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A Real-World Retrospective Cohort Study of Combined Therapy with Bevacizumab and Paclitaxel in Japanese Patients with Metastatic Breast Cancer

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Objective: Combined therapy with bevacizumab and paclitaxel (BP regimen) as a first-line treatment has proven highly effective with good tolerance for patients with metastatic breast cancer (MBC). The objective of this study was to examine the efficacy and safety of the BP regimen for Japanese patients with MBC in real-world clinical settings.

Methods: From June 2012 through May 2014, we recruited 94 patients at 10 medical institutions. The primary endpoint was time to treatment failure (TTF), and the secondary endpoints were overall survival (OS) and safety. Objective response was assessed according to the Response Evaluation Criteria in Solid Tumors. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0-Japan Clinical Oncology Group.

Results: Nighty patients with MBC (mean 58 years, range: 34–80 years) were enrolled, and 60 (66.6%) and 52 (57.7%) had undergone prior chemotherapy as adjuvant treatment and treatment for MBC, respectively. Median TTF was 6.2 months (95% confidence interval [CI], 4.2–8.3 months), and median OS was 15.4 months (95% CI, 12.0–18.9 months). The overall response rate was 67.8% (95% CI: 57.1–77.2%). A total of 28 patients (31.1%) required a dose reduction of paclitaxel. Forty-five, 42, and 3 patients received the initial doses of 90, 80, and 60 mg/m^2, respectively. Among patients who received the initial doses of 90 mg/m^2, 13 patients (28.9%) unexpectedly required a dose reduction of ≥20 mg/m^2. The BP regimen was discontinued for 66 (73.3%) of the 90 patients, 52 (57.7%) of whom experienced "disease progression." Grade 3/4 hematologic AEs developed in 51 patients (56.6%), with leukopenia and neutropenia in 16 patients (17.8%) and 21 patients (23.3%), respectively. Grade 3 nonhematologic AEs developed in 8 patients (8.9%), with the most common nonhematologic AE of peripheral neuropathy in 4 patients (4.4%). No Grade 4 nonhematologic AEs developed. Peripheral neuropathy [56 patients (62.2%)], nail discoloration [53 patients (58.9%)], and fatigue [51 patients (56.7%)] were the most predominant AEs—the known AEs of paclitaxel.

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Conclusions: The BP regimen was active and well tolerated in the real-world clinical settings. As many as 28.9% of patients who received the initial dose of 90 mg/m^2 required a dose reduction of paclitaxel by 20 mg/m^2. Therefore, there is a need to find a therapeutic regimen that is less likely to result in dose reductions for patients with MBC who undergo a BP regimen using the initial paclitaxel dose of 90 mg/m^2. (J Nippon Med Sch 2017; 84: 215–223)

Key words: metastatic breast cancer, bevacizumab, paclitaxel, combined therapy, cohort study

Introduction

Metastatic breast cancer (MBC) is generally incurable and few patients with such tumors achieve long-term disease-free survival[1]. Nevertheless, efforts have been made to improve their clinical outcomes by implementing diversified chemotherapy regimens. In an open-label, randomized Phase 3 clinical trial for patients with MBC[2], combined chemotherapy with a humanized monoclonal antibody directed against all isomers of the vascular endothelial growth factor-A—bevacizumab and the diterpenoid compound—paclitaxel was conducted as first-line treatment. The therapy significantly prolonged progression-free survival (PFS) when compared with paclitaxel alone (median, 11.8 months versus 5.9 months), but overall survival (OS) was comparable for the two arms. In a randomized Phase 3 clinical study in patients with locally recurrent or metastatic breast cancer[3], first-line treatment was conducted that used bevacizumab in combination with paclitaxel 90 mg/m^2, nab-paclitaxel 150 mg/m^2, or ixabepilone 16 mg/m^2. Median PFS for paclitaxel, nab-paclitaxel, and ixabepilone were 11.0, 9.3, and 7.4 months, respectively. Furthermore, combined therapy with bevacizumab and weekly treatment with paclitaxel in the United States[4] prolonged median PFS compared with paclitaxel alone (11.3 months versus 5.8 months). A first-line Phase 2 clinical study in Japanese patients with MBC[5] yielded a median PFS of 12.9 months. Thus, combined chemotherapy with bevacizumab and paclitaxel as first-line treatment has shown efficacy for these patient populations. To date, however, limited clinical evidence has been obtained for combined chemotherapy with bevacizumab and paclitaxel (BP regimen) in patients with MBC.

