

ORIGINAL ARTICLE

Outcomes of Palliative Weekly Low-Dose Gemcitabine-Cisplatin Chemotherapy in Anthracycline- and Taxane- Pretreated Metastatic Breast Cancer Patients

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Purpose: The combination of gemcitabine and cisplatin (GP) has been shown to be safe and efficacious for patients with metastatic breast cancer (MBC), pretreated with anthracyclines and taxanes. We assessed the efficacy and safety of weekly low-dose GP in patients with MBC. **Methods:** We collected clinicopathological data from MBC patients who had been treated with gemcitabine, 800 mg/m² plus cisplatin, 30 mg/m² intravenously, on days 1 and 8 every 3 weeks, between January 2001 and November 2011 in Korea. **Results:** The analysis included 294 patients previously treated anthracycline- and taxane-based chemotherapies prior to GP (median age, 48 years [range, 28–78 years]; median follow-up duration, 63.9 months). Seventeen patients (5.8%) discontinued GP because of toxicities. The median progression-free survival (PFS) was 3.9 months (95% confidence interval [CI], 3.3–4.4 months) and the median overall survival (OS) was 27.7 months (95% CI, 17.6–37.8 months) months. Statisti-

cally significant factors for PFS were performance status (Eastern Cooperative Oncology Group, ≥ 2 vs. < 2 ; hazard ratio [HR], 1.37; 95% CI, 1.02–1.85; $p = 0.037$), distant disease-free interval (DDFI; ≤ 2 years vs. > 2 years; HR, 1.66; 95% CI, 1.28–1.95, $p < 0.001$), time interval from the diagnosis of metastasis to GP therapy (≤ 1 year vs. > 1 year; HR, 1.48; 95% CI, 1.13–1.95, $p < 0.001$), and presence of brain metastasis (HR, 1.47; 95% CI, 1.03–2.10; $p = 0.031$). Similarly, DDFI (≤ 2 years vs. > 2 years; HR, 2.07; 95% CI, 1.36–3.14; $p < 0.001$) and the presence of brain metastasis (HR, 2.14; 95% CI, 1.27–3.61; $p = 0.004$) were important factors for OS after GP treatment. **Conclusion:** Weekly low-dose GP chemotherapy appears safe and effective for heavily pretreated MBC patients.

Key Words: Breast neoplasms, Drug therapy, Neoplasm metastasis

INTRODUCTION

Breast cancer is the second most common cancer after thyroid cancer in Korean women [1]. Approximately, 35% to 40% of patients experience disease recurrence in spite of improved adjuvant treatments [2,3]. Anthracyclines and taxanes are the principal chemotherapeutic agents in both the adjuvant and metastatic settings [4]. However, there is no standard therapeutic option for metastatic breast cancer (MBC) patients beyond anthracycline- and taxane-based chemotherapy.

Gemcitabine is a nucleoside analogue that affects the synthesis phase of the cell cycle. It has cytotoxic activity as a single

agent, but a combination approach with other agents could lead to higher response rates than those seen with monotherapy [5–7]. Currently, gemcitabine is often used together with other drugs including taxanes, cisplatin, carboplatin, or vinorelbine in MBC [8]. Cisplatin is one of the most potent platinum agents and is active in MBC with comparable response rates and manageable toxicities to gemcitabine [9]. The combination of gemcitabine and cisplatin (GP) is known to be synergistic, and several studies demonstrated the clinical efficacy of GP therapy in heavily pretreated MBC patients, including those with triple-negative breast cancer [10,11]. Many studies have been conducted to investigate the efficacy and safety of GP using various dosages and schedules of administration; however, no consensus has been reached [12–14]. In this study, we assessed the clinical efficacy of weekly low-dose GP in heavily pretreated patients with MBC.

