Cisplatin, Etoposide, and Paclitaxel in the Treatment of Patients With Extensive Small-Cell Lung Carcinoma

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Purpose: **The combination of cisplatin, etoposide, and paclitaxel was studied in patients with extensive small-cell lung cancer in a phase I component followed by a phase II trial to determine the maximum-tolerated dose (MTD), characterize toxicity, and estimate response and median survival rates.**

Patients and Methods: **Forty-one patients were treated between October 1993 and April 1997. Doses for the initial cohort were cisplatin 75 mg/m^2 on day 1, etoposide 80 mg/m^2/d on days 1 to 3, and paclitaxel 130 mg/m^2 on day 1 over 3 hours. Cycles were repeated every 3 weeks for up to six cycles. The MTD was reached in the first six patients. In these six patients and in the next 35 patients, who were entered onto the phase II trial, response and survival were estimated.**

Results: **At the initial dose level, one of six patients developed febrile neutropenia, and five of six achieved targeted neutropenia (nadir absolute granulocyte count, 100 to 1,000/μL) without any other dose-limiting toxicity, defining this level as the MTD. Grade 4 neutropenia was observed in 88 (47%) of 188 total courses administered at or less than the MTD. Neutropenia was associated with fever in only 17 (9%) of 188 courses, but two patients experienced neutropenic sepsis that was fatal. Nonhematologic toxicity greater than grade 2 was observed in 10 (5%) of 188 total courses, with fatigue, peripheral neuropathy, and nausea/vomiting most common. The overall objective response rate was 90% of 38 assessable patients: six complete responses (16%) and 28 partial responses(74%). Median progression-free and overall survival durations were 31 and 47 weeks, respectively.**

Conclusion: **The combination of cisplatin, etoposide, and paclitaxel produced response and survival rates similar to those of other combinations and was well tolerated.**

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SMALL-CELL LUNG cancer (SCLC) represents 20% to 25% of total lung cancer cases diagnosed in the United States, with the number of cases in 1998 estimated at 34,300.[1] Sixty-five percent to 70% of patients with SCLC present with extensive disease, ie, metastasis beyond the ipsilateral lung and regional lymph nodes. Combination chemotherapy forms the cornerstone of treatment for extensive SCLC and significantly improves the quality and duration of survival. However, despite more than two decades of intense investigation with various combination regimens with or without irradiation of multiple sites, survival at 5 years and thus apparent cure remains rare (1% to 5%) in patients who have clinically evident metastatic disease at presentation.[2,3]

Paclitaxel has been studied intensively over the past 5 years and has shown promising activity in a diverse array of malignancies. Two phase II trials of paclitaxel in patients with previously untreated small-cell lung cancer produced response rates of 34%[4] and 41%.[5] In view of its unique mechanism of action, and in some cases of resistance, paclitaxel is an attractive drug to add to current combinations.

The combination of etoposide and cisplatin has become a common first-line regimen in the treatment of SCLC because it offers both lowered toxicity and at least equal efficacy compared with cyclophosphamide- or doxorubicin-based combinations.[6-8] One randomized trial of patients with extensive SCLC demonstrated no differences in response rate or survival in patients who received etoposide 80 mg/m^2 intravenously (IV) on days 1 to 3 and cisplatin 80 mg/m^2 IV on day 1 and those who received a 67% increased dose of both drugs during the first two cycles of chemotherapy. Because the former regimen was very well tolerated, we elected to add paclitaxel to etoposide and cisplatin at those doses. We performed an initial dose-finding phase to define a safe dose of paclitaxel in the regimen and then estimated response and survival in a formal phase II trial.

