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ORIGINAL ARTICLE

The efficacy and safety of gemcitabine plus paclitaxel combination first-line therapy for Japanese patients with metastatic breast cancer including triple-negative phenotype

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Abstract
Purpose Gemcitabine (GEM)–paclitaxel combination therapy has been confirmed as a standard therapy for metastatic/recurrent breast cancer (MBC) in Western countries. This study was conducted to assess the efficacy and safety of GEM–paclitaxel combination therapy in Japanese MBC patients.
Methods Patients were administered paclitaxel 175 mg/m^2 on day 1, and GEM 1,000 or 1,250 mg/m^2 on days 1 and 8 of 21-day cycle. The primary endpoint of this study was overall response rate; secondary endpoints were duration of response, time to progression, survival time and rate.
Results Paclitaxel 175 mg/m^2 plus GEM 1,250 mg/m^2 was determined as the recommended dose. A total of 56 patients received 506 cycles of treatment (median: 7.5 cycles) with a relative dose intensity of 79.6% for GEM and 85.8% for paclitaxel. The response rate was 44.6% (25/56 patients), median time to progression 8.6 months and median survival time 27.1 months. In triple-negative patients, the response rate was 35.7% (5/14 patients), and the median time to progression was 6.0 months. The most frequent grade ≥ 3 toxicities were neutropenia (82.1%), leukopenia (62.5%) and ALT increase (14.3%).
Conclusions This study confirmed the efficacy and safety of GEM–paclitaxel combination therapy in Japanese MBC patients.

Keywords Anthracycline-pretreated metastatic breast cancer · Triple negative · Gemcitabine · Paclitaxel · Phase I/II trial

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Introduction

Since 1990, the age-standardized breast cancer death rate has declined in many developed countries [1]; however, the mortality rate is still increasing in Japan [2].

Metastatic breast cancer remains an incurable disease despite progress in current treatment that has resulted in improved survival rates and quality of life. Chemotherapy is currently the treatment of choice for women with Her2/neu negative, endocrine-resistant MBC, or for women with extensive visceral localizations or life-threatening disease. The most used drugs are anthracyclines, taxanes, alkylating agents, anti-metabolites, and vinca-alkaloids. Anthracycline-based combinations remain the standard first-line treatment for MBC, but despite objective response rates in 50–60% of patients, median survival period does not exceed 2–3 years [3–5].

Combination first-line chemotherapy usually provides a higher response rate and longer progression-free survival compared with single-agent chemotherapy [6]. However, due to the availability of very effective second-line, third-line, or even fourth-line chemotherapy along with the recent development of effective molecular targeted therapy, very few trials show overall survival benefit for a combination strategy [7]. One of the exceptions is the combination of an anti-metabolite such as capecitabine or gemcitabine (GEM) with taxane.

Combination therapy with GEM (a nucleoside analog) and taxane offers specific advantages because of their distinct mechanisms of action with no overlapping toxicity, including lack of cardiotoxicity [8]. GEM has demonstrated synergistic effects with taxanes in preclinical tumor models [9, 10], and the two-drug combination of GEM–paclitaxel was studied in various other malignant conditions including non-small cell lung cancer [11], bladder [12], ovarian [13], and breast cancer [14]. In recent years, two phase III randomized clinical trials [15, 16] have shown the beneficial effects of combined therapy with GEM and taxane for the treatment of MBC. Further, an analysis of the global QoL endpoint favored the GEM–paclitaxel combination therapy over paclitaxel monotherapy despite an increase in myelosuppression [17]. Consequently, GEM in combination with paclitaxel has been approved in several countries including the United States and the European Union for the treatment of unresectable, locally recurrent, or metastatic BC in patients following anthracycline-based adjuvant/neoadjuvant chemotherapy.

Japanese patients are known to suffer from more bone marrow toxicity compared with patients from Western countries when treated with a paclitaxel containing regimen [18]. Although paclitaxel 175 mg/m^2 plus GEM 1,250 mg/m^2 has been established as a standard regimen for MBC in Western countries, the optimal dose, schedule, and sequence of administration still need to be determined in Japanese MBC patients. The present phase I/II clinical study was thus conducted using the same regimen to assess the efficacy and safety of GEM–paclitaxel combination therapy in Japanese MBC patients.