In the clinical settings, complete healing is difficult to obtain for MBC because 10-year survival is 10 to 20% after relapse and only 2% of all survivors experience complete healing[6,7]. These facts drive patients with MBC to seek treatment for the extension of their survival and the improvement in their quality of life through symptom palliation. Pharmacotherapy is the core therapeutic modality for these patients, and therapeutic strategies are determined based on organs of metastasis, status of HER2 expression, disease-free interval, age, state of menopause, and other factors. Hortobagyi[8] proposed a therapeutic algorithm as the fundamental concept of current pharmacotherapy—the initiation of hormone therapy, followed by chemotherapy if the patient becomes unresponsive to hormone therapy. Current guidelines follow this therapeutic algorithm[9].

In our previous clinical study of paclitaxel that was administered weekly at a dose of 80 mg/m^2 for Japanese patients with MBC[10], the drug was effective and well tolerated in the study population, with an overall response rate (ORR) of 40.5%, a median time to progression of 4.8 months, and a median OS of 15.8 months. Thus, a clinical study on combined therapy containing paclitaxel was warranted.

Patients and Methods

Patient Eligibility

Patients were eligible if they had histologically confirmed MBC, were 20 years of age or older at time of recruitment, and had not received, were receiving, or received bevacizumab/paclitaxel. Patients gave written informed consent when required by the medical institution's rules. The presence of measurable lesions was not required for eligibility in this study.

Patients were excluded if they had a history of hypersensitivity to bevacizumab/paclitaxel or were pregnant, lactating, or of childbearing age. Patients were also excluded if they were receiving antithrombotic drugs for thrombosis, required antiplatelet drugs (aspirin ≥325 mg/day or nonsteroidal anti-inflammatory drugs) for chronic inflammatory diseases (e.g., rheumatoid arthritis), had bleeding diathesis, coagulopathy, or coagulation factor disorders. Patients were also excluded if they had uncontrolled peptic ulcer or hypertension, were complicated by, or had a history of gastrointestinal perforation within 1 year before recruitment, acquired nephropathy or had had proteinuria (≥2+) within 2 weeks before recruitment, had symptomatic or treatment-requiring heart disease at the time of recruitment, or a history of myocardial infarc-

tion within 1 year before recruitment, or were otherwise considered by the attending physician as ineligible for the present study. The study protocol was approved by the Institutional or Central Ethics Committee.

Study Design and Treatment Plan

We conducted the present cohort study under real-world clinical settings in Japanese patients with MBC. Patients underwent standard premedication and a BP regimen that consisted of bevacizumab 10 mg/kg administered intravenously on days 1 and 15 of each cycle, in combination with paclitaxel 60 to 90 mg/m^2 administered intravenously on days 1, 8, and 15 every 28-day cycle. The dose of paclitaxel was transiently reduced when any toxic effects occurred. Patients continued the treatment until the occurrence of disease progression, unacceptable toxicities, drug withdrawal, or at the request of the patient, or physician. The study was registered at University Hospital Medical Information Network (UMIN number: 000009090).