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METHODS

Patients and treatment

We reviewed the medical records of patients diagnosed with MBC who received palliative GP chemotherapy at the National Cancer Center, Korea between January 1, 2001 and November 19, 2012. Cisplatin, 30 mg/m² and gemcitabine, 800 mg/m² were administered intravenously on days 1 and 8, and the cycle was repeated every 3 weeks. A total of 384 patients were included in this study. Of these 90 patients were excluded for the following reasons: more than 3 lines of prior chemotherapy (n=59); not evaluable for response to GP treatment as lost to follow-up or death after the first day of the first cycle (n=18); diagnosis of other malignancies (n=12); and male sex (n=1) (Figure 1). All patients received 1 or more cycles of GP treatment. This study was approved by the National Cancer Center's Institutional Review Board (number: NCC2014-0165).

Statistical analysis

We defined the distant disease-free interval (DDFI) as the time from first diagnosis of breast cancer to detection of distant metastasis. Time-to-GP (TTGP) was defined as the time interval from the date of diagnosis of distant metastasis to the start of GP treatment. Progression-free survival (PFS) was calculated from the date of the first day of the first cycle of GP chemotherapy until the date of progression or death from any cause. Overall survival (OS) was calculated from the date of the first day of the first cycle of GP chemotherapy until the date of death from any cause or last follow-up date. For patients who were lost to follow-up, data were censored on the date of their last visit. Survival analyses were conducted using the Kaplan-Meier method and compared with the log-rank

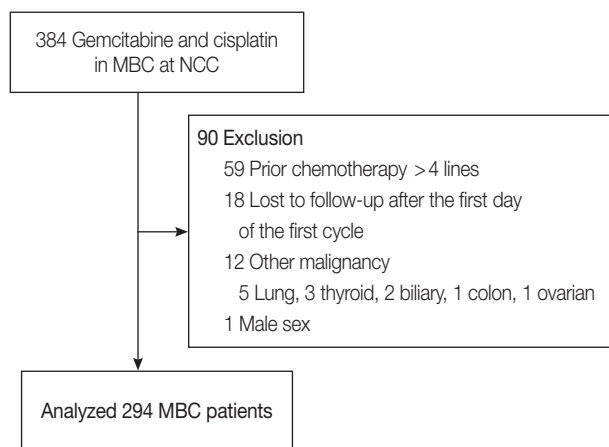


Figure 1. CONSORT diagram.

MBC=metastatic breast cancer; NCC=National Cancer Center, Korea.

test. The Cox proportional hazards model was used to find predictive factors for GP treatment. A *p*-value less than 0.05 was considered significant. SPSS version 12.0 for Windows (SPSS Inc., Chicago, USA) was used for all statistical analyses in this study.

RESULTS

A total of 384 patients were enrolled in the study, and the clinical data from 294 were eligible for analysis. The median age was 48 years (range, 28–78 years) and the median follow-up duration was 63.9 months (range, 7.1–218.7 months). All patients had been previously treated with anthracycline- and taxane-based chemotherapy in either the adjuvant or palliative setting, and approximately 75% received more than one cytotoxic chemotherapy regimen in the palliative setting prior to GP treatment. The baseline patient characteristics are summarized in Table 1. One hundred nineteen patients (40.6%) received GP treatment as third-line therapy, and 99 (33.4%) as

Table 1. Patient baseline characteristics

Characteristic	No. (%)
No. of patients	294
Age (yr)*	48 (28–78)
≤50	173 (58.8)
>50	121 (41.2)
DDFI (yr)*	3.1 (0–16.4)
TTGP (mo)*	24.1 (0–105.1)
Receptor status	
ER or PR (+)/HER2 (-)	138 (47.1)
ER or PR (±)/HER2 (+)	80 (27.0)
Triple-negative	76 (25.9)
Distant metastases	
Bone	159 (53.9)
Brain	47 (15.7)
Visceral	210 (71.3)
No. of prior palliative chemotherapy regimens	
0	12 (4.1)
1	64 (21.8)
2	119 (40.6)
3	99 (33.4)
Hormone therapy for MBC	131 (44.7)
Adjuvant chemotherapy	226 (77.1)
ECOG PS	
0	13 (4.4)
1	205 (70.0)
2	73 (24.6)
3	3 (1.0)

DDFI=distant disease-free interval; TTGP=time interval from the diagnosis of metastasis to GP therapy; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; MBC=metastatic breast cancer; ECOG=Eastern Cooperative Oncology Group; PS=performance status.

