A Phase I/II Trial of Paclitaxel, Carboplatin, and Gemcitabine in Untreated Patients with Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Paclitaxel and carboplatin is widely used in the treatment of patients with advanced non-small cell lung cancer (NSCLC); however, median survival remains <1 year. One strategy to improve survival is to add a third active drug with a differing mechanism of action. Gemcitabine is a novel antimetabolite with considerable activity in NSCLC. The primary objective of this Phase II/II study was to determine the maximally tolerated dose of gemcitabine administered with fixed doses of paclitaxel and carboplatin in untreated patients with advanced NSCLC.

INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women in the United States, accounting for 28% of all cancer deaths (1). More than 75% of patients with lung cancer have non-small cell histology, and 50% will present with incurable stage IIIB or IV. Treatment for patients with advanced stage disease is cisplatin-based chemotherapy, which produces a significant improvement in overall survival as compared with best supportive care (2). In meta-analyses of randomized trials, cisplatin-based chemotherapy increased median survival from 16 to 26 weeks, and the 1-year survival rate improved from 15 to 25% as compared with best supportive care (3, 4). Recently, several new agents with novel mechanisms of action have shown activity in lung cancer (5). These agents include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and the topoisomerase I inhibitors (irinotecan and topotecan). Randomized trials have demonstrated that single-agent taxanes and vinorelbine improve survival compared with supportive care (6–8). Randomized trials also showed that several two-drug combinations produced superior survival compared with cisplatin alone or cisplatin and etoposide, with median survivals ranging from 32 to 57 weeks and 1-year survival rates of 26–61% with the two-drug combinations (9–11).

A recently completed Phase III SWOG study comparing two novel doublets, paclitaxel and carboplatin to cisplatin and vinorelbine, demonstrated similar efficacy with median survivals of 32 weeks for both arms and a 1-year survival rate of 38 and 36%, respectively (12). The paclitaxel/carboplatin arm was more convenient and had less toxicity but was more expensive. Thus, although paclitaxel and carboplatin is a reasonable regimen for the first-line treatment of advanced stage NSCLC, survival remains suboptimal for these patients. Continued research to further improve survival remains important, especially in a time when there are multiple new combinations to investigate. One strategy is to add a new active drug with a different mechanism of action to the active doublet of paclitaxel and carboplatin. Gemcitabine is an excellent candidate because of its single-agent activity in NSCLC and favorable toxicity profile. Phase II studies demonstrated a response rate of 21%, with median survivals of 32–37 weeks (13–15). Myelosuppression was the most common toxicity, with grade 3–4 neutropenia occurring in 25% of patients, but no patient developed clinically significant infection. Nonhematological toxicity was mild. In combination with cisplatin, a Phase III trial showed that gemcitabine plus cisplatin produced a significant survival advantage over cisplatin alone (11).

This study was designed to determine the maximally tolerated dose of gemcitabine with fixed doses paclitaxel and carboplatin in untreated patients with advanced NSCLC. The starting dose of gemcitabine was arbitrarily selected at 600 mg/m² and escalated in 100-mg/m² increments. The secondary objectives were to determine the response rate, response duration, and survival of patients receiving this combination.

PATIENTS AND METHODS

Eligibility. Patients with histologically or cytologically confirmed NSCLC, stage IIIB (with a malignant pleural effusion) or stage IV were eligible to participate in this trial if they had measurable or evaluable disease. Patients with asymptomatic or controlled brain metastasis were also eligible. All patients were required to have normal organ function according to protocol guidelines, a SWOG performance status PS of 0–2, and no active or uncontrolled medical condition. Patients with a prior history of malignancy other than nonmelanoma skin cancer or...
cervical carcinoma in situ were excluded if their disease-free interval was <3 years. Patients could not have received prior chemotherapy, but previous surgery or radiotherapy was allowed after recovery from side effects. All patients were required to give written informed consent.

Pretreatment and Follow-Up Evaluations. Before enrollment, all patients underwent a history and physical examination, complete blood counts, electrolytes, renal and liver function tests, urinalysis, and an electrocardiogram. Required radiographs included a baseline chest X-ray and computed tomography of the chest and abdomen. A computed tomography scan or magnetic resonance imaging of the brain and a bone scan were performed only if there was clinical suspicion of disease. Physical examinations were required before every cycle. Complete blood counts were drawn weekly. Renal and liver function tests were obtained before each cycle. Radiographs for tumor assessment were obtained after every two cycles.