Primary and Secondary Endpoints

The primary endpoint was time to treatment failure (TTF), defined as the interval between the onset of study therapy and the termination of the therapy for any reason, death due to primary disease, or all-cause mortality. For patients who had measurable lesions, disease status was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST)[11] at baseline and every 8 to 12 weeks there after until disease progression. Tumor imaging was repeated every 2 to 3 cycles. In patients who had no measurable lesions, disease progression was defined as the development of new lesions or "unequivocal progression" of existing lesions. The secondary endpoints were OS and safety in OS, defined as the interval between the onset of study therapy and death, and the event as all-cause mortality. Clinical status was assessed and laboratory tests (hematology, blood chemistry, and urinalysis) were conducted before each cycle. Safety was evaluated for hypertension, proteinuria, and oral bleeding after the onset of combined therapy. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Japanese version 4.0-Japan Clinical Oncology Group[12].

Response Criteria

Response to therapy as defined in RECIST was assessed as follows: complete response (CR)—the evanescence of all target lesions; partial response (PR)—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease (PD)—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD)—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started; and not evaluable (NE).

Statistical Analyses

All eligible patients in the efficacy and safety analysis sets were subject to statistical analyses. Categorical variables were given as incidences and proportions, and continuous variables, as fundamental statistics. TTF and OS distributions were estimated according to the Kaplan-Meier method. The study design required the enrollment of 66 patients at an α error of 0.05 (one-tailed) and a power of 80% when setting the median values of 4.0 and 5.6 months for threshold TTF and expected TTF, respectively, and when based on the enrollment and follow-up periods of 2 and 3 years, respectively. All statistical analyses were made using SPSS version 19 (IBM, Armonk, NY).

Results

Patient Population

From June 2012 through May 2014, 94 patients were recruited at 10 medical institutions of the Saitama Breast Cancer Clinical Study Group (SBCCSG)—90 of whom were enrolled in the study after the exclusion of 4 patients because of paclitaxel's initial dose of <60 mg/m^2. Baseline demographic and clinical characteristics of patients are shown in **Table 1**. Median age was 58 years (range, 34–80 years). Sixty patients (66.6%) and 52 patients (57.7%) had undergone prior chemotherapy as adjuvant treatment and treatment for MBC, respectively. In addition, 49 patients (54.4%) had undergone anthracycline-inclusive chemotherapy, and 28 patients (31.1%), in the adjuvant setting. Ninety patients were evaluated for efficacy and safety. The majority (81.1%) of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Most (>75%) patients had undergone two or less cycles of prior hormone therapy or chemotherapy. The median number of cycles delivered was 5 (range, 1–21). The median duration of follow-up for all surviving patients was 10.3 months, with a maximum of 27.3 months. The numbers of patients with estrogen receptor-positive, progesterone receptor-positive, human epithelial growth factor receptor 2 (HER2)-

Table 1 Baseline demographic and clinical characteristics of patients

Characteristics	N=90
Age, years	
Median	58
Range	34–80
Menopausal status, n (%)	
Premenopausal	28 (31.1)
Postmenopausal	62 (68.9)
ECOG performance status, n (%)	
0	46 (51.1)
1	27 (30.0)
2	16 (17.8)
3	0 (0.0)
4	1 (1.1)
Clinical presentation, n (%)	
Advanced	5 (5.6)
Relapsed	85 (94.4)
Histology, n (%)	
Invasive ductal carcinoma	81 (90.0)
Special type	7 (7.8)
Unknown	2 (2.2)
Number of regimens of hormone therapy/prior chemotherapy, n (%)	
0	45 (50.0)/36 (40.0)
1	15 (16.7)/17 (18.9)
2	12 (13.3)/17 (18.9)
3	13 (14.4)/4 (4.4)
4	2 (2.2)/8 (8.9)
5	2 (2.2)/2 (2.2)
≥6	0 (0.0)/5 (5.6)
Unknown	1 (1.1)/1 (1.1)
Hormone receptor status, n	
ER-positive/-negative/unknown	58/31/1
PR-positive/-negative/unknown	42/47/1
HER2-positive/-negative/unknown	6/75/9
Triple-negative/unknown	25/2
Treatment with chemotherapeutic agents, n	
Paclitaxel, postsurgery/progression or relapse/absence/unknown	9/20/59/2
Docetaxel, postsurgery/progression or relapse/absence/unknown	23/11/54/2
Anthracyclines, postsurgery/progression or relapse/absence/unknown	28/21/39/2
Number of metastasis organs, n (%)	
<3	50 (55.6)
≥3	40 (44.4)
Bone modifiers, n (%)	
Zolendronic acid	31 (34.4)
Denosumab	7 (7.8)

