original research report

# A phase 2 study of the combination of gemcitabine and cisplatin in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines with/without taxanes

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**BACKGROUND AND OBJECTIVES:** Many patients with relapsed metastatic breast cancer are pre-treated with taxanes and anthracyclines, which are usually given in the neoadjuvant/adjuvant setting or as first-line treatment for metastatic disease. The primary objective of this study was to determine the overall response rate for combination treatment with gemcitabine and cisplatin in patients with locally advanced or metastatic breast cancer who had relapsed after receiving one adjuvant/neoadjuvant or first-line metastatic chemotherapy regimen containing an anthracycline with/without a taxane. Secondary endpoints included duration of response, time to progression, one-year survival probability, and toxicity.

**DESIGN AND SETTING:** A single-arm, open-label, phase 2 study conducted at 17 investigative sites in Egypt.

**PATIENTS AND METHODS:** Treatment consisted of gemcitabine (1250 mg/m$^2$) on Days 1 and 8 and cisplatin (70 mg/m$^2$) on Day 1 of each 21-day cycle. Treatment continued until disease progression or a maximum of 6 cycles.

**RESULTS:** Of 144 patients all were evaluable for safety and 132 patients were evaluable for efficacy. The overall response rate was 33.3% and 45.5% of the patients with stable disease as their best response. The median time to progression was 5.1 months and the one-year survival probability was 73%. The most common grade 3/4 adverse events were nausea/vomiting (20.1%), neutropenia (19.4%), anemia (13.9%), asthenia (11.1%), diarrhea (9.7%), stomatitis (7.6%), leucopenia (7.6%), and thrombocytopenia (6.2%). Twelve (8.3%) patients had serious adverse events.

**CONCLUSIONS:** The results of this study indicate that gemcitabine and cisplatin were active and generally well tolerated in pretreated patients with locally advanced or metastatic breast cancer.

In Egypt, breast cancer is the most common cancer among women.[1] Many patients with relapsed metastatic breast cancer are pre-treated with taxanes and anthracyclines, which are usually given in the neoadjuvant/adjuvant setting or as first-line treatment for metastatic disease. These women require effective and well-tolerated treatment options, particularly after early relapse following adjuvant taxane-based treatment.

Gemcitabine has previously been studied in phase 1 and 2 clinical trials as monotherapy or combination therapy for advanced or metastatic breast cancer. Response rates of 12% to 46% have been observed

when gemcitabine was given as a single agent to previously treated or untreated patients with advanced or metastatic breast cancer.[2-10] Response rates of 26% to 50% have been observed for gemcitabine in combination with cisplatin in heavily pretreated patients with metastatic breast cancer.[11-13]

We conducted a phase 2 study to examine the efficacy and safety of combination therapy with gemcitabine and cisplatin in patients with locally advanced or metastatic breast cancer who had relapsed after receiving one prior chemotherapy regimen containing an anthracycline (with or without a taxane) as adjuvant or neoadjuvant therapy or as first-line therapy for metastatic disease.

## METHODS

This single-arm, non-randomized, open-label phase 2 study was conducted at 17 investigative sites in Egypt. The first patient was enrolled in July 2002 and the last patient visit was in March 2005. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the ethics review board at each investigative site. All patients provided written informed consent before participating in the study.

Female patients, aged 18 to 75 years, with a histological or cytological diagnosis of breast cancer with evidence of unresectable, locally recurrent or metastatic disease (not amenable to surgery or radiation treatment of curative intent) were eligible for this study. Other inclusion criteria included a Karnofsky performance status of >70%; prior treatment with one anthracycline-containing chemotherapy regimen (with or without taxanes) in the neoadjuvant/adjuvant setting or as first-line treatment for metastatic disease with subsequent documented disease progression, a bidimensionally measurable lesion with clearly defined margins on x-ray, computed tomography (CT) scan, or physical examination, an estimated life expectancy of ≥6 months and adequate bone marrow reserve, liver and renal function. Previous hormonal therapy in the adjuvant setting or for local recurrence of metastatic disease was allowed and previous therapy with humanized anti-HER2 antibody was permitted. Prior radiation therapy was permitted if the irradiated area was not the only source of measurable disease and there was ≥2 weeks between the end of radiotherapy and study entry. Exclusion criteria included known brain metastasis, serious concomitant systemic disorders, bone metastasis, pleural effusion, or ascites as the only site of disease, and radiation of >20% of the total bone marrow producing areas.

