Gemcitabine, Paclitaxel, and Carboplatin for Advanced Non–Small-Cell Lung Cancer

July 01, 2000
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The purpose of this study was to evaluate the combination of gemcitabine (Gemzar), paclitaxel (Taxol), and carboplatin (Paraplatin) in patients with advanced non–small-cell lung cancer (NSCLC). Previously untreated

Introduction

Treatment options for patients with advanced non–small-cell lung cancer (NSCLC) have greatly improved during the last decade. A number of new agents have shown activity both when administered alone or in combination, most commonly with cisplatin (Platinol) or carbo-platin (Paraplatin). These agents include paclitaxel (Taxol), docetaxel (Taxotere), gemcitabine (Gemzar), irinotecan (CPT-11 [Camptosar]), topotecan (Hycamtin), and vinorelbine (Navelbine).[1-6] A large meta-analysis showed that compared with supportive care alone, cisplatin-based chemotherapy increased median survival by more than 6 weeks. [7] The newer agents alone or in combination have yielded median survivals of 8 to 10 months in large multicenter, phase II and III trials. These results represent an increase in absolute improvement in median survival of approximately 2 to 3 months, and in 1-year survival of about 25% to about 40%. The combination of paclitaxel and carboplatin has proven to be well tolerated and active in the treatment of advanced NSCLC.[8,9] Studies have shown reproducible median survivals of > 8 months and 1-year survival rates of about 40%. Paclitaxel plus carbo-platin has become the community standard throughout much of the United States.

Gemcitabine, alone and in combination with cisplatin, has shown promising response rates, with a median survival of approximately 9 months. [10,11] Gemcitabine is very well tolerated by most patients, and as a single agent, it appears to be as useful as the older cisplatin-based therapies. Designing a three-drug regimen for treating NSCLC includes combining agents that are potentially synergistic, with non-overlapping toxicity profiles, and with unique mechanisms of action. The incorporation of a third agent may lead to even greater improvement in median survival. Gemcitabine is an attractive agent to consider because of its demonstrated single-agent activity, favorable toxicity profile, and unique mechanism of action.

Phase I Trial of Gemcitabine/ Paclitaxel/Carboplatin

We conducted a phase I trial to confirm the feasibility of combining gemcitabine, paclitaxel, and carboplatin in a single regimen.[12] A total of 15 patients were treated at two dose levels (7 patients with paclitaxel 200 mg/m², day 1; carboplatin, area under the curve (AUC) 6.0, day 1; gemcitabine 800 g/m², days 1 and 8; 8 patients with paclitaxel 200 g/m², day 1; carboplatin, AUC 5.0; gemcitabine 1,000 mg/m², days 1 and 8). In this trial, leukopenia was the most common toxicity, with a moderate degree of thrombocytopenia. The myelosuppression reversed rapidly and did not delay the administration of subsequent cycles. Furthermore, the lack of severe nonhematologic toxicity with gemcitabine (including the lack of neuropathy and arthralgia/myalgia) resulted in no difference in the nonhematologic toxicity profile of the triple regimen in comparison to the paclitaxel/carboplatin regimen. Phase II dose levels of gemcitabine 1,000 mg/m² on days 1 and 8; paclitaxel 200 mg/m² on day 1; and carboplatin at an AUC of 5.0 on day 1, were selected for further study.

Phase II Trial of Gemcitabine/Paclitaxel/Carboplatin

Patients and Methods
Between December 1996 and September 1997, 69 patients were enrolled in the phase II portion of
this triplet combination study. Entry criteria were the same as for the phase I portion. Therefore, a total of 77 patients were entered and treated at the recommended dose levels (including the 8 patients from the phase I trial). Patients had previously untreated, pathologically confirmed stage IIIB or IV NSCLC.

Previous radiation therapy was permitted as long as the evaluable disease was outside the radiation therapy field. Other requirements were as follows: measurable disease; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; age > 18 years; life expectancy of ≥ 12 weeks; a white blood cell (WBC) count > 3,000/µL; a platelet count > 100,000/µL; and normal creatinine and bilirubin levels.

Exclusion criteria were brain metastases, active cardiac disease, or other serious, ongoing medical problems. Informed consent was obtained from all patients.

**Dosage and Administration**

Chemotherapy was administered on day 1 of each 21-day cycle as follows: paclitaxel 200 mg/m² was given first, followed by gemcitabine 1,000 mg/m², and then carboplatin (AUC = 5.0).

This administration sequence was chosen because other phase I studies[13,14] of gemcitabine and members of the taxane family have reported an acceptable toxicity profile and antitumor efficacy when the taxane was administered before gemcitabine. Additionally, with short paclitaxel infusions, there has been no obvious sequence-related toxicity with carboplatin.

Premedications included oral dexamethasone 20 mg administered 12 and 4 hours prior to paclitaxel dosing; dexamethasone 20 mg; cimetidine (Tagamet) 300 mg; diphenhydramine 50 mg (30 minutes prior to paclitaxel); and a serotonin antagonist antiemetic.

The gemcitabine dose was repeated on day 8, based on a day-8 blood count. Carboplatin dosing was calculated using the Calvert formula: carboplatin = target AUC × glomerular filtration rate (GFR) + 25. The GFR was calculated using the Cockcroft-Gault formula. Cytokines were not routinely administered as part of this therapy.

Blood counts were measured weekly during therapy and were used to modify dosages on the day of therapy. On day 1 of each cycle, full doses were administered if the WBC count was > 3,000/µL, and if the platelet count was > 100,000/µL.

