

# Twice-Weekly Paclitaxel and Weekly Carboplatin With Concurrent Thoracic Radiation Followed by Carboplatin/Paclitaxel Consolidation for Stage III Non-Small-Cell Lung Cancer: A California Cancer Consortium Phase II Trial

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**Purpose:** Recent studies have suggested the superiority of concurrent chemoradiotherapy and the efficacy of paclitaxel/carboplatin in advanced non-small-cell lung cancer (NSCLC). In view of those results, we sought to examine the safety and efficacy of administration of radiosensitizing paclitaxel twice weekly and carboplatin weekly with concurrent thoracic radiation therapy (XRT) followed by consolidation paclitaxel and carboplatin for stage III NSCLC in a multi-institutional phase II trial.

**Patients and Methods:** Induction chemoradiotherapy consisted of paclitaxel 30 mg/m<sup>2</sup> delivered intravenously (IV) for 1 hour twice weekly for 6 weeks, carboplatin at a dose based on an area under the concentration-time curve (AUC) of 1.5 mg/mL × min, given IV once weekly for 6 weeks, and concomitant XRT of 1.8 to 2.0 Gy daily for a total of 61 Gy. Patients who achieved a complete response, partial response, or stable disease received two 21-day cycles of consolidation chemotherapy consisting of paclitaxel 200 mg/m<sup>2</sup> IV for 3 hours and carboplatin at a dose based on an AUC of 6 mg/mL × min.

**Results:** Thirty-four patients were eligible. Their median age was 62 years (range, 39 to 73 years), 59% were female, 41% were male, 94% had a performance status of 0 or 1, 38% had stage IIIA NSCLC, and 62% had stage IIIB NSCLC. Common grade III and IV toxicities during the induction chemoradiation phase included esophagitis (38%) and neutropenia (12%). The most common adverse reaction during consolidation chemotherapy was grade III neutropenia in five patients (15%). The overall response rate was 71%, which was achieved in the induction phase. The median follow-up was 20 months, the median survival was 17 months, and 2-year actuarial survival rate was 40% (95% confidence interval, 20% to 65%).

**Conclusion:** This regimen is tolerable and results are promising. We recommend further evaluation of this regimen in a phase III trial.

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PACLITAXEL IS a potent radiosensitizer, as demonstrated in preclinical models.<sup>1</sup> Radiosensitizing doses of paclitaxel with concurrent radiation therapy (XRT) have been studied in phase I and II trials for treatment of unresectable stage III non-small-cell lung cancer (NSCLC). Choy and Browne<sup>2</sup> determined the maximum-tolerated dose (MTD) of paclitaxel to be 60 mg/m<sup>2</sup> given intravenously (IV) in a 3-hour infusion once per week for 6 weeks with daily XRT for stage III NSCLC. In that study, esophagitis

was the dose-limiting toxicity. The response rate was 86% and the median survival time was 20 months.<sup>3</sup> Because paclitaxel blocks the cell cycle in the highly radiosensitive G<sub>2</sub>-M phase, we reasoned that a frequent schedule of paclitaxel administration is more likely to optimize its radiosensitizing efficacy.<sup>4</sup> A phase I trial was conducted using a twice-weekly schedule of paclitaxel with concurrent XRT.<sup>5</sup> In this trial, the MTD of paclitaxel was 35 mg/m<sup>2</sup> IV given as a 1-hour infusion twice weekly for 6 weeks concurrently with daily XRT. Esophagitis and skin reaction were the dose-limiting toxicities, and response and survival data were encouraging.

Regimens combining paclitaxel and carboplatin have demonstrated efficacy and tolerability in the treatment of metastatic NSCLC. Langer et al<sup>6</sup> reported a response rate of 62% and 1-year survival rate of 54% with the 3-week regimen of paclitaxel 135 to 215 mg/m<sup>2</sup> given either as a 1-hour or a 24-hour infusion and carboplatin at a dose based on an area under the concentration-time curve (AUC) of 7.5 mg/mL × min. Vafai et al<sup>7</sup> reported a response rate of 63% with paclitaxel 150 to 250 mg/m<sup>2</sup> given as a 3-hour infusion, and carboplatin at a dose based on an AUC of 6 mg/mL × min. More recently, a Southwest Oncology

