Phase II Trial of Weekly Paclitaxel and Concurrent Radiation Therapy for Locally Advanced Non-Small Cell Lung Cancer

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ABSTRACT

We conducted a prospective Phase II study to determine the response rate, toxicity, and 2-year survival rate of concurrent weekly paclitaxel and radiation therapy (RT) for locally advanced unresectable non-small cell lung cancer. The weekly paclitaxel regimen was designed to optimize the radiosensitizing properties of paclitaxel. Thirty-three patients with unresectable stage IIIA and IIIB non-small cell lung cancer from six institutions were entered into the study between March 1994 and February 1995. Weekly i.v. paclitaxel (60 mg/m²; 3-h infusion) plus concurrent chest RT (60 Gy over 6 weeks) was delivered for 6 weeks. Twenty-nine patients were evaluable for response. Three patients achieved a complete response (10%), and 22 patients (76%) achieved a partial response, for an overall response rate of 86% (95% confidence interval, 68–96%). One patient progressed during the therapy, and three patients had stable disease. Esophagitis was the principal toxicity. Grade 3 or 4 esophagitis occurred in 11 patients (37%). One patient died of pneumonia after completion of therapy. Additional grade ≥3 toxicities included pneumonitis (12%) and neutropenia (6%). One patient had a grade 3 hypersensitivity reaction. The median overall survival duration for all 33 patients who entered the study was 20 months, and 1-, 2-, and 3-year overall survival rates were 60.6%, 33.3%, and 18.2%, respectively. The median progression-free survival duration for all 33 patients was 10.7 months, and 1-, 2-, and 3-year progression-free survival rates were 39.4%, 12.1%, and 6.1%, respectively. Weekly paclitaxel plus concurrent RT is a well-tolerated outpatient regimen. The survival outcome from this regimen is encouraging and seems to be at least equivalent to that of other chemotherapy/radiation trials. These findings warrant further clinical evaluation of weekly paclitaxel/RT in Phase II trials in the neoadjuvant setting and in combination with other cytotoxic agents.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in the United States. NSCLC³ comprises nearly 75% of all lung cancers diagnosed in smokers and over 90% of smoking-associated lung cancers (1). Prolonged survival depends on the stage of the disease and on the possibility of resection. However, almost 60% of patients with NSCLC will have metastatic disease or locally advanced disease at initial assessment. Overall, the 5-year survival rate for locally advanced lung cancer patients is less than 5% (2). This low figure reflects the inability of standard RT to cure locally advanced disease and the disappointing activity (in the range of 15–20%) of the chemotherapeutic agents used in NSCLC (3). Chemotherapy followed by definitive chest irradiation is, however, superior to chest irradiation alone (4–7). Randomized studies have shown that the addition of cisplatin to radiotherapy modestly enhances survival in patients with locally advanced NSCLC (8, 9). In addition, several pilot studies of concurrent chemotherapy and RT have yielded results similar to those observed in the combined modality arms of randomized sequential studies (4). These studies suggest that chemotherapy plus chest irradiation is a desirable treatment option for locally advanced NSCLC.

Paclitaxel is an attractive agent to study in the setting of concurrent chemotherapy and RT (10, 38). Paclitaxel, a complex plant product extracted from the bark of the Pacific yew Taxus (Taxus brevifolia), has demonstrated substantial anticancer activity in solid tumors (11–14). The drug promotes the polymerization of tubulin and thus disrupts normal microtubule function causing cell death (15). Paclitaxel interferes with mitotic spindle function by enhancing the rate and yield of microtubule assembly and preventing microtubule depolymerization (16–18). In addition to this direct cytotoxic action on tumor cells, in vitro studies have shown that paclitaxel can potentiate the effects of radiation on malignant cells (19–24). Paclitaxel results in the arrestment of cells in the G2-M phase of the cell cycle (25), which is particularly sensitive to ionizing radiation (26). In vitro, paclitaxel is a potent radiation sensitizer for some but not all tumor cell lines (22). This unique mechanism of action may be responsible for much of the radiosensitizing ability of paclitaxel.

The abbreviations used are: NSCLC, non-small cell lung cancer; RT, radiation therapy; CT, computed tomography; ANC, absolute neutrophil count; CALGB, Cancer and Leukemia Group B; CR, complete response; PR, partial response; SD, stable disease.

