection
MD220	14	(8.8, 21.6)	Drop MD220 due to estimated incidence rate exceeding 10%
LD180	5.9	(2.3, 14.6)	Retain LD180

CI, confidence interval.
[a] If HR<0.75 or >1.33, the inferior one was excluded.
[b] The dose with its estimated incidence rate exceeding 10% was excluded.

Table 3
Adverse events.

Events	SD260: n, (%)		MD220: n, (%)		LD180: n, (%)	
	Any Grade	≥3	Any Grade	≥3	Any Grade	≥3
No. of patients	n = 47		n = 45		n = 48	
Leukopenia	31 (66.0)	9 (19.1)	35 (77.8)	12 (26.6)	29 (60.4)	7 (14.6)
Neutropenia	27 (57.4)	12 (25.4)	33 (73.3)	17 (37.7)	24 (50.0)	7 (14.6)
Hemoglobin	27 (57.4)	1 (2.1)	22 (48.9)	1 (2.2)	28 (58.3)	2 (4.2)
ALT elevation	26 (55.3)	1 (2.1)	20 (44.4)	2 (4.4)	18 (37.5)	0 (0.0)
Fatigue	38 (80.9)	1 (2.1)	35 (77.8)	0 (0.0)	34 (70.8)	0 (0.0)
Sensory neuropathy	43 (91.5)	15 (31.9)	38 (84.4)	4 (8.9)	39 (81.3)	4 (8.3)
Arthralgia	35 (74.5)	4 (8.5)	30 (66.7)	5 (11.1)	27 (56.3)	0 (0.0)
Myalgia	34 (72.3)	6 (12.8)	26 (57.8)	3 (6.7)	19 (39.6)	0 (0.0)
Rash	16 (34.1)	0 (0.0)	14 (31.1)	0 (0.0)	12 (25.0)	0 (0.0)
Anorexia	24 (51.1)	1 (2.1)	23 (51.1)	0 (0.0)	20 (41.7)	1 (2.1)

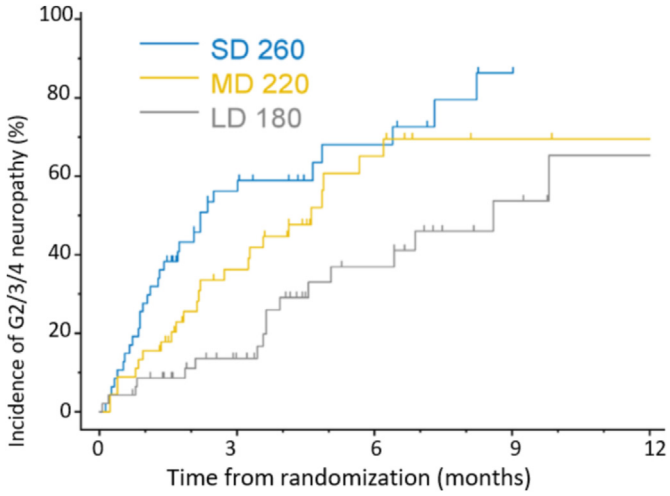

Fig. 3. Accumulated incidences of G2/3/4 neuropathy are shown by the treatment groups.

grade3/4 CIPN.

Gradishar and colleagues have reported that the administration of nab-PTX at 260 mg/m^2 q3w improved clinical outcomes, such as ORR and PFS, and had a more favorable safety profile, when compared to administration of sb-PTX at 175 mg/m^2, in previously untreated patients with MBC [2]. Nonetheless, compared to the results of the pivotal study [2], the incidence of grade 3/4 neuropathy was higher in the group with the SD260 (10.4 vs 31.9%, respectively), and the grade 3/4 myalgia was not trivial in the current study (12.8%) unlike in the pivotal study. The cause of this inconsistency between the studies, in terms of the incidence of CIPN and myalgia is not clear, but may be attributed it to the differences in ethnicity between the subjects enrolled in both studies. Another study reported that the incidence and degree of CIPN were extremely high and severe, respectively, among Japanese patients with the SD regimen (84% grade 3/4) [10]. The common and severe CIPN and myalgia requiring interruption or reduction of the dose would rationalize further modification of the SD260 regimen in Japanese patients to ensure a good QoL.

To this end, multiple studies, including the current one, have evaluated the lower dose of nab-PTX, q3w to establish modified doses that can alleviate the CIPN and myalgia [6–8]. These have reported that the regimen of 180 mg/m^2 of nab-PTX achieved 23–41% of ORRs and 23–26 weeks of PFS with 0–6% of grade3/4 CINP. Their results are consistent with those of the current study, with regard to the efficacy and toxicity of the LD180 regimen compared to the SD260 treatment, highlighting the increased tolerability of this treatment without compromising the efficacy.

Table 5
Relative dose intensity (RDI).

	n	RDI	95% CI	
LD180	48	0.63	0.61	0.65
MD220	45	0.77	0.75	0.8
SD260	46	0.87	0.84	0.91

CI, confidence interval.

