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First-line Gemcitabine *Versus* Treatment of Physician's Choice for Metastatic Breast Cancer: A Prospective Cohort Study

SHINYA YAMAMOTO[1], KAZUTAKA NARUI[1], TAKASHI ISHIKAWA[1], SHOKO ADACHI[1], KAZUHIRO SHIMADA[1], DAISUKE SHIMIZU[1], AKIMITSU YAMADA[2], SADATOSHI SUGAE[2], MIKIKO TANABE[3], MARI OBA[4], SATOSHI MORITA[5], TAKAKO DOI[6], SATOSHI HASEGAWA[7], TOMOYUKI MORITA[8], AYAKO KITO[9], TAKASHI CHISHIMA[10], YASUSHI ICHIKAWA[11], ITARU ENDO[2] and YOKOHAMA CLINCAL ONCOLOGY GROUP

[1]Yokohama City University Medical Center, Department of Breast and Thyroid Surgery, Yokohama, Japan;
[2]Yokohama City University Graduate School of Medicine, Department of Gastroenterological Surgery, Yokohama, Japan;
[3]Yokohama City University Medical Center, Department of Pathology, Yokohama, Japan;
[4]Yokohama City University Medical Center, Department of Biostatics and Epidemiology, Yokohama, Japan;
[5]Kyoto University Graduate School of Medicine, Department of Biomedical Statistics and Bioinformatics, Kyoto, Japan;
[6]Shonan Kinen Hospital, Breast Center, Kamakura, Japan;
[7]Saiseikai Yokohama-shi Nanbu Hospital, Department of Surgery, Yokohama, Japan;
[8]Yokosuka Kyosai Hospital, Department of Surgery, Yokosuka, Japan;
[9]Yokohama Municipal Citizen's Hospital, Department of Breast Surgery, Yokohama, Japan;
[10]Yokohama Rosai Hospital, Department of Breast Surgery, Yokohama, Japan;
[11]Yokohama City University Graduate School of Medicine, Department of Clinical Oncology, Yokohama, Japan

Abstract. *Background/Aim: This study aimed to investigate the efficacy of first-line gemcitabine monotherapy for metastatic breast cancer (MBC) and its effect on health-related quality of life (HRQoL) compared with treatment of physician's choice (TPC). Patients and Methods: We enrolled 96 patients into the first-line gemcitabine group (n=47) or other treatment of physician's choice (TPC) group (n=49) from May 2010 to April 2013. HRQoL was evaluated every 4 weeks. Results: There was no significant difference in the median time to treatment failure (5.3 vs. 4.6 months, hazard ratio=0.87, p=0.546) and the incidence rates of grade 3/4 haematological toxicity (10.6% vs. 8.1%, p=0.677) and grade 3/4 non-haematological toxicity (4.2% vs. 8.1%, p=0.429) between the gemcitabine and TPC groups. Changes in HRQoL from baseline to 12 weeks were not significantly different. Conclusion: Gemcitabine achieves similar efficacy and HRQoL benefit to other chemotherapy and can be used as first-line treatment for MBC.*

Correspondence to: Kazutaka Narui, Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, 4-57 Urafune-cho, Naka-ku, Yokohama city, Kanagawa 232-0024, Japan. Tel: +81 452615656, Fax: +81 452311846, e-mail: nr1@gc5.so-net.ne.jp

Key Words: Metastatic breast cancer, gemcitabine, treatment of physician's choice.

In contrast to early-stage breast cancer for which most treatment options are supported by high-level evidence, there are few recognised therapeutic standards for metastatic breast cancer (MBC) (1). Because of the low curative rate of MBC, the main purpose of treatment is to alleviate symptoms, extend survival, and improve patients' quality of life (2).

Gemcitabine is a pyrimidine nucleoside analogue mainly used for several cancers, including pancreatic, non-small-cell lung, and breast cancers (3-5). However, data on its efficacy for MBC are lacking. To our knowledge, only one randomised controlled trial on first-line gemcitabine monotherapy has been conducted (6). The efficacy of gemcitabine was compared with that of epirubicin for postmenopausal women with MBC aged at least 60 years. The results showed that epirubicin was superior to gemcitabine with respect to time to progression (TTP) and overall survival (OS), but its effect on health-related quality of life (HRQoL) was not evaluated. Thus, this study investigated the efficacy of first-line gemcitabine monotherapy and its effect on HRQoL compared with chemotherapy treatment of physician's choice (TPC).

