Docetaxel Plus Cisplatin: An Active Combination Regimen in Non-Small-Cell Lung Cancer

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Docetaxel (Taxotere) is a semisynthetic taxoid that possesses significant activity as a single

Introduction

The introduction of several new chemotherapeutic agents has encouraged the development of combination regimens with the potential for enhanced activity in patients with non-small-cell lung cancer. Based on older studies that demonstrated some improvement in survival with cisplatin (Platinol)-based regimens, nearly all the new agents have been tested in combination with cisplatin. This paper outlines the rationale and current progress in the development of combination chemotherapy regimens using docetaxel (Taxotere) plus cisplatin in non-small-cell lung cancer. Docetaxel is a new agent with established activity in several malignancies, including non-small-cell lung cancer. As with paclitaxel (Taxol), evidence of its single-agent activity is based on several single-arm phase II trials rather than on random-assignment comparison studies. Both taxoids share several preclinical and clinical features; however, their differences have the potential to result in varying clinical outcomes.

Phase I Docetaxel Trials

Testing of docetaxel as a single agent involved different schedules in typically escalating dosing steps. While the most prominent toxicity was myelosuppression, especially neutropenia, other side effects of a more unusual nature, such as finger nail changes, skin rash, and fluid retention, were observed in many of the trials. The majority of these side effects have been relatively easy to prevent or ameliorate, largely through the use of short courses of corticosteroids. The schedule that appeared to have the greatest clinical activity, based on dose-intensity and activity in preclinical models, was intravenous injection given over 1 hour every 3 weeks. Neutropenia continued to be the most common dose-limiting toxicity of docetaxel at doses in the 75 to 100 mg/m² range in the every 3-week trial schedule.[1] Fluid retention was an unexpected side effect, occurring after severaladministrations of docetaxel. This effect was noted as edema or pleural effusion, even in patients with evidence of major clinical response.[2] Prevention or marked diminution of the frequency and severity of fluid retention is now achieved with the prophylactic use of corticosteroids. In a recent prospective evaluation, fluid retention was not apparent in any of the 33 patients receiving a twice-daily oral dose of 8 mg of dexamethasone, beginning 1 day prior to docetaxel and continuing for 3 or 4 more days.[3] Fluid accumulation or edema generally cleared while patients continued on trial, with several of the patients continuing for a year on the every-3-week chemotherapy plus the dexamethasone regimen.

Single-Agent Docetaxel Activity

A number of phase II studies have been completed in different settings using the every 3-week schedule of docetaxel. Five studies have shown a consistent high degree of activity, with the median survival reported in the range of 7 to 13 months.[4-8] It is also of interest that the response and survival rates were similar in two studies conducted at the same institution, but using different doses of docetaxel (100 or 75 mg/m²) on the same schedule.[4,5] Although the studies are small, they suggest that the lower dose range may be equivalent to the higher dose while producing less toxicity. If this lower dose is equally effective, it could have relevance for combination trials. Docetaxel has also been tested in patients who have previously been treated with cisplatin-containing regimens.[8,9] The observed 17% response rate is remarkable in that no other
single agent has been reported to produce a major response rate over 10% in previously treated patients. The estimated survival of the patients in these two trials is 8 months. As a group, these patients had good prognostic factors at the time of enlistment, with the majority being women and with a high overall performance status. These results suggest that docetaxel may not be very cross-resistant with cisplatin, which would be important in the design of combination studies. At present, random-assignment studies with docetaxel have not been completed. Two trials based on the data from the studies with previously treated patients are continuing to enlist patients. The first of these is an international study in which patients previously treated with cisplatin regimens are assigned to receive either docetaxel or supportive care. Enlistment in this study has been relatively slow, while the second trial in this population, comparing docetaxel with either vinorelbine (Navelbine) or ifosfamide (Ifex), has had more rapid case accession. These trials should clarify the role of docetaxel in a second-line setting, and will also outline the activity of the comparator agents in previously treated patients.

