

## Gemcitabine in Combination with Vinorelbine for Heavily Pretreated Advanced Breast Cancer

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**Abstract.** Purpose: To evaluate the activity and toxicity of gemcitabine and vinorelbine in patients with metastatic breast cancer (MBC), previously treated with anthracyclines alone or with taxanes. Patients and Methods: A total of 86 pretreated patients with MBC (median age 62 years), entered the study. Thirty-six patients had been pretreated with anthracyclines and 8 were resistant. The combination of gemcitabine (1000 mg/m<sup>2</sup>) and vinorelbine (25 mg/m<sup>2</sup>) was administered on days 1 and 8 every 3 weeks, for a total of 6 cycles. Results: A total of 344 cycles of chemotherapy were administered (median 4 cycles per patient). Partial responses were observed in 31 patients (36.0%; 95% CI: 23-56). The median duration of response was 7 months (range 3-11 months) and the median overall survival was 14 months (range 6-21). The scheme was well tolerated. Conclusion: The combination of vinorelbine and gemcitabine is an active scheme in pretreated MBC, demonstrating an acceptable toxicity profile, and may well represent a valuable therapeutic choice after anthracycline/taxane regimens.

Chemotherapy plays an important role in the management of metastatic breast cancer, with anthracyclines (doxorubicin, epirubicin) and taxanes (paclitaxel, docetaxel) being considered the most effective agents for patients with advanced disease (1-4).

In the last 10 years, several newer agents have been incorporated into the advanced setting. Gemcitabine and vinorelbine are two such agents that have demonstrated good antitumor activity and favorable toxicity profiles as single-agent therapy for advanced breast cancer. Gemcitabine is a

nucleoside analog with a novel mode of action involving DNA chain termination, showing broad and potent activity across many cancer types (5).

Vinorelbine is a cytostatic of the vinca-alkaloid class of chemotherapeutic agents. The drug causes metaphase arrest by altering microtubule assembly dynamics at the ends of the mitotic spindle, impairing chromosomal segregation and blocking cells in G2/M (6).

When vinorelbine is used as a single agent, neutropenia is the dose-dependent limiting toxicity. This is, however, non-cumulative and rapidly reversible. When combined with other agents, in two- or three-drug combinations, the toxicity profile is again dominated by neutropenia. Like other vinca-alkaloids, vinorelbine demonstrates neurotoxicities as the most common non-hematological toxicity. The reported peripheral neuropathy and constipation associated with its use as a single agent is generally 2-3% (a few studies have reported above 10%). In general, other toxicities are also fairly mild with nausea and vomiting being reported at between 1-5%, while alopecia and cardiotoxicity are virtually absent (7, 8). Gemcitabine also offers a mild and well-tolerated profile of side-effects, demonstrating limited overlapping toxicities when combined with other chemotherapeutic agents. For these reasons, it is a good candidate for inclusion into combination chemotherapies (5, 9-12).

In chemotherapy-naive patients with metastatic breast cancer (MBC), vinorelbine demonstrates single agent efficacy of approximately 35-60% overall response (OR), with 5.3 to 9 months median duration of response (7, 13-15). In this patient population, gemcitabine demonstrates 14 to 37% OR with a median duration of response of 5 to 6.3 months (5, 16-18). Both have also proven effective in heavily- pretreated and anthracycline- resistant patients, vinorelbine demonstrating 16-46% OR with a 2- to 7.8-month median duration of response and gemcitabine demonstrating 23 to 42% and a median duration of response of approximately 8.1 months (5, 8, 15, 19- 22).

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**Table I.** Patient characteristics and previous treatments.

Eligible patients	86	%
Age (years)		
Median	62	
Range	35-75	
ECOG performance status		
0	11	(12.8%)
1	53	(61.6%)
2	32	(37.2%)
Site of metastasis (dominant)		
Bone	17	(19.7%)
Liver	28	(32.6%)
Lungs	8	(9.3%)
Lymph nodes/ skin	33	(38.4%)
No metastatic sites: 1	32	(37.2%)
: ≥2	54	(62.8%)
Premenopausal	17	(19.8%)
Postmenopausal	69	(80.2%)
Hormone receptor -positive	51	(59.3%)
Previous therapy		
Adjuvant chemotherapy		
CMF	42	(48.8%)
FEC	21	(24.4%)
Other	23	(26.7%)
Metastatic disease		
FEC	15	(17.4%)
Docetaxel and mitoxantrone	47	(54.7%)
Tamoxifen, letrozole (or anastrazole)	11	(54.7%)
Other	13	(15.1%)

Because gemcitabine and vinorelbine have different mechanisms of antitumor activity and good therapeutic indices, they have been evaluated as a combination regimen for the treatment of advanced breast cancer (23). This combination has demonstrated favorable efficacy with manageable toxicity as first- and as second-line therapy (24-29).