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2 To whom requests for reprints should be addressed, at Center for Radiation Oncology, Vanderbilt Medical Center, The Vanderbilt Clinic B-902, Nashville, TN 37232-5671.
On this premise, we recently conducted a Phase I trial of concurrent paclitaxel and RT for locally advanced NSCLC (10). In this trial, 27 patients received paclitaxel at 7 dose levels ranging from 10–70 mg/m²/week for 6 weeks as a 3-h infusion with 60 Gy of chest irradiation. The maximum tolerated dose was 60 mg/m²/week, and reversible esophagitis was the dose-limiting toxicity. One patient had grade 3 neutropenia. The overall response rate was 74%. Based on the favorable toxicity profile and antitumor activity observed in the Phase I study, we initiated a multi-institutional Phase II study of concurrent paclitaxel at the maximum tolerated dose (60 mg/m²/week over 6 weeks) and radiation for locally advanced NSCLC. We now report on the response, toxicity, and survival rate of this Phase II study.

PATIENTS AND METHODS

Patient Eligibility. Previously untreated patients with histologically documented inoperable stage IIIA or stage IIIB NSCLC were eligible for this study. Patients with direct vertebral body invasion or a malignant or exudative pleural effusion were not eligible. All patients had measurable or assessable disease. Further eligibility criteria included: (a) age > 18 years; (b) CALGB performance status < 2; (c) weight loss < 10% during the 3 months preceding diagnosis; (d) no prior chemotherapy; (e) no prior lung RT; (f) platelet count ≥ 100,000/μl; (g) ANC ≥ 1,800/μl; (h) hemoglobin ≥ 10 g/dl; (i) BUN < 1.5 times normal; (j) creatinine < 1.5 mg/dl; (k) bilirubin < 1.5 times the upper limit of normal; (l) AST < 2 times the normal level; (m) PO₂ > 50 mm Hg and PCO₂ < 50 mm Hg in a sample of arterial blood; (n) 1-s forced expiratory volume > 800 ml; and (o) no serious medical or psychiatric illness. All patients signed an informed consent. Height, weight, performance status, and tumor stage were recorded. Before initiation of protocol therapy, all patients underwent a medical history and physical examination; a complete blood cell count with differential and platelet counts; a chemistry panel; a posterior-anterior and lateral chest radiograph; a CT scan of the head, chest, and upper abdomen (to include the liver and adrenals); and a bone scan.

Paclitaxel Dosage. Paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) was administered weekly as a 3-h i.v. infusion in an outpatient setting for 6 weeks. Paclitaxel was usually given at the beginning of the week, before the first weekly dose of radiation treatment. All patients were premedicated with dexamethasone (20 mg, p.o.) the night before the paclitaxel infusion; and dexamethasone (20 mg, i.v.), diphenhydramine (25 mg, i.v.), and ranitidine (50 mg, i.v.) were administered 30 min before the paclitaxel infusion. Vital signs were obtained every 15 min for the first hour of the infusion and every 30 min thereafter.

RT. Radiation was delivered as 200-cGy fractions 5 days weekly for 6 weeks. The original and boost volumes were irradiated sequentially. The original treatment volume included the primary disease site with a margin of 2 cm around the mass and ipsilateral hilum. The entire width of the mediastinum was included, with a 2-cm margin around the radiographically visible area of involvement as determined by the pretreatment chest film and CT scan. The inferior margin was extended to 4 cm below the carina or 2 cm below the radiographically demonstrated tumor mass. For upper lobe lesions or patients with metastatic lesions in the supraclavicular lymph node, ipsilateral supraclavicular fossa was treated from the cricoid cartilage laterally to the midclavicular line. The boost treatment volume included the original tumor volume with a margin of 2 cm. The dose to the original volume was 40 Gy in 20 fractions of 2.0 Gy/fraction to the prescription point over a period of 4 weeks. The boost volume was 20 Gy in 10 fractions of 2.0 Gy/fraction to the prescription point over a period of 2 weeks. All of the radiation treatment records were sent to the Clinical Oncology Group of Rhode Island central data management office and reviewed for quality assurance.

