Phase II Trial of Weekly Dose-Dense Paclitaxel in Extensive-Stage Small Cell Lung Cancer

Cancer and Leukemia Group B Study 39901

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Introduction: Paclitaxel is an active agent in extensive-stage (ES) small cell lung cancer (SCLC). Nevertheless, the optimal schedule is uncertain. A dose-dense schedule was previously evaluated in a Cancer and Leukemia Group B study of patients with non-SCLC, resulting in a 42% response rate and median survival of 12.3 months. Because of these promising results, this dose and schedule of paclitaxel was evaluated in patients with ES-SCLC.

Methods: Patients were eligible for this phase II trial (Cancer and Leukemia Group B 39901) if they had documented ES-SCLC, no prior chemotherapy, and performance status of 0 to 2. Paclitaxel was administered as an intravenous infusion at 150 mg/m^2 over 3 hours weekly for 6 consecutive weeks every 8 weeks.

Results: Thirty-six patients with median age of 65 were enrolled. Of them 25 were men and 33 with a performance status 0 to 1. A median of two 8-week cycles were delivered. The percent of patients with grade 3/4 toxicity included neutropenia 22%, anemia 9%, febrile neutropenia 6%, fatigue 20%, sensory neuropathy 26%, motor neuropathy 11%, and dyspnea 17%. There were two treatment-related deaths, both from pneumonitis. The overall response rate was 33% (3% complete response and 30% partial response). Median progression-free and overall survivals were 3.7 and 9.2 months, respectively. One-year progression-free and overall survivals were 17% and 36%, respectively.

Conclusions: For patients with ES-SCLC, dose-dense weekly paclitaxel was associated with fairly mild hematologic toxicity. Nevertheless, nonhematologic toxicities, including neuropathy, fatigue, and dyspnea required frequent dose delays and reductions. The overall response rate is disappointing and much lower than that seen with standard platinum-based combinations. Paclitaxel in this dose and schedule should not be used as front-line therapy for patients with ES-SCLC.

Key Words: Small cell lung cancer, Extensive stage, Paclitaxel, Chemotherapy.

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Lung cancer remains the leading cause of cancer-related mortality in the United States.[1] Of the expected 174,000 new cases reported in 2006, approximately 13% will be small cell lung cancer (SCLC).[2] Although advances in the treatment of limited-stage SCLC, such as the addition of thoracic radiation therapy[3] and the use of prophylactic cranial irradiation,[4] have improved survival, advances in extensive-stage (ES) SCLC have been less apparent. Etoposide in combination with cisplatin or carboplatin has been the most often used regimen for the past two decades. Various strategies such as maintenance topotecan[5] or oral etoposide[6] have not made meaningful improvements in the overall survival of ES-SCLC patients. There has been interest in substitution of irinotecan for etoposide in combination with cisplatin as demonstrated in Japan Clinical Oncology Group 9511 trial.[7] Nevertheless, this experience has not yet been confirmed in the United States. One recently reported trial showed no difference in survival outcomes,[8] and a Southwest Oncology Group phase III trial, similar in design to Japan Clinical Oncology Group 9511, has recently completed accrual and has not yet been reported. Certainly, new and novel strategies are needed in this setting.

Paclitaxel is an active agent in SCLC with initial phase II trials showing response rates of 34 to 53% as a single agent in previously untreated patients. The North Central Cancer Treatment Group gave paclitaxel 250 mg/m^2 over 24 hours with granulocyte colony stimulating factor (G-CSF) every 3 weeks and reported a response rate of 53% and a median survival of 9.1 months.[9] Using a similar regimen, the Eastern Cooperative Oncology Group reported a 34% response rate and a median survival of 9.9 months.[10] In previously treated

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patients, Smit et al. reported a response rate of 29%. All patients had refractory disease (relapse within 3 months of cytotoxic therapy), and median survival was only 3.3 months.[11] In another small study of second-line chemotherapy of patients who received weekly paclitaxel 80 mg/m^2 for 6 weeks in an 8-week cycle, 33% achieved a partial remission.[12]