*Median (range).

fourth line. The median DDFI was 3.1 years (range, 0.2–16.4 years) and the median TTGP was 24.1 months (range, 0.2–105.1 months). Half of the patients had hormone receptor-positive disease and 25.9% had triple-negative tumors. Eighty patients (27.0%) with human epidermal growth factor receptor 2 (HER2)-positive tumors were included because anti-HER2 therapy was not available to them during the study period.

Table 2. Reasons for discontinuing gemcitabine and cisplatin treatment

Reason	No. (%)
Ongoing	14 (4.8)
Disease progression	217 (73.7)
Chemotherapy holiday	5 (1.7)
Adverse effects	17 (5.8)
Death	9 (3.1)
Others*	32 (10.9)

*Lost to follow-up or patient refusal.

More than 70% of patients had visceral metastasis and 47 (15.7%) had brain metastasis. The most common cause of discontinuation of GP treatment was disease progression (Table 2). Only 5.8% of patients stopped receiving GP chemotherapy due to toxicities and the median number of GP cycles administered to them was 8 cycles (range, 1–14 cycles). The median PFS after GP treatment was 3.9 months (95% confidence interval [CI], 3.3–4.4 months) and the median OS was 27.7 months (95% CI, 17.6–37.8 months) (Figure 2).

According to Cox regression analysis, significant predictive factors for PFS were Eastern Cooperative Oncology Group (ECOG) performance status (PS, ≥ 2 vs. < 2 ; hazard ratio [HR], 1.37; 95% CI, 1.02–1.85; $p = 0.037$), DDFI (≤ 2 years vs. > 2 years; HR, 1.66, 95% CI, 1.28–2.15; $p < 0.001$), TTGP (≤ 1 year vs. > 1 year; HR, 1.48; 95% CI, 1.13–1.95; $p < 0.001$), and the brain metastasis (HR, 1.47; 95% CI, 1.03–2.10; $p = 0.031$) (Table 3). All of these factors remained significant after multi-

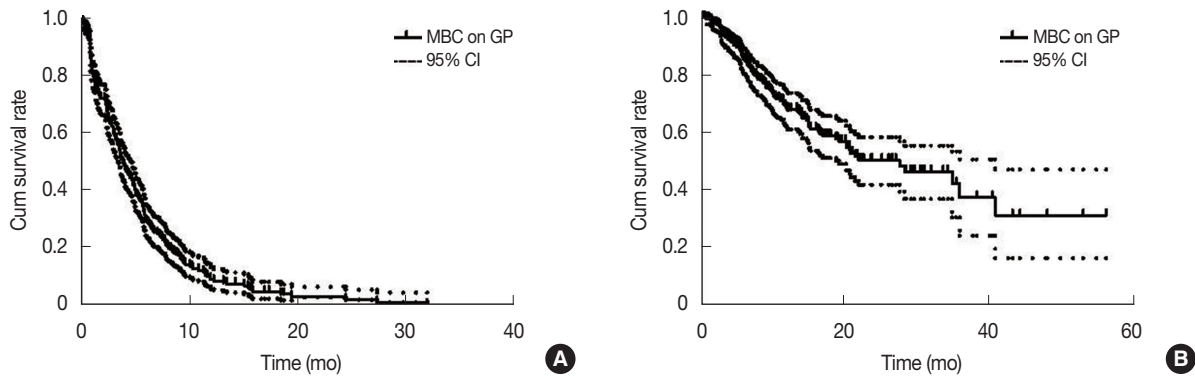


Figure 2. Progression-free survival (PFS) and overall survival (OS) after gemcitabine and cisplatin (GP) treatment. (A) Median PFS was 3.9 months (95% confidence interval [CI], 3.3–4.4 months). (B) Median OS was 27.7 months (95% CI, 17.6–37.8 months). MBC=metastatic breast cancer; cum=cumulative.

