Paclitaxel, Carboplatin, and Extended-Schedule Oral Etoposide for Small-Cell Lung Cancer

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We evaluated the feasibility and efficacy of combination paclitaxel (Taxol) (via 1-hour infusion), carboplatin (Paraplatin), and oral etoposide (VePesid) in the first-line treatment of patients with small-cell lung cancer.

Small-cell lung cancer currently accounts for approximately 20% of all lung cancers in the United States. Although this subtype of lung cancer is initially highly chemosensitive, treatment responses are usually temporary and cure is elusive. Most patients develop a high degree of chemotherapy resistance within several months of diagnosis. In the early 1980s, the combination of cisplatin (Platinol) and etoposide (VePesid) became a widely used regimen, demonstrating superiority over previous non-cisplatin-containing regimens. However, the past decade has offered little further advance in the treatment of patients with small-cell lung cancer. The outcome of treatment continues to be highly dependent on initial disease stage; median survival is only 7 to 10 months if extensive-stage disease is present and 15 to 24 months if patients have limited-stage disease at diagnosis.[1,2]

A number of antineoplastic agents with novel mechanisms of action have recently been developed. One such agent, paclitaxel (Taxol) has demonstrated activity against small-cell lung cancer in several phase II trials, exemplified by response rates of 34% in trials by the Eastern Cooperative Oncology Group and 64% in trials by the North Central Cancer Treatment Group. [3,4] In both of these studies, previously untreated patients with extensive-stage small-cell lung cancer received single-agent paclitaxel 250 mg/m² by 24-hour continuous infusion. Since its introduction, paclitaxel has been administered on much shorter infusion schedules (1 to 3 hours vs 24 hours in initial recommendations). Because of the ease of administration, and to facilitate the development of combination regimens, we routinely administer paclitaxel by 1-hour infusion.[5] Accordingly, in patients with small-cell lung cancer, we added paclitaxel to a regimen of carboplatin (Paraplatin) and etoposide. In our initial study, relatively low doses of paclitaxel (135 mg/m²) and carboplatin (dosed to a target area under the concentration-time curve [AUC] of 5.0) were used.[6,7] This regimen was extremely well tolerated, and in a subsequent phase II trial we increased the doses of both agents to paclitaxel to 200 mg/m² and carboplatin to a target AUC of 6.0. This article summarizes the results of these two sequential phase II trials with this novel regimen.

Patients and Methods

In June 1993, we empirically designed a three-drug regimen containing paclitaxel, carboplatin, and extended-schedule oral etoposide. At that time, limited information concerning paclitaxel-containing combination regimens was available, so the doses of paclitaxel and carboplatin in the initial regimen were relatively low. After treating 38 patients, we observed extremely good tolerance of the regimen, as well as a level of efficacy similar to other reported regimens. Details of data from our initial 38 patients have been reported previously.[7] Subsequently, we increased the doses of paclitaxel and carboplatin and treated another cohort of 79 patients using these higher doses. The first group (38 patients) was treated at The Sarah Cannon-Minnie Pearl Cancer Center in Nashville, Tennessee. The second study was performed in The Minnie Pearl Cancer Research Network, a group of 20 community-based oncology groups located predominantly in the Southeast. Thirty-nine of the 79 patients in this study were enrolled from the Sarah Cannon Center and 40 from the other participating community-based oncology groups.

Eligibility

To be eligible for these studies, all patients were required to have histologically confirmed small-cell lung cancer, previously untreated with chemotherapy or radiation therapy. Additional entry criteria included Eastern Cooperative Oncology Group performance status ≤ 2, measurable or evaluable disease, leukocyte count ≥ 4,000/µL, platelet count ≥ 100,000/µL, serum bilirubin ≤ 1.5 mg/dL, and
serum creatinine $\leq 1.5$ mg/dL. These studies were approved by the Institutional Review Boards at the participating institutions, and all patients provided written informed consent before enrollment.

**Staging**

All patients underwent routine staging for small-cell lung cancer, including chest x-ray; chemistry profile; computed tomography of the chest, abdomen, and brain; and bone scan. Bone marrow aspiration and biopsy were performed in patients who had no evidence of extensive-stage disease after completion of the previous evaluations.

