Phase II study of gemcitabine plus cisplatin in metastatic breast cancer

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Our objectives were to assess the efficacy and toxicity of gemcitabine plus cisplatin as first-line therapy in metastatic breast cancer (MBC). Patients with stage IV MBC and no prior chemotherapy for metastatic disease were treated with gemcitabine 1200 mg/m^2 on days 1 and 8, and cisplatin 75 mg/m^2 on day 1 every 21 days. Up to 6 cycles were given. A total of 46 patients with a median age of 49 years (range 24–77) and Karnofsky performance status of 80 or above were enrolled. In total, 238 cycles were administered. Of the 42 patients evaluable for response, seven (17%) achieved a complete response and 27 (64%) a partial response, for an overall response rate of 81% [95% confidence interval (CI) 69–93%]. Median time to progression was 14.9 months (95% CI 0–30.2 months). Median duration of response was 24.2 months (95% CI 11.2–37.3 months). The median survival was 27.9 months (95% CI 23.1–32.7 months), and the 1- and 2-year survival probabilities were 71.4 and 61.4%, respectively. All patients were evaluable for toxicity, and grade 3/4 WHO toxicities included neutropenia (41.3%), anemia (8.7%), thrombocytopenia (8.7%), alopecia (26.1%) and nausea/vomiting (32.6%). We conclude that gemcitabine plus cisplatin is a highly effective and safe first-line treatment for patients with MBC. The time to progression of 14.9 months compares favorably with other standard treatments (anthracyclines, taxanes). A randomized study is required to further investigate the role of this combination as first-line treatment for MBC. *Anti-Cancer Drugs* **17:565–570 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Breast cancer is a cause of significant cancer-related mortality worldwide [1]. For patients with resectable disease, chemotherapy given in the adjuvant setting can yield meaningful improvements in both time to disease progression and overall survival [2]. Unfortunately, most patients develop metastatic disease with limited survival (about 3 years from diagnosis), and require chemotherapy to palliate symptoms and improve health-related quality of life (HRQoL) [2].

Anthracyclines are among the most active agents used in the treatment of advanced breast cancer, yielding response rates of approximately 20–40% as single agents and up to 60% when given as part of combination regimens in the first-line setting [3]. However, many patients who have relapsed from prior anthracycline exposure in the adjuvant setting are resistant to anthracyclines. Additionally, anthracyclines can cause considerable cardiac toxicity. Because of anthracycline resistance and its potential cardiotoxicity and low overall survival rates in metastatic breast cancer (MBC), it is important to find new treatment options in the management of this disease.

Gemcitabine (difluorodeoxycytidine), a pyrimidine antimetabolite [4], has undergone considerable testing in various malignancies, and has exhibited activity in pancreatic cancer, non-small cell lung cancer, cisplatin-refractory ovarian carcinoma, bladder cancer and advanced breast carcinoma [5–9]. Phase II studies investigating the role of single-agent gemcitabine in the treatment of breast cancer differ in efficacy rates based on the dosing regimen and pre-treatment status of the patients [9–16]. Gemcitabine, however, has shown response rates of around 25% even in mostly pre-treated patients with MBC [9,12–16]. Gemcitabine therapy is well tolerated, with moderate myelosuppression being the primary toxicity. The unique mechanism of action and manageable toxicity profile of gemcitabine make it an ideal partner for combination therapy.

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Cisplatin has significant activity in most solid tumors, but was not considered an active agent for breast cancer until the 1990s [17]. Many clinical studies have shown that it has marked activity, especially in previously untreated patients with MBC in whom overall response rates have been up to 54% [18,19]. Predominant toxicities associated with cisplatin administration are nephrotoxicity, peripheral neuropathy and ototoxicity.