ECOG, Eastern Cancer Oncology Group; ER, estrogen receptor; PR, progesterone receptor; HER2, human epithelial growth factor receptor 2

negative, and triple-negative breast cancer were 58, 42, 74, and 25 patients, respectively.

Treatment Exposure

Twenty-four patients remained on therapy at the data cutoff date of April 30, 2014. Median cumulative exposures to bevacizumab and paclitaxel for the 90 patients were 100 mg/kg (range, 10–420 mg/kg) and 1,040 mg/m^2 (range, 80–5,550 mg/m^2), respectively.

Efficacy

Median TTF was 6.2 months (95% CI, 4.2–8.3 months) (**Fig. 1**, Panel A), and median OS was 15.4 months (95% CI, 12.0–18.9 months) (**Fig. 1**, Panel B). Best overall response is shown in **Table 2**. The median duration of response for 61 responders was 6.2 months (range, 2.0–24.8

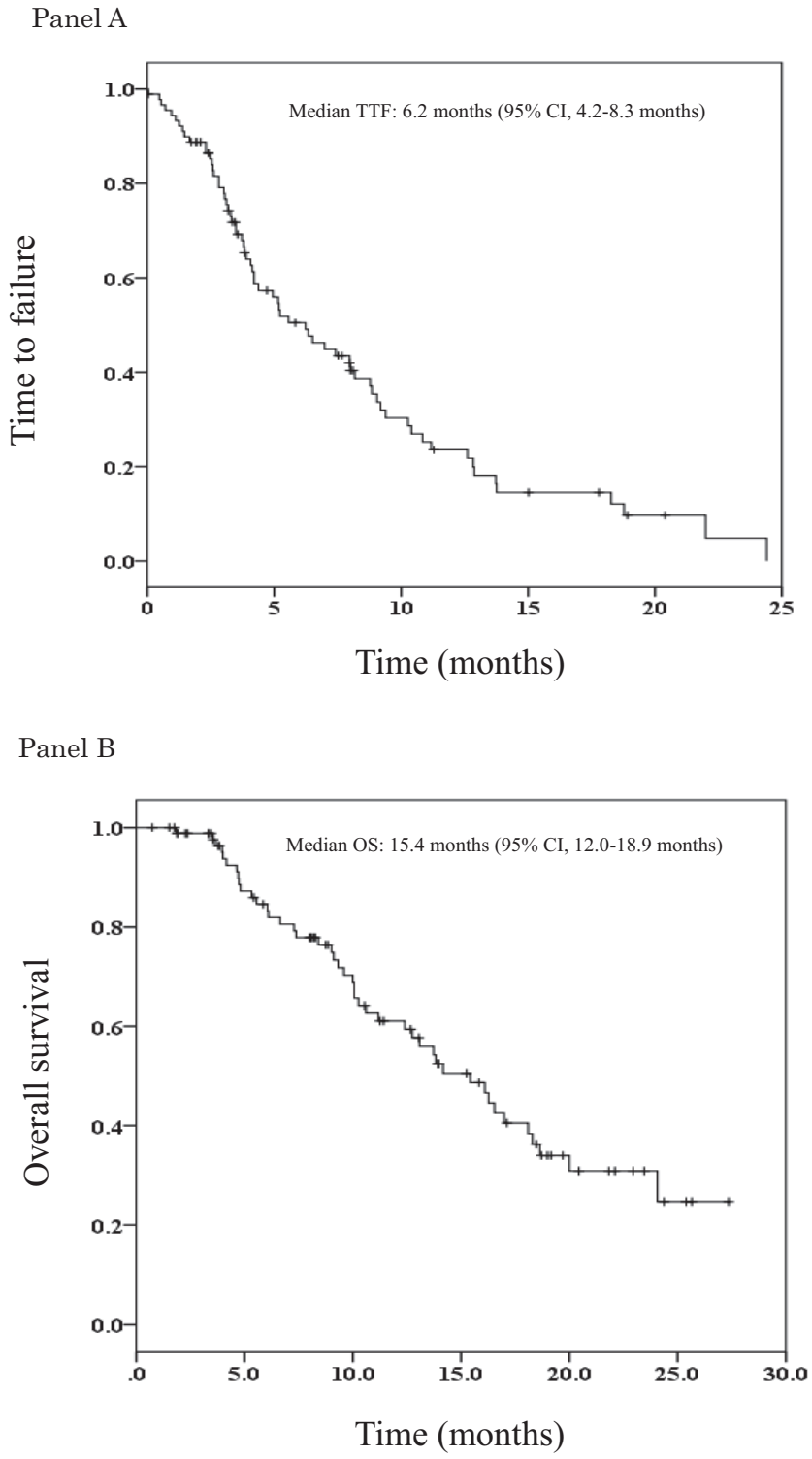

Fig. 1 Time to treatment failure (Panel A) and overall survival (Panel B) in all eligible patients who were analyzed according to the Kaplan-Meier method.

months). The ORR was as high as 67.8% (95% CI, 57.1−77.2%), including PR in 66.7% of patients. SD was achieved in 15.6% of patients, with 11.1% of patients who had PD. The ORR rates of 71.4% and 42.1% were for patients with local lesions and patients with 3 or more prior anticancer regimens, respectively. At the data cutoff date of April 30, 2014, 43 patients had died of cancer, one diabetic patient had died of a disease other than breast cancer, and one patient was lost to follow up due to hospital transfer. Therefore, the BP regimen was active for most of the study population. Furthermore, the BP regimen was also active for subgroups of patients with pri-

