Docetaxel/Vinorelbine Combination Therapy in Non-Small-Cell Lung Cancer

By Jeffrey Crawford, MD

Docetaxel/Taxotere has demonstrated significant activity as a single agent in the treatment of non-small-cell lung cancer.

Introduction

Docetaxel (Taxotere) and vinorelbine (Navelbine) are two of a number of new third-generation chemotherapeutic agents that have become available in recent years. A series of single-agent and combination therapy studies are underway to determine the efficacy of these agents in the treatment of patients with non-small-cell lung cancer. Although docetaxel and vinorelbine are considered tubulin-binding agents, their use in combination therapy is promising because each has different effects on microtubule assembly.

Docetaxel, like other taxoids, promotes tubulin polymerization, whereas vinorelbine, like other vinca alkaloids, promotes tubulin depolymerization. Preclinical tests of docetaxel in combination with other vinca alkaloids failed to demonstrate synergy in a variety of in vivo experiments. However, docetaxel and vinorelbine, when administered either simultaneously at 100% of the highest nontoxic dose or 24 hours apart at 80% of the highest nontoxic dose, produced a synergistic response in the MA 16/C mammary adenocarcinoma model.

This review deals essentially with the safety profiles of vinorelbine and docetaxel and presents preliminary data supporting continued investigation aimed at defining the optimal combination regimen of these agents in patients with non-small-cell lung cancer. Docetaxel, like other taxoids, promotes abnormal polymerization of tubulin into stable microtubule bundles, rather than the long filaments normally used for the mitotic spindle and other microtubule-based structures. Unlike the vinca alkaloids, docetaxel binds specifically with the beta-tubulin subunit of microtubules and inhibits the disassembly of the important cytoskeletal protein. This results in the inhibition of microtubule depolymerization.

Results from in vitro studies indicate that docetaxel is approximately twice as potent as paclitaxel (Taxol) as an inhibitor of microtubular depolymerization. The stabilizing effect of taxoids on microtubule bundles does not stop after concentrations of taxoids are removed. Jordan and colleagues demonstrated that HeLa cells did not resume proliferation after removal of taxoids; instead, the cells entered an interphase-like state. DNA degradation into nucleosome-sized fragments characteristic of apoptosis began during drug incubation and increased after drug removal. Cells died within 48 to 72 hours.

In contrast, vinca alkaloids bind specifically to the alpha- and beta-tubulin subunits and block the ability of the protein to polymerize into microtubules, leading to the inability of chromosomes to segregate correctly during mitosis, and thereby leading to apoptosis.

Vinorelbine departs from the traditional vinca alkaloids in both chemical and functional characteristics. First, vinorelbine is a semisynthetic vinca alkaloid with substitutions on the catharanthine ring instead of the vindoline ring of the molecule. From a functional perspective, the selectivity of vinorelbine for mitotic microtubules lessens the toxicity to axonal microtubules that is typically associated with vinblastine and vincristine.

Binet and colleagues demonstrated that vinorelbine causes complete depolymerization of mitotic microtubules at concentrations lower than vincristine and vinblastine. In addition, preclinical tests with intact tectal plates from mouse embryos showed that depolymerization of axonal microtubules with vinorelbine occurred at a dose of 40 µM/L, compared with 5 and 30 µM/L for vincristine and vinblastine, respectively. Thus, the differences in mitotic and axonal activity imply an improved therapeutic index of vinorelbine compared with vincristine and vinblastine.

Antitumor Activity and Pharmacokinetics
Antitumor Activity
By correlating antitumor activity with total dosage, preclinical tests showed that docetaxel is schedule-independent.[10-12] In several cell lines in vitro, including those resistant to conventional antineoplastic drugs, the antitumor activity of docetaxel appeared to be largely independent of the specific extended dosing schedule used, indicating that prolonged drug exposures may not be required to produce maximum antitumor effect.