Dose Modifications. Complete blood cell counts were performed weekly on the day of paclitaxel administration. Paclitaxel dosage was reduced by 50% if the ANC was less than 1,800/μl, or if the platelet count was less than 100,000/μl. Paclitaxel was not given if the ANC was less than 1,000/μl, or if the platelets were less than 75,000/μl. Radiation was withheld if the ANC was < 500/μl, or if the platelets were < 50,000/μl. Hematopoietic growth factors were not administered.

Response and Toxicity Criteria. Standard CALGB criteria were used to assess response. CR was defined as the disappearance of all measurable and evaluable disease for at least 4 weeks. PR required a reduction of 50% in the sum of the products of the perpendicular diameters of all measurable lesions or a 50% decrease (for assessable disease) in the area of the tumor mass estimated by two independent observers and lasting at least 4 weeks. SD was defined as less than a 50% reduction or a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions. Progressive disease was defined as a >25% increase in the sum of the products of two perpendicular diameters of any measured lesion or any new lesion. Local progression was defined as tumor regrowth within the radiation field. A CT scan performed 3–4 weeks after completion of paclitaxel/RT determined the response. Disease-free survival and overall survival were calculated from the time of registration into the study. Standard CALGB toxicity criteria were used to assess toxicity.

Statistical Design and Analysis. This study was prospectively designed as a two-stage Phase II trial to detect a response rate of 50% or more for the paclitaxel treatment versus the null hypothesis that the response rate is 30% or less (5, 27, 28). The study protocol required that a minimum of 24 evaluable patients be accrued to provide 73% statistical power with 7% statistical significance. An interim analysis was conducted after 16 evaluable patients were accrued.

The paclitaxel response rate was determined by the ratio of complete and partial responders (the total number of evaluable patients. The 95% confidence interval for the response rate was computed based on exact binomial probabilities, rather than a normal distribution approximation. Fisher’s exact test was used to compare response rates in patient subgroups defined by sex, performance status, histology, and stage. The product-limit method was used to estimate overall survival and progression-free survival. Overall survival was defined as the time from study enrollment to death; progression-free survival was defined as the time from study enrollment until documented disease.
progression or death. The log-rank test was used to compare survival for subgroups of patients.

RESULTS

Patient Characteristics. Between March 1994 and February 1995, 33 patients entered this study. The characteristics of all 33 patients are listed in Table 1. The age range was 40–80 years, and the median age was 66 years. There were 19 males and 14 females. Twelve patients had stage IIIA disease, and 21 had stage IIIB disease. The most common histological type was squamous carcinoma (55%). Most patients (79%) had a CALGB performance status of 1.

Doses Administered. Of the 33 patients enrolled, 1 patient was removed from the study after the discovery of s.c. metastatic disease during the first week of treatment. During the second week of treatment, one patient withdrew from the study due to disease progression. One patient refused to receive any additional chemotherapy after only 1 week of treatment; another patient developed a hypersensitivity reaction to her first dose of paclitaxel and was not rechallenged. Twenty-seven of 29 patients received all 6 cycles of weekly paclitaxel treatments. Two patients received only five treatments due to esophagitis. Thus, a total of 172 cycles of weekly paclitaxel were administered for the 29 evaluable patients or 99% of the planned paclitaxel doses. Twenty-seven of 29 patients received the planned 60 Gy of radiation. Radiation dosage was reduced to 48 and 50 Gy in two patients due to esophagitis.

Toxicity. Toxicity is described in Table 2. Toxicities were recorded weekly during the treatment using the CALGB common toxicity table. Esophagitis was the most significant toxicity noted in this study. Six patients (20%) had grade 3 esophagitis (requiring narcotics to eat solids). Five patients (17%) had grade 4 esophagitis (requiring parental or enteral support or hospitalization for i.v. hydration). Only one patient required a jejunostomy tube for enteral nutrition to complete therapy, and no patient required total parental nutrition. Esophagitis generally began in the final 2 weeks of treatment and was resolved within 2 weeks of completing treatment in all patients. Two patients (6%) had grade 2 peripheral neuropathy characterized by numbness and hyperesthesia of the hands and feet, which resolved within a few weeks of completing treatment. Four patients had a pulmonary toxicity of ≥3. One patient had asymptomatic bilateral pneumonitis; two patients had pneumonitis with shortness of breath, hypoxia, and interstitial infiltrates. The pneumonitis improved rapidly with corticosteroids. One patient died of nonneutropenic pneumonia without bilateral pneumonitis. The only significant hematological toxicity was thrombocytopenia. The only significant hematological toxicity was grade 3 neutropenia in two patients. One patient had a fever that persisted for 4 weeks during treatment as an outpatient without an identified source of infection. One patient had a grade 3 supraventricular tachycardia with a near syncopal episode. No other cardiac toxicity was observed. One patient had a grade 3 hypersensitivity reaction during her first cycle of paclitaxel with hypotension and rash and was not retreated. No other cardiac toxicity was observed. One patient had a grade 3 hypersensitivity reaction during her first cycle of paclitaxel with hypotension and rash and was not retreated. No patient had grade 3 or 4 nausea, vomiting, or complete alopecia.

