

Cisplatin, Etoposide, and Paclitaxel with Granulocyte Colony-Stimulating Factor in Untreated Patients with Extensive-Stage Small Cell Lung Cancer: A Phase II Trial of the Southwest Oncology Group^{1,2}

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ABSTRACT

Purpose: This study was designed to determine the efficacy and toxicity of cisplatin, etoposide, and paclitaxel (PET) in patients with extensive-stage small cell lung cancer (ES-SCLC).

Experimental Design: Chemo-naïve adult patients with a performance status (PS) of 0–2 and adequate organ function were eligible. Patients received cisplatin 80 mg/m² i.v., etoposide 80 mg/m² i.v., and paclitaxel 175 mg/m² i.v. over a 3-h period on day 1 followed by etoposide 160 mg/m² p.o. on days 2 and 3 every 21 days for six cycles. G-CSF 5 µg/kg was injected s.c. on days 4–14.

Results: Eighty-eight patients were assessable. The median age was 60 years; 50% were male, 78% had PS of 0–1, 28% had PS of 2, 53% had multiple sites, and 13% had brain involvement. The overall response rate was 57% with 10 (12%) of 84 patients achieving a complete response. Median progression-free survival was 6 months [95% confidence interval (CI), 5–7 months] with a median survival of

11 months (95% CI, 8–13 months) and a 1-year survival rate of 43% (95% CI, 33–54%). Six patients (7%) died from toxicity. Grade 5 toxicity occurred in 3 (14%) of 22 patients (with a PS of 2) versus 3 (5%) of 61 patients (with a PS of 0–1; *P*, not significant). Grade 4 neutropenia developed in 40% of patients. Grade 3 nonhematological toxicities were primarily nausea (20%), vomiting (16%), and fatigue (14%).

Conclusion: The survival result achieved was superior to prior SWOG experiences; however, the toxic death rate was unacceptably high in PS-2 patients. These results provide the largest database for the ongoing randomized Inter-group trial comparing PET to cisplatin+etoposide in PS-0–1 patients with ES-SCLC.

INTRODUCTION

SCLC³ is one of the most aggressive and lethal cancers in humans. In the year 2000, ~40,000 new cases will be diagnosed in the United States, and the majority of these patients will succumb to their disease within this year (1). Two-thirds of patients will present with extensive-stage disease for which combination chemotherapy is the treatment of choice. Current chemotherapy regimens produce response rates of 65–85% with 10–15% complete-responses rates. However, the median survival time is about 9 months (2). The most common combinations used in the United States are the two-drug combinations of PE or CE. Although these combinations are no more effective than the regimens from the 1970s, such as CAV, they are less toxic (3). This makes two-drug combinations candidates for the addition of new agents (4).

One promising new agent is paclitaxel. Two Phase II trials evaluated single-agent paclitaxel in SCLC. The ECOG administered paclitaxel at 250 mg/m² i.v. over a 24-h period every 3 weeks to 32 untreated patients with ES-SCLC (5). Patients were switched to cisplatin+etoposide after four cycles of paclitaxel. Patients who responded to paclitaxel and then switched to cisplatin+etoposide were scored as unconfirmed responses. Thus, the confirmed response rate was 34%, and the total response rate (confirmed plus unconfirmed) was 53%. The median survival was 10.8 months. The major toxicity was grade

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³ The abbreviations used are: SCLC, small cell lung cancer; ES, extensive stage; PE, cisplatin-etoposide; PET, PE+paclitaxel; ECOG, Eastern Oncology Cooperative Group; SWOG, Southwest Oncology Group; PS, performance status; LDH, lactate dehydrogenase; CI, confidence interval; CAV, cyclophosphamide-Adriamycin-vincristine; GLCCG, Greek Lung Cancer Cooperative Group; CE, carboplatin-etoposide; CET, paclitaxel-CE; G-CSF, granulocyte colony-stimulating factor.

4 leukopenia, which occurred in 56% of patients. A similar trial was conducted by the North Central Cancer Treatment Group (6). Forty-three chemo-naïve patients with ES disease received paclitaxel 250 mg/m² i.v. over 24 h with G-CSF. An objective response rate of 53% was observed in 23 patients. The median survival was 10 months. Grade 3 and 4 neutropenia developed in 56%, but this was associated with infection in only two patients.