The schedule of dependency for vinorelbine was determined using P388 intraperitoneal implanted xenografts.[13] As shown in Table 1, the ratio of survival time in treated vs control was greatest with a once-weekly dosing schedule (days 1, 7, and 13), compared with either a day 1 only, day 1 through 5, or a twice-weekly regimen (days 1, 5, and 9). The once-weekly dosing schedule resulted in an approximate threefold increase in survival as compared with controls.[13]

Pharmacokinetics
Docetaxel exhibits dose-independent pharmacokinetics that are consistent with a linear, 3-compartment model, with half-lives for the alpha, beta, and gamma phases of 4 minutes, 11 minutes, and 11.1 hours, respectively.[14] The docetaxel area under the curve was dose proportional after intravenous doses of 70 to 115 mg/m². Mean total body clearance and steady-state volume of distribution were 21 L/h/m² and 113 L, respectively. Docetaxel is extensively metabolized and is highly bound to plasma proteins (greater than 95%). Although docetaxel pharmacokinetic characteristics are not affected by age or gender, the clearance of docetaxel is decreased in patients with impaired hepatic function. Docetaxel did not demonstrate sequence-dependent effects when administered with cisplatin (Platinol).[14]

Pharmacokinetic studies have determined that vinorelbine follows a 3-compartment model.[15] Intravenous administration of vinorelbine results in a rapid distribution to peripheral tissues, with an average terminal half-life of 27.7 ± 15.7 hours. This long half-life is advantageous for use in combination regimens. The mean plasma clearance rate of vinorelbine ranges from 0.97 to 1.26 L/h/kg. The steady-state volume of distribution is large, ranging from 25.4 to 40.1 L/kg. Vinorelbine is highly bound in blood, especially to platelets and lymphocytes, but no drug interactions from displacement of bound drug have been reported. The liver is the primary site of metabolism. The pharmacokinetic profile of vinorelbine is not significantly altered in the elderly or when the drug is administered with cisplatin. Compared with the other vinca alkaloids, vinorelbine has a larger volume of distribution and a higher clearance.[15]

Safety Considerations

Docetaxel
There is an extensive safety database on the administration of 100 mg/m² of docetaxel in patients (N = 1,435) with breast, non-small-cell lung cancer, ovarian, and other tumor types. The dose-limiting side effect of docetaxel was short-lasting neutropenia (less than 500 cells/mm³), which occurred in 76% of patients. Neutropenia resolved in less than 1 week in approximately 11% of patients. Patients who developed febrile neutropenia (12%) were effectively managed by reducing the dosage of docetaxel for subsequent courses, without the use of colony-stimulating factors.

The other frequent hematologic adverse event was leukopenia (less than 1,000 cells/mm³), which was noted in 31% of patients. The incidence of thrombocytopenia (less than 100,000 cells/mm³; 7.5%) and anemia (less than 8 g/dL; 8.4%) associated with docetaxel was low.

Nonhematologic side effects associated with 100 mg/m² of docetaxel included alopecia (80%), gastrointestinal side effects (nausea, 40%; diarrhea, 40%; vomiting, 24%), stomatitis (42%), and nail changes (28%). These were common, but usually only grade 1 or 2 in severity. Neurosensory changes, such as mild paresthesias, were uncommon (less than 5% of patients). In patients receiving corticosteroid premedication, mild hypersensitivity reactions, such as flushing and pruritus, occurred in 16% of patients, and severe reactions were observed in only 0.9% of patients.

Vinorelbine
The safety of vinorelbine was recently reported in a prospective multicenter trial[16] in 216 patients with stage IV non-small-cell lung cancer. Patients were randomized to receive either vinorelbine, 30 mg/m², infused over 20 minutes once weekly or an intravenous bolus of 425 mg/m² of fluorouracil (5-FU) plus 20 mg/m² of leucovorin administered for 5 consecutive days every 4 weeks. The predominant toxicity associated with the use of single-agent vinorelbine at 30 mg/m² was granulocytopenia (Table 2).[16]

Grade 3 or 4 granulocytopenia was noted in 54% of patients receiving vinorelbine, compared with 24% of the 5-FU/leucovorin-treated patients. Despite the wide difference in the incidence of grade 3
or 4 granulocytopenia, only 7% and 6% of the patients in both groups experienced infections related to granulocytopenia. Other hematologic toxicities included anemia, which was seen in 70% of the vinorelbine-treated patients and 42% of the 5-FU/leucovorin-treated patients. Anemia was of grade 1 or 2 severity, with 18% of vinorelbine-treated patients and 12% of 5-FU plus leucovorin-treated patients requiring blood products.