Gemcitabine (1250 mg/m$^2$) was given intravenously over approximately 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin (70 mg/m$^2$) was given intravenously over approximately 3 hours on Day 1 of each 21-day cycle. Cisplatin was given according to institutional guidelines with appropriate pre- and post-infusion hydration. Study treatment was intended to continue for a maximum of 6 cycles, but was discontinued prematurely in the event of disease progression, unacceptable toxicity, or the patient or physician requested discontinuation.

Study treatment could be delayed for up to 4 weeks to allow patients time to recover from treatment-related toxicity. Patients were discontinued if a cycle was delayed for >4 weeks due to toxicity. Study drug doses were reduced by one level at the start of a cycle (a maximum of two dose level reductions were allowed) in the event of an absolute neutrophil count (ANC) $<0.5\times10^9$/L for >5 days or $<0.1\times10^9$/L for >3 days; febrile neutropenia; platelets $<25\times10^9$/L for ≥3 days; a cycle delay of >1 week due to toxicity; or grade 3 non-hematologic toxicity (except nausea, vomiting, or alopecia). Dose level -1 was 1000 mg/m$^2$ gemcitabine on Days 1 and 8 and 50 mg/m$^2$ cisplatin on Day 1. Dose level -2 was 800 mg/m$^2$ gemcitabine on Days 1 and 8 and cisplatin was omitted. Study treatment was withheld in the event of grade 4 non-hematologic toxicity.

The following dose adjustments were required within a cycle. The gemcitabine dose on Day 8 was reduced to 1000 mg/m$^2$ if the patient's ANC was between 1 to $\leq1.5\times10^9$/L and/or the thrombocyte count was between 75 to $99\times10^9$/L. The gemcitabine dose on Day 8 was omitted if neutrophil and/or thrombocyte counts were $<1\times10^9$/L and $<75\times10^9$/L, respectively. Gemcitabine was discontinued in the event of ≥grade 3 pulmonary toxicity. In the event of grade 3 non-hematologic toxicity (other than nausea, vomiting, or alopecia), the gemcitabine dose on Day 8 was reduced to 1000 mg/m$^2$ or withheld. Gemcitabine was omitted on Day 8 in the event of grade 4 non-hematologic toxicity (except alopecia). Cisplatin was reduced to 80% or withheld, at the discretion of the investigator, due to tinnitus or clinically significant hearing loss.

Full supportive care therapies were permitted during the study except for the prophylactic use of growth factors. Concomitant therapy with any other anti-cancer therapy or experimental treatment was not allowed. Palliative radiation was permitted for painful metastases if indicator lesions were not irradiated, a limited target volume was used, and it did not interfere with study therapy continuation.

The clinical investigators performed all of the assessments. Screening assessments occurred within 1 to

2 weeks before study therapy initiation and included a medical history, physical examination, tumor assessment, and electrocardiogram and assessment of concomitant medications, vital signs, performance status (PS), and the collection of blood samples. At the beginning of each cycle, weight, PS, concomitant medications, pre-existing conditions, and adverse events were assessed and a limited physical exam was performed. Blood samples for standard laboratory tests were collected within 48 hours of the start of chemotherapy on Days 1 and 8 of each cycle.

Tumor assessments were completed within 2 weeks before study therapy initiation and approximately every 6 weeks during study therapy. Tumor responses were categorized according to the World Health Organization's (WHO) response criteria.[14] After study treatment discontinuation, follow-up visits were scheduled every 3 months and included the assessment of additional anti-cancer treatment, tumor assessment (for patients without documented progression), and survival. Adverse events were monitored up until 30 days after the last dose of study drug, after which only serious, study drug-related adverse events were reported. Toxicity was graded according to the WHO's recommendations[14] except for neurotoxicity, which was graded according to the National Cancer Institute's Common Toxicity Criteria (NCI CTC).