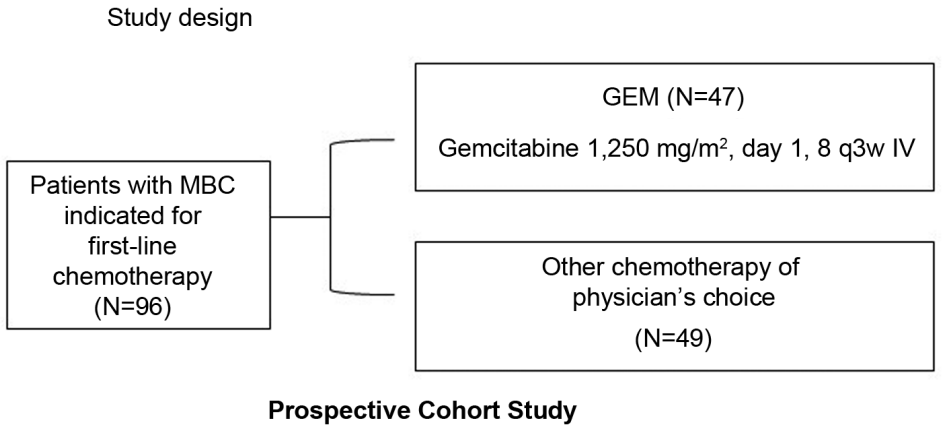

Figure 1. *Study flowchart*.

Patients and Methods

Study design and patients. This multicentre prospective cohort study (YCOG1005) of gemcitabine *versus* TPC in patients with MBC was conducted by the Yokohama Cooperative Oncology Group (Figure 1). From May 2010 to April 2013, 96 patients receiving first-line chemotherapy for MBC were enrolled and administered gemcitabine or other chemotherapy of physician's choice at Yokohama City University Medical Center, Yokohama City University Graduate School of Medicine, Shonan Kinen Hospital, Saiseikai Yokohama-shi Nanbu Hospital, Yokosuka Kyosai Hospital, Yokohama Municipal Citizen's Hospital, and Yokohama Rosai Hospital.

The inclusion criteria were 1) female sex; 2) age 20-80 years; 3) histologically or cytologically confirmed breast cancer; 4) metastatic, locally advanced, or recurrent breast cancer; 5) an Eastern Cooperative Oncology Group performance status of 0-2; 6) adequate bone marrow, liver, and renal function; 7) no prior treatment for MBC; 8) irradiation range <20% of the whole bone marrow; and 9) no history of anthracycline regimens. The exclusion criteria were 1) previous treatment with gemcitabine, 2) inflammatory breast cancer, and 3) brain metastases with symptoms. Among the 96 patients, 47 and 49 patients were treated with gemcitabine and TPC, respectively.

The study protocol (UMIN000013002) was approved by the ethics committees of all participating institutions, and the study was conducted according to the tenets of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all enrolled patients.

Treatment protocol. The patients in the gemcitabine group were intravenously administered 1250 mg/m^2 gemcitabine for 30 min on days 1 and 8 of a 21-day cycle. Those in the TPC group received single-agent cytotoxic chemotherapy of the physician's choice. Treatment continued until disease progression, unacceptable toxic effects, or patient or physician request for discontinuation. Grade ≥3 adverse events were managed by dose modifications. Trastuzumab was added if the human epidermal growth factor receptor 2 (HER2) status was positive. After this trial, additional treatment was administered according to the physician's choice.

Endpoints. The primary endpoint was the time to treatment failure (TTF) in the two groups. The secondary endpoints were severe toxicity (defined as grade 3 or 4 treatment-related toxicities following the National Cancer Institute-Common Toxicity Criteria, version 3.0) and HRQoL [assessed every 4 weeks using the Functional Assessment of Cancer Therapy -Breast Cancer Version 4.0 (FACT-B) questionnaire].

Examination protocol. Diagnostic imaging (*e.g.* computed tomography) and tumour marker evaluation were performed as deemed necessary by the attending physician. The FACT-B survey was conducted before each course.