Combination chemotherapy is commonly used in the treatment of breast cancer with the rationale that bringing together active agents with different mechanisms of action and non-overlapping toxicities, such as gemcitabine and cisplatin, will increase the treatment benefit without significantly increasing morbidity or worsening in HRQoL. Gemcitabine and cisplatin have also demonstrated synergy in preclinical studies [20]. Exposure to cisplatin causes an activation of DNA repair polymerases and thereby enhances the incorporation of gemcitabine triphosphates into DNA repair patches. Once integrated into DNA, gemcitabine is not readily recognized and excised by proofreading exonucleases, and may trigger signaling pathways leading to apoptosis.

On this basis, we conducted a study to evaluate the efficacy and toxicity of combination therapy with gemcitabine plus cisplatin in patients with MBC. The main objective of the study was to determine the tumor response rate of the combination. Secondary objectives were to characterize the nature of the toxicity, and to evaluate the duration of response, time to progressive disease and overall survival. A preliminary report of this investigation was presented earlier [21].

Patients and methods

Eligibility criteria

To be eligible for enrollment, female patients had to be 18 years or older; with histologically or cytologically confirmed diagnosis of stage IV MBC as per the American Joint Committee on Cancer; measurable disease, as defined by a bidimensionally measurable lesion of at least 1 cm × 1 cm upon evaluation by physical examination, chest X-ray, computerized tomography (CT) scan or magnetic resonance imaging (MRI); a Karnofsky performance status (PS) ≥ 60; and a life expectancy of > 12 weeks. Prior radiation therapy was allowed as long as the radiation therapy was completed 4 weeks before receiving the study drug and the irradiated area was not the only source of measurable disease. Patients may have received prior adjuvant therapy (excluding gemcitabine) at least 6 months prior to enrollment, but prior chemotherapy for metastatic disease was not allowed. Hormonal therapy was permitted until the time of enrollment. Additional inclusion criteria included adequate bone marrow reserve [white blood cell count $\geq 3.0 \times 10^9$/l, absolute neutrophil count (ANC) 1.5×10^9/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin $\geqslant 90$ g/l), signed informed consent, and geographic proximity to the treatment center to facilitate patient compliance and adequate follow-up.

Patients were excluded from the study if they had extensive radiation therapy involving $> 30\%$ of the hemopoietic bone marrow in the 4 weeks preceding study therapy, or central nervous system metastasis, or if they had bone metastasis, pleural effusion or ascites as the only site of metastasis. Additional exclusion criteria were inadequate liver and renal function, creatinine levels > 1.25 times the upper normal limit, calcium above the upper normal limit, previous cancer within the last 5 years or a second primary malignancy (except *in situ* carcinoma of the cervix or adequately treated basal cell carcinoma of the skin). Pregnancy was not allowed during the study and for 3 months after the study.

Study design and treatment

This was a multicenter, unblinded, non-randomized phase II study of gemcitabine and cisplatin in patients with MBC. Up to 46 patients were planned in a two-stage sequential study. Of the 15 patients enrolled in the first stage, if less than six patients responded to the gemcitabine plus cisplatin therapy, then the accrual was to be stopped and the study discontinued. If at least six patients responded to the above treatment, another 31 patients were to be enrolled in the second stage of the study. This strategy was to ensure that a response in 23 of the 46 patients (response rate of 50%) would produce a 95% confidence interval (CI) of 38–62%.

Gemcitabine 1200 mg/m^2 was administered i.v. over 30–60 min on days 1 and 8, and cisplatin 75 mg/m^2 was given i.v. over 30–120 min after the gemcitabine infusion on day 1 of each 21-day cycle. Patients received i.v. hydration prior to treatment according to institutional guidelines. Patients also received full supportive care and growth factors for prolonged myelosuppression. Patients who demonstrated complete response (CR) or partial response (PR) were given 2 additional cycles of treatment, after confirmation of best response, for a maximum of 6 cycles. All patients received a maximum of 6 cycles of treatment except when discontinued for disease progression, unacceptable toxicity or patient decision.