Table 2 Best overall response in Japanese patients with metastatic breast cancer who underwent the BP regimen

	n	Response rate (%), N=90				
		CR	PR	SD	PD	NE
All		1 (1.1)	60 (66.7)	14 (15.6)	10 (11.1)	5 (5.6)
Sites of metastasis						
Local lesion	35	1 (2.9)	24 (68.6)	5 (14.3)	5 (14.3)	0 (0.0)
Regional lymph nodes	40	2 (5.0)	24 (60.0)	8 (20.0)	6 (15.0)	0 (0.0)
Lung	43	1 (2.3)	22 (51.2)	11 (25.5)	6 (14.0)	3 (7.0)
Liver	50	2 (4.0)	30 (60.0)	8 (16.0)	6 (12.0)	4 (8.0)
Bone	49	1 (2.0)	6 (12.2)	31 (63.3)	3 (6.1)	8 (16.3)
Distant lymph nodes	26	0 (0.0)	16 (61.5)	5 (19.2)	4 (15.4)	1 (3.8)
Pleura/pleural effusion†	15	2 (13.3)	12 (80.0)	0 (0.0)	1 (6.7)	0 (0.0)
Peritoneum/ascites‡	8	0 (0.0)	6 (75.0)	0 (0.0)	1 (12.5)	1 (12.5)
Brain	9	0 (0.0)	1 (11.1)	5 (55.6)	0 (0.0)	3 (33.3)
Prior anticancer regimens (≥3)	19	0 (0.0)	8 (42.1)	4 (21.1)	6 (32.5)	1 (5.3)

†: CR: disappearance of pleural effusion; PR: a reduction in pleural effusion

‡: PR: a reduction in ascites

BP, bevacizumab and paclitaxel; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

mary tumor/metastases as manifested by the following ORR rates (≥40%): patients with metastases to the pleura (93.3%), peritoneum (75.0%), local lesion (71.5%), regional lymph nodes (65.0%), liver (64.0%), distal lymph nodes (61.5%), and lung (53.5%).