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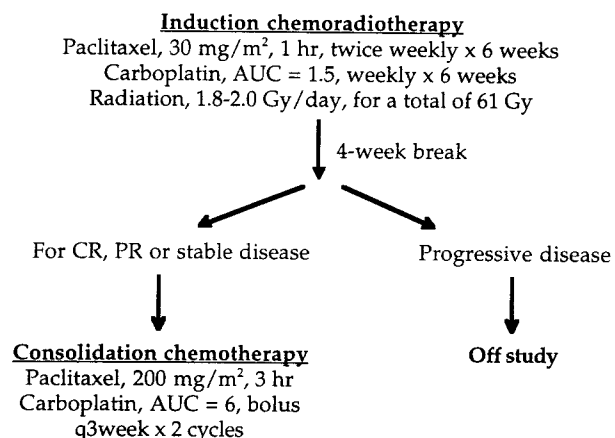


Fig 1. Treatment schema. CR, complete response; PR, partial response.

Group (SWOG) randomized phase III trial demonstrated equal efficacy but better tolerability of paclitaxel and carboplatin compared with vinorelbine and cisplatin.<sup>8</sup> These results have led to a number of clinical studies that incorporate paclitaxel and carboplatin into chemoradiotherapy for stage III NSCLC.<sup>9,10</sup>

To build on our previous phase I trial of twice-weekly paclitaxel and XRT for stage III NSCLC,<sup>5</sup> we examined the safety and efficacy of twice-weekly paclitaxel, weekly carboplatin, and XRT, followed by consolidation with paclitaxel and carboplatin for locally advanced NSCLC, in a phase II trial conducted by the three institutions of the California Cancer Consortium.

PATIENTS AND METHODS

Patients were enrolled onto the study according to the following criteria: a biopsy-proven diagnosis of stage IIIA or IIIB NSCLC; measurable disease on a chest computed tomographic scan; a SWOG performance status of 0 to 2; adequate hematologic (WBC and platelet counts within normal limits), hepatic (total bilirubin level ≤ two times the upper limit of normal), and renal (creatinine clearance ≥ 50 mL/min) functions; and no prior chest XRT or chemotherapy. All patients signed informed consent in accordance with guidelines of the institutional review boards of each of the three participating institutions.

The treatment schema is illustrated in Fig 1. During the first week of paclitaxel infusions, patients were premedicated with dexamethasone 20 mg IV, diphenhydramine 25 mg IV, and cimetidine 300 mg IV 30 minutes before infusion of paclitaxel. If no hypersensitivity reaction was observed during the first two paclitaxel administrations, dexamethasone premedication was deleted in the subsequent weeks of paclitaxel therapy. Paclitaxel was given at a dose of 30 mg/m<sup>2</sup> IV for 1 hour before daily XRT on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, and 39 for a total of 12 doses during a period of 6 weeks. Carboplatin at an AUC of 1.5 mg/mL × min was administered IV on days 1, 8, 15, 22, 29, and 36. If the absolute neutrophil count was less than 1,000/μL or the platelet count was less than 100,000/μL during the chemoradiation phase, the subsequent weekly carboplatin dose was reduced to a dose

based on an AUC of 1.0 mg/mL × min. Starting on day 1, XRT was given from Monday to Friday each week at a daily fraction of 1.8 to 2.0 Gy for a total dose of 61 Gy. The primary tumor and lymph nodes received 45 Gy via anteroposterior-posteroanterior fields with a 1.5- to 2.0-cm margin around the tumor, followed by an off-cord boost of 16 Gy through reduced oblique fields with a 1.0-cm normal tissue margin. The ipsilateral hilar (1.0- to 1.5-cm margin), superior mediastinal (suprasternal notch as the superior margin and 1.0 to 1.5 cm for the lateral margins), and subcarinal (5-cm inferior margin) lymph nodes were included in the radiation fields. Ipsilateral supraclavicular nodes were included only if they were grossly involved or if the primary tumor was in the upper lobe, with a superior margin adequately covering the supraclavicular fossa, a lateral margin extending two-thirds the length of clavicle, and an inferior margin extending 1.0 cm below the lower border of clavicle. Mediastinal nodes more than 5 cm inferior to the carina were included only if the primary tumor was in the lower lobe or the subcarinal nodes were grossly involved with an inferior margin extending to the diaphragm. Interruptions and delays of XRT and chemotherapy were allowed for up to 2 weeks for grade 3 to 4 toxicities.

For patients who achieved a complete response, partial response, or stable disease 4 weeks after induction chemoradiotherapy, two cycles of consolidation chemotherapy were administered 3 weeks apart. Consolidation chemotherapy consisted of paclitaxel 200 mg/m<sup>2</sup> IV during a 3-hour period and carboplatin at a dose based on an AUC of 6 mg/mL × min.

