Non–Platinum-Based Paclitaxel Combinations in Advanced Non–Small-Cell Lung Cancer

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Patients with advanced non–small-cell lung cancer benefit mainly from chemotherapy using cisplatin (Platinol)-based combinations. Platinum compounds, however, due to their toxicity profile, have limited use in combination.

Introduction

With an overall response rate of about 20% to 25%, paclitaxel (Taxol) is one of the most active cytotoxic drugs currently available for chemonaive patients with advanced non–small-cell lung cancer. Cisplatin (Platinol) is a major agent in the treatment of this disease and is most frequently used in combination with other drugs. The benefit of chemotherapy in patients with advanced non–small-cell lung cancer has been reported mainly with cisplatin-based combinations.[1] Nevertheless, the toxicity profile of platinum compounds limits their use in combination with several cytotoxic drugs. Paclitaxel has been combined with various other agents considered active in non–small-cell lung cancer with the hope of obtaining synergistic or additional antitumor activity with better tolerance.

Paclitaxel and Etoposide

The combination of paclitaxel and etoposide has been tested in more than 100 patients (Table 1).[2-4] It appears to be schedule-dependent in the study reported by Rosell et al,[3] where 175 mg/m² of paclitaxel was given on day 4, after 100 mg/m² of etoposide on days 1, 2, and 3; a 41% response rate in 21 patients was achieved, compared to no response in 18 patients in whom paclitaxel was given on day 1 followed by etoposide at a same dose. The addition of a platinum compound to this combination has offered a promising response rate in the study reported by Dow et al.[5] Paclitaxel was given at a dose of 35 to 50 mg/m² per day for 5 consecutive days; cisplatin at a dose of 15 mg/m² per day for 5 consecutive days; and etoposide at a dose of 35 to 50 mg/m² per day for 5 consecutive days. An objective response rate of 76% was observed in 37 patients. In a second study by Neill et al[6] paclitaxel was administered at 200 mg/m², carboplatin at an area under the concentration-time curve of 6 (AUC in mg/mL · min), and etoposide at 80 to 100 mg/m² for 3 days plus granulocyte colony-stimulating factor (G-CSF) (filgrastim [Neupogen]). No response was observed among four patients with advanced non–small-cell lung cancer.

Paclitaxel and Gemcitabine

Gemcitabine (Gemzar), with an overall response rate of 22% in 535 chemonaive patients with advanced non–small-cell lung cancer, is also active in this disease setting. The combination of paclitaxel at doses ranging from 90 to 240 mg/m² on day 1 and gemcitabine at a dose of 900 to 1,000 mg/m² on days 1 and 8 of each 3-week cycle has given overall response rates ranging from 29% to 42% in 100 patients.[7-9] The impact of this combination on survival is still to be determined, however (Table 2).

Paclitaxel and Ifosfamide

Ifosfamide has been reported to be one of the most active single drugs in patients with advanced non–small-cell lung cancer, with a response rate of 27% in 130 untreated patients. The combination of paclitaxel and ifosfamide at a dose of 3 to 5 g/m² (plus mesna) has been evaluated in a total of 141 patients.[10-13] The response rate ranges from 21% to 34%, and median survival, when available, does not reach 40 weeks (Table 3). No synergistic effect of these two drugs has been
observed. The addition of vinorelbine (Navelbine) to paclitaxel and ifosfamide (plus G-CSF) has been evaluated in 55 patients, and only a 17% objective response rate was observed.[14]

The triplet paclitaxel/ifosfamide/carboplatin (AUC of 5) has been reported in 26 patients with a promising 64% response rate,[15] but the addition of etoposide to this triplet offered only a 27% response rate in 34 patients.[16]

## Paclitaxel and Doxorubicin

Doxorubicin (Adriamycin) is not recognized as a major drug in the treatment of advanced non-small-cell lung cancer. Nevertheless its combination with paclitaxel has shown a high level of activity in advanced breast cancer, so it was logical to evaluate this doublet in non-small-cell lung cancer.

Two studies[17,18] have included 29 and 15 patients, respectively. In the first study, paclitaxel was given at a dose of 150 mg/m², administered over 3 hours with 40 mg/m² of doxorubicin; an objective response rate of 30% in the whole population was achieved, including an objective response of 53% in chemonaive patients. In the second study, paclitaxel was delivered at a dose of 135 mg/m² over 24 hours and doxorubicin at a dose of 50 mg/m². The response rate was 33%. This range of activity merits further studies with the combination of paclitaxel and anthracyclines in advanced non-small-cell lung cancer.

## Paclitaxel and Vinorelbine

Vinorelbine has been shown to be active in the treatment of non-small-cell lung cancer with an objective response rate of 32% in 165 chemonaive patients. Two studies have evaluated the combination of paclitaxel and vinorelbine.[19,20] In the first, paclitaxel was given at a dose of 100 to 135 mg/m² over 1 hour on day 1 and vinorelbine at a dose of 20 to 25 mg/m² on days 1 and 8 of each 3-week cycle. The objective response rate was 24% in 18 patients. In the second study, paclitaxel was given at 175 mg/m² and vinorelbine at 25 mg/m² (plus G-CSF) with the same schedule; the response rate was 18% in 20 patients with a median survival of 22 weeks. The response rate for the combination does not appear higher than the one observed for each of the drugs used alone.

## Paclitaxel and Topotecan

Wiesenfeld et al[21] reported a combination of paclitaxel given at the dose of 190 mg/m² and topotecan (Hycamtin) 1 mg/m² on days 1 through 5 (plus G-CSF). The objective response rate was 24% in 61 patients with a median survival of 26 weeks. These results do not appear superior to paclitaxel alone.

## Paclitaxel and Hydroxyurea

Finally, Stewart et al[22] have evaluated the activity of the combination of paclitaxel at a dose of 135 to 200 mg given over 1 hour and hydroxyurea (Hydrea) at a dose of 500 mg orally 3 days a week in patients with previously treated non-small-cell lung cancer. Results were negative with an objective response rate of 3% in 30 patients and a median survival of 20 weeks.

## Conclusion

In conclusion, at this stage of development of paclitaxel combinations, it appears that the most promising association of paclitaxel with a non-platinum compound is the combination of paclitaxel and etoposide. The addition of cisplatin or carboplatin (Paraplatin) to this doublet offers a higher response rate and an apparent impact on survival, both of which warrant confirmatory studies.

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filgrastim (G-CSF) versus topotecan and paclitaxel (Taxol) with filgrastim in patients with advanced


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