On the basis of the high degree of activity, incorporating paclitaxel into combination chemotherapy regimens for ES-SCLC was logical. The University of Colorado Cancer Center conducted a Phase I/II trial to determine the optimal doses of paclitaxel, cisplatin, and etoposide (PET). The more convenient 3-h schedule of paclitaxel was used. Paclitaxel at doses of 135–225 mg/m², day 1 with fixed doses of cisplatin (50 or 80 mg/m², day 1) plus etoposide (50 or 80 mg/m²) i.v. on day 1 and 100 or 160 mg/m² p.o. on day 2 and 3 were evaluated in this study. Twenty-eight previously untreated ES-SCLC patients were assessable for toxicity and 23 patients were evaluable for response (7). Dose-limiting peripheral neuropathy occurred at a paclitaxel dose of 225 mg/m² with cisplatin 80 mg/m² and etoposide 80/160 mg/m². Grade 4 neutropenia, which developed in 82% of patients, was the most common toxicity observed. However, febrile neutropenia was uncommon (14%). With the addition of G-CSF in subsequent cycles, grade 4 neutropenia and febrile neutropenia were greatly reduced. The overall objective response rate was 83%, with 5 patients (22%) achieving a complete response (CR) and 14 patients (61%) having a partial response. The median survival was 10 months, and the 1-year survival rate was 39%. The recommended doses for Phase II studies were paclitaxel 175 mg/m², cisplatin 80 mg/m², and etoposide 80 mg/m² on day 1 with oral etoposide 160 mg/m² on day 2 and 3 with routine G-CSF on days 4–14 because of the high rate of grade 4 neutropenia without growth factor. This SWOG Phase II study was designed to determine the efficacy and toxicity of this three-drug regimen.

PATIENTS AND METHODS

Patient Selection. All of the patients had histologically or cytologically confirmed ES-SCLC. ES disease was defined as disease that could not be encompassed within a tolerable, single radiation port. Patients with controlled brain metastases were eligible. Patients had to have measurable or evaluable disease, a PS of 0–2, and adequate bone marrow, renal, cardiac, and liver function. Patients could not have received prior systemic or biological therapy. Prior surgery and/or radiation was allowed. All of the patients gave written informed consent in accordance with institutional and federal regulations. Descriptive factors at the time of registration included PS, 0–1 *versus* 2; LDH, normal *versus* abnormal; and metastatic sites, single *versus* multiple.

Treatment Plan. Patients received paclitaxel 175 mg/m² i.v. over 3 h, cisplatin 80 mg/m² i.v. over 30 min, and etoposide 80 mg/m² i.v. over 30–60 min on day 1 with the appropriate premedications and hydration. The antiemetic regimen was dictated by the treating physician. On day 2 and 3, etoposide 160 mg/m² was given p.o. G-CSF 5 µg/kg/d was administered s.c. on days 4–14. The cycle was repeated every 21 days for 6 cycles.

Table 1 Patient characteristics (n = 88)

	No. of pts ^a	%
Age (range)	60 (36–77)	
Male:Female	44:44	50:50
PS, 0–1:2	63:25	72:28
Metastatic Sites		
None	5	5
Single	37	42
Multiple	47	53
Brain	11	13
LDH, normal:abnormal	32:56	36:64

^a pts, patients.

Dose Modifications. Patients experiencing a nadir granulocyte count of <500/µl or a nadir platelet count of <50,000 or requiring a 2-week delay in hematological recovery were required to undergo a dose reduction of all three agents (dose level 1: paclitaxel 150 mg/m², cisplatin 65 mg/m², and etoposide 70/140 mg/m²; dose level 2: paclitaxel 125 mg/m², cisplatin 50 mg/m², and etoposide 60/120 mg/m²). Patients experiencing grade 2 or greater neurological toxicity had a dose reduction of paclitaxel. Patients with a creatinine of 1.6–2.0 and a creatinine clearance of ≥50 ml/min required a dose reduction of cisplatin. No cisplatin was administered to patients with a creatinine clearance of ≤50 ml/min. Dose modifications for other toxicities were stipulated in the protocol. Patients who required greater than a 2-week delay in treatment or a third dose reduction were removed from the study.