The primary objective of this phase 2 study was to determine the overall response rate for combination therapy with gemcitabine and cisplatin in patients with locally advanced or metastatic breast cancer who had relapsed after receiving one prior chemotherapy regimen containing an anthracycline (with or without a taxane) as adjuvant or neoadjuvant therapy or as first-line therapy for metastatic disease. The secondary objectives of this study were to determine the duration of response, time-to- disease progression (TTP), 1-year survival, overall survival (OS), and to characterize the nature of toxicity.

The primary outcome measure was the overall tumor response rate, which was calculated by dividing the number of patients with a best clinical response of a complete response (CR) or a partial response (PR) by the number of patients in the tumor analysis population and multiplying by 100. The enrollment target for this study was 150 patients, which was estimated to allow an accurate determination of a tumor response rate of 50% with a 95% confidence interval (CI) of 42% to 58%. Secondary efficacy endpoints were Kaplan-Meier analyses for the duration of response, TTP, one-year survival, and OS. Duration of response was calculated from the date of the first documentation of a CR or PR until the date of disease progression or death due to any cause, and was censored at the date of the last tumor assessment for patients who had not died and did not have disease progression. TTP was calculated from the date of randomization to the date of documented progression, and was censored at the date of the last tumor assessment for patients without documented progression or the date of death for patients who died before disease progression. OS was calculated from the date of randomization to the date of death, and was censored at the last contact date for patients who were still alive at the end of the study.

All enrolled patients were included in the tumor response analysis if they had received prior chemotherapy with an anthracycline-based regimen (with or without a taxane) and no more than one previous chemotherapy regimen for metastatic disease, had not received any excluded concomitant therapy, and had bidimensionally measurable disease. Responding patients in the tumor analysis population were included in the analysis of duration of response. All other secondary efficacy measures were analyzed using all the enrolled patients, and the safety measures were analyzed using all of the enrolled patients who received ≥1 dose of study therapy.

Statistical analyses were performed by statisticians at Eli Lilly and Company (the sponsor of this study) using SAS® software, versions 8 and 9 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

A total of 144 patients were enrolled and received at least one dose of study therapy. All 144 patients were included in the safety analysis population and 132 (91.7%) patients with evaluable tumor responses were included in the efficacy analysis population. A total of 56 (38.9%) patients completed study treatment and 88 (61.1%) patients discontinued early, predominantly due to PD (n=55; 38.2%), but also because of patient (n=14; 9.7%), or physician decision (n=7; 4.9%).

**Table 1** summarizes baseline characteristics of the patients. The median age was 47.5 years and 68.1% of the patients were postmenopausal. Most (91.0%) patients had a pathological diagnosis of ductal breast carcinoma and metastatic disease (99.3%) at study entry. Most patients had received prior surgery (91.7%) and/or prior adjuvant chemotherapy (83.3%). Less than half of the patients (41.7%) had received prior chemotherapy for locally advanced or metastatic disease. A total of 108 (75.0%) patients had received prior anthracycline treatment in the adjuvant setting and 42 (29.2%) patients had received prior anthracycline treatment for locally advanced or metastatic disease.