Patients and methods

Study design

This study was a multicenter, non-randomized, open-label, phase I/II study conducted in Japanese patients with metastatic/recurrent breast cancer (MBC) to assess the efficacy and safety of the GEM–paclitaxel combination therapy. This study consisted of two steps. At Step 1, the officially approved GEM dose for other cancers in Japan (GEM 1,000 mg/m^2) was administered with paclitaxel 175 mg/m^2 to the first group of patients as the initial dose of the study treatment. After confirmation of the safety at GEM 1,000 mg/m^2 plus paclitaxel 175 mg/m^2, an escalated dose of GEM 1,250 mg/m^2 plus paclitaxel 175 mg/m^2 was administered to a second group of patients. This specific dose was chosen because the combination of GEM 1,250 mg/m^2 and paclitaxel 175 mg/m^2 has been recommended in countries other than Japan according to the results from a phase III study [15].

Six patients were enrolled for each group in Step 1. Paclitaxel 175 mg/m^2 was administered intravenously over 3 h on day 1 and GEM 1,000 mg/m^2 was given intravenously over a 30-min infusion on days 1 and 8 in a 3-week cycle, 2 consecutive administration weeks followed by a 1-week rest period. If dose-limiting toxicity (DLT) occurred in less than 2 out of 6 patients at GEM 1,000 mg/m^2, the dose was increased to GEM 1,250 mg/m^2 and paclitaxel 175 mg/m^2, and then administered to a second group of patients.

In Step 2, an additional 50 patients were enrolled and evaluated for the efficacy and safety at the recommended dose determined in Step 1. Treatment was repeated every 21 days until disease progression, intolerable toxicity or patient withdrawal.

Patients

Female patients with histologically or cytologically confirmed MBC or inoperable locally advanced BC were enrolled in the study. All MBC patients had relapsed after receiving anthracycline-based chemotherapy regimen in a neo-adjuvant/adjuvant setting, but no prior chemotherapy for metastatic disease. Neo-adjuvant/adjuvant chemotherapy

including taxanes must have been completed more than 12 months before registering in this study. Other inclusion criteria were as follows: good performance status (ECOG) 0 or 1, at least one bidimensionally measurable lesion, adequate function of major organs [hemoglobin $\geq$ 9.0 g/dL, neutrophils $\geq$ 2,000/mm^3, platelets $\geq$ 100,000/mm^3, AST/ALT $\leq$ 2.5 times upper limit of normal (ULN), ALP $\leq$ 2.5 times ULN, $\leq$ 5.0 times ULN for patients with liver or bone metastases] and an estimated life expectancy of at least 12 weeks. Written informed consent was obtained from all patients enrolled in the study.

This study was conducted in compliance with the guideline of good clinical practice and the Declaration of Helsinki, and the study protocol was approved by the local institutional review boards. The Efficacy and Safety Evaluation Committee, an independent review board, was consulted if any efficacy or safety issues arose in the study.

Efficacy measures

The primary objective of this study was to confirm that the lower limit of the 95% confidence interval (CI) of the response rate at the recommended dose exceeded the threshold response rate of 25%. Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 2000). Responder was defined as a patient who met either the complete response (CR) or partial response (PR) criteria for overall response assessment. CR or PR was confirmed at least 4 weeks after first observation of the response.

Secondary objectives included the median duration of response, time to progression, median survival time, and 1- and 2-year survival rates. The duration of response was the period from the day when the patient first satisfied either the CR or PR criteria to the day when the patient first met the criteria of progressive disease (PD). Time to progression (TTP) was defined as the period from the registration day to the time when any indication of disease progression (including increased size of tumor, identification of a new lesion, death, and aggravation of symptoms) was observed. Survival time was defined as the period from the date of registration to the date of death (regardless of the cause of death). Patients alive at the end of the follow-up period were treated as censored cases.

Safety measures

The safety evaluation included the type and incidence of adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0; toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

DLT was defined as a toxicity occurring in cycle 1 that met one of the following criteria: neutropenia of $\geq$grade 3 with a fever of $\geq$38.0°C, thrombocytopenia of <25,000/mm^3 or thrombocytopenia with bleeding that required platelet transfusion(s), non-hematotoxicity of $\geq$Grade 3 (excluding nausea, vomiting, anorexia). A delay in the start of cycle 2 was also classified as a DLT if cycle 2 could not be started within 42 days after the initiation of cycle 1 due to study drug toxicity.