Treatment Plan. The patients received chemotherapy according to the dose escalation schedule shown in Table 1. Five patients were entered at each dose level. The MTD was defined as the dose level below the level in which two of five patients developed febrile neutropenia with or without G-CSF, grade 4 neutropenia or leukopenia on G-CSF, or any other grade 4 toxicity. If no patient or one patient developed grade 4 toxicity at a given dose level, accrual continued to the next higher dose level. At the MTD, an additional 15 patients were planned to be treated.

Initial patients received paclitaxel (175 mg/m² over 3 h) and carboplatin at an (AUC = 6) on day 1 every 3 weeks. After 14 patients were treated on three dose levels, grade 3 and 4 thrombocytopenia was observed in course 4, 5, or 6 in seven patients. Thus, all newly enrolled patients were treated with a carboplatin AUC = 5. For subsequent cycles, a platelet count of <75,000 at any time required a dose reduction of carboplatin to an AUC of 4. Gemcitabine was administered on days 1 and 8, starting at 600 mg/m² and increasing in increments of 100 mg/m². One patient enrolled on level 2 came off the study after receiving day 1 of cycle 1 only and was not felt to be evaluable for toxicity; thus, another patient was added to dose level 2. One patient enrolled in level 5 erroneously received the doses of level 4 and was reclassified into level 4. Because the MTD was not reached at dose level 5, a sixth dose level was added, with paclitaxel given at 200 mg/m². Dose-limiting toxicity occurred on level six. Subsequently, 16 patients were accrued to MTD (level 5).

All patients were premedicated with oral or i.v. dexamethasone (20–40 mg), cimetidine (300 mg, i.v.), and benadryl (50 mg, i.v.). Paclitaxel was then given i.v. over 3 h, followed by a gemcitabine (i.v. over 30 min), then carboplatin (i.v. over 30 min) on day 1 of each cycle. Carboplatin AUC dosing was calculated using the Calvert formula: Carboplatin dose (mg) = Target AUC × (GFR + 25) (16). The GFR was calculated using the Cockcroft-Gault formula:

\[
GFR = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85 (\text{female})}{72 \times \text{serum creatinine}}
\]

Gemcitabine was repeated on day 8. Cycles were repeated every 21 days for a minimum of six cycles, unless the patient had progressive disease or intolerable toxicity.

G-CSF was not given prophylactically but was allowed subsequently for patients who developed grade 4 leukopenia or neutropenia, febrile neutropenia, or failure to recover neutrophil count by day 28 of a cycle. If a patient on G-CSF developed grade 4 leukopenia or neutropenia, prolonged neutropenia, or febrile neutropenia, the dose of gemcitabine was reduced by 25%.

The dose of gemcitabine on day 8 was based on the absolute granulocyte count and the platelet count obtained on day 8. If day 8 gemcitabine was held because of toxicity, it was not given at a later time. Two dose reductions were allowed prior to removal from the study. Other dose modifications for hematological and nonhematological toxicity were instituted per the protocol guidelines. Treatment toxicity was graded according to the SWOG criteria (17).

Statistical Analysis. Patients with measurable or evaluable disease were assessed for response according to SWOG Criteria (17). Time to progression curves and the Kaplan-Meier survival curves were produced in SAS 6.10 using Proc Lifetest. Time to progression was calculated from the time of diagnosis to progressive disease. Patients who died without progression or who had not progressed were censored at the date of death or last follow-up. Overall survival was calculated from the time of enrollment into the study until death. Living patients were censored at the date of last follow-up.

RESULTS

Fifty-one patients were enrolled in this trial between October 1996 and September 1998. One patient was ineligible because of SWOG PS of 3 at enrollment. Patient characteristics for the 50 eligible patients are listed in Table 2. The patients were between 45 and 76 years of age, with a median age of 61

| Table 1 Dose levels of paclitaxel, carboplatin, and gemcitabine |
|------------------|-------------------|-------------------|-------------------|
| Level | Patients | Paclitaxel\(^a\) (mg/m²) | Carboplatin\(^a\) (AUC) | Gemcitabine\(^b\) (mg/m²) |
| 1 | 5 | 175 | 6 | 600 |
| 2 | 6 | 175 | 6 | 700 |
| 3 | 5 | 175 | 6/5\(^c\) | 800 |
| 4 | 6 | 175 | 5 | 900 |
| 5 | 21 | 175 | 5 | 1000 |
| 6 | 7 | 200 | 5 | 1000 |

\(^a\) Day 1.
\(^b\) Days 1 and 8.
\(^c\) Last two patients started with an AUC of 5.

