Phase I Study of Combination Therapy With Weekly Nanoparticle Albumin-bound Paclitaxel and Cyclophosphamide in Metastatic Breast Cancer Patients

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Abstract. *Background/Aim:* The objective of this phase I study was to determine the maximum-tolerated dose (MTD) and recommended dose (RD) of combination therapy with weekly nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and cyclophosphamide (CPA) in metastatic breast cancer (MBC) patients. *Patients and Methods:* Five patients who had human epidermal growth factor receptor 2 (HER2) negative MBC were recruited in this study. They received nab-paclitaxel at dose levels of 100-150 mg once a week for three weeks, repeated every 4 weeks, and CPA (600 mg/m²) administered on day 1. *Results:* No patient had grade 4 toxicity, however, two patients discontinued protocol treatment due to adverse events at level 2. Thus, the Data and Safety Monitoring Committee recommended the MTD of nab-paclitaxel and CPA to be determined at level 2. *Conclusion:* The combination therapy with weekly nab-paclitaxel and CPA was tolerable, and the RD for these drugs for MBC were 100 and 600 mg/m², respectively.

In Japan, the incidence and mortality rate of patients with breast cancer are increasing (1); effective treatments after recurrence of breast cancer are thus necessary not only to prolong prognosis, but also to improve or maintain the quality of life of patients. Anthracycline- and taxane-containing regimens are the gold standard treatments for breast cancer and are globally administered. Fujii and colleagues have reported that sequential doxorubicin and CPA followed by a taxane (AC-T) might yield longer overall

survival than AC or CPA, methotrexate, and 5-fluorouracil (CMF), in a meta-analysis (2). Anthracycline-containing regimens play a key role in both neoadjuvant and adjuvant chemotherapy, although they tend to induce cardiotoxicity as the total cumulative anthracycline dose increases, and are therefore associated with a risk of congestive heart failure (3). Thus, alternatives to anthracycline-containing regimens have been developed. In particular, the combination of docetaxel and CPA (TC) has become an important adjuvant therapy regimen for patients with breast cancer. Compared to the standard combination of doxorubicin and CPA (AC), disease-free survival (81% vs. 75%, $p=0.033$, respectively) and overall survival (87% vs. 82%, $p=0.033$, respectively) rates at 7 years following initiation of TC are significantly better (4). However, febrile neutropenia occurred more frequently in patients receiving TC than in patients treated with AC (5% vs. 2.5%, respectively; $p=0.07$). Furthermore, Takabatake *et al.* have reported that the TC regimen can be safely administered in a feasibility study of Japanese women with breast cancer (5). In their study, grade 4 neutropenia occurred in 71.4% of patients and febrile neutropenia occurred in 28.3%, while grade ≥ 1 fatigue and rash occurred in 79.2% and 54% of patients, respectively.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a human albumin-bound formulation of paclitaxel that does not contain absolute ethanol or any solubilizing agents has shown good response and safety profile for patients with solid tumor including MBC (6). Solvent-based paclitaxel is considered a standard of care for the treatment of MBC and is administered as adjuvant chemotherapy for patients with early-stage disease. It contains a combination of polyethylated castor oil (Cremophor EL; BASF, Ludwigshafen, Germany) and ethanol as the vehicle. Nab-paclitaxel was developed to avoid hypersensitivity without premedication and permit safe infusion and achieve better delivery of the drug to the tumor microenvironment. In the CA024 randomized Phase II trial, the patients were randomly assigned to docetaxel or nab-

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Table I. Therapeutic regimen and dose level.

Level	Nab-paclitaxel	Cyclophosphamide
	Day 1, 8, 15	Day 1
1	100 mg/m ²	600 mg/m ²
2	125 mg/m ²	600 mg/m ²
3	150 mg/m ²	600 mg/m ²

Nab-paclitaxel and CPA combination regimens. Nab-paclitaxel was administered on days 1, 8, and 15 and CPA was administered on day 1. The regimen was repeated every 3 weeks.

paclitaxel, and prolonged progression-free survival in patients with MBC compared to docetaxel. The results showed that 100 or 150 mg/m² every week (qw) may represent the effective dosing of nab-paclitaxel for MBC patients, rather than the dose of 300 mg/m² qw (7). The most efficacious dose of nab-paclitaxel has been shown to be a weekly regimen of 100 or 150 mg/m² for patients with MBC who have not received previous chemotherapy.