Dose adjustments

Within a cycle, the gemcitabine dose was reduced by 25% for ANC between 0.5 and 0.99×10^9/l or platelet counts between 50 and 74×10^9/l, or held for ANC or platelet counts below the above described numbers. Similarly, the gemcitabine dose was reduced by 25% for WHO grade 3 non-hematologic toxicities (except nausea, vomiting and alopecia) and was held for grade 4 non-hematologic toxicities depending upon the judgment of the physician. If a day 8 gemcitabine dose was held or missed, the cycle

was continued per protocol with one dose not given. If calculated creatinine clearance was below 45 ml/min/1.73 m^2 or grade 3 or 4 neurotoxicity occurred, cisplatin was withdrawn. When the calculated creatinine clearance was 45–59 ml/min/1.73 m^2, hydration was intensified and cisplatin treatment continued.

For subsequent cycles, the cisplatin dose and both gemcitabine doses were reduced by 25% in the event of grade 4 thrombocytopenia, bleeding associated with thrombocytopenia or febrile neutropenia. If grade 3 or 4 neurotoxicity occurred, the treatment cycle was delayed until the toxicity resolved to grade 2 or less. For any other grade 3 toxicity (except nausea/vomiting and alopecia), the cisplatin dose was reduced by 25% and both gemcitabine doses were reduced by 50%. In the event of grade 4 toxicity, both the cisplatin and gemcitabine doses were reduced by 50% or held, depending on the judgment of the physician. A patient who could not be administered treatment for 6 weeks was discontinued from the study.

Baseline and follow-up evaluations

Baseline assessments performed in the week before enrollment included medical history, physical examination, measurement of palpable or visual lesions, Karnofsky PS and chest X-ray. If necessary, radiologic imaging tests (CT scan, MRI and nuclear medicine scan) for measuring tumors were carried out within 2 weeks of enrollment. Efficacy was evaluated at the beginning of each cycle via measurements of weight, PS and physical examination, and before every other cycle via chest X-ray and/or radiologic imaging methods. For a given patient, the evaluation technique for tumor measurement was consistent throughout the study. After completion of study treatment, patients were evaluated at 3-month intervals until progressive disease (PD).

All patients who completed 1 cycle of treatment were included in the response analysis using the modified WHO criteria [22]. The duration of PR was measured from the time of initial administration of gemcitabine and cisplatin until the date of the first observation of PD. The duration of CR was measured from the time of documentation of CR until the date of the first observation of PD. Time to PD was defined as the time from the start of the treatment to the date of PD, lost to follow-up or death. Survival was measured from the administration of the first dose until death.

Safety assessments carried out prior to enrollment and throughout the study were complete blood counts, blood chemistries, urinalysis and vital signs. The number of units required for transfusion at every cycle was also noted. Toxicity was evaluated at the end of each cycle using WHO criteria. All patients who received at least one dose of gemcitabine and cisplatin were evaluated for safety.

This study was conducted according to the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual.

Statistical methods

Tumor response rate evaluations included 95% CIs. Estimates of time to PD, duration of response and survival were calculated using the Kaplan–Meier method. Kaplan–Meier analyses were conducted using the PROC LIFETEST in Statistical Application Software.

Results

Patient characteristics

The study was completed between August 1999 and December 2000. A total of 46 women with MBC from six institutions in Mexico were entered into the study. Patient demographics and baseline clinical characteristics are summarized in Table 1. The median age was 49 years (range 24–77 years). Most patients had a high Karnofsky PS (83% of patients 90 or above) and 35% of patients had visceral metastases. Half of the patients received prior adjuvant anthracycline-based chemotherapy.

Tumor response

Of the 46 patients enrolled, four patients were not considered evaluable for response because they received less than 1 cycle of study therapy. Of the 42 evaluable patients, 34 had CR or PR, for an overall response rate (ORR) of 81% (95% CI 69–93%); eight patients (19%) had PD. The median duration of response was 24.2 months (95% CI 11.2–37.3 months).