All 144 patients received at least one dose of study

**Table 1.** Baseline patient characteristics (N=144).

| Characteristics | n (%) |
|---|---|
| **Age, years** | |
| Median | 47.5 |
| Range (minimum-maximum) | 26-67 |
| **Karnofsky performance status** | |
| Median score | 90 |
| >70% to ≤ 80% | 55 (38.2) |
| >80% to ≤ 100% | 89 (61.8) |
| **Menopausal status** | |
| Post-menopausal | 98 (68.1) |
| Pre-menopausal | 46 (31.9) |
| **Estrogen receptor (ER) status** | |
| ER negative | 41 (28.5) |
| ER positive | 60 (41.7) |
| Unknown | 43 (29.9) |
| **Progesterone receptor (PR) status** | |
| PR negative | 46 (31.9) |
| PR positive | 49 (34.0) |
| Unknown | 49 (34.0) |
| **Pathological diagnosis** | |
| Ductal breast carcinoma | 131 (91.0) |
| Lobular breast carcinoma | 8 (5.6) |
| Medullary breast carcinoma | 1 (0.7) |
| Others | 4 (2.8) |
| **Time since initial diagnosis, years** | |
| Median | 2.3 |
| Range (minimum-maximum) | 0.3-12.9 |
| **Disease stage at study entry** | |
| Locally advanced | 1 (0.7) |
| Metastatic | 143 (99.3) |
| **Previous treatment** | |
| Surgery | 132 (91.7) |
| Adjuvant chemotherapy | 120 (83.3) |
| Adjuvant hormonal therapy or immunotherapy | 72 (50.0) |
| Radiotherapy | 99 (68.7) |
| Chemotherapy for LA or MBC | 60 (41.7) |
| Hormonal therapy for LA or MBC | 34 (23.6) |

**Table 1 cont.** Baseline patient characteristics (N=144).

| Characteristics | n (%) |
|---|---|
| **Prior adjuvant chemotherapy** | |
| Median time since treatment ceased, years | 1.9 |
| Median number of cycles given | 6 |
| **Prior chemotherapy for LA or MBC** | |
| Median time since treatment ceased, years | 0.3 |
| Minimum-maximum time since treatment ceased, years | 0.0-2.6 |
| **Measurable disease** | |
| Median number of sites | 2 |
| 1 site | 50 (34.7) |
| 2 sites | 47 (32.6) |
| ≥3 sites | 47 (32.6) |

n=number of patients with data; LA=locally advanced breast cancer; MBC=metastatic breast cancer.

therapy (cisplatin and gemcitabine on Day 1 of Cycle 1) and 527 complete cycles of study therapy were administered. A total of 88 patients received both study drugs on Day 1 of Cycle 4 (76 of these patients also received the Day 8 dose of gemcitabine in Cycle 4), and 63 patients received both study drugs on Day 1 of Cycle 6, of whom 59 patients also received the Day 8 dose of gemcitabine in Cycle 6. A total of 56 patients (38.9%) successfully completed the 6 cycles of study therapy, according to the study protocol's requirements. The most common reasons for premature study therapy discontinuation were disease progression (n=55), patient's decision (n=14), physician's decision (n=7), and less to follow-up (n=5).

A total of 46 (31.9%) patients received at least one dose of additional anticancer therapy after study therapy discontinuation, which was predominantly chemotherapy (36/46, 78.3%) and/or hormonal, biological or immunotherapy (23/46, 50.0%).

In the tumor response population, 5 patients (3.8%) had a CR as their best clinical response and 39 patients (29.5%) had a PR, resulting in an overall response rate of 33.3%. An additional 60 patients (45.5%) had stable disease (SD) as their best response and, therefore, the disease control rate was 78.8%. The median duration of response for the 44 responding patients was 5.8 months (95% CI: 4.5-12.4 months).

The median TTP was 5.1 months (95% CI: 4.2-6.2 months). The Kaplan-Meier (KM) curve for TTP is