The optimal schedule of paclitaxel has not been defined. Weekly schedules have been tested in a number of disease sites, including ovary, breast, and non-SCLC (NSCLC), with similar activity but perhaps less toxicity compared with more-conventional every 3-week strategy.[13–15] Akerley et al. have previously explored a dose-dense schedule of single-agent paclitaxel in advanced NSCLC.[16,17] In the Cancer and Leukemia Group B (CALGB) phase II trial, 38 patients received a dose of paclitaxel of 150 mg/m^2/wk for 6 consecutive weeks every 8 weeks. The overall response rate was 42% with a median survival time and 1- and 2-year survival rates of 12.3 months, and 52% and 26%, respectively. The primary toxicities of this strategy were neutropenia, neuropathy, and hyperglycemia. Given this level of activity in advanced NSCLC and the need for novel strategies in ES-SCLC, the CALGB evaluated weekly dose-dense paclitaxel in ES-SCLC.

PATIENTS AND METHODS

Patients entered onto this phase II trial (CALGB 39901) were required to have ES-SCLC documented histologically or cytologically. ES was defined as those patients with extrathoracic metastatic disease, malignant pleural effusion, or contralateral supraclavicular or hilar adenopathy (precluding definitive radiation therapy). No prior chemotherapy for SCLC was allowed and patients had to be at least 2 weeks from any prior radiation therapy. A performance status of 0 to 2 was required, and patients had to be at least 18 years old. Patients were also required to have an absolute neutrophil count (ANC) of $\geq$1500/μl, platelet count of $\geq$100,000/μl, serum glutamic oxaloacetic transaminase (SGOT) $<$ 2 $\times$ upper limits of normal (ULN), and bilirubin $<$1.5 mg/dl. Measurable disease was required. Before entry onto this trial, patients were required to have a chest radiograph, computed tomography scan, or magnetic resonance imaging of the chest and abdomen, bone scan, and computed tomography or magnetic resonance imaging of the brain.

Paclitaxel was administered as an intravenous (IV) infusion at 150 mg/m^2 over 3 hours weekly for 6 consecutive weeks every 8 weeks. Before receiving paclitaxel, patients received standard prophylactic medications, including dexamethasone 20 mg orally 12 and 6 hours before or 20 mg IV 30 minutes before paclitaxel, diphenhydramine 50 g IV 30 minutes before paclitaxel and cimetidine (300 mg IV), ranitidine (50 mg IV) or famotidine (20 mg IV) 30 minutes before paclitaxel. A total of four 8-week cycles were planned, assuming the patient had acceptable tolerance of the treatment and no evidence of disease progression.

A complete blood count and toxicity assessment was performed weekly whereas liver enzymes were assessed every 8 weeks. The weekly dose of paclitaxel was omitted if the ANC was $<$1000/μl or the platelets were $<$75,000/μl. If the ANC was 1000 to 1499/μl or the platelets were 75,000 to 99,000/μl, the paclitaxel dose was reduced by 50%. A 50% dose reduction was also required for grade 2 or higher neuropathy after the first cycle. Paclitaxel was held for any grade 3 or higher neurotoxicity during any cycle. If recovery to $\leq$grade 2 neurotoxicity occurred, paclitaxel could be reinstituted at a 50% dose reduction for all subsequent cycles. Paclitaxel was also dose reduced by 50% for elevations in the SGOT of 2 to 5 $\times$ ULN and omitted for $>$5 $\times$ ULN in SGOT or elevations in the bilirubin to $>$1.4 mg/dl. Doses were also omitted for any other grade 3/4 nonhematologic toxicities.

Patients were to receive full supportive care, including transfusions, erythropoietin, antibiotics, and antiemetics, as appropriate. The routine use of myeloid growth factors (G-CSF and granulocyte macrophage colony stimulating factor) was discouraged. They were not used to avoid dose reductions, delays, or to allow for dose escalation and could not be used prophylactically because of concern about myelosuppression. For the treatment of febrile neutropenia, the use of CSFs could be used according to American Society of Clinical Oncology guidelines.