Response by tumor site is summarized in Table 2; all tumors at the primary site, and in lung and bone, showed a response of 100%. Only liver and soft tissue showed comparatively smaller responses.

Table 1 Patient characteristics

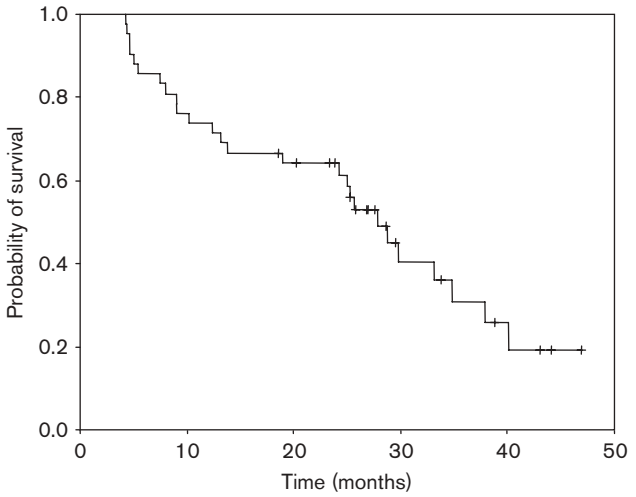
No. patients	46
Median age [years (range)]	49 (24–77)
Karnofsky PS [*n* (%)]	
100	17 (37%)
90	21 (46%)
80	8 (17%)
Major tumor metastatic sites [*n* (%)]	
bone	1 (2.1%)
liver	8 (16.3%)
soft tissues	32 (65.3%)
lung	8 (16.3%)
No. metastatic sites [*n* (%)]	
1	43 (93.5%)
2	3 (6.5%)
Prior adjuvant therapy [*n* (%)]	23 (50%)

Table 2 Tumor response by site

Site[a]	No. responses/total no. sites	%
Primary tumor	17/17	100
Lung metastases	7/7	100
Bone metastases	1/1	100
Liver metastases	4/7	57
Soft tissue metastases	24/29	83

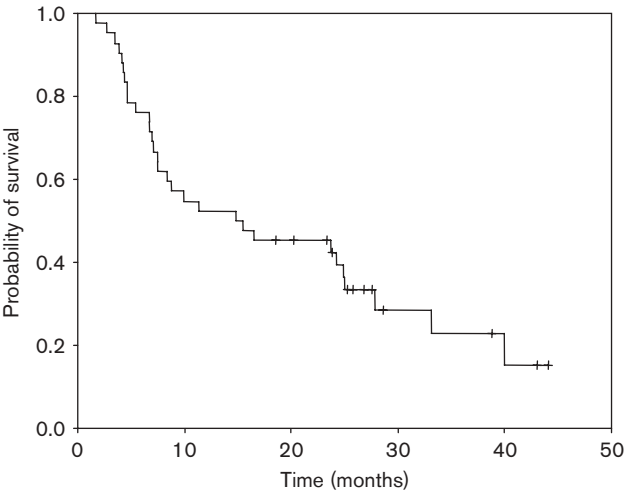
[a]There were 44 metastatic sites evaluated in 42 evaluable patients; two patients had two metastatic sites (liver/soft tissue and lung/soft tissue, respectively).

Fig. 1



Kaplan–Meier estimate of overall survival (months).

Fig. 2



Kaplan–Meier estimate of time to progressive disease (months).

Of the 23 patients who received prior adjuvant therapy, 18 (78.3%) achieved responses (five CR and 13 PR). Of the 19 patients who did not receive prior adjuvant therapy, 16 (84.2%) achieved responses (two CR and 14 PR). There were no statistically significant differences between the ORRs of the subgroups ($P = 0.62$).