Response and Toxicity Criteria. Standard SWOG criteria were used for response determination (8). Toxicity grading was done according to the Common Toxicity Criteria, version 2.0. Criteria for removal of patients from the study included progression of disease, unacceptable toxicity as determined by the treating physician in consultation with the study coordinator, a delay in treatment of greater than 2 weeks, requirement for palliative radiotherapy, or patient refusal.

Statistical Design and Analysis. The primary objective of this study was to determine whether the PET regimen was efficacious for the treatment of SCLC. The regimen would be considered efficacious if the true median survival were ≥13.5 months and of no further interest if the median survival was ≤9 months (9). A sample size of 75 eligible patients, accrued over 18 months with 1 additional year of follow-up, was calculated with a power of 0.90 using a one-sided 0.05 level log-rank test of 9 *versus* 13.5-month median survival. Response rate and rates of specific toxicities were estimated to within ±12% at worst with a 95% CI.

RESULTS

Patient Characteristics. Ninety-nine patients were registered in this study between September of 1997 and June of 1998. A total of nine patients were ineligible because of insufficient data (two patients), incorrect histology (two patients), outdated radiographs (two patients), administration of radiotherapy within 2 weeks (two patients), and uncontrolled central nervous system disease (one patient). Two additional patients never received therapy and are not evaluable for any end point. Patient characteristics for the remaining 88 patients are shown in

Fig. 1 Overall survival for the 88 eligible patients.

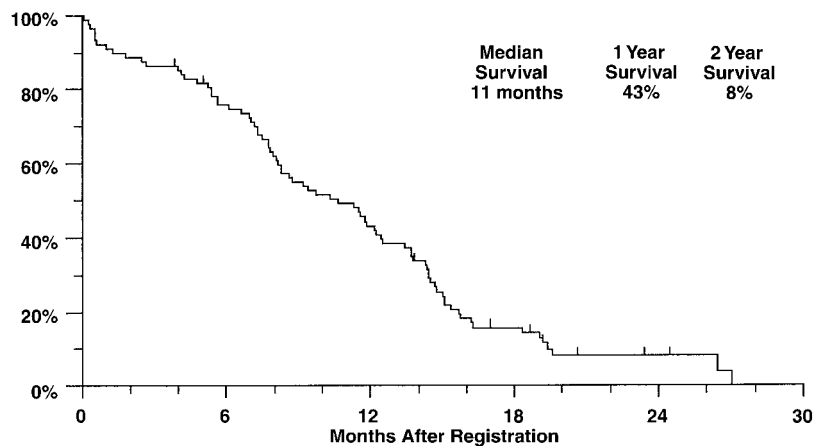


Table 1. The median age was 60 years old (range, 36–77) and 50% of the patients were female. The majority of patients had a PS of 0–1, but 28% of patients had a PS of 2. Most patients (53%) had multiple sites of disease with an elevated LDH (64%). Thirteen % of patients had brain metastases.

Efficacy. An objective response was observed in 48 (56%) of 84 patients, with 10 patients (12%) achieving a complete response. Stable disease was documented in 4 patients (5%) and progressive disease or early death occurred in 11 patients (14%). Response assessment could not be completely determined in 21 patients (25%), primarily because of failure to repeat the bone scan. The median progression-free survival was 6 months (95% CI, 5–7 months), with a median overall survival of 11 months (95% CI, 8–13 months; Fig. 1). The 1- and 2-year survival rates were 43% (95% CI, 33–54%) and 8% (95% CI, 2–15%). Patients with a PS of 0–1, or a normal LDH, or a single metastatic site of disease had a median survival of 14 months as compared with 8 months for patients with a PS of 2, or an elevated LDH, or multiple sites of disease.

