Treatment of Advanced Breast Cancer With Gemcitabine and Vinorelbine

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Breast cancer is sensitive to several cytotoxic drugs. Combination cytotoxic regimens are associated with higher response rates and longer durations of response and, occasionally, survival, than are single-agent regimens.

Introduction

In the past 30 years, the diagnosis and treatment of breast cancer have advanced considerably. Combination cytotoxic regimens developed in the 1970s produced higher response rates and longer durations of response and survival in metastatic breast cancer than did single-agent regimens.[1,2] However, these regimens have not changed the course of the disease.

In the past decade, in addition to targeted therapeutic interventions such as monoclonal antibodies and tyrosine kinase inhibitors, numerous newer cytotoxic agents—including gemcitabine (Gemzar), vinorelbine (Navelbine), and the taxanes (paclitaxel [Taxol] and docetaxel [Taxotere])—have been developed. Combination regimens with newer and older agents as well as combinations of newer cytotoxic drugs provide enhanced activity with a more favorable toxicity profile for the treatment of patients with metastatic breast cancer or high-risk patients with primary breast cancer.[1]

Gemcitabine/Vinorelbine Combination Therapy

Gemcitabine is a nucleoside analog of deoxycytidine that is metabolized by the same pathways as arabinoside-C and has a broad spectrum of antitumor activity in monotherapy.[3] This favorable antitumor activity, combined with its modest toxicity in patients with advanced breast cancer, prompted its evaluation in combination with other effective cytotoxic chemotherapeutic agents—including vinorelbine—that act by a different mechanism of action.

Vinorelbine is a mitotic inhibitor with a higher therapeutic index and lower neurotoxicity than older vinca alkaloids.[4,5]

Phase II studies in patients with advanced breast cancer have found efficacy rates of 25% to 46% with gemcitabine monotherapy, depending on starting dose and status of previous chemotherapy for metastatic disease; neutropenia has been the principal dose-limiting toxicity.[6,7] (Other studies, however, have shown efficacy rates of 20%. [8-14]) Vinorelbine is associated with response rates of 30% to 40% in previously untreated patients with advanced breast cancer[15-19] and 17% when administered as second-line or salvage chemotherapy.[20-25] Similar to gemcitabine, neutropenia is the primary dose-limiting toxicity with vinorelbine.

Dose-Finding Study

In a dose-finding study of 22 women (median age: 55 years) with advanced breast cancer (82% with metastasis to the liver, lung, or both) and a World Health Organization (WHO) performance status of 0, the maximum tolerated doses were 1,200 mg/m² of gemcitabine and 30 mg/m² of vinorelbine administered in combination.[26] Patients were treated with an intravenous bolus of vinorelbine and a 30-minute infusion of gemcitabine on days 1 and 8 every 3 weeks in one of the following dosage regimens of vinorelbine/gemcitabine: 15/800 mg/m², 20/800 mg/m², 25/800 mg/m², 30/800 mg/m², 30/1,000 mg/m², 30/1,200 mg/m², or 30/1,400 mg/m².

Dose-limiting toxicity was observed in only one patient at the highest dose level. The patient...
developed grade 4 neutropenia and thrombocytopenia and died of a cerebral hemorrhage. Seven patients experienced grade 3 neutropenia as their worst hematologic toxicity. Other toxicities were generally mild to moderate in severity, including nausea and vomiting in 77% of patients (10% with grade 3 toxicity) and flu-like symptoms in 40% (grade 1/2). Reversible alterations in liver transaminases were noted in 68% of patients (grade 1/2), with one case being grade 3. Doses on day 1 were held in 24/195 cycles and on day 8 in 19/195 cycles. The overall response rate in 20 evaluable patients was 45%.

**Ongoing Phase II Trial**

Based on the maximum tolerated dose established in this study, the efficacy of gemcitabine at 1,200 mg/m² and vinorelbine at 30 mg/m² is being assessed in a phase II trial of women with recurrent or metastatic breast cancer, measurable or evaluable disease, and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.[27] Chemotherapy is administered on days 1 and 8 of a 21-day cycle and continues until there is disease progression or unacceptable toxicity. Preliminary data from 26 women (median age: 50 years) indicate encouraging response rates and a favorable toxicity profile with the combination.

The gemcitabine/vinorelbine combination regimen was third-line chemotherapy in 7 (26%) patients, second-line in 12 (~ 50%), and first-line in 6 (23%). Most patients were anthracycline refractory (65%) or resistant (31%), and all but one patient had two or more metastatic sites, including soft tissue (69%), bone (58%), lung (58%), and liver (42%).

