Combination Docetaxel/Vinorelbine for Metastatic Breast Cancer and Non-Small-Cell Lung Cancer

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Docetaxel (Taxotere) and vinorelbine (Navelbine) have both demonstrated activity as single agents for the treatment of patients with metastatic breast cancer and non-small-cell lung cancer.

**Introduction**

The rationale for the use of docetaxel (Taxotere) and vinorelbine (Navelbine) in combination chemotherapy regimens is based on a number of factors. One is attributable to their mechanisms of action, because both of these agents exert complementary effects on microtubules. Docetaxel promotes abnormal polymerization of tubulin into stable microtubule bundles by binding specifically with the b-tubulin subunit of microtubules, thereby leading to the inhibition of microtubule depolymerization.[1-3] Vinorelbine, on the other hand, binds specifically to the a- and b-tubulin subunits and blocks the ability of the protein to polymerize into microtubules. This action leads to the inability of chromosomes to segregate correctly during mitosis, thereby inducing apoptosis.[4,5]

The interest in these two compounds is also generated by specific characteristics within their respective chemical classes—i.e., the taxoids and Vinca alkaloids. For example, docetaxel possesses greater potency as an inhibitor of microtubular depolymerization, estimated as twice that of paclitaxel (Taxol).[2,3] Other differentiating in vitro characteristics of docetaxel include higher binding affinities for microtubules, higher intracellular concentrations, and prolonged retention in tumor cells as compared with paclitaxel.[6,7]

It is believed that vinorelbine is less neurotoxic than other Vinca alkaloids because of the selectivity of vinorelbine for mitotic microtubules.[5] Moreover, results from preclinical tests[8] demonstrate that depolymerization of axonal microtubules with vinorelbine occurs at a concentration of 40 µM/L as compared with 5 and 30 µM/L for vincristine and vinblastine, respectively. Thus, the therapeutic index of vinorelbine can potentially be greater than that of either vincristine or vinblastine, as indicated by its actions on mitotic and axonal activity.

Preclinical tests conducted by Bissery and colleagues[6] revealed that docetaxel and vinorelbine produce a synergistic response in the MA 16/C mammary adenocarcinoma model. Synergy was demonstrated whether both agents were administered simultaneously or 24 hours apart at 80% of the highest nontoxic dose.[6,9] Additional toxicity at these doses was not observed. In contrast, synergy was not demonstrated with either vincristine or vinblastine.[6] Thus, the results from preclinical studies and the well-established antitumor activity as first-line single agents in metastatic breast cancer, non-small-cell lung cancer, and a variety of other cancers support the use of docetaxel and vinorelbine in combination regimens.

**Clinical Trials with Docetaxel and Vinblastine**

**Phase I/II Studies in Metastatic Breast Cancer**

A phase I/II dose-finding study by Fumoleau and colleagues[10] established the maximum tolerated doses for the combination of docetaxel and vinorelbine, determined major pharmacokinetic parameters, and identified a recommended dose for future phase II studies. Dose-limiting toxicity was defined as febrile neutropenia of more than 3 days' duration and/or grade 4 neutropenia lasting more than 7 days and/or grade 3 to 4 nonhematologic toxicity. Patients entered in this trial had metastatic breast cancer, a World Health Organization performance status of 2 or less, and no prior chemotherapy for advanced disease.

The treatment plan included vinorelbine administered as a 30-minute intravenous infusion on days 1 and 5 followed immediately by a 1-hour intravenous infusion of docetaxel on day 1 of a 21-day cycle. The dose levels of vinorelbine/docetaxel administered were 20/60, 20/75, 22.5/75, 20/85, and 20/100 mg/m². All patients received premedication with 8 mg/day of dexamethasone for 3 days.
starting 1 day prior to chemotherapy. Because of the potential for neurotoxicity with the use of vinorelbine, neurological examinations including nerve conduction studies were performed at baseline, and then following every 2 cycles thereafter.

Overall, responses were observed at each dose level. Two maximum tolerated doses were reached: 22.5 mg/m² of vinorelbine followed by 75 mg/m² of docetaxel and 20 mg/m² of vinorelbine followed by 100 mg/m² of docetaxel. Febrile neutropenia was observed in 37% and 11% of the cycles at the 2 dose levels. Based on these results, the authors concluded that 20 mg/m² of vinorelbine (days 1 and 5) followed by either 75 or 85 mg/m² of docetaxel on day 1 was recommended for phase II studies. At the recommended doses, 11 of 16 patients had an objective response.

