original research article

A phase II study of gemcitabine combined with vinorelbine as first-line chemotherapy for metastatic breast cancer

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BACKGROUND AND OBJECTIVES: There is an unmet need for new combination treatments, especially for aggressive, visceral, and high tumor burden metastatic breast cancer. Gemcitabine (GEM) has shown synergy with vinorelbine (VRL) in preclinical models, and has a toxicity profile that is different from VRL, another recently approved cytotoxic drug that seems to be effective in the treatment of breast cancer.

PATIENTS AND METHODS: We studied the efficacy and side effects of the GEM-VRL combination as first-line chemotherapy in patients in an open-label, single arm, phase II study in patients with locally advanced or metastatic breast cancer who had been previously treated with an anthracycline-based regimen in the adjuvant/neoadjuvant setting.

RESULTS: Of the 74 patients enrolled, 72 patients were evaluable for the primary treatment outcome (tumor response rates). Four patients (6%) had a complete response and 26 patients (36%) had a partial response. Nineteen patients (26%) had stable disease. The median time to disease progression was 37 weeks (range, 1-60 weeks). Median duration of response was 43 weeks (range, 8.6 to 55 weeks) and one-year survival was 77% (95% confidence interval, 64% to 86%). Grade 3-4 neutropenia without fever was reported in 10% of patients, thrombocytopenia in 1%, and febrile neutropenia in 11%. The most common clinical grade 3-4 toxicities were nausea (24%) and diarrhea and stomatitis (11% each). Hospitalizations for adverse events mainly due to anemia, febrile neutropenia, septic shock and hepatic failure occured in 7%.

CONCLUSION: With an overall response rate of 42%, the GEM-VRL combination had promising efficacy and good tolerability in metastatic breast cancer patients.

Breast cancer is the most prevalent malignancy in women and metastatic breast cancer is a leading cause of mortality, accounting for more than 400 000 deaths annually worldwide.[1] Even though anthracyclines and taxanes are the most active agents in breast cancer, treatment failure occurs in a substantial number of patients and median survival for metastatic breast cancer remains 2 to 3 years.[2-4] Resistance to antineoplastic agents, and in particular anthracyclines and taxanes, is a limiting factor in breast cancer therapy, either after metastatic or adjuvant treatment.[3,5] With increasing use of anthracyclines and taxanes for early breast cancer, fewer effective options are available for patients with metastatic disease.[3,4] Capecitabine is commonly used for the treatment of anthracycline- and/or taxane-pretreated metastatic breast cancer; however, objective response rates in phase II studies are only 20% to 28%.[6,7] Therefore, there is an unmet need for new combination treatments, especially for aggressive, visceral and high tumor burden metastatic breast cancer.

Gemcitabine (GEM) and vinorelbine (VRL) are two of the most recently approved cytotoxic drugs that seem to be effective in the treatment of several solid tumors including breast cancer. Single VRL chemotherapy has been administered as first- and second-line treatment in advanced breast cancer. The response rate as first-line treatment has varied from 35% to 41%.[8,9] As second-line treatment, the overall response rate has been reported to be 16%, 27%, and 32%.[8,10,11] When given in combination with other drugs, the second-line response

rate was higher.[12,13] GEM is also active against breast cancer and has demonstrated single-agent response rates of approximately 20%.[14]

A short pilot study of pretreated patients[15] and a dose-finding study,[16] both in patients with metastatic breast cancer, indicated promising results, although myelotoxicity was again the dominant side effect. Data on this combination in Egyptian patients is needed to assess it as a possible option for metastatic breast cancer patients pretreated with anthracyclines in this population of patients.

PATIENTS AND METHODS

In an open label, single arm, non-randomized, unblinded phase II study in patients with locally advanced or metastatic breast cancer who had been previously treated with one anthracycline with/without taxane-based regimen in the adjuvant/neoadjuvant or first-line metastatic setting, we studied the GEM-VRL combination in a 3-weekly schedule as first-line chemotherapy. The study was conducted in five different oncology centers in Egypt. The primary objective of this study was to assess the efficacy of this combination by determining overall response rate. Secondary endpoints were the assessment of the toxicity of GEM in combination with VRL, as well as the time to disease progression and the survival at one year.