**Table 2.** Summary of the most common treatment-emergent adverse events (≥10.0% overall).

| Adverse event | Grade 1 or 2 n (%) | Grade 3 or 4 n (%) | Overall n (%) |
|---|---|---|---|
| Nausea/vomiting | 56 (38.9) | 29 (20.1) | 85 (59.0) |
| Anemia | 33 (22.9) | 20 (13.9) | 53 (36.8) |
| Neutropenia | 24 (16.7) | 28 (19.4) | 52 (36.1) |
| Leucopenia | 28 (19.4) | 11 (7.6) | 39 (27.1) |
| Asthenic conditions | 22 (15.3) | 16 (11.1) | 38 (26.4) |
| Appetite disorder | 29 (20.1) | 5 (3.5) | 34 (23.6) |
| Diarrhea[a] | 20 (13.9) | 14 (9.7) | 34 (23.6) |
| Stomatitis and ulceration | 14 (9.7) | 11 (7.6) | 25 (17.4) |
| Gastritis[a] | 23 (16.0) | 0 (0.0) | 23 (16.0) |
| Bone-related signs and symptoms | 18 (12.5) | 1 (0.7) | 19 (13.2) |
| Thrombocytopenia | 9 (6.2) | 9 (6.2) | 18 (12.5) |
| Alopecia | 16 (11.1) | 0 (0.0) | 16 (11.1) |

Values based on World Health Organization (WHO) severity criteria.
[a]Excluding infective diarrhea or gastritis.

shown in **Figure 1**. Fifty-one patients died during the study period, and 41 of these deaths were related to study disease, 1 was considered to be study drug-related, and 9 were due to other causes. The KM estimate of one-year survival probability was 73.4% (95% CI: 65.1-81.6%). Median OS was not reached. The KM curve for OS is shown in **Figure 2**. Ninety-three patients (64.6%) were censored in the KM analysis of OS and the median follow-up time for OS was 15.6 months (95% CI: 14.3-16.6 months).

The most common (≥10.0%) treatment-emergent adverse events (TEAEs) are summarized in **Table 2**. The most common (≥5.0%) grade 3 or 4 TEAEs were nausea/vomiting (20.1%), neutropenia (19.4%), anemia (13.9%), asthenic conditions (11.1%), diarrhea (9.7%), stomatitis and ulceration (7.6%), leucopenia (7.6%), and thrombocytopenia (6.2%). There were a total of 12 serious adverse events reported, including diarrhea (n=3), vomiting (n=1), abdominal cramps (n=1), acute myocardial infarction (n=1), and cardiac arrest (n=1). Four patients were hospitalized during the study due to adverse events. Thirty patients required 98 transfusions during the study (packed cell, n=74; whole blood, n=16; platelets, n=6; other, n=2).

## DISCUSSION

Due to the frequent use of anthracycline- and taxane-based regimens in the adjuvant and neoadjuvant settings, there is a need for effective, non-cross-resistant chemotherapeutic agents with minimal toxicity for the treatment of advanced breast cancer. The combination of gemcitabine and cisplatin is one of the most widely investigated gemcitabine combinations in metastatic breast cancer. To our knowledge, this was the largest phase 2 study conducted to date to examine the efficacy and safety of gemcitabine and cisplatin in women with unresectable, locally recurrent or metastatic breast cancer whose disease had progressed following prior treatment with one anthracycline-containing chemotherapy regimen (with or without taxanes). The results of our study showed that the study therapy was active and generally well-tolerated. The overall response rate was 33.3%, which is within the range of response rates (26.0%-62.5%) observed in previous phase 2 trials in minimally and heavily pretreated patients with advanced breast cancer following anthracycline and/or taxane failure.[12,13,15-24]

In our study, the median duration of response in the responding patients was 5.8 months and the median time to progression was 5.1 months. These time-to-event measures were not reported for most of the previous phase 2 trials, but the median duration of response ranged from 5.3 to 10.6 months in 4 of the previous studies[12,19,22,24] and median TTP ranged from 5.2 to 11.2 months in 5 previous studies.[19-23] In our study, the median TTP was relatively short, but most of the patients (99%) had metastatic disease and 33% of the patients had ≥3 sites of measurable disease. The variability in the reported efficacy outcomes following combination treatment with gemcitabine and cisplatin is at least partly due to differences in the drug doses, chemotherapy schedules, and the number of patients and their characteristics. The methodology used to calculate time-to-progression and duration of response (i.e. censoring methods) has not been reported for the majority of previous studies and may also account for some of the observed variability.