**Treatment**

All patients received combination therapy with paclitaxel (delivered by 1-hour infusion), carboplatin, and extended-schedule oral etoposide. In the first 38 patients, the doses were as follows: paclitaxel 135 mg/m², via 1-hour intravenous infusion, day 1; carbo-platin dosed to an AUC of 5.0, intravenously, day 1; oral etoposide 50 mg alternating with 100 mg, days 1 to 10. In the second group of 79 patients, the regimen was identical, but the doses of paclitaxel and carboplatin were increased to paclitaxel 200 mg/m² and carboplatin to a target AUC of 6.0. The carboplatin dose was calculated using the Calvert formula (dose [mg] = \([\text{glomerular filtration rate} + 25] \times \text{desired AUC}\)), with GFR calculated by the Cockcroft-Gault formula and creatinine determined by the colorimetric method. Standard antihypersensitivity premedications preceded paclitaxel administration. Cytokines were not routine with either regimen.

In both regimens, courses were repeated at 21-day intervals, and patients were reevaluated after the first two courses. Responding and stable patients continued on therapy for at least four courses; treatment was discontinued in most patients after four courses, although some who achieved partial responses and definite clinical benefit received an additional two to four courses.

**Radiation Therapy**

Patients with limited-stage small-cell lung cancer also received radiation therapy, which was administered concurrently with the third and fourth courses of full dose chemotherapy, beginning on day 42. A total of 45 Gy was given, using standard, once-daily 1.8-Gy fractions. The size of the radiation therapy field was based on the size of the primary tumor at the time that radiation was started.

Prophylactic whole-brain irradiation was not administered routinely in the first group of patients; however, whole-brain irradiation was given routinely to patients in the second group who had complete or near-complete remissions after treatment.

**Dose Modification Plan**

Complete blood counts were monitored weekly during therapy. The etoposide dose was evaluated based on day 8 blood counts as follows: leukocytes $> 3,000/\mu L$ and platelets $> 100,000/\mu L$, etoposide continued at same dose; leukocytes 2,000 to 3,000/\mu L or platelets 75,000 to 100,000/\mu L, etoposide continued at 75% dose; leukocytes $< 2,000/\mu L$ or platelets $< 75,000/\mu L$, etoposide discontinued for the remainder of the course.

Blood counts on day 21 were used to modify doses in subsequent courses as follows: leukocytes $\geq 3,000/\mu L$ and platelets $\geq 100,000/\mu L$, all drugs continued at full dose; leukocytes $< 3,000/\mu L$ or platelets $< 100,000/\mu L$, treatment delayed 1 week or until counts rose above the values cited when patients were retreated with full doses of all agents. Patients who required hospitalization for febrile neutropenia received 75% doses of all drugs in subsequent chemotherapy courses.

**Follow-up and Evaluation**

At study completion, all patients were assigned a response category using standard response criteria (complete response = total disappearance of clinically and radiologically detectable disease for at least 4 weeks; partial response = $\geq 50\%$ reduction in size of all measurable lesions, with no new lesions; nonresponders = all others). Treatment-related toxicity was graded according to the World Health Organization Common Toxicity Criteria. After all treatment was completed, patients were followed at monthly intervals until progression.

Actuarial survival curves for the various patient subsets were constructed using the Kaplan and Meier method, and survival curves were compared using the Wilcoxon log rank method.

**Results**

The patient characteristics of the 79 patients in the higher-dose study are typical for patients with small-cell lung cancer. Median age was 62 years (range, 35 to 76 years); 45 patients (57%) were male. Forty-one patients (52%) had limited-stage disease, and 67 patients (85%) had Eastern Cooperative Oncology Group performance status ratings of 0 or 1.

Of the 79 patients, 74 (94%) received the planned four courses of therapy. Five patients did not complete therapy due to treatment-related deaths (two patients) and disease progression (three
patients). All 79 patients were evaluable for toxicity and response. A total of 262 courses (89%) were administered at full dose.