At the time of the final analysis, 16 patients were alive and 30 patients had progressed. From the start of chemotherapy to the time of final analysis, the median follow-up time was 25.1 months. The median survival time was 27.9 months (95% CI 23.1–32.7 months) with a 38.1% censoring rate and median time to PD was 14.9 months (95% CI 0–30.2 months) with a 28.6% censoring rate. Kaplan–Meier curves for overall survival and time to PD are provided in Figs 1 and 2, respectively. The 1- and 2-year survival rates were 71.4 and 61.4%, respectively.

Dose intensity

In total, 238 cycles were administered with a median of 6 cycles per patient (range 2–6). Of all the planned infusions, there were 83 dose reductions (18%) and 26 dose omissions (6%) for gemcitabine. All of the gemcitabine dose omissions were associated with day 8. For cisplatin, there were 10 dose reductions (4%) and no dose omissions. Thirteen patients (28%) had cycle delays. Dose delays occurred for gemcitabine in 22 cycles (9%) and for cisplatin in 46 cycles (19%). The most common reason for these dose adjustments was febrile neutropenia. The relative dose intensities for gemcitabine and cisplatin were 78.7 and 90.1%, respectively.

Toxicity

All 46 patients were evaluable for toxicity. No deaths occurred during the study. WHO grade 3 and 4 toxicities are reported in Table 3. Neutropenia was the most commonly reported toxicity (36% of patients), followed by nausea/vomiting (33%) and alopecia (26%). Febrile neutropenia occurred in two patients (4.3%). None of the patients developed grade 3/4 neurotoxicity, nephrotoxicity or ototoxicity. The four patients who had grade 3/4 thrombocytopenia required platelet transfusions. Grade 3/4 anemia was seen in 9% of the patients. Three of the four patients who had grade 3/4 anemia received red blood cell transfusions. No patients were discontinued from the study due to treatment-related toxicities.

Discussion

The present study, exploring activity of gemcitabine plus cisplatin as first-line treatment for patients with MBC, found the treatment to be highly effective and well tolerated. Of the 42 efficacy evaluable patients, 17% achieved CR and 64% achieved PR, for an impressive ORR of 81%. The median survival of 27.9 months and median time to PD of 14.9 months are also highly encouraging.

Single-agent gemcitabine has been shown effective as both first- and second-line treatment of MBC. Single-agent gemcitabine, administered at 1200 mg/m^2 on days 1, 8 and 15 of a 4-week cycle, has achieved an ORR of 37% in the first-line setting (median time to PD of 5.1 months) [10] and 29% in the second- or third-line setting [13].

Single-agent cisplatin, applied in the first-line setting at a dose of 30 mg/m^2 on days 1–4 over 4-week cycles, produced ORRs of 47 to 54% [18,19]. In pre-treated patients with MBC, however, cisplatin at doses of 15–120 mg/m^2 given over 3- or 4-week treatment cycles produced low response rates not exceeding 15% [23–27]. Thus, single-agent cisplatin appears more effective in the first-line setting.

There is speculation that prior treatment with anthracyclines or other drugs may induce cisplatin drug resistance, thereby causing lower cisplatin responses in the pre-treated patients. Alternatively, it has been suggested that drug resistance to cisplatin may be overcome when used in combination chemotherapy [28]. This and the fact that gemcitabine and cisplatin are usually not given as adjuvant or neoadjuvant chemotherapy supports the use of this combination as first-line treatment of patients with MBC.

The combination of gemcitabine and cisplatin in patients with MBC has only been tested in phase II studies to date. Various doses and schedules of gemcitabine and cisplatin have been explored using 3- or 4-week treatment cycles (Table 4) [29–33]. Compared to the results of these studies, our present regimen obtained superior efficacy (ORR of 81%, median time to PD of 14.9 months); however, our patients were either chemonaive or treated only in adjuvant settings compared to mostly pre-treated patients (for metastatic disease) in the published studies.