Patients were observed weekly during treatment to monitor toxicity, which was graded according to the SWOG toxicity criteria. Objective response was assessed with a chest computed tomographic scan 4 weeks after completion of induction chemoradiotherapy and 4 weeks after consolidation chemotherapy. Patients were then observed at 2-month intervals for disease status and survival. Complete response was defined as complete disappearance of all measurable lesions; partial response was defined as a decrease of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions; and progression was defined as an increase of 50% or more from baseline in the sum of products of perpendicular diameters of all measurable lesions or the appearance of any new lesion.

A two-stage design proposed by Simon<sup>11</sup> was used for the study, with the assumption that a response rate of less than 50% would not warrant further study and a response rate of 70% or greater would be considered promising for further study of this regimen. In the first stage, 23 assessable patients were entered. If fewer than 13 responses were observed, accrual would stop with the conclusion that the regimen did not hold promise for further study. If 13 or more responses were observed, an additional 11 or more patients would be accrued in the second stage of the study. The actuarial median survival time and 2-year survival rates were estimated by the Kaplan-Meier method.<sup>12</sup>

RESULTS

Thirty-six patients were enrolled. Two patients were not eligible; one had an inadequately evaluated pleural effusion and one had a performance status of 3. The characteristics of the 34 eligible patients are listed in Table 1. The median age was 62 years (range, 39 to 73 years). Thirty-two patients had a SWOG performance status 0 or 1. Thirty-six percent and 64% of the patients had stage IIIA and IIIB NSCLC, respectively. The median follow-up time was 20 months.

Table 1. Patient Characteristics

No. of patients	34
Age, years	
Median	62
Range	39-73
Sex	
Female	20
Male	14
Performance status	
0	14
1	18
2	2
Stage	
IIIA	13
IIIB	21

For the chemoradiotherapy phase of the trial, 94% of the 34 patients completed the planned 61 Gy of XRT, and 79% completed the planned concurrent chemotherapy. The most common reasons for noncompletion of the planned chemoradiotherapy were grade 3 or 4 esophagitis and/or neutropenia. Twenty-eight patients (82%) proceeded to receive consolidation chemotherapy. Of these 28 patients, 26 received the planned two cycles of paclitaxel and carboplatin, and two patients received only one cycle because of disease progression.

Among the 34 assessable patients, the grade 3 and 4 toxicities observed are listed in Table 2. The most common grade 3 and 4 toxicities observed during the chemoradiation phase were esophagitis in 13 patients (38%) and neutropenia in four patients (12%). One patient developed oxygen-dependent radiation pneumonitis and one developed corticosteroid-dependent pericarditis. One patient had grade III hypersensitivity reaction on initial exposure to paclitaxel but subsequently was able to complete the planned twice-weekly paclitaxel therapy without recurrence of the allergic reaction observed during the induction phase of the trial. During the consolidation phase, the only grade 3 toxicity observed was neutropenia in five patients (15%). No patient died as a result of toxicity during the induction or consolidation phase of the trial.

Table 2. Grade 3 and 4 Toxicities During the Induction and Consolidation Treatment Phases

Toxicity	Induction		Consolidation	
	No.	%	No.	%
Esophagitis	13	38	0	0
Neutropenia	4	12	5	15
Hypersensitivity	1	3	0	0
Radiation pneumonitis	1	3	0	0
Radiation pericarditis	1	3	0	0

Table 3. Responses to Treatment

	No. of Patients	%
Complete response	7	21
Partial response	17	50
Stable disease	5	15
Progression	3	9
Not assessable	2	6
Total	34	100

The analysis of responses is listed in Table 3. Seven patients (21%) achieved a complete response, and 17 patients (50%) achieved a partial response, which yielded an overall response rate of 71%. All responses were observed during the chemoradiotherapy phase of treatment. Five patients (15%) had stable disease and three patients (9%) had progressive disease after consolidation chemotherapy. Two patients (6%) were not assessable for response because they refused further evaluation and treatment after chemoradiotherapy. Of 13 patients with documented progression, three had local and 10 had distant recurrence.

A Kaplan-Meier curve of overall survival is illustrated in Fig 2. After a median follow-up of 20 months, the actuarial median survival time was 17 months and the 2-year survival rate was 40% (95% confidence interval, 20% to 65%).