Statistical analysis. Categorical variables were compared using the Mann–Whitney *U*-test. TTF and OS were estimated using the Kaplan–Meier method and were compared between the two groups using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox regression model. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Patient characteristics. Patient characteristics are shown in Table I. The proportion of patients with positive HER2 status was significantly larger in the TPC group. Details of TPC are shown in Table II. Approximately half of the patients in the TPC group received vinorelbine and capecitabine.

TTF and OS. The median follow-up period was 9.9 months (range=0.2-119.2 months). As shown in Figure 2, the median TTF were 5.3 and 4.6 months in the gemcitabine and TPC groups, respectively. There was no significant difference between the two groups (hazard ratio=0.87, p=0.546). The median overall survival (OS) was 26.8 and 26.8 months in the gemcitabine and TPC groups, respectively (Figure 3), with no significant difference (hazard ratio=0.85, p=0.649).

Table I. *Patient characteristics*.

	GEM group (n=47)	TPC group (n=49)	*p*-Value
Age (years), median (range)	63 (38-79)	60 (31-77)	0.224
Oestrogen receptor			
Positive	40	35	0.105
Negative	7	14	
HER2 (combined FISH and IHC)			
Positive	2	10	0.023*
Negative	43	39	
Unknown	2	0	
Disease-free interval			
<2 years	8	8	0.787
2-5 years	11	16	
≥5 years	17	15	
No surgery	11	10	
Liver metastasis			
Yes	12	16	0.442
No	35	33	

GEM: Gemcitabine; HER2: human epidermal growth factor receptor 2; FISH: fluorescence *in situ* hybridisation; IHC: immunohistochemistry. *statistically significant.

Table II. *Details of treatment of physician's choice*.

Treatment	Number of patients
Vinorelbine	15
Capecitabine	9
Paclitaxel	7
Eribulin	4
EC	6
AC	2
S-1	2
nab-Paclitaxel	2
FEC (50)	1
UFT	1

EC: Epirubicin and cyclophosphamide; AC: doxorubicin and cyclophosphamide; FEC: 5-fluorouracil, epirubicin, and cyclophosphamide; UFT: uracil tegafur.

Adverse events. Grade 3/4 adverse events are shown in Table III. Grade 3/4 haematological toxicity occurred in 10.6% and 8.1% of patients in the gemcitabine and TPC groups, respectively, with no significant difference (p=0.677). Particularly, the incidence rates of grade 3/4 neutropenia were 10.6% and 8.1% in the gemcitabine and TPC groups, respectively. Neutropenia was the most common adverse event in both groups, but no patient developed febrile neutropenia. Grade 3/4 non-haematological toxicity occurred in 4.2% and 8.1% of patients in the gemcitabine and TPC groups, respectively. There was no significant difference in the incidence of non-haematological toxicity between both groups (p=0.429).

HRQoL. The FACT-B survey results are summarised in Figure 4. From baseline, the FACT-B score changed to –4.2 at 4 weeks, –1.4 at 8 weeks, and –3.8 at 12 weeks in the gemcitabine group and to +0.7, –5.9, and –7.8, respectively, in the TPC group. There was no significant difference in the changes from the baseline scores between the two groups at all time points (4 weeks, p=0.652; 8 weeks, p=0.440; 12 weeks, p=0.615).

Discussion

Data to support the usefulness of gemcitabine as first-line treatment for MBC are limited. Our results showed that gemcitabine as first-line monotherapy for MBC is non-inferior to other chemotherapy of the physician's choice with respect to TTF, adverse events, and HRQoL.

There have been several studies on gemcitabine for MBC, with most using gemcitabine in combination with other chemotherapy agents (7), including paclitaxel, docetaxel, and vinorelbine (8-10). A recent clinical trial on combination therapy with gemcitabine, trastuzumab, and pertuzumab after prior pertuzumab-based therapy for HER 2-positive MBC (11) reported that the regimen was well tolerated. Further, the median PFS was 5.5 months. Meanwhile, evidence on the efficacy of gemcitabine monotherapy for MBC is scarce. Suzuki *et al*. used gemcitabine monotherapy in the late line setting after anthracycline and taxane treatment (12). Gemcitabine was administered in the same dose and schedule as our study, and the median TTP was 3.0 months. For first-line gemcitabine monotherapy for MBC, Blackstein *et al*. conducted a phase 2 study of 39 patients. The TTP was 5.1 months, although the dose and schedule of gemcitabine were different from those in our study. In other studies with different treatment line, dose, and schedule of gemcitabine, the TTP ranged from 1.9 to 6.3 months (13-16). Despite the differences, our result of a median TTF of 5.3 months is similar with those in previous reports.