Statistics

All patients who received at least one dose of the study drug were included in the efficacy and safety analysis. The primary efficacy endpoint was response rate. A statistical test against the null hypothesis of "the response rate is less than 25%" was performed by obtaining an exact *P*-value based on the binomial distribution with a significance level of 2.5% (one-sided). The other efficacy endpoints of duration of response, time to progression (TTP), survival time and 1- and 2-year survival rates were estimated using the Kaplan–Meier method. Two-sided 95% CIs for all endpoints were obtained.

The sample size was determined by reference to the results of a global phase III study [15]. The expected response rate of the GEM–paclitaxel combination treatment and the threshold response rate were set at 45% and 25% respectively. Assuming that the true response rate is 45%, the number of 48 subjects is needed to achieve 80% power when the statistical test is applied based on the binomial distribution with a significance level of 2.5% (one-sided). As this was the first time of the GEM–paclitaxel combination treatment to Japanese patients with MBC, given adequate consideration for feasibility, it was necessary to treat at least 55 patients with the recommended dose to evaluate the safety profile.

Results

Patient disposition and characteristics

This study was carried out from June 2006 to August 2009 at 24 study centers in Japan. Sixty-two female patients were enrolled into this study. At Step 1, 12 patients were divided into two groups of 6 patients each and administered paclitaxel 175 mg/m^2 plus GEM 1,000 mg/m^2 or GEM 1,250 mg/m^2 to determine the recommended dose for Step 2. At Step 2, an additional 50 patients were enrolled at the recommended dose of GEM plus paclitaxel 175 mg/m^2.

The mean age was 58.2 years (range 51–63) in the GEM 1,000 mg/m^2 dose group and 54.4 years (range 30–73) in the GEM 1,250 mg/m^2 dose group. All 62 patients had a history of prior chemotherapy; 27 were anthracycline and taxane pretreated patients and 35 anthracycline pretreated patients. Fifty-five patients had metastases: 32 lung, 25 bone, 22 liver and 20 lymph nodes (Table 1).

Table 1 Baseline demographic and characteristics of patients

	G 1000 group	G 1250 group
Patient number (%)	6 (100.0)	56 (100.0)
Age: mean (SD)	58.2 (4.5)	54.4 (8.7)
Height (cm): mean (SD)	153.5 (8.0)	154.7 (6.2)
Body weight (kg): mean (SD)	57.2 (15.3)	55.8 (8.7)
PS (ECOG)		
0	4 (66.7)	50 (89.3)
1	2 (33.3)	6 (10.7)
Metastatic sites		
Patients without metastases	1 (16.7)	6 (10.7)
Patients with metastases	5 (83.3)	50 (89.3)
Lung	3 (50.0)	29 (51.8)
Bone	1 (16.7)	24 (42.9)
Liver	2 (33.3)	20 (35.7)
Brain	0 (0.0)	2 (3.6)
Lymph node	2 (33.3)	18 (32.1)
Skin	0 (0.0)	4 (7.1)
Other sites	1 (16.7)	14 (5.0)
Estrogen receptor status		
Positive	1 (16.7)	35 (62.5)
Negative	5 (83.3)	21 (37.5)
Progesterone receptor status		
Positive	1 (16.7)	26 (46.4)
Negative	5 (83.3)	30 (53.6)
Her2/neu expression status		
0	4 (66.7)	19 (33.9)
1+	2 (33.3)	22 (39.3)
2+	0 (0.0)	1 (1.8)
3+	0 (0.0)	9 (16.1)
Unknown	0 (0.0)	5 (8.9)
Prior therapy		
Surgical therapy	3 (50.0)	42 (75.0)
Chemotherapy	6 (100.0)	56 (100.0)
Radiotherapy	2 (33.3)	25 (44.6)
Hormonal therapy	1 (16.7)	33 (58.9)
Other	2 (33.3)	16 (28.6)
Prior chemotherapy		
Anthracycline plus taxane	2 (33.3)	25 (44.6)
Anthracycline	4 (66.7)	31 (55.4)

PS performance status, *ECOG* Eastern cooperative oncology group, *Her2* human epidermal growth factor receptor 2

Triple-negative patients were defined as those with negative estrogen receptor (ER) and progesterone receptor (PR) status and an Her2/neu status of 0 or 1+. Fourteen of the 56 patients in the GEM 1,250 mg/m^2 dose group met the triple-negative criteria.