Toxicity. Eighty three patients were assessable for toxicity. Grade 3 and 4 toxicities are shown in Table 2. The major toxicity was grade 4 neutropenia, which developed in 33 patients (40%) despite the use of G-CSF. Grade 4 thrombocytopenia and anemia were infrequently observed. The frequency of Grade 3 hematological toxicity was 7% neutropenia, 18% thrombocytopenia, and 12% anemia. Grade 4 nonhematological toxicity was rarely observed and included decreased electrolyte values (6%), dehydration (4%), and renal failure (2%) which were most likely related to cisplatin; hypersensitivity reaction (2%) secondary to paclitaxel; fatigue (2%), and diarrhea (1%). The most frequent grade 3 toxicities were nausea (20%), vomiting (16%), fatigue (14%), diarrhea (8%), weakness (7%), and dehydration (6%). Grade 3 peripheral neuropathy developed in 2 patients (2%) and grade 2 neuropathy was seen in 22 patients (27%). No patient had grade 3 arthralgia/myalgia and nine patients (11%) reported grade 2 toxicity.

Six patients (7%) died from toxicity with five patients dying during cycle 1. Four patients died from neutropenic sepsis, one patient died from infection without neutropenia, and one patient died from renal toxicity. Four of the six patients were female, and three of these patients had a PS of 2. Overall, 3

Table 2 Grade 3 and 4 toxicity (n = 83)

Toxicity	Grade 3		Grade 4	
	No. of pts ^a	%	No. of pts	%
Hematological				
Neutropenia	6	7	33	40
Thrombocytopenia	15	18	3	4
Anemia	10	12	2	2
Nonhematological				
Decreased Na, K, Mg	6	7	5	6
Dehydration	5	6	3	4
Fatigue	12	14	2	2
Hypersensitivity	2	2	2	2
Renal failure	0	0	2	2
Diarrhea	7	8	1	1
Nausea	17	20	0	0
Vomiting	13	16	0	0
Weakness	6	7	0	0

^a pts, patients.

(14%) of 22 patients with a PS of 2 died from toxicity as compared with 3 (5%) of 61 patients with PS of 0–1 (*P*, not significant).

Forty-nine patients (56%) completed all six cycles, nineteen patients (22%) discontinued treatment because of toxicity, and 19 patients were removed from the study for progressive disease (11%), death (6%), or other reasons (3%).

DISCUSSION

This cooperative group multicenter study confirms the results of single-institution Phase I-II studies, which indicated that full doses of the three-drug combination of cisplatin, etoposide, and paclitaxel can be given safely with the use of G-CSF support. The regimen is active with response rates and survival times that compare favorably to prior SWOG experience with two drugs and alternating drug combinations (11). In this study, the confirmed objective response rate was 57%, the median survival was 11 months, and the 1-year survival rate was 43%. Furthermore, our experience with the PET regimen was similar to that reported from three other trials evaluating this regimen and the trial in which carboplatin was substituted for cisplatin (Table 3; Refs. 7, 10, 12, 13).

Table 3 A summary of PET trials in SCLC

Study	Regimen	No. of pts ^a	RR %	CR %	MS mo	1 YR %	ANC % Gr 4	TD %
Kelly <i>et al.</i> (7)	P, 50–80 mg/m ² E, 50/100–80/100 mg/m ² T, 135–200 mg/m ²	28	83	22	10	39	82	4
Glisson <i>et al.</i> (10)	P, 75 mg/m ² E, 80 mg/m ² T, 130 mg/m ²	41	90	16	11	NR	47 ^b	5
Mavroudis <i>et al.</i> (12)	P, 80 mg/m ² E, 80 mg/m ² T, 175 mg/m ² G-CSF	33	45	NR	7	NR	39 ^c	13 ^c
Birch <i>et al.</i> (13)	C, AUC = 6 E, 50 mg/100 mg T, 200 mg/m ²	34	94	18	10.6	NR	31 ^c	5 ^c
SWOG	P, 80 mg/m ² E, 80/160 mg/m ² T, 175 mg/m ² G-CSF	88	57	12	11	43	40	7

^a pts, patients; Gr 4, Grade 4; RR, response rate; CR, complete response; MS, median survival; 1 YR, one-year survival rate; ANC, absolute neutrophil count; TD, toxic death rate; P, cisplatin; E, etoposide; T, paclitaxel; C, carboplatin; AUC, area under the curve; NR, no response.

^b Percent of courses.

^c Include patients with limited-stage disease.