Based on the results of the phase I study,[10] a multicenter phase II trial was initiated to evaluate the combination of docetaxel and vinorelbine as first-line therapy in patients with metastatic breast cancer. Patients in this ongoing trial will receive 20 mg/m² of vinorelbine administered as a 30-minute intravenous infusion on days 1 and 5 followed immediately by 85 mg/m² of docetaxel on day 1 of a 21-day cycle.

**Phase I/II Studies in Non-Small-Cell Lung Cancer**

Although the initial studies of docetaxel and vinorelbine combinations were performed in patients with metastatic breast cancer, subsequent studies have concentrated on non-small-cell lung cancer. Douillard and co-workers[11] conducted a phase I dose-escalation trial to determine the dose-limiting toxicity, maximum tolerated dose, and the recommended dose of docetaxel plus vinorelbine for future trials. Inclusion criteria included previously untreated patients with histologically proven advanced or metastatic non-small-cell lung cancer with at least one bidimensionally measurable lesion and who had a World Health Organization performance status less than or equal to 2.

During the 3-week cycle, vinorelbine was administered as a 30-minute intravenous infusion on days 1 and 8 followed immediately by a 1-hour intravenous infusion of docetaxel on day 8. The dose levels are shown in Table 1. Patients were premedicated with 8 mg of dexamethasone twice daily for 3 days, beginning 1 day prior to the administration of docetaxel.

To date, 26 patients have entered this ongoing trial, with evaluable data on 23 patients (Table 2). The median age is 52 years (range: 39 to 68 years) with a median World Health Organization performance status of 1. The maximum tolerated dose was 25 mg/m² of vinorelbine on days 1 and 8 and 100 mg/m² of docetaxel on day 8. At this dose, 3 patients developed dose-limiting toxicities (1 incidence of febrile neutropenia, 1 neurosensory, and 1 neutropenia with infection). Data are not yet available for patients receiving 25 and 20 mg/m² of vinorelbine on days 1 and 8, and 100 mg/m² of docetaxel on day 8. The authors concluded that the maximum tolerated dose found in this study was close to the recommended dose of each drug as a single agent.

**Use of a 2-Week Cycle**

Investigators at Memorial Sloan-Kettering Cancer Center[12] evaluated an every-2-week dose schedule in a phase I/II trial of docetaxel and vinorelbine in previously untreated patients with advanced non-small-cell lung cancer. Based on preliminary observations, the authors noted that the toxicity of this combination appears to be minimized when docetaxel and vinorelbine are administered at approximately the same time.

Using a 2-week cycle, patients in this ongoing study receive either 15, 20, 25, 30, or 37.5 mg/m² of vinorelbine as a 10-minute intravenous infusion followed immediately by a 1-hour IV infusion of 50 mg/m² of docetaxel. Patients are also receiving granulocyte colony-stimulating factor (G-CSF) (filgrastim [Neupogen]) support, and premedication with dexamethasone.

Preliminary data are available on 17 patients who have received a total of 83 cycles (Table 2). The median age of patients was 56 years. Overall, partial response was achieved in 29% of patients (range: 10% to 56%; 95% confidence interval). As with Douillard and colleagues,[11] no cases of neurotoxicity were noted. Only 2 episodes of febrile neutropenia were observed. Other nonhematologic toxicities (grade 1 to 2) included mucositis (2/17), diarrhea (1/17), bacteremia (1/17), and upper extremity thrombosis (1/17). Patient accrual is ongoing and more data are needed before identifying the maximum tolerated dose and the dose-limiting toxicity.

Schiller et al[13] performed a phase I study evaluating the maximum tolerated dose of docetaxel and vinorelbine in patients with advanced non-small-cell lung cancer who had failed platinum-based chemotherapy. Dose-limiting toxicity was defined as grade 4 neutropenia of at least 5 days' duration, febrile neutropenia, a 2-week or greater delay in the administration of vinorelbine, and/or a grade 3 or greater nonhematologic toxicity in the first cycle.

