Docetaxel Combined With Vinorelbine: Phase I Results and New Study Designs

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This was a phase I dose-finding and pharmacokinetic study of vinorelbine (Navelbine) and docetaxel (Taxotere) as first-line chemotherapy for metastatic breast cancer. Vinorelbine dose, 20 or 22.5 mg/m², on days 1 and 5, was followed on day 1 by docetaxel every 21 days, in doses increasing from 60 to 100 mg/m².

Introduction

The large number of patients with metastatic breast cancer resistant to anthracyclines suggests a need to develop nonanthracycline combination chemotherapies. The differing mechanisms of action of docetaxel (Taxotere) and vinorelbine (Navelbine) suggest a rationale for their use in combination. Docetaxel promotes tubulin polymerization and stabilizes the formed microtubules.[1] In contrast, vinorelbine inhibits the polymerization of tubulin into microtubules.[2] Both compounds have demonstrated high antitumor activity as first-line chemotherapy in metastatic breast cancer, with overall response rates of 61% for docetaxel and 41% to 50% for vinorelbine.

In addition, preclinical research has shown a therapeutic synergy between the two drugs in mice bearing subcutaneous transplantable tumors.[3] Moreover, the combination toxicity index was between 1.8 and 1.55, indicating that approximately 78% to 90% of the maximum tolerated dose of the two drugs could be administered together without additional toxicity.

These observations led to a phase I dose-finding study of the combination of docetaxel and vinorelbine, conducted at Centre René Gauducheau, Nantes, France.[4] Ongoing and future research will compare the docetaxel/vinorelbine combination with other regimens routinely used as first-line therapy for patients with advanced breast cancer or as second-line therapy after the failure of anthracycline treatment.

Objectives

The objectives of this phase I study were to determine the dose-limiting toxicities and the recommended dose for further phase II trials. A secondary objective was to define the major pharmacokinetic parameters in order to assess potential interactions between the two drugs when administered in combination.

Patients and Study Procedures

Patients

All patients had evaluable and/or measurable metastatic breast cancer, with no prior chemotherapy for advanced disease. Previous adjuvant chemotherapy was allowed, provided that there was a 1-year interval between the end of adjuvant chemotherapy and entry into the study. Performance status on the Eastern Cooperative Oncology Group (ECOG) scale was 2 or less, with normal hematologic, liver, and renal function. All patients gave written consent.

Treatment

Vinorelbine was administered as a 20-minute intravenous infusion on days 1 and 5, followed by docetaxel as a 1-hour infusion on day 1, repeated every 3 weeks. Vinorelbine doses were 20 or 22.5 mg/m², while docetaxel doses increased from 60 to 100 mg/m². At least three patients were accrued at each dose level (Table 1).

Patients received 3 days of corticosteroid premedication (8 mg of oral dexamethasone every 6 hours, starting the day before therapy and continuing through the day after). They also received 500 mg of diosime (Daflon), 2 g/d, starting the day before the first infusion and continuing through the entire course of therapy. (Diosime is a flavonoid approved in France as a "vascular tonic" to stabilize
capillary endothelium.)

Assessments
Dose-limiting toxicities were defined as grade 4 absolute neutrophil count for more than 7 days, febrile neutropenia for more than 3 days, grade 3 or 4 infection, grade 4 thrombocytopenia, and/or any other grade 3 or 4 adverse event, except anemia or alopecia. The maximum tolerated dose was defined as the dose at which a dose-limiting toxicity occurred in two or more of three patients entered, or in three or more of six patients entered.

Neurologic function was evaluated prospectively by the same neurologist at baseline, every two cycles during the study, and at the end of the study. This included a clinical examination and measurement of nerve conduction velocities.

Results

Patient Characteristics
Over 1 year, 29 patients were enrolled in the study. The majority of patients had visceral disease, mainly liver involvement.

Safety
Table 1 summarizes the overall safety results. The incidence of grade 4 neutropenia was high at all dose levels, with febrile neutropenia highest at level III. Grade 3 or 4 mucositis occurred in two patients at level III and in one patient each at levels IV and V. Symptomatic peripheral neuropathy was not observed. Neurologic adverse events were no higher than grade 1. The treatment regimen, which included corticosteroid prophylaxis, resulted in only mild fluid retention.

Table 2 summarizes the dose-limiting toxicities, which were first observed at level III. At level III, three (75%) of the four patients had dose-limiting toxicities. Dose-limiting toxicities were also high at level V (four of six patients; 67%).

Two maximum tolerated doses were reached. The first, at 75 mg/m² of docetaxel and 22.5 mg/m² of vinorelbine, included the dose-limiting toxicities of febrile neutropenia plus mucositis (two patients) or febrile neutropenia alone (one patient). The second maximum tolerated dose was reached at 100 mg/m² of docetaxel and 20 mg/m² of vinorelbine; dose-limiting toxicities were febrile neutropenia, febrile neutropenia plus mucositis, febrile neutropenia plus sepsis, or grade 4 mucositis (one patient each).

From these results, the recommended doses for phase II studies were determined to be 75 to 85 mg/m² of docetaxel on day 1 and 20 mg/m² of vinorelbine on days 1 and 5, every 3 weeks (level IV); at these doses, only one dose-limiting toxicity occurred in 10 patients.

Pharmacokinetics and Efficacy
Based on the maximum concentration, bioavailability, and clearance data, the pharmacokinetics of docetaxel and vinorelbine were not altered by combining them at the doses and schedule studied. The data indicate that under these conditions the two drugs can be administered together without any relevant drug interactions.

The responses observed were promising, with an 80% overall response rate at the higher recommended dose, 85 mg/m² of docetaxel on day 1 and 20 mg/m² of vinorelbine on days 1 and 5, and a 67% overall response rate at 75 mg/m² of docetaxel and 20 mg/m² of vinorelbine at the same schedule. At all dose levels, the overall response rate was 66%. It is noteworthy that in the 11 patients with evaluable liver metastases, the overall response rate was 82%, with one complete response.

Discussion
These results correlate well with the preclinical data. Bissery et al[2,3] performed three experiments in mice: one in the MA/16 model and two with MA 13/C to determine the mean combination toxicity index; ie, the sum of the percentages of the highest nontoxic doses of each of the agents used in the combination. They found a mean combination toxicity index of 1.79 for docetaxel/vinorelbine. When considering the recommended dose in humans--ie, 75 to 85 mg/m² of docetaxel on day 1 and 20 mg/m² of vinorelbine on days 1 and 5 of a 21-day course--the combined dosages correspond to 87% of the actual dose intensity of docetaxel (98 mg/m² every 3 weeks) and 95% of the actual dose intensity of vinorelbine (21 mg/m²/wk). This corresponds to an overall combined toxicity index of 1.82, which correlates well with the preclinical data.

Future study designs will continue to investigate the combination of docetaxel and vinorelbine, as first-line therapy for patients with advanced breast cancer, and as second-line therapy after the failure of an anthracycline-containing treatment.

Future investigations may attempt to raise the rate of complete responses by increasing the dose...
density to every 14 days, dosing with additional granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) or by administering several therapies alternately or sequentially.

**Conclusions**

Based on the results of this trial, the recommended dosage regimen for the docetaxel/vinorelbine combination in phase II studies is docetaxel, 75 to 85 mg/m² on day 1, and vinorelbine, 20 mg/m² on days 1 and 5, every 3 weeks. This combination will play an important role in the treatment of patients with advanced breast cancer.

**References:**


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