Table 3. Cox regression analysis for progression-free survival after treatment with gemcitabine and cisplatin

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
ECOG PS (≥ 2 vs. < 2)	1.32 (0.99–1.76)	0.022	1.37 (1.02–1.85)	0.037
Age (> 50 yr vs. ≤ 50 yr)	1.06 (0.81–1.38)	0.655		
No. of prior chemotherapies (≥ 2 vs. < 2)	1.14 (0.85–1.53)	0.364		
Receptor status				
ER or PR (+)/HER2 (-)	1.0			
ER or PR (\pm)/HER2 (+)	1.19 (0.89–1.59)	0.239		
Triple-negative	1.16 (0.86–1.55)	0.329		
DDFI (≤ 2 yr vs. > 2 yr)	1.76 (1.37–2.27)	< 0.001	1.66 (1.28–1.95)	< 0.001
TTGP (≤ 1 yr vs. > 1 yr)	1.67 (1.28–2.19)	< 0.001	1.48 (1.13–1.95)	0.004
Metastases				
Bone	1.03 (0.80–1.33)	0.799		
Brain	1.45 (1.03–2.04)	0.029	1.47 (1.03–2.10)	0.031
Visceral	1.14 (0.86–1.51)	0.356		

HR=hazard ratio; CI=confidential interval; ECOG=Eastern Cooperative Oncology Group; PS=performance status; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; DDFI=distant disease-free interval; TTGP=time interval from the diagnosis of metastasis to gemcitabine and cisplatin therapy.

Table 4. Coxregression analysis for overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
ECOG PS (≥ 2 vs. < 2)	1.22 (0.77–1.92)	0.390		
Age (> 50 yr vs. ≤ 50 yr)	1.02(0.67–1.53)	0.924		
No. of prior chemotherapies (≥ 2 vs. < 2)	1.02 (0.65–1.62)	0.912		
Hormonal status				
ER or PR (+)/HER2 (-)	1.0			
ER or PR (\pm)/HER2 (+)	1.16 (0.75–1.81)	0.493		
Triple-negative	1.06 (0.67–1.67)	0.794		
DDFI (≤ 2 yr vs. > 2 yr)	2.18 (1.45–3.27)	< 0.001	2.07 (1.36–3.14)	< 0.001
TTGP (≤ 1 yr vs. > 1 yr)	1.52 (0.99–2.03)	0.049	1.29 (0.84–1.98)	0.186
Metastases				
Bone	1.15 (0.76–1.72)	0.479		
Brain	1.95 (1.16–3.27)	0.011	2.14 (1.27–3.61)	0.004
Visceral	1.50 (0.92–2.43)	0.100		

HR=hazard ratio; CI=confidential interval; ECOG=Eastern Cooperative Oncology Group; PS=performance status; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; DDFI=distant disease-free interval; TTGP=time interval from the diagnosis of metastasis to gemcitabine and cisplatin therapy.

