One-Hour Paclitaxel Plus Carboplatin for Advanced Non-Small-Cell Lung Cancer

We report here the preliminary results of a large phase II multicenter study done in the community setting, using paclitaxel (Taxol) (given by 1-hour infusion) plus carboplatin (Paraplatin) to treat patients with advanced non-small-cell lung cancer (NSCLC). In this study, 155 chemotherapy-naive patients with stage IIIb, stage IV, or recurrent metastatic non-small-cell lung cancer received the two drugs in 21-day cycles. Paclitaxel 225 mg/m² was given by 1-hour intravenous infusion followed immediately by carboplatin at a targeted area under the concentration-time curve of 6.0 (calculated according to the Calvert formula). Colony-stimulating factors were not used routinely. Objective responses occurred in 53 of 155 patients (34%) (53 of 144 [36%] evaluable patients) including three complete responses and 50 partial responses. Fifty-two other patients had stable disease at initial reevaluation. The median survival among all 155 patients was 8 months; the 1-year survival rate was 42%, and the 2-year survival rate was 20%. Leukopenia and cumulative peripheral neuropathy occurred consistently but rarely were severe or affected the course of therapy. One patient died due to sepsis. Other grade 3 and grade 4 toxicities were uncommon. This paclitaxel-carboplatin combination chemotherapy appears to be a relatively convenient, safe, and active regimen in advanced non-small-cell lung cancer.[ONCOLOGY 12(Suppl 2):71-73, 1998]

Although the ideal dose and schedule of paclitaxel (Taxol) has not been definitively determined, we have investigated a 1-hour infusion schedule and found it to be safe and easy to administer.[1,2] Response rates among patients with advanced non-small-cell lung cancer generally are around 25% in phase II trials, including even patients previously treated with cisplatin (Platinol)-based regimens.[3-5] We attempted to corroborate these findings in a large, phase II, multicenter, community-based study of 1-hour paclitaxel and carboplatin (Paraplatin) for the treatment of patients with advanced non-small-cell lung cancer. Preliminary results are presented here.

Patients and Methods

This phase II trial was initiated in The Minnie Pearl Cancer Research Network in March 1995. Seventeen community-based oncology groups entered patients (see Table 1). Data management was coordinated at The Sarah Cannon-Minnie Pearl Cancer Center. The study was approved by the Investigational Review Board of Centennial Medical Center (Nashville, Tennessee), and all patients gave written informed consent before beginning treatment.

Eligibility

Eligibility required histologically documented stage IIIb, stage IV, or recurrent metastatic non-small-cell lung cancer and no previous systemic treatment. Previous radiotherapy was acceptable. All patients had uni- or bidimensionally measurable disease by chest radiograph or computerized tomography. Additional characteristics included age older than 18 years, Karnofsky performance status ≥ 70%, life expectancy ≥ 12 weeks, adequate bone marrow function (leukocyte count ≥ 3,500/µL, platelets ≥ 100,000/µL), adequate liver function (bilirubin ≤ 1.25 × upper normal limit, aspartate aminotransferase ≤ 2.5 × upper normal limit), adequate renal function (serum creatinine ≤ 1.5 × upper normal limit or calculated glomerular filtration rate [GFR] > 50 mL/minute).

Treatment

All patients received the following chemotherapy regimen: paclitaxel 225 mg/m² administered by 1-hour intravenous infusion and followed immediately by carboplatin at an area under the concentration-time curve (AUC) of 6.0 given intravenously over 30 to 60 minutes. Treatment courses were repeated every 21 days. The carboplatin dose was calculated using the Calvert formula to achieve an estimated AUC of 6.0 as follows:

Carboplatin dose (mg) = 6.0 × (GFR + 25)
The GFR was calculated using the formula:

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\text{GFR} = \frac{[(140 - \text{age}) \times \text{weight in kg}]}{\text{serum creatinine} \times 72} \times 0.85 \text{ (for women)} \text{ or } 1.00 \text{ (for men)}
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Before receiving paclitaxel, all patients were premedicated with dexamethasone 20 mg given orally 12 and 4 hours before therapy. Thirty minutes before paclitaxel infusion, the following drugs were administered intravenously: dexamethasone 20 mg, diphenhydramine 50 mg, and cimetidine (Tagamet) 300 mg. Paclitaxel was mixed in normal saline at a concentration not to exceed 1.2 mg/mL.

Response to therapy was determined at week 6 (after two courses). Therapy was discontinued in patients with progressive disease. Patients with stable disease or objective response continued treatment, and response was reassessed after each two courses of treatment. Responding or stable patients received a minimum of six and a maximum of 10 courses of treatment.