## DISCUSSION

Chemoradiotherapy has become standard treatment for unresectable locally advanced NSCLC.<sup>13</sup> However, the optimal regimen of chemoradiotherapy, including radiation dose schedule, choice of chemotherapeutic agents, and

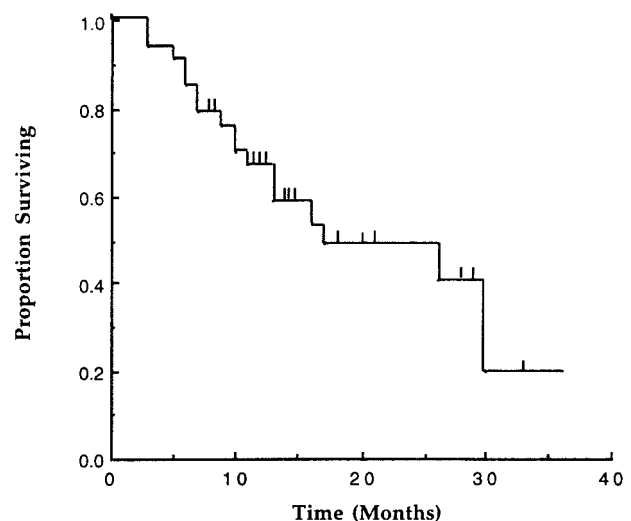


Fig 2. Kaplan-Meier curve of overall survival.

sequence of chemotherapy and radiation has not been defined.<sup>13,14</sup> More recently, Furuse et al<sup>15</sup> showed that concurrent XRT in combination with mitomycin, vindesine, and cisplatin resulted in a better response rate and survival than a sequential regimen. Nevertheless, a number of randomized trials are underway in the continued effort to identify an optimal chemoradiation regimen for unresectable stage III NSCLC.<sup>13</sup>

In an attempt to explore novel strategies for chemoradiotherapy in stage III NSCLC, we conducted a phase I trial previously, in which we aimed to optimize the radiosensitizing effect of paclitaxel through delivery of it twice weekly with concurrent XRT.<sup>5</sup> In that trial, the MTD of twice-weekly paclitaxel was 35 mg/m<sup>2</sup> given for 1 hour twice weekly for 6 weeks with daily XRT to a total dose of 61 Gy. On the basis of reports of the therapeutic efficacy and safety of combination carboplatin and paclitaxel for NSCLC, weekly carboplatin was added to the twice-weekly paclitaxel with concurrent XRT, followed by consolidation therapy with paclitaxel and carboplatin. In this study, paclitaxel 30 mg/m<sup>2</sup> twice weekly and carboplatin at a dose based on an AUC of 1.5 mg/mL × min weekly were delivered for 6 weeks with concurrent daily XRT to a total dose of 61 Gy. As compared with twice-weekly paclitaxel and XRT, the addition of weekly carboplatin resulted in a similar incidence of grade 3 and 4 esophagitis (38% for paclitaxel/carboplatin/XRT v 44% for paclitaxel/XRT). The incidence of grade 3 and 4 esophagitis in our trial was similar to that observed in other paclitaxel-plus-carboplatin-based chemoradiotherapy regimens.<sup>9,10</sup> On the other hand, concomitant carboplatin resulted in grade 3 neutropenia in 12% of patients compared with none in patients who received twice-weekly paclitaxel and XRT.<sup>5</sup> Other serious but rare toxicities during the chemoradiotherapy phase included hypersensitivity reaction, radiation pneumonitis, and radiation pericarditis. Despite the apparent added toxicity, 79% of the patients completed the planned chemoradiotherapy.

For paclitaxel given once weekly or twice weekly, there has been concern regarding frequent premedication with dexamethasone for prevention of hypersensitivity reactions. Frequent use of high-dose dexamethasone as premedication for paclitaxel may predispose patients to opportunistic infections.<sup>16</sup> In our previous phase I trial using twice-weekly paclitaxel with XRT, two patients developed *Pneumocystis carinii* pneumonia.<sup>5</sup> On the basis of the observation that the incidence of hypersensitivity reactions to paclitaxel on first exposure was only 5%, and that subsequent hypersensitivity reactions to paclitaxel probably would not occur if they were not observed during the first exposure,<sup>17</sup> we adopted a premedication strategy by which dexamethasone was deleted if a patient experienced no allergic reaction after the first two doses of paclitaxel.