The aforementioned data indicate that, although the efficacy of TC regimen was established, neutropenia was frequently observed in Japanese breast cancer patients and could be likely to decrease their quality of lives. Therefore, instead of the TC regimen, we selected nab-paclitaxel that seems likely to be equivalent or more effective for breast cancer and to relieve adverse events of breast cancer patients, compared to docetaxel. Herein we report the results of a phase I study to determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT) and recommended dose (RD) of combination therapy with weekly nab-paclitaxel and CPA in MBC patients.

Patients and Methods

Patient eligibility. The eligibility criteria were female patients age 20-75 years with invasive, metastatic or recurrent, pathologically-confirmed adenocarcinoma of the breast that was human epidermal growth factor receptor type 2 (HER2)-negative by immunohistochemistry or *in situ* hybridization, regardless of hormone receptor status, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1, and at least one measurable lesion. Laboratory value requirements included normal renal function (serum creatinine, ≤ 1.2 g/dl), normal hepatic function (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), <100 IU/l and total bilirubin, ≤ 1.5 mg/dl) and normal hematologic function (white blood cells, $\geq 4,000/\text{mm}^3$; neutrophils, $\geq 2,000/\text{mm}^3$; platelets, $\geq 100,000/\text{mm}^3$; and hemoglobin, ≥ 9.0 g/dl). Patients who had received adjuvant paclitaxel or docetaxel were included, if 6 months had passed since completion of that therapy. Patients were excluded if they had severe complications in other organs, had undergone any surgery within 4 weeks prior to enrollment, had received more than two regimens for MBC, had received first-line paclitaxel or docetaxel or nab-paclitaxel for MBC, or had grade ≤ 2 sensory neuropathy. Inclusion was not dependent on the presence or absence of measurable lesions.

Table II. Patient characteristics.

	Level 1 n=3	Level 2 n=2	Total n=5
Median age	60	47	56
ECOG performance status 0	3	2	5
Estrogen receptor positive and HER2 negative	3	2	5
Metastatic site			
Liver	2	2	4
Lung	3	0	3
Bone	2	1	3
Lymph node	3	1	4
Adjuvant therapy			
Endocrine	2	1	1
Chemotherapy	0	1	1
Prior endocrine therapy for MBC	1	1	2

Study design. This phase I, dose-finding study was approved by the Institutional Review Board at Mitsui Memorial Hospital and registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN 000010945). All patients provided written informed consent.

Three escalating dose levels of nab-paclitaxel and CPA were planned. The dose of CPA was fixed at 600 mg/m². Nab-paclitaxel was increased from 100 mg/m² (level 1) to 125 mg/m² (level 2) and then to 150 mg/m² (level 3). Nab-paclitaxel was administered on days 1, 8 and 15 of each 21-day cycle, and CPA was administered on day 1. The dosage schedule at each dose level is shown in Table I.

Nab-paclitaxel was dissolved in physiological saline (100 mg/20 ml) and was intravenously infused into each patient over 30 min. CPA was dissolved in 500 mL physiological saline and was infused intravenously for 90 min.

On days 8 and 15 of each cycle, the full doses were administered if the following criteria were met: white blood cells, $\geq 3,000/\text{mm}^3$; neutrophils, $\geq 1,500/\text{mm}^3$; platelets, $\geq 75,000/\text{mm}^3$; hemoglobin, ≥ 9.0 g/dl; temperature, $<38^\circ\text{C}$; non-hematologic toxicity, grade ≤ 2 ; AST, <100 IU/l; ALT, <100 IU/l; total bilirubin, ≤ 1.5 mg/dl; and serum creatinine, ≤ 1.2 g/dl.

Dose levels were assigned at recruitment, and no dose escalation was allowed within the same patient. The protocol stipulated that at least 3 patients should be treated at each dose level.

Three patients were accrued at the starting dose of 100 mg/m² nab-paclitaxel. If no DLTs occurred in the first 3 patients, then the patients were entered into the next dose level. The present phase I study only enabled a shift to the next level when the incidence of DLTs was $\leq 33\%$. The MTD was defined as the dose level at which 2 out of 3-6 patients developed a DLT.

DLTs. DLTs were defined as any of the following drug-related events occurring in the first cycle: grade 4 neutropenia (neutrophils, $<500/\text{mm}^3$); grade 3 or 4 febrile neutropenia; grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring blood transfusion; grade 3 or 4 non-hematological toxicity; and other adverse events that led to discontinuation for at least 2 consecutive weeks.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria ver.4.