The purpose of this study was to evaluate the overall response rate, duration of response and associated toxicity of the combination of gemcitabine and vinorelbine in heavily pretreated MBC patients.

## Patients and Methods

**Patient selection.** Eligible patients had histologically confirmed MBC, measurable or assessable, with documented progression within 2 months prior to study entry regardless of prior chemotherapy. Adequate bone marrow (WBC >3.5x10<sup>9</sup>/L, platelets >100x10<sup>9</sup>/L), hepatic (serum bilirubin ≤1.5 mg/dL and serum transaminases ≤3 times upper normal limit; or <5 times upper normal limit for patients with liver metastases) and renal function (serum creatinine ≤1.5 mg/dL) were required. Patients aged ≥18 to ≤75 years, with a life expectancy of greater than 3 months, were eligible.

Exclusion criteria included: prior treatment with either of the study drugs, prior radiation to any of the present areas of measurable or evaluable disease, active secondary malignancy, psychiatric or addictive disorders, pregnant or lactating women.

**Table II.** Toxicities.

	Grade 1/2	Grade 3	Grade 4
Leucopenia	48 (55.8%)	4 (4.7%)	0
Thrombocytopenia	2 (2.3%)	2 (2.3%)	0
Febrile neutropenia	0 (0%)	0 (0%)	0
Anemia	12 (14.0%)	13 (15.1%)	0
Neurotoxicity	2 (2.3%)	0 (0%)	0
Nausea	24 (27.9%)	0 (0%)	0
Fatigue	25 (29.1%)	0 (0%)	0
Fever	12 (14.0%)	0 (0%)	0
Phlebitis	1 (1.2%)	0 (0%)	0
Treatment-related deaths	0 (0%)	0 (0%)	0

The study was performed according to the Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Approval was obtained from the local ethical boards, and written informed consent was obtained from all patients.

**Treatment plan.** The patients received gemcitabine (1000 mg/m<sup>2</sup>) as a 30-minute intravenous (*i.v.*) infusion, and vinorelbine (25 mg/m<sup>2</sup>) by (*i.v.*) 20-minute infusion on days 1 and 8. The treatment was repeated every 3 weeks, with an intention to administer a total of 6 cycles, in the absence of progression, significant toxicity or patient refusal. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not routinely used. Treatment for control of pain and other symptoms were allowed if they did not significantly interfere with the chemotherapy.

The primary end-point of this phase II trial was the overall response rate (CR + PR), while the secondary end-points were duration of response and toxicity.

**Criteria for response and toxicity evaluation.** Before study entry, all patients received a physical examination, ECG, full blood count, liver and kidney function tests and urinalysis. Staging was determined by chest X-ray or computed tomography (CT) scan, and CT scan of the abdomen and pelvis, bone scan and bone radiographs (following abnormal bone scan), within 3 weeks prior to study entry. The assessments were repeated following cycle 3, following clinical signs indicative of disease progression, at the end of treatment and every 3 months until disease progression. Blood counts, urea and serum creatinine were measured before each treatment administration and 7 days later.

The Eastern Co-operative Oncology Group (ECOG) criteria were used to define response and performance status (PS) (30). Toxicity was evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria (31). All documented side-effects were included, regardless of their relationship to study treatment.

The duration of response (DR) was defined as: the number of days from the date of first documented response to the earlier of (a) death (from any cause) or progression and (b) the last on-study tumor assessment. If the duration did not correspond to the patient's death or progression then it was to be censored. The DR was derived for each patient with a best objective tumor response of complete response or partial response. For the purposes of overall clinical benefit (OCB), patients were assessed if they obtain a complete (CR) or partial response (PR) and/or maintained stable disease (SD).