| Table 2 Patient characteristics (n = 50) |
|-------------------------------|----------------|
| Median age | 61 (range, 45–76) |
| Male/Female | 32/18 |
| Stage IIB/IV | 4/46 |
| Brain metastases | 8 |
| PS 0/1/2 | 17/30/3 |
| Histology | |
| Adenocarcinoma | 33 |
| Squamous | 10 |
| Large cell/poorly differentiated | 6 |
| Mixed NSCLC | 1 |
years. Sixty-four % were men, and 36% were females. Ninety %
of patients had stage IV disease (16% with controlled brain
metastases), and 10% had stage IIIB disease with malignant
pleural effusion. The majority of patients had a PS of 0 –1
(94%), whereas 6% had a PS of 2. Adenocarcinoma was the
most frequent histology observed, but various other histolog-
cal subtypes were reported. Forty-seven patients were evalu-
able for toxicity and response. Three patients were inevalu-
able: one patient was lost to follow-up, and two patients
refused protocol treatment. All 51 patients were included in
the survival analysis.

Hematological Toxicity. Hematological toxicity is sum-
marized in Table 3. The most frequent grade 4 toxicity was
neutropenia, occurring in 19 patients (40%) and 13% of courses.
Grade 3 neutropenia occurred in 25 patients (53%) and in 21% of
courses. No patient developed febrile neutropenia. Four pa-
tients received G-CSF. Overall, grade 4 thrombocytopenia oc-
curred in 10 patients (21%) and 6% of courses. Grade 3 throm-
bocytopenia developed in 17 patients (36%) and 9% of courses.
Initially, 4 of 14 patients (29%) treated with carboplatin at an
AUC = 6 on dose levels 1, 2, and 3 developed grade 4 throm-
bocytopenia during cycles four to six, necessitating a dose
reduction of carboplatin to an AUC = 5 for all new patients and
a liberal dose modification for all subsequent cycles. Once
these modifications were instituted, grade 4 thrombocytopenia
occurred in 6 of 33 patients (18%), but dose-limiting thrombocy-
topenia was observed in two patients on dose level 6. One
patient developed grade 4 thrombocytopenia during both cycles
1 and 2 of therapy, and the other patient died suddenly from
acute exsanguinating hemoptysis on day 17 of cycle 1 (presum-
ably related to thrombocytopenia). Overall, three patients re-
ceived platelet transfusions. Grade 4 anemia occurred in 1
patient, and grade 3 anemia occurred in 5 patients. Ten patients
received blood transfusions.

One additional toxic death was observed in a patient on
level 1. This patient developed epistaxis on day 15 of cycle 5
and was found to have a platelet count of 17,000 with an
international normalized ratio of 3.3 (secondary to anticoagulant
therapy). He was transfused with platelets, and his coumadin
dose was decreased; however, a few hours later, he was found
unresponsive; resuscitation efforts failed, and the patient died. A
platelet count at this time was 33,000.

Nonhematological Toxicity. Nonhematological toxicity
was mild (Table 4). Grade 4 nausea and vomiting developed in
two patients (4%); no other grade 4 toxicities occurred. The
most frequent grade 3 toxicity was fatigue, which developed in
five patients (11%). Other grade 3 toxicities were infrequent.
Grade 1 or 2 peripheral neuropathy was observed in 15 patients
(32%), and 2 patients developed grade 3 toxicity. Grades 1 and
2 fatigue and myalgia/arthralgia were seen in 38% (18 pa-
tients) and 25% (12 patients), respectively.

Dose Intensity. Forty-seven patients received at least one
complete cycle of chemotherapy. The median number of cycles
administered per patient was four. No patient on dose level 6
completed the six planned cycles of therapy. During the first
four courses of therapy, 163 cycles were administered to 47
patients. The patients received a mean of 99, 90, and 90% of the
planned doses of paclitaxel, carboplatin, and gemcitabine, re-

Table 3 Hematological toxicity

| Dose level | No. of eval. ptsa | No. of courses | Neutropenia | | | | Thrombocytopenia | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | No. of pts | % of courses | No. of pts | % of courses | No. of pts | % of courses | No. of pts | % of courses |
| 1 | 5 | 32 | 3 | 28 | 2 | 6 | 2 | 6 | 4 | 13 |
| 2 | 6 | 26 | 3 | 19 | 3 | 15 | 3 | 15 | 0 | 0 |
| 3 | AUC=6 | 3 | 11 | 2 | 27 | 2 | 45 | 1 | 9 | 0 | 0 |
| AUC=5 | 2 | 11 | 2 | 18 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 6 | 25 | 2 | 20 | 2 | 16 | 2 | 12 | 1 | 8 |
| 5 | 19 | 96 | 12 | 22 | 7 | 11 | 7 | 10 | 4 | 5 |
| 6 | 7 | 18 | 1 | 6 | 3 | 18 | 2 | 11 | 1 | 1 |
| Total | 47 | 219 | 25 | 21 | 19 | 13 | 17 | 9 | 10 | 6 |

a eval pts, evaluable patients.