Patients were included in the study only if they met all of the following criteria: histological or cytological diagnosis of breast carcinoma with evidence of unresectable, locally recurrent, or metastatic disease, or the presence of metastatic or local-regional recurrent disease, according to the American Joint Committee on Cancer.[17] Also required were uni-dimensionally measurable lesions with clearly defined margins that were clearly measurable by CT, chest x-ray or clinical examination, according to RECIST criteria;[18] no prior chemotherapy for metastatic or loco-regionally recurrent disease, or prior radiotherapy must have been completed at least 30 days before study entry; no concurrent hormonal therapy for metastatic breast cancer, a Karnofsky performance status of ≥70, an estimated life expectancy of at least 6 months, patient compliance and geographic proximity that allowed for adequate follow-up, adequate organ function and signed informed consent from the patient or legal representative. Patients were excluded from the study if there was concurrent administration of other tumor therapy, pregnancy or breast-feeding, serious concomitant disorders that would compromise the safety of the patient or compromise the patient's ability to complete the study, a second primary malignancy that was clinically detectable at the time of consideration for study enrollment, known or suspected brain metastasis, bone metastasis, pleural effusion or ascitis as the only sites of disease.

GEM and VRL were given on days 1 and 8 every 3 weeks. GEM was used at a dose of 1000 mg/m^2 and VRL at 25 mg/m^2. Every cycle, VRL was administered before GEM. Therapy was continued until there was evidence of progressive disease, the patient experienced unacceptable toxicity, the investigator decided that the patient should be discontinued, the patient requested discontinuation, or the patient received 6 cycles of the regimen. Any adverse event considered at least possibly related to treatment was defined as toxicity.

After baseline evaluation, tumor status was assessed every other treatment cycle (approximately 6 weeks) while on study therapy and every 6 to 8 weeks during post-treatment follow-up until documented disease progression, death or 12 months after study enrollment, whichever occured first. Responses were assessed according to Response Evaluation Criteria in Solid Tumors, version 1.0,[17] and required confirmation at least 4 weeks after first evidence of response.

Patients having documented disease progression were monitored for survival approximately every 2 months, until death or 12 months after study enrollment, whichever occured first. Patients were assessed for toxicity according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.[19]

The Simon two-stage design was used to test the null hypothesis that the response rate was ≤40% versus the alternative hypothesis that the response rate was ≥55%.[20] Setting the type-I error rate at 0.04 and type-II error rate at 0.2, 35 patients were to be enrolled in the first stage of the trial. At the end of the first stage, if 15 or fewer responses were observed the trial was to be terminated. Otherwise, the trial was to go to a second stage, enrolling an additional 45 evaluable patients. If at least 40 of a total of 80 evaluable patients responded, the treatment was then considered promising enough to warrant further development.

The primary endpoint of this study was tumor response rate, which was defined as the number of patients with a confirmed response (complete response [CR] or partial response [PR] divided by the number of patients who qualified for tumor response analysis, i.e., the enrolled eligible patients with measurable disease and at least one dose of study therapy). These qualified patients were the basis of the duration of response analysis, one of the secondary endpoints. The other secondary end points of this study included time to disease progression and one-year survival rate, which were analyzed on the intent-to-treat basis including all enrolled eligible patients. The Kaplan-Meier method was used to estimate

the medians for time to disease progression, duration of response as well as the one-year survival rate.[21] All patients who received at least one dose of study drug were evaluated for safety.

RESULTS

The 74 patients enrolled in this study had a median age of 45 years (Table 1). The majority were postmenopausal. Seventy-two (97%) had a Karnofsky performance status of 80% and above. Seventy-one patients (96%) were metastatic and only three patients had locally advanced disease (4%). All patients had previously received adjuvant chemotherapy with anthracyclines for breast cancer. Thirty-seven patients (50%) had lung metastasis, 34 (46%) had liver metastasis, and 44 (60%) had metastasis in three or more sites.

The overall response rate was 42% (95% CI, 30% to 54%) (n=30) in 72 evaluable patients, with a complete response in 4 patients (6%) and a partial response of in 26 patients (36%) (Table 2). Stable disease was reported in 19 patients (26%) and progressive disease in 17 patients (24%). Disease progression was not assessable in 6 (8%). The median duration of response was 43 weeks (range 8.6-55 weeks) (Figure 1).The median time to disease progression (Figure 2) was 36.7 weeks (range, 1-60 weeks). The one-year survival rate was 77% (95% CI, 64% to 86%).

Toxicity data was available for all patients (Table 3). The most common grade 3-4 toxicities were vomiting (24%) diarrhea (11%) and stomatitis (11%) (Table 4). Serious clinical adverse events included 18 hospitalizations; 5 (7%) due to adverse events, 2 for platelet transfusions and 14 for packed-RBC transfusions (Table 5). The mean (SD) number of cycles received for both GEM and VRL was 4.4 (1.8). Dose reductions occurred in 9.5% of cycles for both GEM and VRL. The dose reduction was mainly due to hematological toxicities for both drugs. None of the patients had more than one dose reduction.