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PATIENTS AND METHODS

Patients

Eligibility criteria included histologically or cytologically documented SCLC and extensive disease, defined as disease beyond the hemithorax of origin and regional lymph nodes and demonstrated by staging that included chest x-ray, computed tomography of chest, abdomen, and brain, and bone scan. Bone marrow aspiration and biopsy were performed only if all other tests were negative for metastasis. Patients with a cytologically positive pleural effusion as the only evidence of extensive disease were eligible, as were patients with clinically silent brain metastasis. Adequate organ function was required, including absolute granulocyte count $\geq$ 1,500/μL, platelet count $\geq$ 100,000/μL, bilirubin level $\leq$ 1.5 mg/dL, creatinine level $\leq$ 1.5 mg/dL, and creatinine clearance $\geq$ 60 mL/min. Patients with serious intercurrent medical illness and those with severe chronic obstructive pulmonary disease (partial pressure of oxygen, $\leq$ 50 and/or partial pressure of carbon dioxide, $\geq$ 50 on room air) were excluded. A performance status of 0 to 2 (Zubrod scale), no previous chemotherapy or radiotherapy, no recent ($<$ 5 years) history of malignancy other than nonmelanoma skin cancer, and ability to provide informed consent were also required. The protocol was approved by the institutional review boards of The University of Texas M.D. Anderson Cancer Center and other participating affiliated institutions. Four of the 41 patients accrued were treated at Harris Methodist Hospital (member of the Texas Community Oncology Network; Fort Worth, TX), and three of the 41 were treated at the M.D. Anderson Cancer Center–Orlando (Orlando, FL). The remaining patients were treated at The University of Texas M.D. Anderson Cancer Center.

Therapy

Chemotherapy was repeated every 21 days for a planned total of six cycles. The treatment plan and dose levels are summarized in Table 1. Premedication for paclitaxel consisted of dexamethasone 20 mg orally 14 and 7 hours before treatment and cimetidine 300 mg IV and diphenhydramine 50 mg IV 30 minutes before treatment. Paclitaxel was administered IV over 3 hours. Dose reduction was required for infection, bleeding, nadir platelet count less than 25,000/μL, and grade 2 irreversible or grade 3 reversible nonhematologic toxicity. Irreversible grade 3 and any grade 4 nonmyelosuppressive toxicity required discontinuation of treatment, except in the case of reversible grade 4 nausea/vomiting. Growth factor use was permitted only for treatment of neutropenic fever with pneumonia or other severe infection. Growth factors were not used in subsequent cycles for prophylaxis. Intrapatient dose escalation was permitted in the absence of myelosuppressive toxicity greater than grade 2 and nonmyelosuppressive toxicity greater than grade 1. A complete blood count with differential and platelet counts was obtained weekly and immediately before a new cycle. Serum chemical assays were obtained before each cycle. Recovery of absolute granulocyte count to 1,500/μL and platelet count to 100,000/μL and resolution of nonhematologic toxicity to $\leq$ grade 1 was required before initiation of a new cycle of treatment.

Patients with brain metastasis who developed progressive disease at any time or who did not have a complete or partial response in the brain after three cycles were removed from the study and referred for whole-brain radiotherapy. Patients with a major response in the brain were referred for radiation after they completed six cycles of chemotherapy.

Table 1. Treatment Plan and Dose Levels*

Treatment	Duration (days)	mg/m²			
		−2	−1	+0	+1
Paclitaxel, IV	1	85	105	130	160
Cisplatin, IV	2	75	75	75	75
Etoposide, IV	2-4	80	80	80	80

*Dose level 0 was the initial dose level in phase I and the MTD. In phase II, patients began therapy at dose level 0, and doses were escalated or reduced according to toxic effects.

Study Design

Guiding the phase I part of the study were the end points of targeted myelosuppression, defined as nadir absolute granulocyte count of100 to 1,000/μL and nadir platelet count of 25,000 to 100,000/μL, and dose-limiting toxicity, defined as febrile neutropenia, grade 4 thrombocytopenia, or bleeding or other grades 3 to 4 nonhematologic toxicity. Dose-limiting toxicity in more than one of three or more than two of six patients in a cohort was deemed above the maximum-tolerated dose (MTD). Alternatively, achievement of targeted myelosuppression in fewer than two of three or fewer than four of six patients in a cohort was deemed below the MTD. If two of three patients achieved targeted myelosuppression and one of three patients experienced dose-limiting toxicity in a given cohort, this led to the accrual of three additional patients at that dose level. The dose level was defined as the MTD if targeted myelosuppression was achieved in at least four of six patients, and if $\leq$ two of six patients experienced dose-limiting toxicity. Patients were accrued in cohorts of three beginning at dose level 0, with dose increase and reduction as indicated in subsequent cohorts (Table 1). A minimum of six patients was to be studied at the MTD before proceeding to phase II.