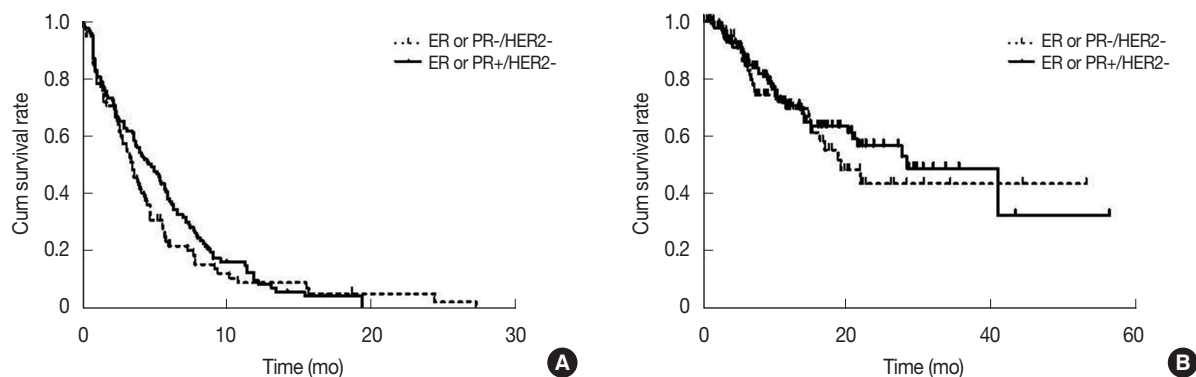


Figure 3. Progression-free survival (PFS) and overall survival (OS) according to receptor status in the patients with human epidermal growth factor receptor 2 (HER2)-negative tumors. (A) Median PFS in patients with estrogen receptor (ER)-/HER2- tumors was 3.3 months, and PFS of ER+/HER2- was 4.3 months. (B) Median OS in patients with ER-/HER2- tumors was 7.6 months and OS in patients with ER+/HER2- tumors was 10.1 months. cum=cumulative.

variate analysis. A shorter DDFI (≤ 2 years vs. > 2 years; HR, 2.07; 95% CI, 1.36–3.14; $p < 0.001$) and the presence of brain metastasis (HR, 2.14; 95% CI, 1.27–3.61; $p = 0.004$) were associated with worse OS outcomes after GP treatment (Table 4). Hormone receptor status was not associated with the clinical efficacy of GP treatment in terms of PFS and OS (Figure 3).

DISCUSSION

Approximately 30% to 50% of early breast cancer patients experience metastatic recurrence despite receiving standard adjuvant chemotherapies including anthracycline and taxane-based regimens [15,16]. Unfortunately, there is no standard chemotherapeutic regimen for anthracycline- and taxane-resistant MBC. Previously, several phase II studies evaluated the efficacy and safety of GP combinations in these. They reported similar

response rates of approximately 30% to 40% after GP chemotherapy, even though the dose and schedules of GP differed between the studies [12–14]. Sánchez-Escribano Morcuende et al. reported that weekly low-dose GP treatment (gemcitabine, 750 mg/m² plus cisplatin, 30 mg/m² on days 1 and 8, every 3 weeks) in heavily pretreated MBC patients showed similar efficacy with better safety profiles when compared to high dose GP treatment (gemcitabine, 1,250 mg/m² plus cisplatin, 75 mg/m² on days 1 and 8, every 3 weeks) [12,17,18]. According to our data, the discontinuation rate of weekly low-dose GP due to overt toxicities was less than 6% and 32 patients (10.9%) discontinued GP because they were lost to follow-up or refused further treatment for other reasons. The significant predictive factors for PFS after GP treatment were PS (ECOG PS, ≤ 2), DDFI (> 2 years vs. ≤ 2 years), TTGP (≥ 1 year), and the presence of brain metastasis. All of the predictive factors

that we found were associated with a less aggressive form of the disease and better response to previous treatment. In contrast with other reports demonstrating the efficacy of platinum agents in triple-negative breast cancer [4,19-21], hormone receptor negativity was not a predictive factor for PFS after GP treatment in our analysis. Previous studies showing the efficacy of platinum agents in triple-negative breast cancer were mostly conducted in a first or second line setting [4,10]. In our study, all patients were heavily pretreated for metastatic breast cancer, and this resulted in resistance to subsequent treatments. This may explain why cisplatin did not show a beneficial effect for triple-negative breast cancer in this study.

There are several limitations in this study, mainly due its retrospective nature. First, we could not collect specific data on the toxicity experienced by patients receiving GP treatment. We assumed that the safety of GP treatment was based on the discontinuation rate. Second, the response of metastatic lesions in the brain was not consistently assessed in patients who had brain metastasis previously. Therefore, many of these patients discontinued GP treatment due to progression in the brain, even when the systemic disease was under control. This could be the reason that brain metastasis was a poor predictive factor for PFS after GP treatment in the current study.

In conclusion, weekly low-dose GP treatment is a good palliative option for heavily pretreated MBC patients regardless of breast cancer subtype. GP showed good tolerability and considerable clinical efficacy in this patient group. Further study would be valuable to confirm the role of low-dose GP treatment in the metastatic setting.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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