Table 4 Nonhematological toxicity

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>Fatigue</th>
<th>Peripheral neuropathy</th>
<th>Myalgia/Arthralgia</th>
<th>Nausea/Vomiting</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Grade 1–2</td>
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<td>Grade 1–2</td>
<td>3</td>
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<td>Total</td>
<td>47</td>
<td>18</td>
<td>5</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

3476 Paclitaxel/Carboplatin/Gemcitabine in Advanced NSCLC
respectively. Thirty-nine patients received more than four cycles of therapy totaling 58 courses. The mean percentage of planned doses was 95, 89, and 92% for paclitaxel, carboplatin, and gemcitabine, respectively.

**Response and Survival.** Forty-seven patients with measurable or evaluable disease who completed at least one cycle of therapy were assessable for response. No complete responses were observed. Ten patients had partial responses (21%; CI, 0.13–0.36), 9 patients had minor responses (19%), and 12 patients had stable disease (25%). Sixteen patients had progressive disease (34%). With a median follow-up time of 8 months, the median survival for all 51 patients was 8 months (CI, 5.5–9.5 months), with a 1-year survival rate of 33% (CI, 19–45%) and a 2-year survival rate of 14% (CI, 2–22%). Four patients are still alive at 24, 26, 28, and 32 months.

**DISCUSSION**

This Phase I/II study showed that four to six cycles of paclitaxel, carboplatin, and gemcitabine could be given at full doses with acceptable toxicity in patients with advanced NSCLC. Dose-limiting thrombocytopenia was observed on dose level six. No increase in other toxicities was noted with the addition of gemcitabine to paclitaxel and carboplatin. Grade 4 neutropenia was the most common toxicity and occurred in 40% of patients, but no patient developed febrile neutropenia. The triplet was active, producing a response rate of 21%, a median survival of 8 months, and a 1- and 2-year survival rate of 33 and 18%, respectively. The recommended doses for future studies are 175 mg/m² paclitaxel i.v. over 3 h, carboplatin AUC = 5, and 1000 mg/m² gemcitabine.

The results observed in this study are similar to those obtained by other investigators evaluating this combination, as shown in Table 5. Hainsworth et al. (18) conducted a Phase I study and also found thrombocytopenia to be dose limiting, with a carboplatin dose AUC = 6. In their subsequent Phase II study, they treated 77 patients with advanced NSCLC, with 200 mg/m² paclitaxel i.v. over 1 h, carboplatin AUC = 5, and 1000 mg/m² gemcitabine on days 1 and 8 and reported a 44% response rate (18). With mature follow-up, the median survival was 9.9 months, and the 1-year survival rate was 47%. The combination produced grade 4 thrombocytopenia in 21% of patients and grade 4 leukopenia in 15% of patients. Favaretto et al. (19) conducted a Phase I/II trial in 28 patients with 175 mg/m² paclitaxel i.v., carboplatin AUC = 6, and 1000 mg/m² gemcitabine on days 1 and 8. Seventeen patients (61%) achieved an objective response. Survival data were not reported (19). Three trials substituted cisplatin for carboplatin (20–22). Frasci et al. (20) conducted a Phase I/II trial to determine the MTD of paclitaxel (50–150 mg/m² i.v. over 1 h) given in combination with fixed doses of cisplatin (50 mg/m²) and gemcitabine (1000 mg/m²), with all drugs repeated on days 1 and 8 of a 21-day cycle. Sixty-five previously untreated patients were accrued to this study. Cumulative dose-limiting toxicity consisted of neutropenia, thrombocytopenia, nausea/vomiting, diarrhea, and fatigue at a paclitaxel dose of 150 mg/m². An objective response was observed in 39 of 64 evaluable patients (61%). The median survival was 15 months for all chemotherapy patients. At the recommended paclitaxel dose of 125 mg/m², 26 of 38 assessable patients (68%) achieved a response. Median survival has not been reached, and the projected 1-year survival rate is 70% (Table 5). At the recommended doses, grade 4 neutropenia occurred in 23% of patients and grade 4 thrombocytopenia in 8% of participants. Sorensen et al. (21) completed a Phase II study of a biweekly regimen of 110 mg/m² paclitaxel i.v. over 3 h with 60 mg/m² cisplatin and 800 mg/m² gemcitabine every 2 weeks in 40 patients with NSCLC. In their preliminary analysis, 80% of patients developed grade 3–4 neutropenia, but only one case of neutropenic sepsis was reported. Nephrotoxicity occurred in 33% of patients. Twenty-one patients (53%) had a documented response with an 8-month median survival. A subsequent trial evaluated a 21-day schedule with 180 mg/m² paclitaxel on day 1, 100 mg/m² cisplatin on day 1 plus 1000 mg/m² gemcitabine on days 1 and 8 (22). Twenty-nine patients were administered this combination. Significant toxicity continued to be observed, with grade 3–4 neutropenia developing in 92% of patients and grade 3–4 thrombocytopenia in 62% of patients. Twelve episodes of febrile neutropenia occurred, resulting in one toxic death. Grade 3 hematological toxicity included nausea and vomiting (41%), nephrotoxicity (33%), and neurotoxicity (7%). Among 22 evaluable patients, there were 13 objective responses (59%). Survival data were not reported.