Response assessments were done with each cycle of treatment (every 8 weeks), and responses were evaluated using RECIST criteria.[18] Measurable disease was required for eligibility. Confirmation of response was to be obtained 4 to 6 weeks later.

The primary goal of the study was to evaluate the activity of weekly dose-dense paclitaxel in ES-SCLC. A one-stage phase II design was used. The study was designed with 90% power at a 0.05 level of significance to differentiate between a complete response (CR) rate of 10% and 30%. Thirty-three patients were to be accrued, and if fewer than six patients experienced a CR, it would be concluded that the treatment regimen had insufficient activity to merit further investigation. Secondary goals included determining overall and progression-free survival, overall response rate (partial + CR rate), and toxicity. Kaplan-Meier curves were used to describe overall and progression-free survival.[19] Survival time was defined as the time from registration until death or last known follow-up. Progression-free survival was defined as the time from registration until disease progression, death, or last known follow-up. The frequency of toxicity was to be tabulated by the most severe occurrence.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. Statistical analyses were performed by CALGB statisticians. As part of the quality assurance program of the CALGB, members of the Data Audit Committee visit all participating institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 10 (27.8%) of the 36 patients under this study.

TABLE 1. Patient Characteristics

Gender	
Male	25 (69)
Female	11 (31)
Age (yr)	
40–49	5 (14)
50–59	9 (25)
60–69	8 (22)
70–79	12 (33)
80+	2 (6)
Median age (range)	65 (41–81)
Performance status	
0	3 (8)
1	30 (83)
2	3 (8)
Weight loss	
Unknown	5 (14)
<5%	19 (53)
5–10%	6 (17)
>10%	6 (17)

Values given are *n* (%) values, unless indicated otherwise.

RESULTS

Thirty-six patients were entered onto this phase II trial between November 2000 and April 2002 (Table 1). The median age was 65 years (range 41–81) and 69% were men. Fourteen of the patients were 70 years or older (39%). The performance status was 0 in 8%, 1 in 83%, and 2 in 8%. Thirty-four percent of the patients had experienced weight loss of 5% or more at the time of entry onto the trial. All patients had measurable disease.

The reasons for removal from study treatment are listed in Table 2. Seventeen patients developed progressive disease during treatment, 2 died, and 11 were removed from protocol therapy because of an adverse event (7) or withdrawal of consent for treatment (4). The seven adverse events included grade 3 neuropathy in five (two also had grade 3 dyspnea), grade 4 diarrhea in one, and multiple grade 2 toxicities, including fatigue, in one patient.

The median number of chemotherapy cycles completed was 2 (16 weeks). Eleven (31%) completed one cycle, 16 (46%) completed two cycles, 5 (14%) completed three cycles, and 3 (9%) completed all four planned cycles (1 patient without progression and 2 patients with progression). One patient did not receive protocol therapy. Twenty-seven patients (77%) required a dose modification or delay in therapy. Of these, 9 patients required one, 10 required two, and 6 required three or more dose modifications or delays. In all, there were 67 instances of dose delays or modifications, occurring during week 1 in 8, week 2 in 8, week 3 in 16, week 4 in 13, week 5 in 9, and week 6 in 13 patients.

TABLE 2. Reason for Removal from Study Treatment ($n = 36$)

Completed all treatment without progression	1 (3)
Progressive disease	17 (47)
Death	2 (6)
Adverse event	7 (19)
Withdrew consent for treatment	4 (11)
Other[a]	5 (14)

Values given are *n* (%) values.

[a] One with missing data, one placed on other therapy, one did not start protocol therapy because of myelodysplasia, and two unknown.

The rates of grade 3 or worse toxicities of dose-dense paclitaxel are listed in Table 3. The primary hematologic toxicity was neutropenia with 22% of patients experiencing grade 3/4 neutropenia. Only 6% of patients experienced febrile neutropenia. The rates of grade 3/4 anemia and thrombocytopenia were less than 10%. The principal nonhematologic toxicities consisted of neuropathy (37%), fatigue (20%), dyspnea (17%) and dehydration (11%). The neuropathy was mainly sensory in nature (26%), although motor neuropathy was reported in 11%. There were two treatment-related deaths, both from pneumonitis.