Nonhematologic toxicities that occurred more frequently in vinorelbine-treated patients than in those given 5-FU/leucovorin combination therapy included constipation (29% vs 6%), peripheral neuropathy (20% vs 4%), and injection-site reactions (i.e., phlebitis and pain; 38% vs 1%). The incidence of grade 3 severity of the same nonhematologic toxicities was substantially lower—i.e., constipation, 2%; peripheral neuropathy, 1%; and injection site reactions, 5%. There were no grade IV nonhematologic toxicities associated with the administration of vinorelbine.

In general, nausea, vomiting, stomatitis, anorexia, and diarrhea were reported to occur more frequently in the 5-FU/leucovorin treatment than in the vinorelbine treatment group. Thus, the hematologic and nonhematologic toxicity profiles of docetaxel and vinorelbine appear to be compatible for concomitant use in patients with non-small-cell lung cancer.

**Docetaxel/Vinorelbine: Preclinical and Clinical Studies**

Data supporting the potential for docetaxel/vinorelbine combination therapy in non-small-cell lung cancer come from single-agent trials as well as preclinical studies.

**Single-Agent Efficacy**

Docetaxel has demonstrated significant activity as a single agent in the treatment of patients with advanced non-small-cell lung cancer. Response rates for docetaxel administered intravenously 100 mg/m² over 60 minutes, once every 3 weeks, in patients with non-small-cell lung cancer have ranged from 33% to 38% in previously untreated patients, with projected median survival duration of 9 months and a 1-year survival rate of 40%. In previously treated patients, response rates have ranged from 21% to 27%, with projected median survival duration of 9 months and a 1-year survival rate of 34%.

As reported in a recent prospective multicenter trial in 216 previously untreated patients with stage IV non-small-cell lung cancer, 30 mg/m² of vinorelbine, infused over 5 to 10 minutes once weekly every 21 days, produced a partial response rate of 12%, with a median survival of 30 weeks and a 1-year survival rate of 25%. This survival time was superior to the control regimen of 5-FU/leucovorin (16% at 1 year) and compares favorably with that achieved by previous combination regimens (28 weeks), as shown in Table 3.

The potential for improving the survival time of vinorelbine was demonstrated by Le Chevalier and colleagues, who reported that survival times could be increased to 40 weeks when cisplatin was used in combination with vinorelbine in patients with non-small-cell lung cancer.

**Preclinical/Phase I Combination Studies**

Bissery and colleagues reported the in vitro synergistic effects of these agents when administered in mice bearing subcutaneous mammary adenocarcinoma MA 16/C. The study used a 3-arm dose-response design to assess the tolerance and efficacy of the combination when administered either simultaneously or 24 hours apart. The highest nontoxic dose of docetaxel (100 mg/m² IV every 21 days) and vinorelbine (21 mg/m² IV once a week) could be administered when given simultaneously. However, scheduling studies 24 hours apart necessitated a 20% reduction in the docetaxel dose, regardless of the order in which the agents were administered.

The results from this preclinical study proved to be predictive of the maximum tolerated dose in patients with breast cancer. The phase I clinical trial performed by the same authors evaluated patients' response to 20 mg/m² of vinorelbine administered intravenously on days 1 and 5 followed immediately by varying doses of docetaxel (60, 75, 85, and 100 mg/m²) on day 1, once every 3 weeks. Each dose level demonstrated significant clinical responses (31% to 34%), with the highest nontoxic dose being 85 mg/m² of docetaxel combined with 20 mg/m² of vinorelbine. These results suggest that the docetaxel/vinorelbine combination has activity in the breast cancer model.