Safety

Hematologic and nonhematologic AEs are shown in **Table 3**. Hematologic AEs of grade 3/4 developed in 51 patients (56.6%), with leukopenia and neutropenia in 16 (17.8%) and 21 patients (23.3%), respectively. Grade 3 nonhematologic AEs developed in 8 patients (8.9%), with the most common nonhematologic AE of peripheral neuropathy in 4 patients (4.4%). No Grade 4 nonhematologic AEs developed. Peripheral neuropathy [56 patients (62.2%)], nail discoloration [53 patients (58.9%)], and fatigue [51 patients (56.7%)] were the most common AEs—known AEs of paclitaxel. Sixty-six of the 90 patients (73.3% of the safety analysis set) were withdrawn from the study due to the following causes: disease progression in 52 patients (57.8%); AEs (2 cases of sensory peripheral neuropathy, as well as 1 case each of diarrhea, duodenal ulcer, heart failure, rash, hematuria, neutropenia, and pemphigus) in 9 patients (10.0%); and others (2 cases of hospital transfer, as well as 1 case each of economical reason, femoral fracture, and CR) in 5 patients (5.6%).

Dose Reductions and Discontinuations

A total of 28 patients (31.1%) required a dose reduction of paclitaxel. Forty-five, 42, and 3 patients received initial doses of 90, 80, and 60 mg/m^2, respectively. Ten patients—4 (8.9%), 5 (11.9%), and 1 (33.3%) patients who received the initial doses of 90, 80, and 60 mg/m^2, respectively—required a dose reduction of 10 mg/m^2. Dose reductions of ≥20 mg/m^2 were made for 13 (28.9%), 4 (9.5%), and 1 (33.3%) patients.

Study treatment was discontinued in 9 patients because of the following AEs: 2 cases of numbness and 1 case each of grade 3 diarrhea, grade 3 duodenal ulcer, grade 3 heart failure, grade 4 neutropenia, grade 3 hematuria, skin reddening, and pemphigus.

Discussion

Bevacizumab has been approved in Japan for the treatment of a number of solid malignant neoplasms: Unresectable advanced colorectal cancer and small-cell lung cancer (NSLC), ovarian cancer, metastatic cervical cancer and breast cancer, as well as malignant glioma. Paclitaxel is among the most active agents in the treatment of breast cancer[13] and also approved for the treatment of ovarian cancer, NSLC, breast cancer, gastric cancer, carcinoma of the uterine body, relapsed or metastatic carcinoma of the head or esophageal cancer, angiosarcoma, metastatic cervical carcinoma or refractory germ cell tumors. Patients with MBC frequently undergo multiple therapies during the clinical course of their malignancy[2] in an attempt to gain better clinical outcomes.

Table 3 Treatment-related adverse events

	Grade†			
	1	2	3	4
Hematologic, n (%)				
Leukopenia	9 (10.0)	25 (27.7)	12 (14.4)	4 (4.4)
Neutropenia	5 (5.6)	19 (21.1)	17 (18.9)	4 (4.4)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Hypochromia	18 (20.0)	14 (15.6)	3 (3.3)	1 (1.1)
Thrombocytopenia	11 (12.2)	1 (1.1)	0 (0.0)	0 (0.0)
Increased total bilirubin	2 (2.2)	1 (1.1)	1 (1.1)	0 (0.0)
Increased aspartate transaminase	24 (26.6)	5 (5.6)	2 (2.2)	0 (0.0)
Increased alanine transaminase	15 (16.7)	3 (3.3)	1 (1.1)	0 (0.0)
Increased creatinine	11 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nonhematologic, n (%)				
Hypertension	6 (6.7)	13 (14.4)	0 (0.0)	0 (0.0)
Oral bleeding	2 (2.2)	2 (2.2)	0 (0.0)	0 (0.0)
Epistaxis	12 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	10 (11.1)	6 (6.7)	0 (0.0)	0 (0.0)
Vomiting	6 (6.7)	4 (4.4)	0 (0.0)	0 (0.0)
Peripheral neuropathy	32 (35.6)	20 (22.2)	4 (4.4)	0 (0.0)
Myalgia	12 (13.3)	2 (2.2)	0 (0.0)	
Arthralgia	16 (17.8)	1 (1.1)	0 (0.0)	
Onycholysis	23 (25.6)	5 (5.6)		
Nail discoloration	53 (58.9)			
Fatigue	36 (40.0)	12 (13.3)	3 (3.3)	0 (0.0)