Responses were assessed by chest x-ray before each course and by reimaging all involved sites after three and six courses were completed. Designation of complete or partial response, no change, or progressive disease were based on standard World Health Organization criteria.[9] Response duration was measured from the first day of documentation of response until the date of disease progression or death if recurrent disease was not evident. Because metastatic disease was not evaluated until completion of three cycles, at least three cycles of treatment were required before a patient's response was deemed assessable. After completing therapy, patients were evaluated every 3 months or more frequently as clinically indicated.

Statistical Methods

Survival was measured from the first day of treatment and estimated by the Kaplan-Meier method.[10]

RESULTS

Patients

Between October 1993 and April 1997, 41 patients were entered onto the study. Their characteristics are listed in Table 2. Sex distribution was essentially equal, and the median age was 59 years. Thirty-one patients (75%) had a Zubrod performance status of 0 to 1, and 13 (32%) had only one site of metastasis. Three patients were not assessable for response. One patient received two courses and refused further therapy at M.D. Anderson Cancer Center. One patient was found retrospectively to have limited disease

Table 2. Patient Characteristics

Characteristic		No. of Patients (N = 41)
Age, years		
Median	59	
Range	35-78	
Sex		
Female		20
Male		21
Zubrod performance status		
0		2
1		29
2		10
Site of metastasis		
Liver		24
Bone		19
Pleura		15
Adrenal		6
Extrathoracic lymph nodes		6
Brain		2
No. of metastatic sites		
1		13
2		11
≥ 3		17

based on magnetic resonance imaging evaluation of an adrenal mass after three courses. This patient was taken off the study to receive thoracic irradiation and continued chemotherapy; he was excluded from the survival analysis. One patient was taken off study on the second day of course 1 after experiencing hypersensitive reactions to both paclitaxel and etoposide. These three patients are included in toxicity assessments but not response analysis. Two patients who died of treatment-related neutropenic sepsis during the first cycle were included in the nonresponding group.

Determination of MTD

Of the first three patients entered at dose level 0, one experienced neutropenic fever and two of three achieved targeted myelosuppression. Three patients were added, and five of the six patients achieved targeted myelosuppression without any additional dose-limiting toxicity. Thus, dose level 0 was defined as the MTD for phase II. Myelosuppressive toxicity in cycle 1 for patients in the phase I segment is summarized in Table 3.

Response

The first six patients who were accrued in phase I were all treated at the MTD and were included in the overall response analysis. A total of 188 cycles was given with a median of six cycles per patient (range, one to eight cycles). Twenty-eight patients (68%) completed the planned six cycles of therapy. Chemotherapy was continued in one patient who achieved a CR after six cycles and received a total of eight cycles and in one patient with partial response who received seven cycles. Chemotherapy was repeated at 21- to 24-day intervals in 65% of courses. Reasons for delay of treatment more than 24 days included delayed recovery of granulocytes (38% of courses), delay after hospitalization for neutropenic fever (23%), fever without neutropenia (10%), persistent mucositis (5%), and personal reasons of the patient (16%). No reason was documented in 10% of courses delayed.

The overall response rate was 90% (34 of 38 patients), with six patients (16%) achieving a complete response, and 28 (74%) achieving a partial response. The 10 patients with a performance status of 2 at presentation had an equivalent response rate of 90% (nine of 10 patients), with one (10%) of 10 achieving a complete response. Of two patients with brain metastases, one had progression in the brain after four cycles and one had treatment-related mortality in the first cycle.