Response and Overall Survival. Of the 33 patients enrolled, 4 were unevaluable for response as discussed in the previous section. Response rates for the 29 evaluable patients are listed in Table 3. The CR rate was 10% (3 of 29 patients), and the PR rate was 76% (22 of 29 patients) for a total response rate of 86% (95% confidence interval, 68–95%). Three patients had SD (10%). One patient had local tumor progression on a chest CT scan at completion of the treatment.

The univariable prognostic factor analysis for 29 evaluable patients was performed. No statistically significant differences in the response rate were noted according to performance status, histology, or stage. The response rate was 100% for women and 76% for men (P = 0.1). The most frequent histological subtype

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>CALGB performance status</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>25</td>
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<td>1</td>
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<th>Age (yr)</th>
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<td>66</td>
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<table>
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<tr>
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<th>Female</th>
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<tr>
<td></td>
<td>19</td>
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<tr>
<th>Histology</th>
<th>Squamous 5</th>
<th>Adenocarcinoma</th>
<th>Large</th>
<th>Poorly differentiated</th>
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<tr>
<td></td>
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<td>8</td>
<td>5</td>
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<thead>
<tr>
<th>Stage</th>
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<th>IIIB</th>
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<tr>
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<td>12</td>
<td>21</td>
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</table>

* Histology was unknown for one patient (Rotondo).

### Table 2 Hematological and nonhematological toxicity (CALGB toxicity table): worst grade (n = 29)*

<table>
<thead>
<tr>
<th>Grade</th>
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<th>%</th>
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<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>48</td>
</tr>
<tr>
<td>Anemia</td>
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<td>17</td>
</tr>
<tr>
<td>Esophagitis</td>
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<td>6</td>
</tr>
<tr>
<td>Pulmonary</td>
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<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
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<td>6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Arrhythmia</td>
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<td>3</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1</td>
<td>3</td>
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</table>

* One patient had a grade 3 hypersensitivity reaction.

### Table 3 Paclitaxel/RT response

<table>
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<th>Responses</th>
<th>No. of patients (n = 29)</th>
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<tbody>
<tr>
<td>PD*</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
<td>76</td>
</tr>
<tr>
<td>CR + PR</td>
<td>25</td>
<td>86</td>
</tr>
</tbody>
</table>

* PD, progressive disease.
in this trial was squamous cell carcinoma. Thirteen of 16 patients (81%) with squamous cell carcinoma responded to treatment. All seven patients with adenocarcinoma had at least PRs (100%). Patients with stage IIIB disease responded equally as well as patients with stage IIA disease (82% and 92%, respectively; \( P = 0.62 \)).

The median follow-up duration of this study is more than 20 months. Overall survival and progression-free survival are shown in Fig. 1 (all 33 patients). The median overall survival time for the total patient sample \((n = 33)\) was 20 months. The 1-, 2-, and 3-year survival rates for all patients were 60.6, 33.3, and 18.2%, respectively. The median progression-free survival duration for all 33 patients was 10.7 months, and the 1-, 2-, and 3-year progression-free survival rates were 39.4, 12.1, and 6.1%, respectively.