**Table III.** Response data.

Patients	Site	PR	(%)	SD	(%)	Overall clinical benefit (OCB %)
All	Bone	4/17	(23.5%)	7/17	(41.2%)	11/17 (64.7%)
	Liver	12/28	(42.9%)	5/28	(17.9%)	17/28 (60.7%)
	Lung	3/8	(37.5%)	3/8	(37.5%)	6/8 (75.0%)
	Lymph nodes/ soft tissue	12/33	(36.4%)	19/33	(57.6%)	31/33 (94.0%)
Anthracycline-resistant		2/8	(25.0%)	2/8	(25.0%)	4/8 (50%)

**Statistical analysis.** Statistical analysis was performed using the statistical package of SPSS version 10.07. All tests were two-sided;  $p < 0.05$  was considered as significant. Continuous data were summarized using descriptive statistics; they are presented as means values, medians or proportions where appropriate, with 95% confidence intervals. All patients were analyzed for toxic side-effects.

## Results

**Patient characteristics.** Eighty-six patients were enrolled in this study; all were evaluable for response and toxicity. The patient characteristics and previous treatments are listed in Table I. The median age was 62 years (range 35-75 years). Thirty-six patients had been pretreated with anthracyclines and 8 were resistant. The median time from their previous treatment(s) was 15 months (range, 1 to 32 months).

**Toxicity.** The major toxicities are listed in Table II. Grade 3 leucopenia was observed in 4 patients (4.7%), all of whom were treated with G-CSF; no patient was hospitalized with febrile neutropenia. A total of 18 cycles were delayed for 1 week due to leucopenia, 2 cycles being delayed on day 8. All of the patients who developed leucopenia grades 1 or 2 received prophylactic G-CSF. Other grade 3 toxicities were limited to thrombocytopenia in 2 patients (2.3%) and anemia in 13 (15.1%). There were no grade 4 toxicities.

Fatigue, nausea and fever were the most commonly observed non-hematological toxicities. Slight rises in transaminases (grade 1/2) were recorded in 3 patients without liver metastases. No grade 3/4 non-hematological events occurred. No patient displayed neurotoxicity. There were no treatment-related deaths.

**Response and survival data.** Among the 86 patients eligible for response evaluation, 65 patients (75.6%; 95% CI: 59-84) demonstrated overall clinical benefit, including 31 patients (36%; 95% CI: 23-56) with PR and 34 patients with SD of greater than 3 months duration, as noted in Table III. The median duration of response was 7 months (range 3-11 months).

**Survival data.** Most patients received additional chemotherapy or endocrine therapy at the investigators' discretion. The median follow-up time was 11 months (range 1-26) and median time to progression was 5 months. The median overall survival for all patients was 14 months (range 6-21).

## Discussion

The most effective drugs for the treatment of women with advanced breast cancer remain the taxanes and anthracyclines. Once these agents are no longer effective, or are contraindicated due to toxicities including myelotoxicity or cardiotoxicity, treatment options are generally palliative. Because gemcitabine and vinorelbine have different mechanisms of antitumor activity and good therapeutic indices, they have been studied as a combination regimen for the treatment of advanced breast cancer.

In this study, the efficacy and safety of the combination of gemcitabine and vinorelbine was evaluated in 86 patients with MBC. The results demonstrated that the combination is highly effective in controlling metastatic disease in previously pretreated patients with an OR of 36% and a median disease-free survival period of 7 months. These data compare well with other similar studies utilizing this combination, that have reported responses ranging from 22-54% with median disease-free periods of between 5.3 to 9.5 months (24-28). In the present study, no significant hematological toxicity was observed with the dosing regimen. The toxicity profile of the regimen was principally restricted to non-hematological grades 1 and 2 nausea and fatigue. Only 4 patients demonstrated grade 3/4 leucopenia; there were no incidences of febrile neutropenia. Other authors have reported higher incidences of myelosuppression with G-CSF support being indicated as essential in the majority of patients (24-28). In this population, there were 48 incidences (55%) of grade 1/2 leucopenia and 4 (4.7%) of grade 3/4. An alternative bi-weekly schedule of gemcitabine plus vinorelbine also resulted in a lower incidence of myelosuppression, following an initial high incidence of grade 3/4 hematological toxicity, without compromising efficacy (27).

In view of these results, it can be concluded that the combination of gemcitabine and vinorelbine is clinically effective for the management of patients with MBC. It is easily manageable on an out-patient basis, providing there is adequate support and monitoring for leucopenia. Therefore, this combination may be regarded as a valuable alternative to the palliative treatment of MBC, as an excellent option for the development of effective combination treatment not only in first-line therapy, but also for intensively pretreated patients, and may well represent an interesting therapeutic choice after anthracycline/taxane regimens.

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