Single-Agent Paclitaxel in Advanced Non–Small-Cell Lung Cancer

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Despite the availability of combination chemotherapy, response rates are poor in patients with non–small-cell lung cancer. Recently, phase II trials have been undertaken with single-agent paclitaxel (Taxol). Good results have

Introduction

Treatment results in patients with advanced non–small-cell lung cancer are still unsatisfactory. In single-institution trials, combination chemotherapy regimens have produced responses in the 20% to 43% range; however, the impact on median survival time is minimal.[1] To improve these results, new cytotoxic agents are needed.

Paclitaxel (Taxol) is one of the new antineoplastic agents with a unique mechanism of action and a wide spectrum of clinical activity. Significant antitumor efficacy has been reported in patients with ovarian and breast cancer. Paclitaxel has also shown activity in patients with lung cancer, including non–small-cell lung cancer and small-cell lung cancer. Single-agent paclitaxel chemotherapy has been investigated in a number of trials in advanced non–small-cell lung cancer using different dosages and schedules (Table 1).

Phase II Studies of Single-Agent Paclitaxel

Long Infusion (24 h)
Two trials of single-agent paclitaxel were conducted in previously untreated patients with advanced non–small-cell lung cancer.[2,3] In one trial conducted by the Eastern Cooperative Oncology Group (ECOG), 250 mg/m² of paclitaxel was administered by 24-hour infusion. In a second trial conducted at M. D. Anderson Cancer Center, 200 mg/m² of paclitaxel was administered by 24-hour infusion. The overall response rate in the Eastern Cooperative Oncology Group trial was 21%, with a 1-year survival rate of 42%. The second trial conducted at M. D. Anderson confirmed these data, with an overall response rate of 24% and a 1-year survival rate of 38%. The results of these two trials generated a lot of interest and several other investigators initiated trials to further explore the activity of paclitaxel in the treatment of patients with advanced non–small-cell lung cancer.

A later trial using a 24-hour infusion of paclitaxel was published by Tan.[4] In this trial, 11 patients were pretreated with cisplatin-containing regimens and the response rate was 16%. The median survival time published to date was in the range of 30 to 40 weeks. The 1-year survival ranged from 22% to 47%.

Short Infusion (3 h)
It has been shown that the administration of paclitaxel by a 3-hour infusion significantly reduces hematologic toxicity, in particular, neutropenia. Consequently, four other phase II trials using a 3-hour infusion schedule have been published by Gatzemeier,[5] Rosell,[6] Furuse,[7] and Millward.[8] The paclitaxel dosages ranged from 175 mg/m² up to 225 mg/m². The response rates were between 24% and 32%. An Australian trial reported a 10% response rate. However, in this trial 57% of the patients had received prior radiotherapy, but more importantly, the investigators had used a different formulation of paclitaxel.[8] Again the median survival time published to date was in the range of 30 to 40 weeks. The 1-year-survival ranged from 22% to 47%.

Short Infusion (1 h)
In one trial published by Hainsworth,[9] between 135 mg/m² and 200 mg/m² of paclitaxel was administered as a 1-hour infusion. The response rate on this trial was 25%, with a median survival time of 33 weeks, and the 1-year-survival probability was 33%.
Weekly Administration
In a study by Akerley,[10] a weekly schedule of 100 mg/m² and up to 175 mg/m² of paclitaxel as a 3-hour infusion yielded a response rate of 38%. The study included 21 patients—all with stage IV disease. Survival data are not available to date.

Toxicity
Looking at the toxicity data suggested that the frequency and intensity of the myelosuppressive side effects are correlated with the infusion length of the paclitaxel administration (Table 2). Episodes of febrile neutropenia have been reported only with the use of the 24-hour schedule. The incidence of grade IV granulocytopenia was found to be significantly less with the 3- or 1-hour infusion schedules compared with the 24-hour schedule. Excluding the Japanese trial, all 3- and 1-hour infusion trials showed a very low level of grade IV neutropenia. Thrombocytopenia (Table 3) was rarely reported with almost no incidence of World Health Organization (WHO) grade II, III, or IV toxicity. The infusion length has no impact on the frequency or severity of thrombocytopenia. Neurotoxicity is usually mild to moderate. It is noteworthy that grade IV neurotoxicity has not been reported in any trials (Table 4).

No major differences were demonstrated between the different trials based on schedule and infusion length. The different dosages and schedules did not lead to differences in the incidence and severity of nausea and vomiting (Table 5). Overall, very few patients experienced WHO grades III and IV gastrointestinal toxicity. Myalgia and arthralgia (Table 6) was rarely reported with almost no incidence of the patients. Very few patients experienced WHO grades III and IV myalgia and arthralgia, again without any difference between the schedules.

Discussion
Paclitaxel is one of the most active agents in advanced non-small-cell lung cancer, with response rates of approximately 22%. The data are very consistent and are based on about 400 patients in phase II trials. In comparison to older drugs,[1] the response rate is in the upper range of the effective drugs. Myelosuppression is the major dose-limiting toxicity, especially when paclitaxel is used as a 24-hour schedule. The incidence of grade IV granulocytopenia was found to be significantly less with the 3- and 1-hour infusion schedules compared with the 24-hour schedule.

The 40% 1-year survival rate of single-agent paclitaxel is double that achieved by the combination of cisplatin and etoposide, which has shown a 1-year survival rate of approximately 20% in several previous studies. Paclitaxel as a single agent is an active drug in non-small-cell lung cancer.

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