Of the 36 patients entered, response data were available for 31 (86%) (Table 4). The confirmed response rate was 33% (95% confidence interval [CI]: 19–51; 3% CR and 30% partial response) whereas 42% had stable disease. Four patients (11%) experienced early progression. The median survival time and median progression-free survival was 9.2 months (95% CI, 6.7–14.8) and 3.7 months (95% CI, 3.3–5.8), respectively (Table 4 and Figure 1). The 1-year survival rate was 36% (95% CI, 23–56%) and the 1-year progression-free survival was 17% (95% CI, 8–35%; Figure 1).

TABLE 3. Toxicity of Weekly Dose-Dense Paclitaxel in ES-SCLC ($n = 35$)[a]

	% of Patients	
	Grade 3	**Grade 4**
Hematologic		
Neutropenia	11	11
Leukopenia	9	9
Anemia	9	0
Thrombocytopenia	3	0
Febrile neutropenia	3	3
Nonhematologic		
Neuropathy		
Sensory	26	0
Motor	11	0
Nausea	6	0
Vomiting	6	0
Diarrhea	3	3
Dehydration	11	0
Fatigue	20	0
Hyperglycemia	6	0
Dyspnea	14	3
Pneumonitis	6	0[b]
Dermatitis	3	0
Thrombosis/embolism	6	0
Infection without neutropenia	3	0

[a] There was no toxicity data for one patient.

[b] There were two treatment-related deaths (grade 5), both from pneumonitis.

TABLE 4. Overall Response and Survival Rates ($n = 36$)

Response ($n = 36$)	
Complete	1 (3)
Partial	11 (30)
Stable	15 (42)
PD	4 (11)
Unassessable[a]	5 (14)
Survival ($n = 36$)	
Median overall (95% CI), mo	9.2 (6.7–14.8)
1-yr overall (95% CI), %	36 (23–56)
Progression-free survival ($n = 36$)	
Median progression-free (95% CI), mo	3.7 (3.3–5.8)
1-yr progression-free (95% CI), %	17 (8–35)

CI, confidence interval.
PD, progressive disease.
Values given are *n* (%) values, unless indicated otherwise.
[a] Two patients died while receiving treatment, but before their initial disease reassessment, two additional patients withdrew from study participation before disease reassessment, and one patient had no response data available.

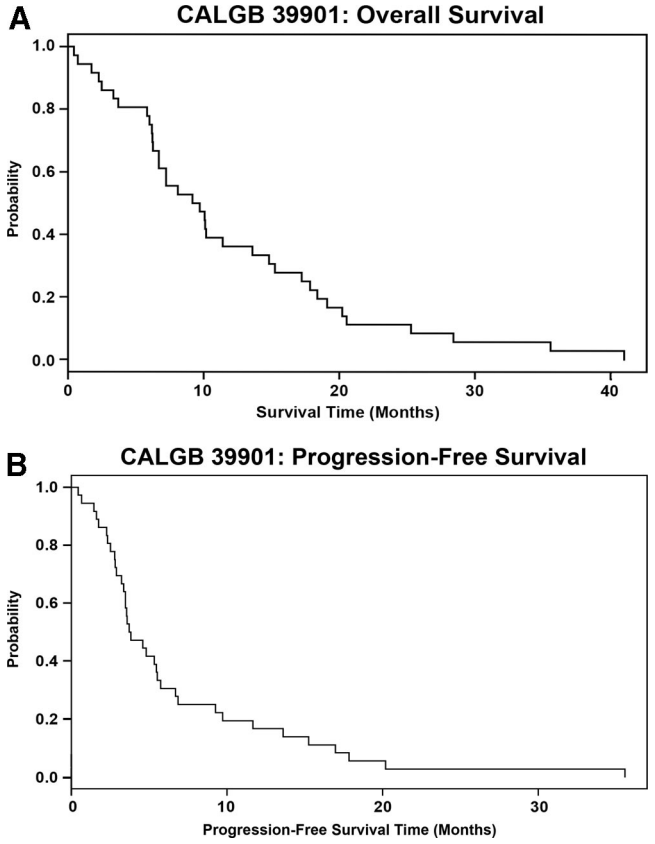

FIGURE 1. Median overall survival (*A*) and median progression-free survival (*B*). The median progression-free survival was 3.7 months, median survival was 9.2 months. The 1-year progression-free survival was 17% and the 1-year overall survival rate was 36%.