Complete blood counts were measured weekly. Dose reductions for myelosuppression and other toxicities were made in a standard fashion. Colony-stimulating factors were not used during the first course of therapy but could be added subsequently, though not as a substitute for a required dose reduction. Moderate or severe hypersensitivity reactions to paclitaxel necessitated removal from the study, although treatment could be reinstituted at the discretion of the treating physician.

**Results**

Between March 1995 and June 1996, 155 patients enrolled in this study. Seventy-five percent of patients had stage IV disease, median age was 63 years, 50% had adenocarcinoma, 70% of patients were men, 60% had Karnofsky performance status \( \geq 90\% \), and 1% had \( \geq 10\% \) weight loss. All 155 patients registered for this study are included in the survival analysis and were evaluated for intent-to-treat response rate. Duration of response was calculated from the first day of treatment until the day that disease progression was documented. Thus far, the first 100 patients who received at least one course of treatment have been evaluated for treatment-related toxicity.

Patients received a median of four courses of paclitaxel and carboplatin.

**Efficacy**

Fifty-three of 155 patients (34%) had major responses to therapy (three complete responses, 50 partial responses). The response rate in the 144 evaluable patients was 36%. An additional 52 patients (36%) had stable disease after two courses of treatment, and 39 (27%) had progressive disease. The median duration of response was 6 months (range, 3 to > 20 months). The median survival for all 155 patients was 8 months, the 1-year survival rate was 42%, and the actuarial the 2-year survival rate was 20%.

There were no statistically significant differences in response rate related to gender, performance status, disease stage, or previous weight loss in this group of patients. Furthermore, there was no difference in survival between stage IIIIB and stage IV patient cohorts.

**Toxicity**

Myelosuppression was the most common toxicity. Grade 3 or grade 4 leukopenia occurred in 32 patients (10% of courses), necessitating dose reductions at some time during treatment in 15 patients. Grade 3 and grade 4 anemia and thrombocytopenia occurred in only 10% and 12% of patients, respectively. Eleven hospitalizations (3% of courses) for fever occurred, and there was one treatment-related death due to sepsis.

Although the arthralgia-myalgia syndrome was common, it was severe (grade 3 or grade 4) in only five patients (5%). Peripheral neuropathy, also frequent, generally developed after the third or fourth treatment course. Grade 3 peripheral neuropathy was encountered in only 15 patients, although an additional 12 patients were electively removed from treatment after four to eight courses due to mild to moderate neuropathy (grade 2). Other grade 3 and grade 4 toxicities were uncommon.

**Discussion**

Several phase II studies have documented a high level of activity for the combination of paclitaxel and carboplatin in advanced non-small-cell lung cancer, although the doses and schedules of administration have varied in these studies.[6-12] The preliminary results presented here from a large, multicenter, community-based trial confirmed these findings.

In 144 evaluable patients treated at 17 centers, a 36% overall response rate was obtained. In all 155 patients the survival rate at 1 year was 42% and at 2 years, 20%. Furthermore, most responding patients and some with stable disease experienced improvement in one or more symptoms, and nearly 50% of these patients gained weight during therapy. These survival results are double those...
of previous historical series of patients treated with the combination of cisplatin and etoposide (VePesid).[12]

Similar response rates, median survival rates, and 1-year survival rates have been reported whether this regimen consisted of longer paclitaxel infusions or, in some instances, higher carboplatin doses. We found, however, that the 1-hour paclitaxel regimen was easily administered and well tolerated in the outpatient setting.

Cumulative peripheral neuropathy frequently occurs when paclitaxel is administered by short infusion, particularly when cisplatin is included in the regimen[6] (15% of our patients experienced grade 3 neuropathy, and 12% discontinued therapy prematurely due to grade 2 neuropathy). However, the short paclitaxel infusions markedly reduce myelosuppression and make administration easier than the 24-hour infusion. A modest reduction in the paclitaxel dose (ie, from 225 mg/m² to 200 mg/m²), as well as limiting the total number of cycles to four to six, potentially could alleviate some of the neuropathy that we noted.

Several randomized trials are comparing the combination of paclitaxel and carboplatin with other standard regimens employed in non-small-cell lung cancer, including cisplatin and etoposide, cisplatin and gemcitabine (Gemzar), cisplatin and vinorelbine (Navelbine), and paclitaxel as a single agent. Results of a recently reported randomized, three-arm Eastern Cooperative Oncology Group trial showed that two different regimens of paclitaxel (administered by 24-hour infusion) plus cisplatin produced superior response rates and survival when compared with a standard cisplatin-etoposide regimen.[12] Paclitaxel and a platinum compound is now accepted as a standard treatment for advanced non-small-cell lung cancer. Of the various regimens used, our 1-hour paclitaxel-carboplatin regimen is the easiest to administer in the outpatient setting and provides a useful and applicable option. This regimen should be evaluated further in phase III trials.

References:


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