Patients were also classified by hormone receptor subtype: 27 patients with ER+ or PR+ and HER2−, 7 patients with ER+ or PR+ and HER2+, 2 patients with ER− and PR− and HER2+.

Dose-limiting toxicity (DLT)

Two DLTs were observed: grade 3 ALT increase (1 patient at 1,000 mg/m^2) and grade 3 fatigue (1 patient at 1,250 mg/m^2). Therefore, GEM 1,250 mg/m^2 plus paclitaxel 175 mg/m^2 was determined as the recommended dose of this study.

Drug exposure

A total of 506 cycles were administered (median 7.5 cycles, range 1–37 cycles) at the GEM 1,250 mg/m^2 dose level. Relative dose intensities were 79.6% for GEM and 85.8% for paclitaxel.

Efficacy

The response rate was 44.6% at the GEM 1,250 mg/m^2 dose level, median duration of response was 7.9 months (95% CI: 5.6, 11.0), and the median TTP was 8.6 months (95% CI: 6.5, 10.3) (Table 2). The 1-year survival rate was 78.6% (95% CI: 67.8, 89.3). The 2-year survival rate was 58.9% (95% CI: 46.0, 71.8), with 30 out of 56 patients surviving at the time of the 2-year survival analysis. The median survival time was 27.1 months (95% CI: 22.9, incalculable) at the median follow-up time period of 24.8 months (Figs. 1, 2).

Among the 14 triple-negative patients, the response rate was 35.7% with 5 patients achieving PR. The median TTP in the triple-negative patients was 6.0 months (95% CI: 1.4, 7.3) compared with 9.6 months (95% CI: 7.4, 13.6) in the non-triple-negative patients (Table 2). The 27 patients with ER+ or PR+ and HER2− hormonal receptor subtype achieved a 59.3% response rate and a median TTP of 9.3 months (95% CI: 7.4, 15.4).

Safety

All 62 patients reported at least one adverse event, and hematological toxicity was commonly observed at the GEM 1,250 mg/m^2 dose level. The most common grade ≥ 3 drug-related adverse events were neutropenia

Table 2 Tumor response and time-to-event (RECIST criteria)

	N	Tumor response *n* (%)						Time to event median (months) (95% CI)	
		CR	PR	SD	PD	NE	RR (95% CI)	DOR	TTP
G 1250 group	56	0 (0.0%)	25 (44.6%)	14 (25.0%)	11 (19.6%)	3 (5.4%)	44.6% (31.3, 58.5)	7.9 (5.6, 11.0)	8.6 (6.5, 10.3)
Triple negative	14	0	5	4	5	0	35.7%	4.5 (2.8, 9.3)	6.0 (1.4, 7.3)
Non-triple negative	42	0	20	13	6	3	47.6%	8.2 (7.3, 13.2)	9.6 (7.4, 13.6)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *DOR* duration of response, *TTP* time to progression, 95% CI: 95% confidence interval

