Docetaxel in Combination With Platinums in Patients With Advanced Non-Small-Cell Lung Cancer

By Chandra P. Belani, MD

Docetaxel (Taxotere) is a semisynthetic taxoid that possesses significant activity as a single agent in the treatment of patients with non-small-cell lung cancer. In previously untreated patients with non-small-cell lung cancer, docetaxel has demonstrated activity in phase II trials, in patients with previously untreated non-small-cell lung cancer (NSCLC), and in those who have progressed after receiving cisplatin (Platinol)-based combinations. The response rates range from 21% to 38% in chemotherapy-naive patients with advanced or recurrent non-small-cell lung cancer, and the median survival in these phase II studies varies from 25.2 to 47.0 weeks. Docetaxel also has modest activity in patients who have either progressed after initial treatment with cisplatin-containing regimens, with response rates of 20% to 21% and median survival of 28 to 42 weeks. Myelosuppression continues to be the main side effect associated with docetaxel in all the studies. Other unique toxicities include nail changes, hypersensitivity reactions, and symptomatic peripheral edema and effusions.

Gandara et al observed a 19% incidence of febrile neutropenia among 80 patients who were treated with docetaxel, and Cerny et al reported a 67% incidence of grade 3 to 4 neutropenia. The fluid retention observed in the study from Memorial Sloan-Kettering Cancer Center reported by Miller and colleagues appeared to be cumulative. Symptomatic pleural effusions developed in 6 of 8 patients who received a total dose of docetaxel greater than 500 mg/m². To further investigate the activity of docetaxel in the salvage setting after initial treatment or failure with cisplatin regimens, two large randomized studies are being conducted.

Development of Docetaxel/Cisplatin/Carboplatin Combination Regimens for Patients With NSCLC

Cisplatin has been used for the treatment of patients with non-small-cell lung cancer over the past two decades. Meta-analysis of randomized studies comparing cisplatin-containing combination chemotherapy to best supportive care in advanced non-small-cell lung cancer demonstrated a modest but significant improvement in survival in favor of chemotherapeutic intervention. Thus, cisplatin appeared to be suitable for combination with docetaxel for further evaluation. The phase I studies established the doses of the two agents in the combination for further evaluation. The recommended dose of 75 mg/m² of docetaxel in combination with 75 mg/m² of cisplatin, with cycles repeated every 3 weeks, was used in our study. In this multicenter trial, 47 previously untreated patients with advanced, metastatic non-small-cell lung cancer received a total of 229 courses of therapy. The salient toxicities were febrile neutropenia (8.5%), grade 4 pulmonary toxicity (4.3%), neuromotor effects (2.1%), and asthenia (12.8%). Symptomatic fluid retention occurred in only 1 patient, and other rare toxicities included nausea, vomiting, diarrhea, and stomatitis. Using stringent response criteria, the observed response rate was 21.3% (10.7% to 35.7%; 95% confidence interval), with 1 complete response and 9 partial responses, and the median survival of all patients is 10+ months.

This combination has been evaluated in three additional studies conducted in Australia.\(^{[16]}\)
France,\cite{17} and Greece,\cite{18} The design and schema of these trials were slightly different, as shown in Table 2. With an increase in dose of either cisplatin to 100 mg/m² \cite{17} or docetaxel to 100 mg/m²,\cite{18} the degree and incidence of myelosuppression was higher. The median survival in all these trials ranges from 8 to 13 months. Based on the activity seen with the combination of docetaxel and cisplatin, this regimen is being evaluated further in the ongoing, randomized Eastern Cooperative Oncology Group (ECOG) study (Figure 2) for patients with advanced and metastatic non-small-cell lung cancer.

Carboplatin (Paraplatin), developed as the less toxic analog of cisplatin, has marginal but consistent activity in non-small-cell lung cancer.\cite{19-21} In a large ECOG randomized study\cite{19} comparing three cisplatin-based combination chemotherapy regimens to single agent therapy with carboplatin or ifoplatin, the best survival was observed on the carboplatin arm. Thus, carboplatin also appeared to be a suitable agent for combination with docetaxel.

We performed a phase I study\cite{22} of the combination of docetaxel and carboplatin to characterize the toxicity and establish the doses of the two agents. The results of this study were presented at the American Society of Clinical Oncology 1997 meeting.\cite{22} The dose of docetaxel was escalated in cohorts from 65 mg/m² to 80 mg/m², 90 mg/m², and 100 mg/m² in combination with a fixed dose of carboplatin. Carboplatin was dosed using the Calvert's formula based on the targeted area under the time-concentration curve (AUC) of 6 mg/mL · min. The cycles were repeated every 3 weeks.

Dose-limiting toxicity was defined as: nonreversible grade 3 or greater nonhematologic toxicity; grade 4 emesis despite the use of antiemetics; grade 4 neutropenia lasting more than 7 days; or febrile neutropenia.

Febrile neutropenia was dose limiting. Other rare salient toxicities observed were hypotension, low back pain, nausea, and fatigue. The recommended phase II doses of docetaxel for further evaluation were 90 mg/m² and 80 mg/m² with and without G-CSF support, in combination with a fixed dose of carboplatin (AUC = 6 mg/mL · min).

Based on the results of this phase I study,\cite{22} a phase II study of the combination of docetaxel and carboplatin has been initiated for patients with stage IIIIB and IV non-small-cell lung cancer (Table 3). In this study, the duration of dexamethasone (8 mg twice daily) administration has been reduced to 3 days from 5 days. The results of this study will provide further insight into the effectiveness of this combination against non-small-cell lung cancer.

**Future Directions With Docetaxel and Platinum Compounds**

The combinations of docetaxel with either carboplatin or cisplatin are being evaluated further in large randomized trials for patients with metastatic and advanced non-small-cell lung cancer. These regimens are also being investigated in patients with earlier stages of non-small-cell lung cancer in the neoadjuvant setting. Supportive care agents such as amifostine and thrombopoietin are being added to further refine these regimens and attempt to decrease the overall toxicity. Future studies will also incorporate new agents with activity in non-small-cell lung cancer, such as vinorelbine (Navelbine) and gemcitabine (Gemzar), with these regimens to develop three-drug combinations for evaluation in non-small-cell lung cancer.

**References:**


7. Watanabe K: Personal communication.