DISCUSSION

The optimal therapy for stage III NSCLC continues to evolve, because no single modality has proven effective. Of those patients with stage IIIA who undergo surgical resection, only 10–15% have long-term survival after surgery. Metastases to paratracheal nodes, extracapsular spread, or stage IIIB disease are relative contraindications to surgery. RT alone provides only 5–10% of patients with long-term survival (27, 29). To improve local control and treat distant micrometastases, the use of chemotherapy with radiation has been explored. Many investigators have tried to improve survival by combining chemotherapy concurrently or sequentially with RT (5–9). CALGB demonstrated the first positive randomized trial with combined modality. The median survival was 13.8 months as compared with 9.7 months for the control RT-alone arm in good performance stage III NSCLC patients. Le Chevalier et al. (6) reported statistically significant survival benefits in the combined modality arm. The 3-year survival rate was 4% in the group that received 65 Gy of radiation alone and 12% in the group that received chemotherapy followed by 65 Gy of RT followed by chemotherapy. This French study also demonstrated statistically significant lower actuarial metastasis rates in the combined modality arm (43%) compared with the radiation-alone arm (60%; Ref. 6). The survival benefits in the combined modality arm may be due to the decreased metastasis rate. Jeremic et al. (30) conducted another randomized trial comparing hyperfractionated RT versus hyperfractionated RT with concurrent daily carboplatin/etoposide. The combined modality group had a significantly longer survival time than did the radiation-alone group, with a median survival of 22 versus 14 months and 4-year survival rates of 23 versus 9%. The median time to local recurrence and 4-year local recurrence-free survival rates were also significantly higher in the combined modality group than they were in the radiation-alone group. The improved local control in the combined modality group may translate the survival improvement.

Several other randomized studies compared RT alone with concurrent cisplatin chemotherapy and RT (8, 28, 31, 32). Only the European Organization for Research and Treatment of Cancer trial had a statistically significant survival benefit in the concurrent daily cisplatin and radiation arm (8). Several other randomized trials compared RT alone with cisplatin-containing chemotherapy plus RT. Although four studies demonstrated statistically significant survival benefits in the cisplatin-containing chemotherapy arm, the survival improvement can be considered only modest (5, 6, 8, 33).

This Phase II study of concurrent weekly paclitaxel/RT for patients with stage III NSCLC demonstrated an overall median survival of 20 months at the 20-month median follow-up. The median progression-free survival of all patients was 10.7 months. The overall 1-, 2-, and 3-year survival rates of all patients were 60.6%, 33.3%, and 18.2%, respectively. The survival outcome from this regimen is encouraging and seems to be at least equivalent to that of more toxic chemotherapy/radiation trials. Responses were noted in all subgroups. There was no statistically significant difference in response rates according to histology or stage.

The activity of paclitaxel/RT seen in this study may have
been due to paclitaxel, radiation, or the combination of the two administered concurrently. Our overall response rate of 86% is greater than the 38% response rate observed with radiation alone in the control arm of the Hoosier Oncology Group study (28) and the 45% response rate reported by Perez (27) for locally advanced NSCLC. Our current response rate is also much greater than the 20–25% response rate anticipated from paclitaxel as a single agent (34, 35). The substantial response and survival rates seen with concurrent paclitaxel/Rt seem to justify the clinical use of concurrent RT/paclitaxel.

Paclitaxel/Rt was safely administered on an outpatient basis. The toxicity was acceptable and compared favorably with other regimens currently used. The major side effect was esophagitis, which occurred predictably, could be easily managed, and abated shortly after completing therapy. Only one patient required enteral nutrition. This profile compares favorably with cisplatin-based concurrent chemotherapy/radiation treatment. The incidence of radiation pneumonitis in our study [4 of 29 patients (13%)] was similar to the reported incidence noted with combined modality therapy in NSCLC (36). This pulmonary toxicity is far less than the toxicity reported by Reckzeh et al. (37).

Therefore, it would seem that the combination of paclitaxel/Rt demonstrates a high response rate with a relatively modest toxicity comparable with cisplatin-based chemotherapy/radiation combinations. A randomized trial will be necessary to fully evaluate the usefulness of the regimen.

Based on this response and toxicity profile, concurrent Rt/paclitaxel seems to offer significant clinical utility for control of both local and distant spread. At present, this investigation of concurrent weekly paclitaxel and Rt is being extended to the neoadjuvant setting for patients with potentially resectable minimal N2 disease. We postulate that early use of effective local and systemic therapy will eventually translate into improvements in survival.

REFERENCES

Phase II trial of weekly paclitaxel and concurrent radiation therapy for locally advanced non-small cell lung cancer.

H Choy, H Safran, W Akerley, et al.