**Efficacy**

Of 79 patients in the higher-dose study, 72 (91%) had major responses to treatment. The response rate was 84% in the 38 patients with extensive-stage disease, including eight complete responses (21%). Fully 98% of patients with limited-stage disease responded, with complete responses in 71%. Actuarial survival curves for the subsets of patients with limited and extensive disease are shown in Figure 1.[8] Median survival for patients with extensive disease was 10 months; the median survival for limited-disease patients has not yet been reached but will exceed 16 months ($P = .005$).

Table 1 compares the response rates of both patient cohorts treated with the lower and higher doses of paclitaxel and carboplatin.[8] Although overall response rates were high with both regimens, the higher-dose regimen yielded an improved overall response rate in patients with extensive disease and improved complete response rates in limited-disease patients.

The median survival of patients with extensive disease was longer with the higher-dose regimen (10 vs 7 months, $P = .008$). Figure 2 compares actuarial survival of these two subsets.[8] At present, no significant difference in survival exists between the limited-disease patients treated with higher doses vs those receiving lower doses, although the median survival of the higher-dose group has not yet been reached.

**Toxicity**

Table 2 details the toxicities encountered with this regimen and compares the frequency of toxicities in the lower- and higher-dose patient cohorts. Myelosuppression was the most common toxicity; as expected, the incidence of grade 3 and grade 4 leukopenia increased (from 8% to 38% of courses) with the increased doses of paclitaxel and carboplatin. However, because of the brief duration of leukopenia, the incidence of hospitalization for treatment of neutropenia and fever did not increase substantially with the higher-dose regimen (11% vs 9% of courses).

Esophagitis occurred exclusively in limited-disease patients receiving concurrent chemoradiotherapy. Grade 4 esophagitis was rare. No other unusual toxicity, including parenchymal lung toxicity, was encountered with concurrent chemoradiotherapy. Peripheral neuropathy was uncommon, probably since most patients received only four courses of therapy. Treatment-related mortality was 3% with each regimen.

**Discussion**

The combination of paclitaxel (given over a 1-hour infusion), carboplatin, and extended-schedule oral etoposide is highly active and well tolerated in the treatment of patients with small-cell lung cancer. In sequential cohorts of patients, we demonstrated that the doses of paclitaxel and carboplatin can be increased to doses commonly used in the treatment of patients with non-small-cell lung cancer, without undue toxicity. The results with the higher-dose regimen were obtained in a cooperative group, community practice setting, and patient and physician acceptance of this novel regimen was excellent.

Several features of this regimen contribute to its relatively acceptable toxicity. First, substitution of carboplatin for the traditional cisplatin component decreases several common nonhematologic toxicities, including nausea, vomiting, and asthenia. Second, the 1-hour paclitaxel infusion limits myelosuppression and facilitates the easy administration of this regimen in the outpatient setting. Third, limitation of the duration of treatment to four courses minimizes cumulative side effects, particularly peripheral neuropathy. Finally, the use of extended-schedule oral etoposide is easily tolerated and obviates the need for intravenous administration on three consecutive days.

Although these trials were sequential rather than randomized, it appears that the higher-dose regimen may be more active. The complete response rate in those with limited-stage small-cell lung cancer improved with the higher doses, and more importantly, median survival in a large group of extensive-disease patients improved from 7 to 10 months as the paclitaxel and carboplatin doses were increased. In spite of these increases, changes in toxicity were minimal; the greatest change was in the incidence of grade 3 and grade 4 leukopenia, which increased from 8% to 38% of courses. Other serious toxicities, as well as hospitalizations and treatment-related deaths, were equally common with both regimens.

Although these phase II studies demonstrate the feasibility of adding full-dose paclitaxel to a standard platinum/etoposide combination, either alone or with concurrent radiation therapy, they do not fully define the role of paclitaxel in the treatment of patients with small-cell lung cancer. The level of efficacy observed with our higher-dose regimen is sufficient to warrant further investigation.
We are currently in the midst of a randomized trial comparing a commonly used regimen of carboplatin and etoposide (carboplatin to a target AUC of 6.0 on day 1, etoposide 120 mg/m² intravenously on days 1 to 3, repeated at 21-day intervals) with the higher-dose regimen of paclitaxel, carboplatin, and oral etoposide. This trial is accruing patients rapidly and should be completed within the next 12 to 18 months.

References:


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