Table III. Adverse events during the first course of therapy.

	Level 1 (n=3)			Level 2 (n=2)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Febrile neutropenia	-	-	0	-	-	0
Neutropenia	0	1	1	0	0	1*
Leukopenia	0	2	0	0	1	0
Anemia	1	0	0	0	1*	0
Thrombocytopenia	0	0	0	0	0	0
Malaise	1	0	-	2	0	-
Nausea	1	0	0	2	0	0
Vomiting	1	0	0	0	0	0
Skin toxicity	2	0	0	0	0	0
Neurosensory toxicity	1	0	0	0	0	0
Dysgeusia	1	1	-	1	0	-
Myalgia	1	0	0	2	0	0
Constipation	1	0	0	1	0	0

*Dose-limiting toxicity.

Definition of MTD and RD. Based on the occurrence of DLTs during cycle 1 of the protocol regimen, the MTD and RD were determined. In principle, the RD was determined as the dose one level lower than the MTD. However, considering the treatment continuation rate of patients in cycle 2 or thereafter, the RD of nab-paclitaxel and CPA was to be determined through a discussion with the Data and Safety Monitoring Committee.

Ethical approval. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent. Informed consent was obtained from all individual participants included in the study.

Results

Patients. Five patients were enrolled from April 2013 to March 2015; three patients were evaluated at level 1 and two patients at level 2. Patient characteristics are listed in Table II. All estrogen receptor-positive and HER2-negative breast cancer, the median age of 55 years (range=44-67 years) and ECOG PS was 0. Distant metastases occurred in all patients; metastatic sites included the liver (n=4), bone (n=3), lung (n=3), and lymph node (n=4). Two patients had not previously undergone surgery due to the presence of distant metastasis at initial diagnosis. One patient was treated with adjuvant chemotherapy. However, two patients were treated with endocrine therapy for metastasis and no patient received chemotherapy for metastasis prior to enrollment.

MTD and DLT. No patients developed DLTs during the first cycle of level 1 at nab-paclitaxel dose of 100 mg/m². However, DLTs occurred in two patients during level 2 at nab-paclitaxel dose of 125 mg/m².

They could not receive protocol treatment due to adverse events; one patient developed grade 2 anemia, and the other patient developed grade 3 neutropenia. No patient had grade 4 toxicities. However, the Data and Safety Monitoring Committee recommend the MTD of nab-paclitaxel and CPA to be determined at level 2. Therefore, the MTD of combination therapy with nab-paclitaxel and CPA was 125 mg/m² and 600 mg/m². The RD of nab-paclitaxel was identified to be the dose at level 1 (100 mg/m²).

Hematologic adverse events. Hematologic adverse events during the first course of therapy are shown in Table III. Febrile neutropenia was not observed at any level. At level 1, one patient developed grade 3 neutropenia, and almost all hematological adverse events could be tolerated. At level 2, grade 3 neutropenia and grade 2 anemia that resulted in discontinuation of nab-paclitaxel 125 mg/m² for 2 consecutive weeks were observed.

Non-hematological adverse events. Non-hematological adverse events during the first course of therapy are shown in Table III. No patient experienced grade 3 non-hematological adverse events at any dose of nab-paclitaxel. Grade 2 alopecia and dysgeusia were observed in one patient each.

Efficacy and time to treatment failure. Treatment appeared to be effective in all patients who received the level 1 dose for >6 months. Complete response and progressive disease were not observed, while partial response was observed in two patients and long-term stable disease was observed in three patients.

Discussion

This study demonstrated that combination of nab-paclitaxel and CPA can be safely administered to patients with MBC. Neutropenia and anemia were identified as the DLTs for nab-paclitaxel 125 mg/m² given weekly and CPA 600 mg/m² given every 3 weeks. The MTD was determined to be nab-paclitaxel 125 mg/m² and the RD was determined to be nab-paclitaxel 100mg/m² and CPA 600 mg/m².

