Cisplatin/Paclitaxel vs Cisplatin/Teniposide for Advanced Non-Small-Cell Lung Cancer

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A total of 332 patients with advanced non-small-cell lung cancer were randomized by the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group

Introduction

Chemotherapy is still considered a controversial issue in the treatment of non-small-cell lung cancer (NSCLC). As single agents, relatively few of the older drugs achieve a more than 15% response rate in advanced NSCLC, but, among them, cisplatin (Platinol) has received considerable attention. Other drugs with some activity are ifosfamide (IFEX), the vinca alkaloids (eg, vinblastine [Velban] and vindesine), mitomycin (Mutamycin), and the epipodophyllotoxins (eg, etoposide [VePesid] and teniposide [Vumon]). The response rate associated with the established active agents in NSCLC is in the range of 15% to 25%.

Cisplatin is considered the backbone agent for use in combination chemotherapy against this disease. Combination chemotherapy regimens including cisplatin have yielded response rates up to 50% and usually include two or three of the drugs mentioned.[1] One combination chemotherapy regimen commonly used in Europe and the United States is cisplatin/etoposide, which produces response rates in the range of 25% to 35%, with tolerable toxicity.

In the European Organization for the Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group, we recently completed a randomized study in which the activity of single-agent teniposide, an analogue of etoposide, was compared with that of combination teniposide/cisplatin.[2] In that same study, teniposide was tested at two different schedules: the same total dose was given either in 1 day or in 3 refracted days. The study accrued over 200 patients and was a 2 x 2 factorial design study.

The results of that study indicated that combination teniposide/cisplatin was superior to teniposide alone in terms of response rate and both progression-free and overall survival.[2] Further, the treatment arm in which teniposide was administered in 1 day only had a 0% response rate, suggesting that the drug has a schedule-dependent activity, as shown for etoposide.[3] For these reasons, we elected to use the teniposide/cisplatin combination as the standard arm for the current randomized study in patients with advanced NSCLC.

In recent years, several interesting new drugs have been developed that exhibit significant activity in advanced NSCLC; among them are the taxanes, paclitaxel (Taxol) and docetaxel (Taxotere); gemcitabine (Gemzar); a new vinca alkaloid, vinorelbine (Navelbine); and water-soluble topoisomerase I inhibitors such as irinotecan. Paclitaxel has shown a response rate of 20% to 25% in previously untreated patients with advanced NSCLC, with a remarkably long 1-year survival. In these studies, paclitaxel was given as a 24-hour infusion, with premedication with three antiallergic agents. We decided to compare our standard arm of cisplatin/teniposide with the new combination of paclitaxel/cisplatin. A report suggesting a possible pharmacologic interaction between paclitaxel and cisplatin,[4] with higher toxicity when paclitaxel was given after cisplatin, prompted us to administer paclitaxel before cisplatin in this study. Further, we decided to administer paclitaxel as a 3-hour infusion instead of a 24-hour infusion, based on a report of lower hematologic toxicity but similar activity with this schedule compared with the more prolonged infusion time, in patients with advanced ovarian cancer.[5]

Patients and Methods
Standard eligibility criteria were required to enter this study: Patients were aged 18 to 75, had had no prior chemotherapy, had histologically proven inoperable non-small-cell lung cancer, and were in relatively good condition (Eastern Cooperative Oncology Group performance status 2 or less and adequate marrow and organ functions). Prior radiotherapy was allowed to areas not used as marker lesions for response assessment, but it had to have been terminated at least 4 weeks before study entry. Patients with brain metastases were not eligible. Informed consent was obtained according to the regulations of each participating center.

Physical examination and complete blood counts and chemistries were performed before study entry, along with imaging procedures appropriate to adequately stage and assess the tumor deposits. Weekly blood counts were performed to determine hematologic toxicity, and blood chemistries, electrocardiogram, and thoracic x-ray were performed before every cycle of therapy. Additional imaging techniques were repeated to evaluate the response to treatment after two, four, and six cycles, and approximately every 2 months thereafter. At treatment completion, patients were seen at approximately 2-month intervals.

**Treatment**

Patients were randomized to receive one of two cisplatin-based combination chemotherapy regimens (Figure 1):

- Paclitaxel 175 mg/m² given on day 1 by 3-hour infusion, followed by 1- to 2-hour infusion of cisplatin 80 mg/m² or
- 1- to 2-hour infusion of cisplatin 80 mg/m² on day 1, followed by teniposide 100 mg/m² given on days 1, 3, and 5.

Cycles were repeated every 3 weeks in both arms. Paclitaxel was dissolved in 500 mL 5% dextrose and infused before cisplatin; teniposide was dissolved in 500 mL normal saline and infused over 1 hour, administered after cisplatin. Cisplatin was dissolved in 500 mL saline or 5% dextrose and infused in a program of forced diuresis consisting of at least 2 L of fluid. Paclitaxel was administered after standard antiallergic premedication, consisting of oral dexamethasone 20 mg 12 and 6 hours prior to infusion and diphenhydramine 50 mg intravenously (IV) and cimetidine 300 mg IV 30 minutes before paclitaxel infusion. Prophylactic antiemetic medication was left to the discretion of the investigators, but usually included ondansetron (Zofran) 8 mg bid IV in combination with dexamethasone 8 mg bid IV during the cisplatin administration.