Among 34 patients in this trial, we observed only one episode of hypersensitivity reaction to the first dose of paclitaxel. When dexamethasone was deleted for subsequent twice-weekly administration of paclitaxel, no hypersensitivity reactions were encountered. No *P carinii* pneumonia was observed in this study. This premedication strategy has been adopted for administration of weekly and twice-weekly paclitaxel at our institution.<sup>17</sup>

In this study, consolidation chemotherapy was initiated 4 weeks after completion of induction chemoradiotherapy and was well tolerated. Twenty-eight patients (82%) received the planned two cycles of paclitaxel and carboplatin. Only five patients experienced grade 3 neutropenia in the consolidation phase. No grade 3 or 4 hypersensitivity reaction or peripheral neuropathy was observed.

In this phase II trial, we anticipated a therapeutic advantage through the addition of carboplatin to the chemoradiation regimen and consolidation with paclitaxel and carboplatin compared with our previous experience with paclitaxel and XRT. In the current trial, the response rate was 71% and the median survival time was 17 months, compared with 80% and 20 months, respectively, in the previous phase I trial of paclitaxel and XRT.<sup>5</sup> Although patient eligibility criteria were similar, direct comparisons between these two phase I and II trials may not be meaningful, and a phase III trial would be required to demonstrate a survival advantage.

In this report, we present the results of twice-weekly paclitaxel, weekly carboplatin, and concurrent daily XRT. The optimal approach to the combination of paclitaxel and carboplatin with concurrent radiation for the treatment of locally advanced NSCLC remains to be determined. Regimens of weekly paclitaxel and carboplatin with concurrent XRT have been studied in phase II trials by other investigators. Chemoradiotherapy schemas and efficacy data for these trials are compared in Table 4. In two studies conducted by Choy et al,<sup>9,18</sup> paclitaxel 50 mg/m<sup>2</sup> and carboplatin at a dose based on an AUC of 2 mg/mL × min were given weekly for 6 to 7 weeks with concomitant XRT either in 2-Gy daily fractions or in 1.2-Gy fractions bid for a total of 66 to 69.6 Gy. In another study reported by Belani et al,<sup>10</sup> paclitaxel 45 mg/m<sup>2</sup> and carboplatin 100 mg/m<sup>2</sup> were given weekly for 6 to 7 weeks with XRT in 1.8- to 2.0-Gy daily fractions for a total of 60 to 65 Gy. In our study as well as in those by Choy et al,<sup>9,18</sup> consolidation therapy with two cycles of paclitaxel and carboplatin also was used. Among these studies, the toxicity profiles were similar, and esophagitis was the dose-limiting toxicity. The short-term efficacy of these studies is comparable also, with response rates ranging from 71% to 78% and 1-year survival rates ranging from 56% to 67%. A number of other paclitaxel/platinum/XRT

**Table 4. Phase II Trials of Paclitaxel and Carboplatin With Radiation for Unresectable Stage III NSCLC**

Study	Chemoradiation Regimen	No. of Patients	Response Rate (%)	1-Year Survival Rate (%)
Choy et al <sup>9</sup>	Chemoradiotherapy: P 50 mg/m <sup>2</sup> , 1 hour C AUC 2 Weekly × 7 weeks XRT 2 Gy daily/66 Gy total Consolidation chemotherapy: P 200 mg/m <sup>2</sup> , 3 hours, days 1, 22 C AUC 6, days 1, 22	40	76	56
Choy et al <sup>18</sup>	Chemoradiotherapy: P 50 mg/m <sup>2</sup> , 1 hour C AUC 2 Weekly × 6 weeks XRT 1.2 Gy bid/69.6 Gy total Consolidation chemotherapy: P 200 mg/m <sup>2</sup> , 3 hours, days 1, 22 C AUC 6, days 1, 22	22	77	63
Belani et al <sup>10</sup>	Chemoradiotherapy: P 45 mg/m <sup>2</sup> , 3 hours C 100 mg/m <sup>2</sup> Weekly × 6-7 weeks XRT 1.8-2.0 Gy daily/60-65 Gy total Consolidation chemotherapy: None	38	NR	63
Lau et al*	Chemoradiotherapy: P 30 mg/m <sup>2</sup> , 1 hour, twice weekly C AUC 2, once weekly × 6 weeks XRT 1.8-2.0 Gy daily/61 Gy total Consolidation chemotherapy: P 200 mg/m <sup>2</sup> , 3 hours, days 1, 22 C AUC 6, days 1, 22	34	71	67

Abbreviations: P, paclitaxel; C, carboplatin; NR, not reported.

\*Current study.

regimens for locally advanced NSCLC are under evaluation in randomized trials.<sup>13</sup> A phase III trial will be needed to evaluate the worth of the twice-weekly paclitaxel/weekly carboplatin/XRT regimen described in this report.

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