A phase III trial that compared docetaxel 100 mg/m² to paclitaxel 175 mg/m² every 3 weeks in MBC demonstrated that docetaxel was superior to paclitaxel with respect to overall survival, time to progression, and overall response rate (8). However, hematologic and non-hematological adverse events were more frequently observed in patients who received docetaxel than in those treated with paclitaxel; febrile neutropenia (14.9% and 1.8%, $p<0.001$, respectively) and skin disorders (37.4% and 14.4%, $p<0.001$, respectively) occurred more frequently in the docetaxel group (8). In a study of Japanese breast cancer patients who received adjuvant TC, febrile neutropenia and skin rash were also frequently observed (28.3% and 54.7%, respectively) (5). These results suggest that the docetaxel every-3-weeks regimen is more likely to induce neutropenia and skin disorders than paclitaxel; therefore, weekly nab-paclitaxel might be considered to be safer and more tolerable. Patients who received weekly nab-paclitaxel treatment are more likely to develop sensory neuropathy than those treated with docetaxel (9); however, prolonged weekly nab-paclitaxel administration does not worsen quality of life scores for sensory neuropathy (10).

Tanaka *et al.* have reported on 44 patients with HER2-positive breast cancer who were treated with an every-3-weeks anthracycline-based regimen followed by nab-paclitaxel 260 mg/m² plus trastuzumab every-3-weeks for four cycles as neoadjuvant therapy. In that study, the pathological complete response rate (defined as no histological evidence of residual invasive tumor cells in the breast and axillary lymph nodes) was 49% and the regimen was shown to be safe and tolerable, although 1 patient required a dose reduction due to peripheral neuropathy associated with nab-paclitaxel (11). Yardly and colleagues have described 8 patients with MBC who received nab-paclitaxel/CPA combined with trastuzumab and developed no severe adverse events (12). Mirtsching *et al.* have also demonstrated the efficacy and safety of weekly nab-paclitaxel and trastuzumab as first-line chemotherapy in 22 patients with HER2-positive MBC; the overall response rate was 52.4% and therapy was tolerated (13). A phase II study of 60 metastatic HER2-positive breast cancer patients, combination of nab-paclitaxel (100 mg/m² on days 1, 8, and 15 of each cycle) every 28 days and lapatinib (1,000 mg once daily on a continuous basis) has revealed an objective

response rate of 53%, with tolerable adverse events (14). Further studies of nab-paclitaxel plus CPA combined with targeted therapy are required to evaluate the efficacy and safety of these regimens in patients with HER2-positive breast cancer.

Several studies evaluating the efficacy and safety of combination therapy with nab-paclitaxel and other agents as first-line treatment for MBC patients have been published. A phase II trial of HER2-negative MBC patients treated with combination of weekly nab-paclitaxel (125 mg/m² on days 1 and 8 of each cycle) and capecitabine (825 mg/m² twice daily for 14 days) every 3 weeks resulted in an objective response rate of 61% and median progression-free survival of 10.6 months (15). Roy and colleagues have reported a response rate of 50% and median progression-free survival of 7.9 months in a phase II study of weekly nab-paclitaxel (125 mg/m²) and gemcitabine (1,000 mg/m²) on days 1 and 8 of each 3-week cycle in previously untreated MBC patients (16).

In neoadjuvant setting, Untch *et al.* compared pathological complete response rate between weekly nab-paclitaxel and solvent-based paclitaxel, it resulted that pCR occurred more frequently in the nab-paclitaxel group than in the solvent-based paclitaxel group (38% vs. 29%, $p<0.00065$) (17). In particular, triple negative breast cancer patients given nab-paclitaxel were more likely to achieve pCR compared to given solvent-based paclitaxel (48% vs. 26%, $p<0.00027$).

Based on these results and to further evaluate the tolerability and efficacy of the RD in the present phase I trial (nab-paclitaxel 100 mg/m² on days 1, 8, and 15 and CPA 600 mg on day 1), we plan to initiate phase II study of the regimen as neoadjuvant therapy.

In conclusion, combination therapy with nab-paclitaxel and CPA resulted in DLTs in 2 patients at level 2 (nab-paclitaxel 125 mg/m²). One patient developed grade 2 anemia, and another patient developed grade 3 neutropenia. These patients withdrew from the treatment protocol due to adverse events. The RD of combination therapy with weekly nab-paclitaxel and CPA was 100 and 600 mg/m², respectively.

Conflicts of Interest

This manuscript has not been published and is not under consideration for publication elsewhere. All the Authors have read the manuscript and have approved this submission. The Authors report no conflicts of interest.

Author's Contributions

Daisuke Ota: Corresponding author, creating the study protocol, recruitment of patients, and writing the manuscript. Sotaro Akatsuka, Tsunehiro Nishi, Takao Kato, Masashi Takeuchi, Munechika Tsuji, and Atsushi Fukuuchi: Recruitment of patients and review of the manuscript.

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