Currently, anthracycline-based regimens are the standard for first-line treatment of MBC. In one long-term follow-up study of more than 1500 patients (84% of patients chemonaive), the fluorouracil, doxorubicin and cyclophosphamide regimen achieved an ORR of 65% and a median progression-free survival of 11.5 months [3]. A phase II study by GEICAM used two of the most widely used drug classes in the first-line treatment of MBC, anthracyclines and taxanes, which were used as single agents or in combination [34]. Patients treated with doxorubicin alone achieved an ORR of 54%, while patients treated with doxorubicin plus docetaxel achieved an ORR of 74%. These results underscore the encouraging results obtained in our study of gemcitabine plus cisplatin in the first-line setting.

Overall, the major hematologic toxicities associated with the combination of gemcitabine and cisplatin have been neutropenia and thrombocytopenia, and the major non-hematologic toxicities have been nausea/vomiting, nephrotoxicity and neurotoxicity [21,29–33]. The most prevalent hematologic toxicities observed in our study were neutropenia and leukopenia, with no severe (grade 3/4) neurotoxicity, ototoxicity or nephrotoxicity observed. The excellent PS, median age of 49 years and no prior chemotherapy in the metastatic setting, with only half of the patients having had chemotherapy in the adjuvant setting, may explain the better tolerability observed with our regimen.

Several studies using gemcitabine plus cisplatin as a 4-week regimen in the treatment of MBC encountered hematologic toxicities that often resulted in the reduction of gemcitabine doses on day 15 [30–32]. In the present study, the 3-week treatment cycle with gemcitabine doses given on days 1 and 8 may have been partly responsible for the acceptable toxicity profile and the

Table 3 WHO grade 3 and 4 toxicities ($n=46$)

Toxicity	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Hematologic		
neutropenia	12 (26.1)	7 (15.2)
leukopenia	12 (26.1)	2 (4.3)
thrombocytopenia	3 (6.5)	1 (2.2)
anemia	4 (8.7)	0
Non-hematologic		
alopecia	12 (26.1)	0
nausea/vomiting	14 (30.4)	1 (2.2)
alanine aminotransferase/aspartate aminotransferase	1 (2.2)	0

Table 4 Phase II studies of gemcitabine plus cisplatin

Author	*n*/response evaluable	Regimen (doses in mg/m^2)	ORR (complete response rate) (%)	Median time to PD (months)
Nagourney *et al.* [29]	30/30	gemcitabine 1000; cisplatin 30; d1, 8, 15; q4w[a]	50 (10)	second or third line: 5.5; fourth line or above: 3.5
Chaudhry *et al.* [30]	28/28	gemcitabine 1000; cisplatin 25 d1, 8, 15; q4w	39 (3)	NA
Burch *et al.* [31]	21/21	gemcitabine 1000; cisplatin 25 d1, 8, 15; q4w	29 (4)	7.1
Galvez *et al.* [32]	41/41	gemcitabine 1200 d1, 8, 15; cisplatin 50 d1; q4w	49 (4)	5.2
Doroshow *et al.* [33]	55/44	gemcitabine 1000 d2, 8; cisplatin 25 d1–4; q3w	34 [moderately pretreated=43 (9); heavily pretreated=26 (8)]	first line: 8.3; second line: 3.7; third line or above: 3.5

[a]After 12 patients, the regimen was changed to gemcitabine 750; cisplatin 30; d1, 8; q3w.

adequate mean dose intensities achieved (79% for gemcitabine and 90% for cisplatin).

In conclusion, the present study applying the combination of gemcitabine and cisplatin therapy as first-line treatment of patients with MBC is highly effective and safe with a manageable toxicity profile. The absence of severe (grade 3/4) neurotoxicity, nephrotoxicity, ototoxicity and the lower incidence of hematologic toxicity compared to those of other published regimens are favorable features of the current regimen. The high response rates (81% ORR with a 17% CR) and the comparatively longer time to progression (14.9 months) place this treatment on par with the best available treatment regimens in the first-line treatment of MBC. Randomized phase III studies are warranted to compare this regimen with widely used regimens to substantiate the best options for the treatment of patients in this setting.

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