The data published by Bissery and colleagues as well as Fumoleau and co-workers provided a basis for testing various schedules of docetaxel plus vinorelbine in patients with non-small-cell lung cancer. Monnier and colleagues reported the results of a French multicenter, phase II trial that evaluated the use of docetaxel/vinorelbine in 39 patients with locally advanced or metastatic non-small-cell lung cancer, 80% of whom had a performance status of 0 to 1. The initial dose was 75 mg/m² of docetaxel administered intravenously on day 1 followed by vinorelbine, 20 mg/m².
administered intravenously on days 1 and 5, once every 3 weeks. Patients also received premedication with prednisone, diosmine, and antiemetics on an outpatient basis. The dose-limiting toxicity was grade 4 neutropenia, which was seen in 77% of the patients (Table 4).[29] Febrile neutropenia was experienced by 42% of patients. Grade 3 to 4 stomatitis and severe asthenia occurred in 11% of the patients. Partial responses were achieved in 23% of the patients. The authors concluded that additional studies are needed to determine whether the efficacy documented in this study is similar to that of docetaxel alone.[17] In addition, the regimen did not include colony-stimulating growth support, which may be appropriate for inclusion in future studies because of the 42% incidence of febrile neutropenia reported in this study.[29]

Other Trials
A second trial, by Kourousis and colleagues[30], examined the combination regimen of 100 mg/m² of docetaxel (as a 3-hour infusion with premedication) and 25 mg/m² of vinorelbine, both administered intravenously once every 21 days, in 43 patients with non-small-cell lung cancer. Patients in this study also received growth factor support in the form of 5 mg/kg of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) beginning on days 4 through 15 to reduce the expected neutropenia. The majority (70%) of patients had stage IV disease, and 81% had a performance status of 0 to 1.[30] The addition of G-CSF minimized the magnitude of grade 3 or 4 neutropenia, which was noted in 19% of patients (Table 4).[30] Further, only 6% of patients experienced febrile neutropenia. The incidence of grade 2 to 3 neurotoxicity was also low, at 8%. Partial response was documented in 47% of patients, with a median survival time of over 6 months (range, 2 to 10 months). The authors noted that the addition of G-CSF to docetaxel/vinorelbine resulted in an active, well-tolerated regimen with acceptable toxicity.[30]

A third approach to the combination of docetaxel and vinorelbine in patients with non-small-cell lung cancer was reported by Viallet and colleagues.[31] In this study, 45 patients with stage IIIB or IV non-small-cell lung cancer received 100 mg/m² of docetaxel on day 1, 100 mg/m² of cisplatin on day 21, and 30 mg/m² of vinorelbine on days 21, 28, and 35 of a 6-week cycle. A maximum of 3 cycles was given to patients with stable disease and a maximum of 2 cycles beyond maximal response to responding patients. Growth factor support was not administered in this study. Febrile neutropenia was noted in 4 patients; 63 cycles were administered (Table 4).[31] A response rate of 55% (15 of 27 patients) was documented, with stable disease being achieved in an additional 5 patients. Recently, Early and colleagues[32] reported preliminary results from a phase I/II trial in patients with stage IIIB and IV non-small-cell lung cancer who received escalating doses of vinorelbine (15 to 37.5 mg/m²) administered intravenously over 10 minutes followed by a 1-hour intravenous infusion of docetaxel, 50 mg/m². The cycle was repeated every 2 weeks. Patients also received prophylactic G-CSF support and dexamethasone premedication. Two episodes of febrile neutropenia were noted in the 83 cycles administered. Antitumor activity has been noted in 5 of the 17 patients enrolled to date in this ongoing study.[32]

Conclusions
The optimal regimen for the combination of docetaxel and vinorelbine in patients with non-small-cell lung cancer remains to be determined. A number of preliminary studies of this combination have had encouraging results in terms of efficacy as well as tolerability. Future studies need to address the role of supportive therapy with G-CSF and whether dose intensification with a docetaxel/vinorelbine regimen can be achieved in patients with non-small-cell lung cancer.

References:
4. Ringel I, Horwitz SB: Studies with RP 56976 (Taxotere): A semisynthetic analogue of taxol. J Natl...


Source URL: http://www.diagnosticimaging.com/review-article/docetaxelvinorelbine-combination-therapy-non-small-cell-lung-cancer

Links:
[1] http://www.diagnosticimaging.com/review-article