Regarding adverse events, the frequency of grade 3/4 neutropenia was 10.6%. Although this was slightly higher than that in the TPC group, the difference was not significant. Furthermore, the gemcitabine group showed a low rate of non-haematological toxicity. This is consistent with the findings reported by Possinger *et al*. who evaluated the efficacy of gemcitabine as first-line treatment for MBC. Grade 3/4 neutropenia and non-haematological toxicity occurred in 19.2% and 15.2% of their patients, respectively (17). Further, drug-induced pneumonia did not occur in our study. Collectively, these findings support that gemcitabine monotherapy has generally low toxicity and good tolerability.

Regarding the effect on HRQoL, the results showed only a minor decline in FACT-B from baseline to all evaluation

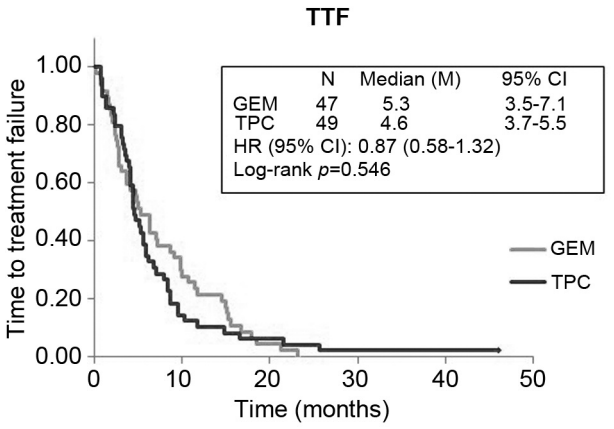

Figure 2. *Time to treatment failure. HR: Hazard ratio; CI: confidence interval. This is a Kaplan–Meier curve. The median time to treatment failure was 5.3 and 4.6 months in the gemcitabine and TPC groups, respectively. There was no significant difference between the two groups (hazard ratio=0.87, p=0.546).*

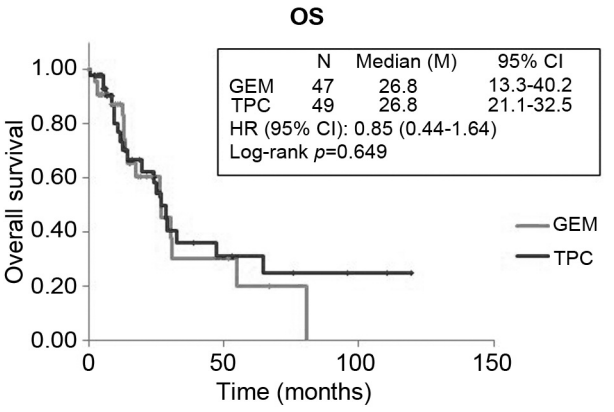

Figure 3. *Overall survival. HR: Hazard ratio; CI: confidence interval. This is a Kaplan-Meier curve. The median overall survival was 26.8 and 26.8 months in the gemcitabine and TPC groups, respectively. There was no significant difference between the two groups (hazard ratio=0.85, p=0.649).*