When the WBC count was between 2,000/µL and 3,000/µL, or the platelet count was between 75,000/µL and 100,000/µL, 75% of all three drugs were administered. If the WBC count was < 2,000/µL or a platelet count was < 75,000/µL, the course was delayed 1 week, and the full dose was administered if the counts recovered.

For day 8 of gemcitabine dosing, full doses were administered if the WBC was > 3,000/µL and the platelet count was > 100,000/µL.

If the WBC was > 2,000/µL to 3,000/µL, and the platelet count was between 75,000/µL and 100,000/µL, 75% of the planned dose was administered. Day-8 doses were omitted if the WBC was < 2,000/µL or if the platelet count was < 75,000/µL.

Patients requiring hospitalization for the treatment of fever and neutropenia had subsequent doses reduced to 75% of all three drugs for the remainder of treatment. For patients developing grade 3 and 4 nonhematologic toxicity, doses were held until the toxicity had recovered to grade 1 or less, and then 75% of planned doses were administered with future cycles.

Patients were evaluated for response after two treatment courses. Those patients with stable disease or response continued treatment, with responses reassessed after each additional two cycles. A minimum of four and a maximum of ten courses of treatment were given to responding or stable patients.

Responses were defined by standard criteria. Complete response required the absence of all clinical evidence of tumor for a minimum of 4 weeks. Partial response required a > 50% decrease in tumor size (a perpendicular sum of the products of measurable lesions) for at least 4 weeks, with no new lesions developing and evaluable lesions remaining stable or improved.

Progressive disease was defined as those patients showing an increase of at least 25% of the product of the measured lesions or the appearance of any new lesions. Patients not meeting partial response definitions and not having developed progressive disease were considered to have stable disease.

Patients for the phase II study were enrolled at 13 sites in the Minnie Pearl Cancer Research Network. All 77 patients treated at the phase II doses of gemcitabine, paclitaxel, and carboplatin are included in the survival analysis (8 patients from the phase I portion and 69 patients subsequently accrued).

**Results**

Patient characteristics are shown in Table 1. Of the 77 enrolled patients, 56 (73%) had stage IV
disease, and 23 (30%) patients were treated at the Sarah Cannon Cancer Center, Nashville, Tennessee. A total of 67 (87%) patients received at least two courses of therapy and were fully evaluable for assessment of response. An additional 4 patients who were included in the response analysis experienced rapid progressive disease prior to completing two treatment cycles and were categorized as nonresponders.

A total of 6 other patients received fewer than two courses of therapy for the following reasons: 2 patients reported a severe hypersensitivity reaction to paclitaxel; 2 patients requested withdrawal from the study because of therapy intolerance; 1 patient suffered sepsis (treatment-related death); and 1 patient died from a cerebral vascular accident (nontreatment related). All 77 patients were both evaluable for treatment-related toxicities and included in the survival analysis.

A total of 291 courses were administered (median, four courses). Full doses were administered in 77% of the courses on day 1, compared with 50% of the full doses given on day 8. Patients received a mean of 92% paclitaxel, 85% gemcitabine, and 94% carboplatin during their first two courses of therapy. More than six cycles were administered to 10 patients.

Table 2 shows intent-to-treat response rates, tumor response, response duration, and survival. A response rate of 48% (34 patients) was documented, including 2 patients with complete responses in the 71 fully evaluable patients. A total of 25 (35%) patients reported stable disease or minor regressions of tumor as their best response to therapy, and 12 patients (17%) progressed. Median duration of response was 6 months, with a range of 3 to 14 months. Among the 21 patients with stage IIIB disease, 11 (52%) responded, including two complete responses. Median survival of all 77 patients was 9.9 months. The minimum follow-up was 24 months (range, 24 to 36 months). At 1 year, the actual survival was 47%, and at 2 years, the survival rate was 21%.

Tables 3 and 4 show the toxicities reported in this phase II trial. Myelosuppression was the most commonly noted toxicity, with 16% of patients experiencing febrile neutropenia. Although 44% (34 of 77) of patients experienced grade 3 or 4 thrombocytopenia (platelet count < 50,000/µL), no bleeding complications were noted and only 9 patients received platelet transfusions. Red blood cell transfusions were administered to 17 (22%) patients.

The addition of gemcitabine to the paclitaxel and carboplatin regimen did not seem to greatly affect the observed nonhematologic toxicities. Fatigue and asthenia were the most common toxicities. Arthralgia/myalgia occurred in approximately one-half (53%) of patients, while severe peripheral neuropathy (grades 3 or 4) was noted in only 8% of patients. Mucositis, dermatitis, nausea, and edema were infrequently reported.

**Conclusion**

Use of the triple-drug combination of gemcitabine/paclitaxel/carboplatin for patients with advanced NSCLC is feasible. The results of this multi-institutional trial are encouraging. Of the 71 fully evaluable patients, 34 (48%) showed documented responses. Also impressive is the fact that only 12 (17%) patients reported progressive disease as their best response to treatment. The actual 1-year survival rate for this group approaches 50%, and the 2-year survival rate is 21%, which is the next threshold to surpass in designing effective NSCLC regimens.

Myelosuppression observed in this trial was brief and quickly reversible. The vast majority of patients received their subsequent cycles of therapy on time. The overall toxicity of this triplet combination was only modestly increased compared to that experienced with paclitaxel plus carboplatin.

Results of the triplet combination with gemcitabine as reported herein compare favorably with recent results from paclitaxel and carboplatin phase II trials, including those from our own center.[9] Prospective, randomized comparisons are now warranted. In addition, this triplet combination may be particularly useful in neoadjuvant and adjuvant settings for patients with earlier stage disease.

**References:**


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