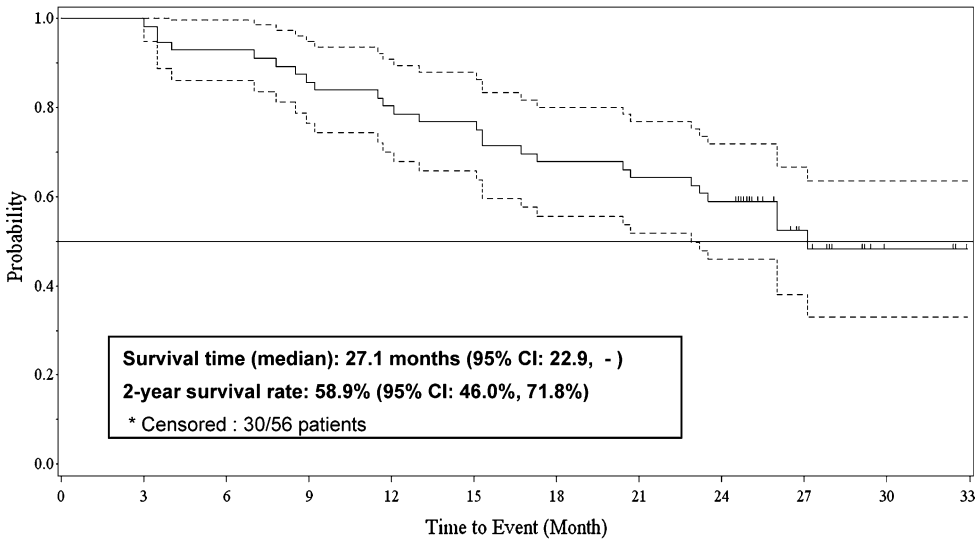

Fig. 1 Kaplan–Meier survival curve

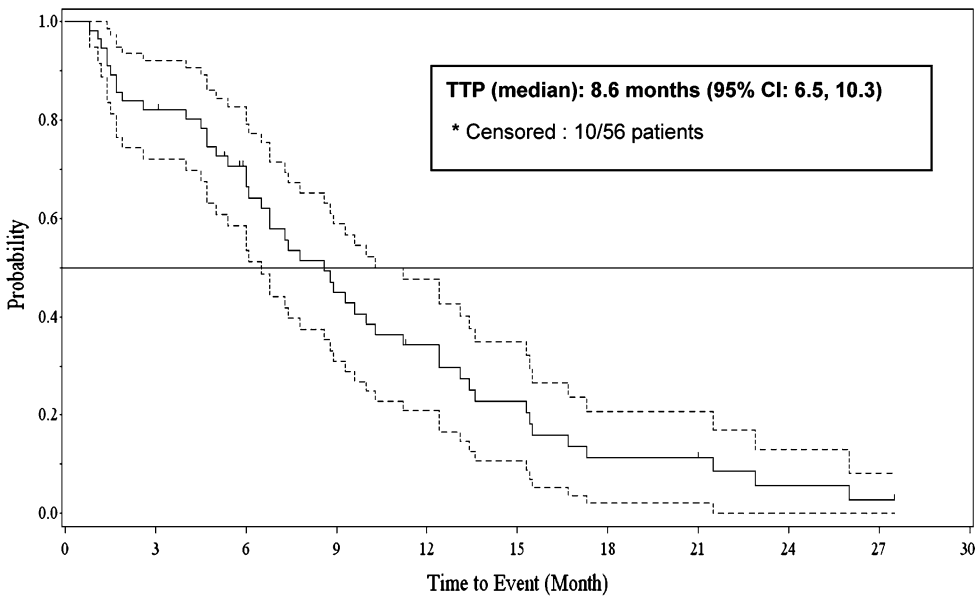

Fig. 2 Kaplan–Meier time to progression (*TTP*) curve

(82.1%), leukopenia (62.5%), lymphopenia and alanine transaminase (ALT) increase (14.3% each). The incidence of grade 3 non-hematological toxicity was low (Table 3). Fourteen of 56 patients (25.0%) reported peripheral neuropathy, but with no grade 3 or 4 toxicities. The incidence of neutropenia was 82.1%; however, no case of febrile neutropenia was reported. Prophylactic use of G-CSF was not allowed in this study, and only 10 patients (10/56, 17.9%) received G-CSF during the 2-year follow-up period. No patients required platelet transfusions.

Table 3 Adverse reactions (CTC grade 2, 3 or 4 toxicities)

Parameters	Toxicity grade[a] ($N = 56$)					
	Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%
Hematologic						
Neutrophil count decreased	7	12.5	18	32.1	28	50.0
White blood cell count decreased	12	21.4	30	53.6	5	8.9
Lymphocyte count decreased	18	32.1	4	7.1	3	5.4
ALT increased	24	42.9	7	12.5	0	0.0
Hemoglobin decreased	21	37.5	4	7.1	0	0.0
Platelet count decreased	8	14.3	5	8.9	0	0.0
AST increased	8	14.3	4	7.1	0	0.0
Red blood cell count decreased	13	23.2	3	5.4	0	0.0
GGT increased	3	5.4	2	3.6	0	0.0
Blood albumin decreased	4	7.1	0	0.0	0	0.0
Febrile neutropenia	0	0.0	0	0.0	0	0.0
Non-hematologic						
Alopecia	25	44.6	0	0.0	0	0.0
Malaise	9	16.1	1	1.8	0	0.0
Pain in extremity	9	16.1	1	1.8	0	0.0
Rash	9	16.1	0	0.0	0	0.0
Arthralgia	8	14.3	1	1.8	0	0.0
Peripheral neuropathy	7	12.5	0	0.0	0	0.0
Constipation	6	10.7	0	0.0	0	0.0
Diarrhea	4	7.1	2	3.6	0	0.0
Myalgia	4	7.1	1	1.8	0	0.0
Fever	4	7.1	1	1.8	0	0.0
Vomiting	4	7.1	0	0.0	0	0.0
Nausea	3	5.4	0	0.0	0	0.0
Anorexia	2	3.6	1	1.8	0	0.0