Table III. *Grade ≥3 adverse events.*

	GEM group (n=47)	TPC group (n=49)	*p*-Value
Haematological toxicity	5 (10.6%)	4 (8.1%)	0.677
Febrile neutropenia	0 (0.0%)	0 (0.0%)	-
Neutropenia			
Grade 3	4 (8.5%)	1 (2.0%)	0.677
Grade 4	1 (2.1%)	3 (6.1%)	
Leucopoenia			
Grade 3	2 (4.2%)	2 (4.0%)	0.680
Grade 4	0 (0.0%)	1 (2.0%)	
Anaemia	0 (0.0%)	0 (0.0%)	-
Thrombocytopenia	0 (0.0%)	0 (0.0%)	-
Non-haematological toxicity	2 (4.2%)	4 (8.1%)	0.429
HFS	0 (0.0%)	1 (2.0%)	0.324
Nausea	0 (0.0%)	0 (0.0%)	-
Diarrhoea	0 (0.0%)	1 (2.0%)	0.324
Heart failure	1 (2.1%)	0 (0.0%)	0.304
Peripheral neuropathy	0 (0.0%)	2 (4.0%)	0.161
Erythema	1 (2.1%)	0 (0.0%)	0.304

GEM: Gemcitabine; HFS: hand-foot syndrome.

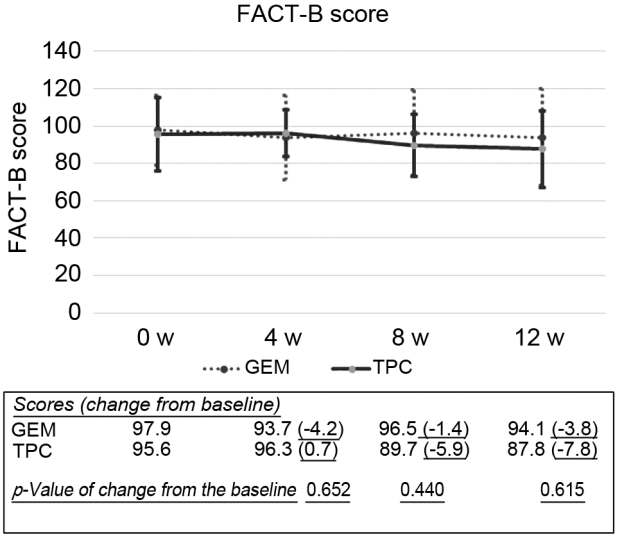

Figure 4. *Changes in FACT-B Score throughout the study period. Bars represent an average value and a standard deviation. From baseline, the FACT-B score changed to –4.2 at 4 weeks, –1.4 at 8 weeks, and –3.8 at 12 weeks in the gemcitabine group and to +0.7, –5.9, and –7.8, respectively in the TPC group. There was no significant difference in the changes from the baseline scores between the two groups at all time points (4 weeks, p=0.652; 8 weeks, p=0.440; 12 weeks, p=0.615).*

timepoints of evaluation. This indicated that there were few adverse events that influenced the patients' HRQoL. The FACT-B, which is a four-subscale questionnaire on physical well-being, social/family well-being, emotional well-being, functional well-being, is a widely used tool for assessing the HRQoL among breast cancer patients (18). In this study, there was no significant difference in the changes from the baseline scores to all timepoints in both groups. Gemcitabine showed comparable tolerability to TPC according to the impact on HRQoL. Therefore, it may be a good option for patients who are reluctant to undergo chemotherapy because of its adverse effects.

This study has some limitations. First, this was a non-randomised trial, and the study population was small. A

larger randomised study is needed to confirm our result. Second, evidence on the efficacy of other treatments for MBC appeared only after the trial, and thus, it was difficult to compare between gemcitabine and later approved drugs.

Compared to S-1, eribulin, and capecitabine, there is a lack of evidence to support the efficacy of gemcitabine monotherapy for MBC. Gemcitabine is not recommended by the National Comprehensive Cancer Network or Japanese Breast Cancer Society guidelines. Although this study does not recommend that gemcitabine should be the standard first-line treatment for MBC, the findings support that gemcitabine can be considered as first-line treatment for MBC patients.

Conclusion

Gemcitabine is non-inferior to TPC with respect to survival benefit and HRQoL impact and can thus be an option for first-line treatment of MBC.

Conflicts of Interest

The Authors disclose no conflicts of interest in relation to this study.

Authors' Contributions

SY wrote the manuscript, and analyzed statistics. KN, AY, TI, YI, and IE designed the study, collected the samples and clinical data., and revised the manuscript. MT contributed to histology review. SA, KS, DS, SS, TD, SH TM, AK, and TC collected the samples and clinical data. MO and SM analyzed the samples and statistics. All Authors have read and approved the manuscript.

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