After a median of four cycles, the response rate in 22 evaluable patients was 45% (two complete, eight partial responses), and the median time to disease progression was 5.5 months.[20] Nine (41%) patients had stable disease for durations ranging from 3.5 to > 8.5 months. Toxicity was acceptable. Grade 3/4 leukopenia was noted in 31% of patients (seven grade 3, one grade 4), but there were no incidences of neutropenic fever. Leukopenia caused delays in day 8 chemotherapy and/or dosage reductions in 13 patients. Grade 3 thrombocytopenia developed in four patients. Nonhematologic toxicities were generally mild. The study is ongoing to achieve full patient accrual and mature survival data.

**Phase II Trial With G-CSF**

Results of a second phase II trial of gemcitabine and vinorelbine plus granulocyte colony-stimulating factor (G-CSF [Neupogen]) to limit myelosuppression also suggest that this combination regimen is associated with encouraging response rates and a favorable toxicity profile for the treatment of patients with advanced breast cancer.[28] (See Figure 1.)

**Patients and Methods**

The study included 60 women (45 previously untreated and 15 for whom palliative chemotherapy failed). The median age was 58 years; they had histologically diagnosed breast cancer with bidimensionally measurable advanced and/or metastatic disease and a WHO performance status < 2.

Patients were treated with gemcitabine at 1,000 mg/m² infused over 30 minutes on days 1, 15, and 21 and vinorelbine at 40 mg/m² infused over 30 minutes on days 1 and 21. In addition, they received G-CSF at 5 mg/kg/d subcutaneously on days 2 to 6 and days 22 to 26 of each cycle. Treatment courses were repeated every 5 weeks and continued in patients who achieved a response or had stable disease for a total of six courses.

The majority of patients (42 out of 60) had two or more metastatic sites, including visceral, bone, and soft tissue, and 38 patients received adjuvant endocrine therapy (19) and/or cytotoxic chemotherapy (19).[28] The median disease-free interval for the entire study population was 23 months, compared with 26 months in patients who had received adjuvant cytotoxic treatment.

Of the 60 women enrolled in the study, 34 had not received prior palliative chemotherapy, 21 had
received hormonal therapy for advanced disease, and 15 had received palliative first-line chemotherapy after a disease-free interval of 4 months. A total of 266 courses of study drug treatment were administered, while the median number of treatment cycles was 6 and the median duration of follow-up was 15 months.

**Response Rates**

The overall response rate was 51.7% (5 complete and 26 partial responses), with 28.3% of patients showing disease stabilization for > 3 months. The median duration of response was 8.5 months.[28] The response rate among the 45 women not previously treated with palliative chemotherapy was 55.6% (5 complete and 20 partial responses), and the median duration of response was 10.8 months.

In the 15 women who had received prior palliative chemotherapy, the response rate was 40% (six partial responses) and 33.3% had disease stabilization. The median duration of response in previously treated patients was 7.4 months. After a median follow-up of 15 months, the median survival duration had not been reached (> 14 months) in previously untreated patients and was 12.2 months in those who had received prior palliative chemotherapy.

While leukopenia was common (77%) in all patients, only eight (13%) experienced grade 3/4 leukopenia.[28] Thrombocytopenia occurred in 20% of patients, but was not severe in any patient. Grade 3 anemia requiring transfusion developed in only two patients. Nonhematologic toxicity was generally mild in severity; the most common complaints were nausea and vomiting on the day of drug administration.

A total of 14 (5%) treatment courses were delayed by 1 week at some time during therapy, and five patients had a 25% reduction in cytotoxic drug dose during treatment. The mean delivered dose intensity of the combination was 95% of the projected dose.

**Conclusions**

Gemcitabine and vinorelbine are newer cytotoxic chemotherapeutic agents that demonstrated good antitumor activity and favorable toxicity profiles as single-agent therapy for advanced breast cancer. Because of their different mechanisms of antitumor activity and good therapeutic indices, they have been evaluated as a combination regimen for the treatment advanced breast cancer. Data from phase II clinical trials suggest that the combination of gemcitabine and vinorelbine with or without G-CSF is effective first- or second-line therapy for advanced breast cancer and has a favorable safety profile. Further studies of the gemcitabine/vinorelbine combination regimen are warranted.

**References:**


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