One difference in the present study was a lower response rate and complete response rate compared with the single-institution studies (7, 10). This can be attributable to multicenter participation and an increased sample size, but additionally, the confirmatory follow-up studies such as bone scans were often not available in this study, so that responses could not be confirmed.

The survival outcome in this SWOG study was superior to recent SWOG and other cooperative group experiences with PE and alternating CAV/PE. The original Southeastern Cooperative Study Group study comparing PE to CAV and CAV/PE showed a median survival of ~8–9 months in both arms and a one-year survival rate of about 33% (14). The most recent SWOG/National Cancer Institute-Canada study comparing cisplatin, vincristine, doxorubicin, etoposide (CODE) to CAV/PE produced a median survival of 11 months for the CAV/PE arm but was restricted to patients ≤68 years of age with PS of 0–1 (for SWOG institutions) and no brain metastases (11). In the present study, response and survival were as good as this study despite the fact that patients had significantly worse prognostic factors. Finally, the recent ECOG study that randomized nonprogressing patients treated with four cycles of PE to topotecan or observation produced a median survival time of 8.9 months for patients on the observation arm and a 1-year survival rate of 27% (15). Patients with a PS of 2 were eligible and accounted for 12% of the patients on the observation arm.

One additional multicenter trial evaluating the PET regimen has been conducted by the GLCCG (Table 3). In this small randomized trial of PET *versus* PE, 33 ES-SCLC patients received PET and 41 ES-SCLC patients received PE. Response rates were 45 *versus* 31%, time to progression was 8 *versus* 6 months, and median survival was 7 *versus* 10 months, respectively, for the PET arm as compared with the PE arm. However, these results should be viewed with caution because this trial

was closed early because of increased toxic deaths on the PET arm, which most likely accounted for the poorer survival in the ES subgroup. Our results compare favorably with the trial by Birch *et al.*, in which carboplatin was substituted for cisplatin (13). In this small randomized Phase II trial comparing CET with CE, 34 patients with ES disease received CET and 31 ES patients received CE. Although the overall response was higher at 96% for CET (*versus* 71% for CE), the median survival was almost identical to the SWOG experience at 10.6 months for CET (*versus* 7.8 months for CE).

Neutropenia was the most common toxicity, but the rates varied widely because of study design and patient characteristics. Nonhematological toxicities were mild and primarily related to cisplatin. The toxic death rate of 7% observed in our study and the 13% toxic death rate reported in the GLCCG study is concerning and merits further comment. We believe that the high percentage of PS-2 patients enrolled in our trial contributed to the death rate. In the Greek study only 7 patients had a PS of 2, but two of these patients died from toxicity (29%) as compared with 6 (11%) of 55 patients with PS of 0–1. Poor PS is a well-recognized risk factor for increased toxicity. For example, ECOG terminated accrual of PS 2 patients to their four-arm trial in advanced stage non-SCLC after an increase in grade 3–5 toxicity was observed in 64 patients with a PS of 2 (16). The toxic death rate was 8%. Perhaps future clinical trials for the treatment of SCLC should be developed separately for PS 0–1 and PS-2 patients, as is being done for advanced non-SCLC. Another factor which may have contributed to the toxicity of our regimen was the use of oral etoposide on days 2 and 3 of treatment. The bioavailability of oral etoposide is highly variable, ranging from 48 to 57%, which could have increased toxicity in individual patients (17).

To clarify the efficacy and safety of the PET regimen, an Intergroup trial coordinated by the Cancer and Leukemia Group

B randomizes ES-SCLC patients to PET, with doses of paclitaxel at 175 mg/m² i.v. over 3 h on day 1, cisplatin 80 mg/m² i.v. on day 1, and etoposide 80 mg/m² i.v. on day 1–3 with G-CSF versus PE with cisplatin 80 mg/m² on day 1 and etoposide 80 mg/m² on day 1–3 in patients with a PS of 0–1. This trial met its 640-patient accrual goal in June 2001. Preliminary toxicity data has been acceptable.

In conclusion, this large, multicenter Phase II trial evaluating the PET regimen revealed the regimen was active but associated with increased toxicity, especially in patients with a PS of 2. Most importantly, this is the largest database regarding the safety profile and efficacy of the PET regimen and provides valuable information for physicians treating patients on the Intergroup trial.

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