Notably, the current study is the only one to randomize patients according to standard or low-dose regimens, to clarify the differences in therapeutic indices of the variable doses [6–8]. Interestingly, all three of these studies showed uncompromising PFS with the LD180 regimen, implying that the dose-PFS relationship, but not the dose-toxicity one, had plateaued at 180 mg/m^2 of nab-PTX q3w, and the therapeutic index of nab-PTX was higher than that of sb-PTX, due to its better delivery to the tumor [1]. Therefore, the LD regimen is sufficient to achieve the most efficacy.

One limitation of this study was the tri-weekly treatment schedule of nab-PTX q3w employed for patients with MBC. Previously, several studies have demonstrated that a weekly sb-PTX might be more effective and less toxic than q3w administration for early or MBC [11,12]. Seidman and colleagues also compared weekly sb-PTX (80 mg/m^2) with q3w sb-PTX (175 mg/m^2) regimens in patients with MBC and have shown that the weekly PTX was superior to q3w administration: ORR, time-to-progression, and OS [11]. Further, Sparano and colleagues enrolled 4950 patients with early breast cancer and randomized sb-PTX either q3w or every week following doxorubicin and cyclophosphamide, and found that disease-free survival and OS were significantly improved [12]. Furthermore, weekly nab-PTX was superior to the q3w regimen, in terms of efficacy and toxicity [13]. The weekly schedule of sb- or nab-PTX is more commonly used to treat patients with breast cancer, and the significance of our findings with the reduced dose of q3w nab-PTX may be limited. Nab-PTX at 100 mg/m^2 can be administered weekly to reduce the incidence and degree of myalgia. Nonetheless, it was not until recently that the weekly nab-PTX regimen was adopted in Japan to treat patients with MBC due to previous failures to demonstrate its superiority to q3w docetaxel [14]. Moreover, there must be room for less frequent and toxic regimens, especially for patients with limited access to clinics or those who may benefit from minimizing the risk of coronavirus infection during the COVID-19 pandemic.

The second limitation of the current study was that this was an exploratory trial with small sample sizes in each treatment group, and 28 patients included in the study withdrew their consent. This can have a major impact on PFS and neurotoxicity data. Neurotoxicity is cumulative, and patients who withdrew their consent would not contribute to disease events. Moreover, patients in the

Table 4
Dose reductions.

	Treatment Arm								
	SD260 (n = 47)			MD220 (n = 45)			LD180 (n = 48)		
Dose reduction	n	%	95% CI	n	%	95% CI	n	%	95% CI
Yes	19	40.4	(26.4, 55.7)	11	24.4	(12.9, 39.5)	7	14.6	(6.1, 27.8)
No. of dose reduction									
1	14	29.8	(17.3, 44.9)	8	17.8	(8, 32.1)	6	12.5	(4.7, 25.2)
2	5	10.6	(3.5, 23.1)	3	6.7	(1.4, 18.3)	1	2.1	(0.1, 11.1)
By treatment course									
By 1st course	0	0	(0, 7.5)	0	0	(0, 7.9)	0	0	(0, 7.4)
By 2nd course	3	6.4	(1.3, 17.5)	1	2.2	(0.1, 11.8)	0	0	(0, 7.4)
By 3rd course	5	8.5	(2.4, 20.4)	2	4.4	(0.5, 15.1)	0	0	(0, 7.4)

CI, confidence interval.

medium-dose arm had both the highest withdrawal rate and the best PFS results. Therefore, the results of such analysis should be interpreted with caution. Further studies are required to affirm whether all patients should receive the reduced dose of nab-PTX from the first cycle; however, a reduced-dose regimen is a treatment option without compromising efficacy before the patients experience severe toxicities, such as grade 3/4 neurotoxicity or myalgia. The reduced initial dose is endorsed by the consistent efficacy observed with favorable toxicity profiles in Japanese patients, although larger studies may be warranted to confirm these findings [7,8].

Finally, we considered only the grade of neurotoxicity to determine the optimal dose; however, the length and reversibility of neurotoxicity are the two very important parameters that should be considered to interpret the results.

5. Conclusion

Intravenous administration of low-dose nab-PTX at 180 mg/m^2 q3w may improve tolerability without compromising PFS in patients with MBC, and further evaluation is warranted to confirm these findings in a larger trial.

Author contributions

Junji Tsurutani: Data analysis and interpretation, Manuscript preparation, Manuscript editing; Fumikata Hara: Study Concepts, Data analysis and interpretation, Statistical analysis, Manuscript preparation; Masahiro Kitada: Data acquisition; Masato Takahashi: Data acquisition; Yuichiro Kikawa: Data acquisition, Statistical analysis; Hiroaki Kato: Data acquisition; Eiko Sakata: Data acquisition; Yoichi Naito: Data acquisition; Yoshie Hasegawa: Data acquisition; Tsuyoshi Saito: Quality Control of data and algorithms; Tsutomu Iwasa: Quality Control of data and algorithms; Naruto Taira: Study Concepts; Tsutomu Takashima: Manuscript review; Kosuke Kashiwabara: Study Design, Formal analysis and interpretation, Statistical analysis, Manuscript preparation; Tomohiko Aihara: Quality Control of data and algorithms; Hirofumi Mukai: Quality Control of data and algorithms

Ethics approval

This study was approved by the Institutional Review Board of Kindai University and conformed to the guidelines of the Declaration of Helsinki.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.12.002.

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