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma glutamyltransferase, *ALP* alkaline phosphatase

[a] Toxicity was graded according to CTCAE v3.0

Discussion

This phase I/II, multicenter study was conducted to evaluate the efficacy and safety of GEM plus paclitaxel combination therapy in Japanese MBC patients who had received prior chemotherapy with anthracycline.

Selection of combination versus serial single chemotherapy in the metastatic setting has been debated. The concepts of non-overlapping resistance mechanisms and toxicity profile have been the guiding principle for modern combination chemotherapy such as used in lymphoma, certain leukemia, and testicular germ cell cancers, but the validity of this concept has not been consistently shown in MBC. In randomized trials where single-agent and combination chemotherapy for MBC were compared, only a few multidrug therapies (capecitabine plus docetaxel or GEM plus paclitaxel) were associated with improvement in overall survival [15, 19], possibly because effective first-line chemotherapy can mask the true efficacy of second or later-line chemotherapy. In a phase III study that compared the GEM–paclitaxel combination with paclitaxel monotherapy, randomized patients were required to have had a history of anthracycline containing chemotherapy, and thus fewer patients in the monotherapy arm responded to paclitaxel monotherapy. In that study, more than 90% of the patients had prior anthracycline therapy resulting in a lower response rate for paclitaxel monotherapy [15].

Although therapy with serial single agents is a reasonable and often preferred alternative to combination regimens, combination therapy may be a more appropriate first-line choice, especially for symptomatic patients or those with rapidly progressive visceral metastases because of the greater likelihood of an objective response. Furthermore, analysis of the global QoL endpoint from a phase III study favored the GEM–paclitaxel combination therapy over paclitaxel monotherapy. The benefits of this combination as shown by QoL differences and mean global QoL scores rated by the Rotterdam Symptom Checklist (RSCL) indicated significant improvement of patients in GEM–paclitaxel combination arm versus paclitaxel monotherapy arm [17]. Capecitabine and docetaxel share hand–foot syndrome as an overlapping toxicity. Retrospective analysis of 1,000 Japanese breast cancer patients showed that the incidence of grade 2 or higher hand–foot syndrome with docetaxel was 16%, which increased to 40% with the docetaxel–capecitabine combination [20]. Results from another phase III study have also suggested that GEM may be a better option than capecitabine in combination with docetaxel for the treatment of advanced BC [16].

The present study also revealed that GEM–paclitaxel therapy was well tolerated in Japanese patients with 19 of 56 patients able to continue the study treatment for more than 10 cycles, adverse events that occurred in this study were manageable with appropriate treatment. The most common clinically significant adverse events encountered with this combination therapy were related to myelosuppresion such as neutropenia (82.1%), leukopenia (62.5%) and lymphocytopenia (12.5%). However, patients were able to continue the treatment over 506 cycles administered in 56 patients (median 7.5 treatment cycles, range 1–37). Grade 3 ALT increases were reported in 7 patients (12.5%); however, the study protocol allowed patients with liver metastases to enroll. At study entry, 20 patients had liver metastases and elevated liver enzymes associated with symptomatic aggravation. Results obtained in the present study were similar to those obtained in an earlier randomized phase III global trial [15] which demonstrated significant benefit of the GEM–paclitaxel combination therapy

over paclitaxel alone in the treatment of advanced breast cancer. Indeed, RR (44.6%) as well as TTP (8.6 months) observed in the present study were numerically better than the results (41.4% and 6.1 months, respectively) reported in the global trial. The 1- and 2-year survival rates observed in the present Japanese study (78.6 and 58.9%, respectively) were also greater than the survival rates (71 and 41%) observed in the global trial. The median survival time in this study was 27.1 months (95% CI: 22.9, incalculable) with more than half the patients were surviving after the 2-year follow-up period. This clearly demonstrates the beneficial effect of the GEM–paclitaxel combination on survival.