Survival

Seven patients remained alive at the time of analysis, with a median follow-up time of 54 weeks in the survivors. Actuarial estimation of median failure-free and overall survival durations for the entire population was 31 weeks (95% confidence interval [CI]), 24 to 36 weeks) and 47 weeks (95% CI, 38 to 76 weeks), respectively (Figs 1 and 2). The 30 patients with a performance status of 0 to 1, compared with the 10 with a status of 2, experienced a nonsignificant trend to improved overall survival: 59 weeks (95% CI, 38 to 78 weeks) versus 39 weeks (95% CI, 21 to not reached; $P = .15$). Progression-free survival was identical in these two groups. The 2-year overall survival rate was 10% for the entire group.

Table 3. Myelosuppression in Cycle 1*

Toxicity Grade†	Dose Level 0 (n = 6)
Neutrophils	
2	1
3	3
4	2
Febrile neutropenia	1
Platelets	
0	1
1	5
Hemoglobin	
0	2
1	2
2	2

*Includes only the six patients in the phase I part of the study.

†According to the National Cancer Institute Common Toxicity Criteria.

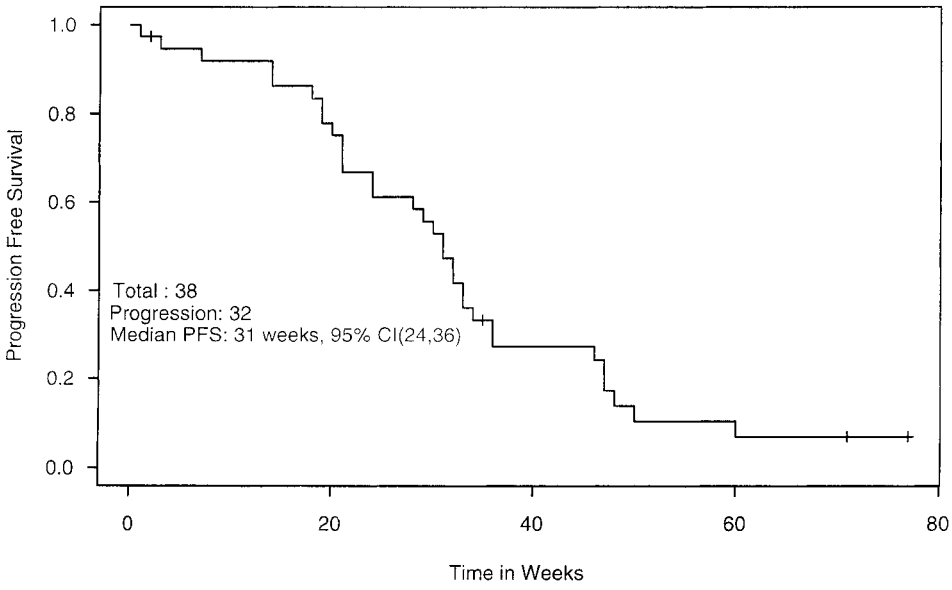

Fig 1. Kaplan-Meier estimate of progression-free survival.

Toxicity

Dose escalation/reduction and myelosuppressive toxicity for all courses in the 41 patients (phase I and II combined) are described in Table 4. Of 16 patients who required dose reduction less than the MTD at any point, 14 were reduced to dose level 1 and maintained at that level. Only two patients required eventual reduction to dose level 2. Notably, 70% of the total courses delivered were at or greater than the MTD. As expected, neutropenia and anemia were most common; however, febrile neutropenia was uncommon, occurring in only 9% of total courses, despite grade 4 neutropenia in 47% of courses. Two episodes of fatal sepsis syndrome were observed, both in the first cycle. Nonhematologic toxicity is summarized in Table 5. Fatigue was most common, followed by gastrointestinal toxicity. Neuropathy was uncommon.