DISCUSSION

There is a clear requirement for alternative cytotoxic drugs or regimens with antitumour activity to treat patients with metastatic breast cancer who have already received anthracyclines. Few standard combination chemotherapy treatments currently exist for this patient population, for which only a few drugs have shown activity as single agents. VRL has been tested in phase II trials in patients with previous treatment with anthracyclines with a reported response rate of 25% and a median time to disease progression of 3 months.[22,23] GEM has shown modest activity (response rate 13%) as a single agent in metastatic breast cancer, especially when used as second-

Table 1. Patient characteristics at baseline.

Patients Characteristics at Baseline (n=74)	n (%)
Age (years)	
Median	45
Range	26-65
Performance status (Karnofsky)	
70%	2 (3)
80%	38 (51)
90%	25 (34)
100%	9 (12)
Menopausal status	
Postmenopausal	41 (55)
Premenopausal	33 (45)
Stage at initial presentation	
I	0 (0)
II	23(31)
IIIa	26 (35)
IIIb	11 (15)
IIIc	6 (8)
IV	7 (10)
Unspecified	1 (1)
Histology	
Ductal	68 (92)
Lobular	3 (4)
Other	3 (4)
Stage at study entry	
Metastatic	71 (96)
Local recurrence	3 (4)
Measurable disease sites	
Lung	37 (50)
Liver	34 (46)
Bone	14 (19)
Lymph nodes	38 (51)
Breast	11 (15)
Prior therapy	
Surgery	67 (91)
Chemotherapy	74 (100)
Anthracyclines	73 (99%)
Adjuvant hormonal	15 (20)
Radiotherapy	56 (76)
Measurable lesions at baseline/patient	
One site	9 (12)
Two sites	21 (28)
Three or more sites	44 (60)

ER; estrogen receptors, PR; progesterone receptors

Table 2. Response rates in 72 evaluable patients with metastatic breast cancer.

	n (%)
Confirmed response[a]	30 (42)
95% Confidence interval[b]	30-54
Complete response	4 (6)
Partial response	26 (36)
Stable disease	19 (26)
Progressive disease	17 (24)
Not assessable	6 (8)

Values are number of patients (percentages)

[a]Complete and partial response, [b]CI : Confidence Interval

Table 3. Common laboratory toxicities.

Laboratory toxicities	Grade 1 and 2 n (%)	Grade 3 and 4 n (%)
Febrile neutropenia	0 (0)	8 (11)
Neutropenia	29 (39)	7 (10)
Leukopenia	24 (32)	4 (5)
Anemia	39 (53)	1 (1.4)
Thrombocytopenia	4 (5)	1 (1.4)
Neutropenia with infection	0 (0)	1 (1.4)

T: Total

Table 4. Common clinical toxicities.

Clinical toxicities	Grade 1 and 2 n (%)	Grade 3 and 4 n (%)
Nausea	18 (24)	2 (3)
Vomiting	12 (16)	18 (24)
Anorexia	1 (1)	0 (0)
Asthenia	11 (15)	0 (0)
Diarrhea	16 (22)	8 (11)
Alopecia	18 (24)	0 (0)
Fever	5(7)	0 (0)
Stomatitis	8 (11)	8 (11)
Injection reaction	11 (15)	10 (14)

Table 5. Serious clinical adverse events related to study drug.

Clinically significant adverse event	n (%)
Hospitalization due to adverse event	5 (7)
Number of transfusions	
Platelets	2 (3)
Packed RBCs	14 (19)
Hepatic failure	1 (1.4)
Septic shock	1 (1.4)

line or third-line treatment.[24] However, GEM in combination with paclitaxel has been approved for the first-line treatment of metastatic breast cancer, after a large multicenter trial reported that the combination was more effective than single-agent paclitaxel in terms of response rate, time to disease progression, and overall survival.[25]

Because of the activity of VRL and GEM as single agents in pretreated metastatic breast cancer, and the lack of overlapping non-hematological toxic effects, phase II studies were initiated to test the activity of the combination of these two drugs, where the response rates ranged from 36% to 80% with an average of 60%.[26-40] There was also one phase III trial of the combination of GEM-VRL versus VRL alone, which reported a response rate for the combination of 36% versus 25 % for VRL alone. In this trial the median progression-free survival for the combination was 6.3 months versus 4.1 months for VRL alone (P=.001). The main grade 3-4 toxicities reported in this phase III trial were neutropenia (65%), febrile neutropenia (10%) and thrombocytopenia (11%).[41] The main reported toxicities in the various trials reported in the literature were grade 3-4 neutropenia ranging from 12%[38] to 42%,[31] grade 3-4 anemia ranging from 1%33 to 17%[25] and thrombocytopenia grade 3-4 ranging from 1%[32] to 18%.[30] Other frequently reported clinical toxicities were nausea, diarrhea and asthenia.[26-40] The response rates and disease progression in our study are consistent with the results of previously reported in phase II and III studies.The median duration of response and median time to disease progression are similar to the reported phase III trial where the progression free survival was 6.3 months in the combination arm versus 4.1 months in the single agent VRL arm.[41] Other phase II studies reported time to disease progression between 3 and 6.8 months.