In this study, the 1-year survival probability was 73.4%, which is similar to that reported for one previous phase 2 study (71.4%) in patients with metastatic or refractory breast cancer who were pretreated with 1 or 2 previous chemotherapy regimens including anthracycline or taxane combinations.[21] Median OS was not reached in our study but ranged from 13.5 to 27.9 months in two previous trials with 16 to 38 patients with refractory or metastatic breast cancer pretreated with anthracycline- or taxane-containing chemotherapy regimens.[21,23] Both of these previous studies used lower doses of gemcitabine and cisplatin than were used in our study.

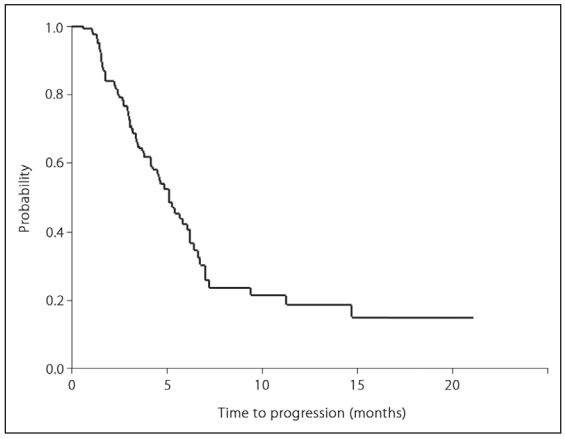


**Figure 1.** Kaplan-Meier distribution of time-to-disease progression.

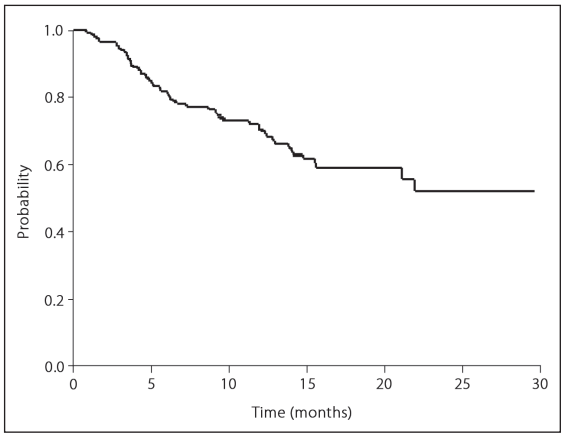


**Figure 2.** Kaplan-Meier distribution of overall survival time.

Consistent with results from previous phase 2 studies in patients pretreated with anthracyclines and/or taxanes, the most prevalent grade 3 or 4 toxicities observed in our study were neutropenia (19.4%), anemia (13.9%), leucopenia (7.6%), nausea/vomiting (20.1%), and asthenic conditions (11.1%).[12,13.15-19,21-24] However, most toxicities were mild to moderate (grade 1 or 2) and, overall, toxicity was generally manageable.

A limitation of our study design was the absence of human epidermal growth factor receptor-2 (HER2) testing. When the study was designed, the importance of the triple negative subset of metastatic breast cancer was not yet evident and HER2 testing was not routinely available at all of the participating investigative sites. Therefore, we have not been able to report the outcomes for patients with triple negative or HER2-positive disease. Nonetheless, the results of this study are consistent with those from previous phase 2 trials and indicate that the combination of gemcitabine and cisplatin was active and had an acceptable toxicity profile in anthracycline- and/or taxane-pretreated patients with advanced breast cancer. Further research is required to investigate the efficacy and safety of this combination regimen in patients with earlier stage disease or triple negative disease.

### Author contributions

*Dr Meshref was involved in the study design and management, statistical analyses, interpretation of data and drafting and reviewing the manuscript. All other authors were clinical investigators in the study and were involved in data collection and critically reviewed and approved the manuscript for submission to this journal. Dr Meshref was a full-time employee of Eli Lilly and Company, the manufacturer of gemcitabine, when the study was conducted. Rabbab Gaafar has been a consultant for Eli Lilly and a member of an advisory board for Eli Lilly. The other authors have no potential conflicts of interest to declare.*

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