Rationale for Combination Studies With Docetaxel

There are several reasons for using docetaxel in combination chemotherapy. While many agents could be combined with docetaxel, the selection of cisplatin is logical, based on the survival advantages previously demonstrated with cisplatin-based combinations.[10-14] Additionally, large, multicenter random-assignment trials have shown that the agents added to cisplatin (when the dose of cisplatin is kept the same in comparison arms) can also influence survival.[15-17] The side-effect profile of cisplatin makes it both logical and difficult for use with docetaxel. Cisplatin is attractive for combining with any agent due to its relatively mild degree of myelosuppression. This factor often allows the cisplatin and the accompanying agents to be given at or near their full phase II single-agent doses. However, the risk of emesis, nephrotoxicity, and fatigue makes cisplatin a difficult agent. Good supportive care techniques have reduced the former risks;[18,19] however, the asthenia associated with this agent has not been easy to control. While combining docetaxel with several other agents could be interesting, the greatest clinical experience has been with the cisplatin/docetaxel combination. The results of these studies will be discussed in the next section.

Docetaxel Plus Cisplatin Trials

There are reports of three trials in which docetaxel was combined with cisplatin in patients with advanced non-small-cell lung cancer previously untreated with chemotherapy.[20-23] Several similarities exist among these trials, allowing for a better overall view of the activity of the regimen. These similarities include the characteristics of the patients enlisted into the studies. All three studies share an every-3-week treatment regimen and at least one common dose level in each trial. Each study incorporated both phase I and phase II objectives. The trials were each single-institution studies, conducted in the United States, France, and Australia.

While generally similar, there were some differences among the trials, such as different combination dose levels. The Australian trial continued with both docetaxel and cisplatin given every 3 weeks, while in the French and the US studies, docetaxel was administered every 3 weeks, but cisplatin was administered on days 1 and 22, and every 6 weeks thereafter. The preliminary results of the trials are outlined in Table 1.

The US trial explored four dose levels.[20,21] The only dose-limiting toxicity was neutropenia, as seen in Table 2. With the prophylactic dexamethasone regimen, outlined earlier in this report, fluid retention and rash were not of clinical significance in any of the patients treated, with several receiving docetaxel for up to 1 year.

In the phase I portion, it was concluded that 85 mg/m² of docetaxel was too high when combined with cisplatin. When giving cisplatin at 100 mg/m², the investigators favor using docetaxel at 65 mg/m², although doses of 75 mg/m² of docetaxel can be given. If the latter dose of docetaxel is used, this trial recommends a cisplatin dose of 75 mg/m². The 50% complete and partial response rate observed (with the majority of patients treated at 75 mg/m² of each agent), was encouraging, as was the projected median survival of 10 months. All patients were treated on an outpatient basis; neither growth factors nor prophylactic antibiotics were used.

The French trial used the same dosing interval for both agents as in the US study. Interestingly, the French study found less neutropenia than any of the other studies, and favored 75 mg/m² of docetaxel plus 100 mg/m² of cisplatin.[22] While the major response rate observed in this trial (30%) was the lowest among the 3 trials (Table 1), it should be realized that the French study had the largest proportion of patients with stage IV non-small-cell lung cancer (85%); nonetheless, the median survival is similar to the other studies and is projected to be 10 months.
The Australian trial--A response-rate intermediate between the French and US trials was reported in the Australian study, as was the amount of neutropenia.[23] This group concluded that the 75 mg/m²-dose of both agents, with each given every 3 weeks, was the phase II level. As in the other studies, their preliminary analysis predicts a 10-month median survival (Table 1).

Conclusions

To date, no random-assignment trials with docetaxel combination regimens have been reported. This is appropriate in that data from the initial combination studies have only recently been available. The above trials indicate reproducible and useful response rates with survival rates as high as or higher than those reported with other combination regimens. The trials have outlined several possible dosing levels. Based on our trial and the other studies, we would make two recommendations for randomized investigations. If cisplatin is given at 75 mg/m² then a 75 mg/m² dose of docetaxel appears to be appropriate. If cisplatin is given at the 100 mg/m² dose level, then docetaxel should be given at a dose of 65 mg/m². We recommend the every-3-week docetaxel schedule, with cisplatin given on days 1, 22, and every 6 weeks thereafter. The only prominent toxicity in the US trial was neutropenia. Fluid retention of clinical significance was completely prevented by using dexamethasone with each docetaxel course. Febrile neutropenia was treated effectively with a new all-oral outpatient regimen.[24]

The results of these studies are encouraging, and outline schedules of docetaxel that could also be useful in patients with other malignancies and that could be combined with other chemotherapeutic agents. The cisplatin/docetaxel regimens warrant further study in lung cancer, in patients with advanced disease, and as part of combined-modality investigations.

References:


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