The response rate in the present study was similar to the other GEM–paclitaxel combination phase II first-line study [21]. Response rates for MBC in that study were 40–50%, while Delfino et al. reported a higher response rate of 66.7% (30/45 patients, 10 CR and 20 PR) in their phase II study [22]. This might be due to differences in patients' background in that more than half of the patients (53.3%) had no history of prior chemotherapy in the Delfino study.

Another important observation made in the present study relates to the effects of the GEM–paclitaxel combination therapy on patients with triple-negative breast cancer (TNBC). It is estimated that over 1 million women worldwide will be diagnosed annually for breast cancer and that 15% of them are likely to be classified as patients with TNBC [23, 24], with 30% of these patients developing metastatic disease [25]. TNBC usually exhibits an aggressive clinical course unlike hormone receptor-positive breast cancer and previously had not been a candidate for target therapy such as HER-2-positive breast cancer. Therefore, patients with TNBC are more likely to develop distant metastasis in locations like the brain earlier than non-TNBC patients, and have shorter overall survival [26]. Lin et al. reported that close to 50% of TNBC develop brain metastasis, and one-third of which were at first site of recurrence [27].

Until recently, the subset of breast cancer patients with triple-negative disease lacked a distinct therapeutic approach, despite this accounting for 15% of breast cancer patients. For patients with TNBC, anti-estrogen therapy and HER2 targeted agents are not useful options, and strategies utilizing both standard cytotoxic agents and novel targeted therapy have evolved [28]. A recent randomized phase II study on the efficacy of a PARP (poly ADP ribose polymerase) inhibitor in combination with GEM and carboplatin in patients with TNBC has shown that the median PFS was 6.9 months [29]. In comparison, combination therapy with GEM–paclitaxel at the recommended dose level (GEM 1,250 mg/m^2) resulted in a 7.9 month median duration of response for the 25 responding patients in this study. It was also found that TTP in triple-negative patients was 6.0 months versus 9.6 months in non-triple-negative patients.

Hormone receptor-positive patients have longer progression-free survival compared with triple-negative (TN) type patients. In the E2100 trial, where paclitaxel was compared with the paclitaxel plus bevacizumab, the PFS of TN patients was shorter compared with hormone receptor-positive patients in the paclitaxel arm (5.3 vs. 10.6 months) [30]. Although cross-trial comparison is limited by many biases and our study used tri-weekly paclitaxel, our results also showed a similar trend (TN 6.0 vs. non-TN 9.6 months). Since weekly administration of paclitaxel has an advantage over tri-weekly administration [31], the combination of GEM with weekly paclitaxel, possibly incorporating bevacizumab might result in better tumor control. This is being tested in ongoing clinical trial [32].

Even though the efficacy of combination therapy in the treatment of TNBC needs to be further studied, the results from the present study are in agreement with similar observations made in the earlier global trial [15] and indicate that GEM–paclitaxel combination therapy would be effective and well tolerated in Japanese patients with MBC.

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Conflict of interest statement The following authors disclose relationships with Eli Lilly Japan: TF and JF are employed by Eli Lilly and MT contributed in an advisory role.

Appendix

The following institutions participated in this study.

Sapporo Breast Surgical Clinic, Iwate University Hospital, Gunma Prefectural Cancer Center, Saitama Red Cross Hospital, Chiba Cancer Center, Kameda General Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, St Luke's International Hospital, Tokai University Hospital, Seirei Hamamatsu General Hospital, Aichi Cancer Center Hospital, Osaka National Hospital, Osaka Medical Center for Cancer and Vascular Diseases, Osaka Breast Clinic, Kinki University Hospital, Sakai Municipal Hospital, Kure Medical Center and Chugoku Cancer Center, Shikoku Cancer Center, Fukuoka University Hospital, Kyushu Cancer Center, Kumamoto Municipal Hospital, Breastpia Namba Hospital, and Sagara Hospital.

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