Patients received 15 mg/m² of vinorelbine administered by intravenous infusion on a weekly basis followed immediately by varying doses of docetaxel (45, 60, and 75 mg/m²) on day 1, once every 3
weeks. This schedule was implemented after an initial trial of vinorelbine on days 1, 2, and 3 was believed by the authors to be too myelosuppressive for the first 2 patients.
Preliminary data are available for 11 patients (Table 2). The median age is 63 years with a World Health Organization performance status between 0 and 1. Patient accrual continues in this study. Results from the first 11 patients suggest that 15 mg/m² of vinorelbine administered by intravenous infusion once weekly followed immediately by 60 mg/m² of docetaxel as a 1-hour intravenous infusion once every 3 weeks is well tolerated.
The recommended dose of docetaxel and vinorelbine reported by Fumoleau and colleagues[10] in patients with metastatic breast cancer was adopted by Trillet-Lenoir and colleagues[14] in a multicenter phase II trial of 39 previously untreated patients with locally advanced or metastatic non-small-cell lung cancer. Inclusion criteria included patients with histologically proven locally or advanced metastatic non-small-cell lung cancer with at least one bidimensionally measurable lesion. Seventy-nine percent of patients had a World Health Organization performance status of 1 and 21% had a WHO performance status of 2. The initial dose was 20 mg/m² of vinorelbine administered as a 30-minute intravenous infusion on days 1 and 5 followed immediately by a 1-hour intravenous infusion of 75 mg/m² of docetaxel on day 1, once every 3 weeks. Patients also received premedication with prednisone, diosmine, and antiemetics on an outpatient basis. Prophylactic growth factor support was not provided in this study.
Partial responses were achieved in 27% of the patients and the median duration of response was 4 months (Table 2). The dose-limiting toxicity was grade 4 neutropenia, which was seen in 85% of the patients.[14] Febrile neutropenia was experienced by 41% of patients. Grade 3 to 4 stomatitis occurred in 11% of the patients. Approximately 18% of the patients experienced grade 1 to 2 neurosensory toxicity. Fluid retention was not observed in any patient. The authors concluded that the combination of 75 mg/m² of docetaxel and 20 mg/m² of vinorelbine is a feasible combination with promising activity. Additional studies are needed to determine if the activity documented in this study is similar to that of docetaxel alone. In addition, future studies incorporating G-CSF may decrease the incidence of febrile neutropenia.[14]
One such trial incorporating the use of G-CSF support was that conducted by Kourousis and colleagues.[15] In 41 previously untreated patients with stage IIIB or IV non-small-cell lung cancer, 25 mg/m² of vinorelbine was administered as a 15-minute intravenous infusion followed immediately by a 1-hour intravenous infusion of 100 mg/m² of docetaxel once every 3 weeks. Patients in this phase II study also received 5 µg/kg of G-CSF beginning on day 4 and continuing through day 15. The majority of patients had stage IV disease (70%) and had a World Health Organization performance status of 0 to 1 (80%).[15] Partial response was documented in 41% of the 37 evaluable patients (range: 25% to 56%; 95% confidence interval), with a median survival of over 5 months (range: 2 to 13 months) (Table 2). The addition of G-CSF support minimized the magnitude of grade 3 or 4 neutropenia, which was noted in 49% of patients. Febrile neutropenia was noted in 24% of patients. Neurotoxicity of grade 3 severity was also low, at 2%, with no cases of grade 4 neurotoxicity. The authors noted that the addition of G-CSF support to docetaxel and vinorelbine was a well-tolerated regimen that provided significant antitumor activity.[15]

Commentary

The combination of docetaxel and vinorelbine is an active and well-tolerated regimen, based on the preliminary results from phase I and II trials in both patients with metastatic breast cancer and non-small-cell lung cancer. Identifying a standard dosage and schedule for this combination continues to be refined, most notably in patients with non-small-cell lung cancer who, as expected, appear to have a different tolerability for such schedules. The majority of studies have used various dosages of vinorelbine that required various dosages of docetaxel (see Table 2).
For docetaxel, it is becoming clear that doses near those recommended for single-agent use (75 to 100 mg/m², 1-hour intravenous infusion, once every 3 weeks) are appropriate. However, defining a dose schedule for vinorelbine has been more difficult, especially in the non-small-cell lung cancer setting. Based on the preliminary data, promising antitumor activity and acceptable safety profile have been noted with 2 regimens: 75 mg/m² of docetaxel on day 1 and 20 mg/m² of vinorelbine on days 1 and 5, once every 3 weeks; 25 mg/m² of vinorelbine on days 1 and 8 and 85 mg/m² of docetaxel on day 8, once every 3 weeks. It is hoped that results from future studies will further define the optimal dose schedules of this combination in both metastatic breast cancer and non-small-cell lung cancer.
non-small-cell lung cancer.

References:


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