†: Adverse events were graded according to the National Cancer Institute Common Terminology Criteria, version 4.03.

To date, first-line combined therapy with bevacizumab and paclitaxel has shown high effectiveness and good tolerability for both non-Japanese[2–4] and Japanese[5] patients with MBC. Specifically, the BP regimen reduced the risk of disease progression by more than half, and more than doubled the ORR, thus confirming the robust effect of bevacizumab treatment[4]. However, no significant difference was found in the OS rate between combined therapy and paclitaxel alone, which led the Food and Drug Administration to disapprove breast cancer as an indication for combined chemotherapy. In Japan, the regimen has been highly effective, and yielded a median PFS of 12.9 months[5] that was equivalent to 11.3 to 11.8 months in Phase 3 clinical studies in the United States[2,4]. There was also a median OS of 35.8 months[5] that was much longer than the 15.8 months in our previous study[10].

PFS, an important variable for the pharmacotherapy of MBC, is known to be affected by the assessment schedule for imaging modalities (e.g., mammography, computed tomography, and positron emission tomography)[14]. This makes it difficult to strictly specify the schedule, especially in the real-world clinical settings. PFS does not precisely indicate treatment discontinuation caused by patient refusal. In contrast, TTF reflects the continuity of treatment and treatment discontinuation resulting from both patient refusal and disease progression. Thus, TTF does not greatly affect the schedule, and it is available for use as a variable in the real-world clinical settings. In the present study, BP regimen yielded a median TTF of 6.2 months—a value that is close to the median TTFs (6.6 and 8.9 months, respectively) which were described in two previous clinical studies in patients with MBC[15,16]. Furthermore, the BP regimen showed a shorter median OS of 15.4 months compared with 35.8 months in a study of first-line combined therapy with bevacizumab and paclitaxel in Japan[5].

We consider that our finding—that the BP regimen was also active for the subgroups of patients who exhibited local relapse, who had metastases to the pleura, peritoneum, and distant/regional lymph nodes, and who had a treatment history of 3 or more chemotherapeutic regimens against the malignant tumor—is of clinical relevance. Specifically, as many as 93.3% and 75.0% of patients showed reductions in pleural effusions and ascites, which indicates that the BP regimen might be clinically effective for improvement in patient quality of life through the alleviation of dyspnea and abdominal distension, and the avoidance of thoracic and abdominal drain-

age.

Grade 3/4 hematologic AEs were mostly caused by leukopenia (17.8%) and neutropenia (23.3%) among hematologic AEs, and by peripheral neuropathy (4.4%) among nonhematologic AEs. No Grade 4 nonhematologic AEs occurred. Hence, the safety profile of combined therapy was similar to profiles reported in previous randomized studies on bevacizumab-containing therapy[2–5,17,18], and treatment-related AEs were manageable clinically. Nevertheless, dose reductions to continue the BP regimen were required in as many as 28.9% of patients who received the initial paclitaxel dose of 90 mg/m^2. Thus, there in a need to look for a chemotherapeutic regimen that is less likely to cause dose reductions in patients with MBC who undergo the BP regimen using the initial paclitaxel dose of 90 mg/m^2.

Conflict of Interest: The authors declare no conflicts of interest.

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