DISCUSSION

Paclitaxel added to the base regimen of etoposide and cisplatin was feasible and reasonably well tolerated. Predictably, the major toxicity was grade 4 neutropenia, which occurred in nearly half of the courses. However, neutropenic

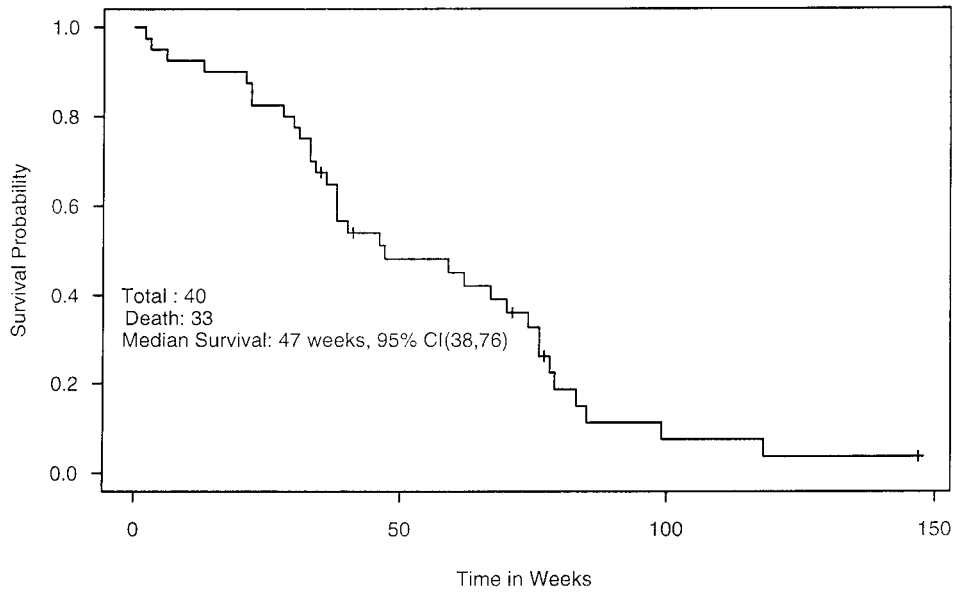

Fig 2. Kaplan-Meier estimate of overall survival.

Table 4. Summary of Dose Escalation/Reduction and Myelosuppressive Toxicity*

Dose Level	Courses/No. of Patients	Grade 4 Neutropenia	Febrile Neutropenia	Grade 4 Thrombocytopenia	Grade 3-4 Anemia
+1	9/4	1	0	0	3
0	123/39	55	12	3	8
−1	50/17	24	3	0	4
−2	8/3	8	2	0	1
Total					
No.	188	88	17†	3	16
%	100	47	9	1	8

*Number of courses associated with toxicity (combined data from phases I and II).

†Two episodes resulted in early septic death.

fever was uncommon. Despite this, two patients died from neutropenic sepsis. The combination was associated with a high response rate and survival similar to other combinations for extensive SCLC.

The MTD we defined in this study for paclitaxel (130 mg/m^2 over 3 hours) is only 52% of the dose used in the phase II trials documenting the single-agent activity of paclitaxel in SCLC (250 mg/m^2 over 24 hours).[4,5] One might argue that the paclitaxel dose we used in the combination regimen was not ''optimal'' and that higher doses (with growth factor support) would have resulted in improved efficacy. There are no randomized trials in SCLC that directly address this question; there are only suggestive data from sequential cohorts in a phase II trial reported by Hainsworth et al[11] (see below). Randomized trials with paclitaxel as a single agent in recurrent ovarian cancer and in combination with cisplatin in recurrent squamous cancer of the head and neck have not shown a dose response or survival benefit for higher doses.[12,13] Furthermore, other drugs such as etoposide are frequently administered in combination regimens for SCLC at less than 50% of the single-agent MTD (eg, 80 mg/m^2 IV on days 1 to 3 *v* 100 mg/m^2 IV on days 1 to 5), and one trial has shown no response or survival benefit for a 67% dose escalation above this level in patients with extensive disease.[7] Clearly, a randomized trial would be required to define a dose response for paclitaxel as a single agent or in combination for SCLC. Certainly, a dose response for paclitaxel in the combination we used will be difficult to demonstrate given the 90% overall response rate we observed with a relatively low dose.