DISCUSSION

This study was undertaken based on the promising results in a number of phase II studies of dose-dense paclitaxel in both NSCLC and other tumors.[13–17] In particular, the CALGB phase II study in patients with advanced NSCLC by Akerley et al. resulted in an overall response rate of 42% and median survival of 12.3 months.[17] Also, paclitaxel has been a component of several combination regimens with demonstrated activity in the second-line treatment of SCLC.[20–22] As has been subsequently demonstrated, however, paclitaxel has not added to the efficacy of cisplatin/etoposide in two phase III trials.[23,24] CALGB has also studied weekly paclitaxel compared with the standard every 3-week schedule in patients with metastatic breast cancer and found the weekly schedule more efficacious.[25]

The results of the present study demonstrated response rates that were not better compared with the more-conventional every 3-week schedule of paclitaxel. The response rates and median survival were nearly identical to those of the North Central Cancer Treatment Group trial of paclitaxel 250 mg/m^2 with G-CSF given every 3 weeks. In this trial, the response rate was 53% and median survival was 9.1 month.[9] Likewise, the response rate was 34% and median survival 9.9 months in the ECOG trial.[10] Fortunately, in our study, survival was not different from that demonstrated in large phase III trials in the Cooperative Group setting. In the CALGB trial of etoposide/cisplatin with or without paclitaxel, median survival was 9.9 months in the standard therapy arm, 1-year survival was 37%, and 1-year progression-free survival was 9%.[23] In the current trial median progression-free survival was 3.7 months but 1-year progression-free survival was 17%. The reason for similar survival despite lower overall response rate is unclear but it is more likely to be the reflection of the effects of salvage therapy given after disease progression. CALGB did not systematically collect details of second-line therapy, but at least 15 patients received subsequent systemic chemotherapy and two received radiation therapy after being removed from dose-dense paclitaxel (data not shown). As expected, the most common second-line regimen was etoposide with either cisplatin or carboplatin.

With weekly paclitaxel, myelosuppression was less severe compared with a standard regimen of cisplatin and etoposide. In the phase III trial, cisplatin/etoposide resulted in grade 3 and 4 neutropenia in 66%, anemia in 17%, and thrombocytopenia in 14%. Nevertheless, nonhematologic toxicity seemed to be more frequent with weekly paclitaxel, particularly peripheral neuropathy, fatigue, and dyspnea. Also, only three patients completed all planned therapy, and withdrawal for adverse events or patient preference was common. This would likely make this an impractical schedule for considering adding additional cytotoxic agents. Nevertheless, it is difficult to directly compare the weekly paclitaxel regimen with more standard combination chemotherapy because one cycle of the current regimen was a full 8 weeks and a standard cisplatin/etoposide regimen is repeated every 3 weeks. In the phase III trial of cisplatin/etoposide ± paclitaxel, the median number of cycles delivered was 6. This would constitute 18 weeks of chemotherapy, quite comparable to two 8-week cycles of the weekly paclitaxel regimen (16 weeks).

In conclusion, for patients with ES-SCLC, dose-dense weekly paclitaxel was associated with fairly mild hematologic toxicity. Nevertheless, nonhematologic toxicities, including neuropathy, fatigue, and dyspnea, required frequent dose delays and reductions. The overall response rate (33%) and CR rate (3%) are disappointing and much lower than those seen with standard platinum/etoposide. Paclitaxel in this dose and schedule should not be used as front-line therapy for patients with ES-SCLC.

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