The toxic effects of the combination were manageable and consisted mainly of grade 3-4 febrile neutropenia and clinical toxicities of nausea, diarrhea and stomatitis. The most commonly reported toxicities in previously reported trials were neutropenia, febrile

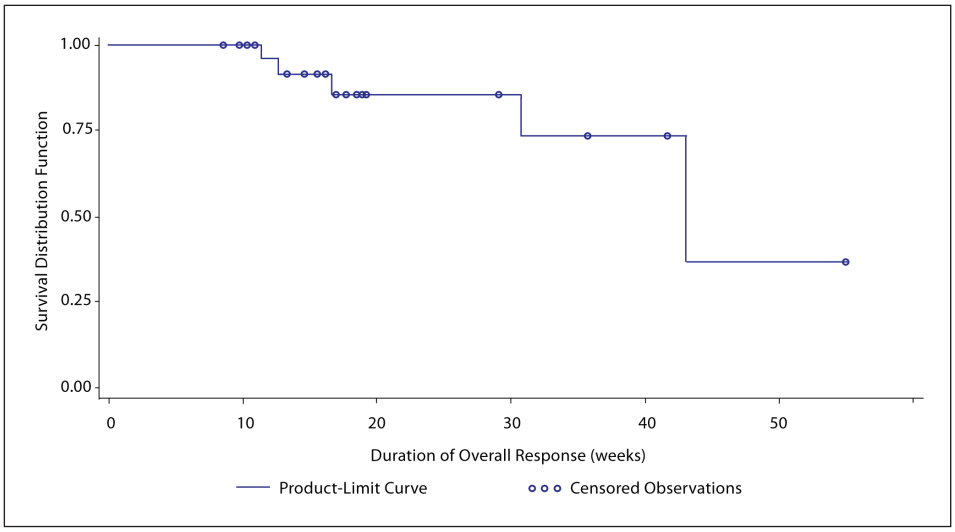

Figure 1. Kaplan-Meier distribution of duration of overall response.

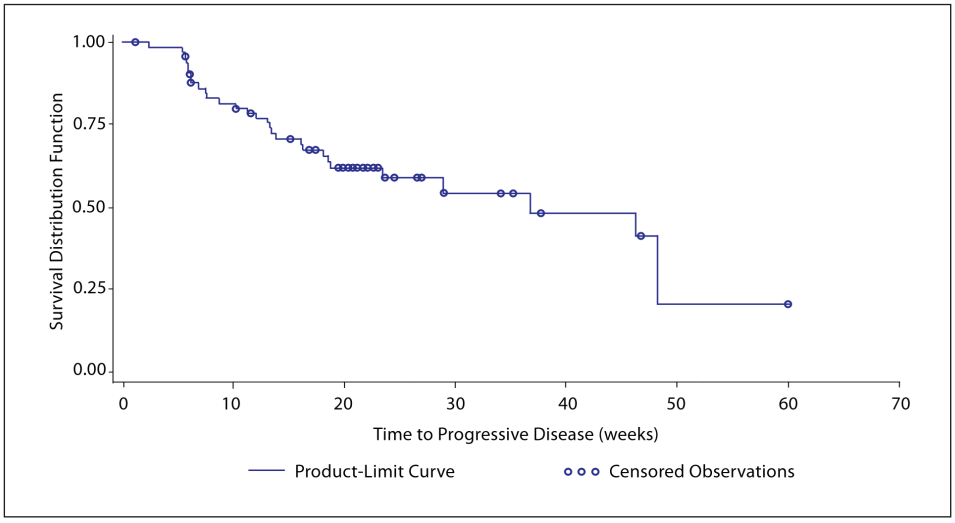

Figure 2. Kaplan-Meier curve of time to disease progression.

neutropenia, neausia and phlebitis.[26-40] With an overall response rate of 42%, the GEM-VRL combination demonstrated promising efficacy and good tolerability in metastatic breast cancer patients.

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