In comparison to other trials, we reported a low response rate of 25% in the small Phase II portion of this trial. Patient selection most likely accounts for this discrepancy, with only

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**Table 5** Results from Phase II studies with gemcitabine, paclitaxel, and carboplatin or cisplatin

<table>
<thead>
<tr>
<th>Author</th>
<th>No of eval. pts</th>
<th>Stage</th>
<th>Objective response</th>
<th>Median survival</th>
<th>1-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hainsworth et al. (18)</td>
<td>77</td>
<td>27%</td>
<td>44%</td>
<td>9.9 months</td>
<td>47%</td>
</tr>
<tr>
<td>Favaretto et al. (19)</td>
<td>28</td>
<td>60%</td>
<td>61%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Frasci et al. (20)</td>
<td>38</td>
<td>33%</td>
<td>68%</td>
<td>NR</td>
<td>70%</td>
</tr>
<tr>
<td>Sorensen et al. (21)</td>
<td>40</td>
<td>NR</td>
<td>53%</td>
<td>8 months</td>
<td>NR</td>
</tr>
<tr>
<td>Sorensen et al. (22)</td>
<td>22</td>
<td>48%</td>
<td>59%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kelly et al.</td>
<td>19</td>
<td>10%</td>
<td>25%</td>
<td>8 months</td>
<td>33%</td>
</tr>
</tbody>
</table>

* eval pts, evaluable patients; NR, not reported.

* Projected.

* Cisplatin-based regimen.

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4 A. Greco, personal communication.
one patient (5%) having stage IIIB disease as compared with 27, 33, 48, and 60% in four of the five trials reporting stage of disease. Furthermore, four patients had brain metastasis, and only one other trial included patients with brain metastases (20). The dosing schedule could also have played a role, with two cisplatin-based trials administering all three drugs twice during a cycle, producing high response rates of 68 and 53% (20, 21). Median survival had not been reached in the first study, but overall survival for all patients including those in the Phase I study was encouraging at 15 months; however, the second trial reported an 8-month median survival, which was the same as our survival time (20, 21). The increased toxicity observed with these dose-intense regimens will require further evaluation.

Overall, these trials suggest a benefit for the triple-drug combination, but their superiority over a two-drug regimen remains to be determined. In comparison to our previous Phase I/II trial of paclitaxel plus carboplatin, there does appear to be a slight survival advantage for the triplet regimen with a median survival of 7 months for paclitaxel/carboplatin versus 8 months for paclitaxel/carboplatin/gemcitabine and 1- and 2-year survival rates of 28% versus 33% and 6% versus 12%, respectively (23). A similar observation was observed by Hainsworth et al. (24), when they compared their Phase II results. An increase in median survival from 8 months for paclitaxel/carboplatin to 9.9 months for paclitaxel/carboplatin/gemcitabine was observed with 1-year survival rates (42% versus 47%), respectively.

In conclusion, this trial demonstrated that the triplet combination of paclitaxel, carboplatin, and gemcitabine could be given at full doses with acceptable toxicity. Furthermore, efficacy was slightly superior to that observed in our Phase II trial of paclitaxel plus carboplatin but similar to the 8-month survival demonstrated recently in the randomized Phase III trial of paclitaxel/carboplatin versus vinorelbine/cisplatin (23, 12). However, other investigators have shown superior survival to ours with the same triple-drug combination (18). The definitive answer awaits the results of ongoing randomized trials comparing paclitaxel plus carboplatin to paclitaxel, carboplatin, with gemcitabine.

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