The duration of treatment was six cycles in patients whose disease did not progress during treatment. In the paclitaxel arm only, however, investigators were allowed to continue administration of paclitaxel alone to a total of 10 cycles of chemotherapy during the initial randomized, phase II part of the study. Following observation of a substantial increase of peripheral neurotoxicity after more than six cycles with this treatment, the recommendation was made to terminate chemotherapy after a maximum of six cycles. This was implemented in the phase III part of the study.

Dose-reduction schemas and treatment delays were provided based on occurrence of severe hematologic toxicities and nonhematologic side effects.

**Trial Conduct and Statistical Analysis**

Patients were stratified according to institution, performance status (0 vs 1 vs 2), and extent of disease (stage III vs IV). Because cisplatin/paclitaxel was a novel combination at the time of design of this study, we started with a randomized phase II study. After analysis of the results of the initial phase, which included a total of 80 patients,[6] it was concluded that the standard arm produced similar activity and toxicity to those observed in the previous study[2] and that the new experimental arm was both feasible and active.

Based on results of the randomized phase II study, it was then decided to proceed with the randomized phase III study for which the major end point was comparison of survival between the arms. An additional end point of the phase III trial was comparison of the two arms for toxicity, response rate, and progression-free survival. At selected centers, quality of life was assessed by the Quality-of-Life-30 instrument with the lung module in the phase III part of this study. Consequently, a secondary end point of the phase III trial became comparison of quality of life issues in the two arms. To ensure detectability of an improvement in median survival of 3 months (from 7 to 10 months), it was planned that a total of 288 patients would be entered into this trial; this number of patients would also suffice to detect an increase in response rate from 24% to 42%.
Results

A total of 332 patients (166 in each arm) were randomized by the EORTC Lung Cancer Cooperative Group from July 1993 to February 1996, and this report represents a preliminary analysis of the results of this phase III trial. These results must be viewed with some caution, however, as external review of radiologic responses is still ongoing and site visits have not been completed yet; further, longer follow-up may reveal some changes in the survival figures. Overall, the two arms were well balanced for major prognostic factors: approximately 70% of patients were male and had lost less than 5% of their body weight, 90% had a performance status of 0 or 1, 50% had adenocarcinoma, and 60% had stage IV disease. The major characteristics of the eligible patients are reported in Table 1. Thirteen patients were considered ineligible.

Toxicity

Hematologic toxicity was definitively more severe and more common in arm B (cisplatin/teniposide) than in arm A (paclitaxel/cisplatin): In the control arm (B) approximately 50% of patients developed grade 3/4 leukopenia, almost 80% developed grade 3/4 neutropenia, and almost 40% developed severe thrombocytopenia. The severe myelosuppression also led to treatment-related infections in a substantial number of patients. These results are in agreement with our prior experience with this regimen.[2] In contrast, the new investigational arm (A) was associated with relatively mild hematologic toxicity, with 18%, 54%, and 3% grade 3/4 leukopenia, neutropenia, and thrombocytopenia, respectively. Primarily due to myelosuppression, there were more treatment delays and dose reductions in the standard arm than in the investigational arm. The nonhematologic side effects were mainly represented by alopecia and nausea and vomiting in both arms. Due to the introduction of more potent antiemetic medications, emesis was better controlled in this study than in our previous study. A slightly higher incidence of peripheral neurotoxicity and arthralgia/myalgia was reported in the paclitaxel arm. Peripheral neurotoxicity did not represent a serious problem for patients who interrupted treatment after a maximum of six cycles of chemotherapy. Low and similar frequencies of severe hypersensitivity reactions and cardiac toxicity were observed in both arms of the study.

Response and Survival

Among 264 patients evaluable so far, responses have been assessed in 47% of those in the paclitaxel-based treatment arm and 29% of those given cisplatin/teniposide. Extramural radiologic response evaluation is still being carried out, however, and these numbers are expected to decrease slightly in both arms. In both arms, the vast majority of responses were partial. Given the preliminary nature of this analysis, it is premature to draw conclusions about the survival comparisons; so far, however, survival appears to be similar in the two arms, with a median survival time in the range of 9 months. At this time, the number of deaths is nearly 200 in total. Longer follow-up is necessary to allow meaningful comparisons.

Discussion

The introduction of new active drugs to treat NSCLC, such as paclitaxel, clearly offers new treatment options in this disease. We tested the new combination of paclitaxel/cisplatin in patients with advanced, previously untreated NSCLC and compared it with our best standard arm, a combination of teniposide and cisplatin. Preliminary analysis of this phase III trial indicates quite clearly a difference in response rate and toxicity between the two arms: Both differences favor the paclitaxel arm. So far, however, no major differences in survival are evident between the two arms. Quality of life has been assessed in selected centers and the data are being analyzed; this analysis will certainly provide additional information useful for comparing the two arms. It should be kept in mind, however, that palliation is the major objective of these treatments in patients with advanced NSCLC. In light of the present preliminary results, it is tantalizing to consider the investigational arm of paclitaxel/cisplatin as the new standard arm for the next randomized study in this disease.

References:


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