Table 5. Summary of Nonhematologic Toxicity Grades 2 to 4

Toxicity	Grade*	No. of Patients/No. of Courses
Gastrointestinal		
Nausea/vomiting	2	12/17
	3	3/3
Diarrhea	2	8/9
	3	1/1
Constipation	2	10/18
	3	1/1
Neurologic		
Sensory	2	4/5
	3	2/2
Motor	2	1/1
Arthralgia/myalgia	2	6/9
Fatigue	2	23/56
	3	2/2

*According to the National Cancer Institute Common Toxicity Criteria.

Other investigators have reported on the use of regimens similar to ours in SCLC (Table 6).[11,14-16] Three of these trials have had dose finding as a major end point, have therefore involved relatively small numbers of patients, and at this time have been reported only in abstract or monograph form. Survival data from these three trials have not been reported.[14-16] The article by Hainsworth et al[11] reports data from a phase II trial with two sequential cohorts, as previously noted. Paclitaxel was added to carboplatin and 10-day oral etoposide and studied at two different dose levels. A total of 61 patients with extensive disease were treated, 23 with the lower dose and 38 with the higher dose. The second dose level studied included an increase in carboplatin from an area under the concentration-time curve of 5 to 6 and in paclitaxel from 135 mg/m^2 to 200 mg/m^2 in 1 hour. Etoposide was kept constant at 50 mg, alternating with 100 mg orally on days 1 to 10. Growth factor support was not used. Experience with the low-dose regimen was disappointing, with an overall response rate of 65% and a median survival duration of only 7 months. In the second cohort, the high-dose regimen seemed more effective, with a response rate of 84% and median survival duration of 10 months. Despite their use of a higher dose of paclitaxel, these results are nearly identical to ours. In addition, toxic effects of the two regimens were similar, especially concerning the incidence of neutropenic fever and grade 4 neutropenia.

The data of Hainsworth et al[11] suggest a dose response for paclitaxel in SCLC, and they also imply that paclitaxel adds efficacy to the base regimen of carboplatin and etoposide. We obtained similar results with a lower dose of paclitaxel in an equitoxic combination regimen, albeit with a minor difference in schedule (3-hour *v* 1-hour infusion time). Furthermore, in terms of efficacy, we observed similar high response rates and equivalent or better median survival durations in previous phase II trials with a similar patient population at The University of Texas M.D. Anderson Cancer Center, all with etoposide/cisplatin as a base (Table 7).[17,18] A randomized trial will be necessary to elucidate the

Table 6. Summary of Cisplatin or Carboplatin, Etoposide, and Paclitaxel Regimens in Extensive SCLC

Study	No. of Patients	Dose/Schedule	Overall Response (%)	Complete Response (%)	Median Survival (months)	2-Year Survival (%)	Grade 4 Neutropenia (% courses)	Treatment-Related Death (%)
Hainsworth et al[11]	23	C (AUC = 5) IV day 1						
		E 50 mg alt 100 mg orally days 1-10	65	17	7	NR	8	3
		T 135 mg/m^2 IV 1 hr day 1						
	38	C (AUC = 6) IV day 1	84	21	10	NR	38	3
		E 50 mg alt 100 mg orally days 1-10						
		T 200 mg/m^2 IV 1 hr day 1						
Levitan et al[14]	8	P 60 mg/m^2 IV day 1*						
		E 80 mg/m^2 IV days 1-3						
		T 135 mg or 200 mg/m^2 IV 3 hr day 1	75	12	NR	NR	12	0
		G-CSF 5 μg/kg SC days 5-14						
Kelly et al[15]	17	P 80 mg/m^2 IV day 1*						
		E 50 or 80 mg/m^2 IV day 1 100 or 160 mg/m^2 orally days 2-3						
		T 135 or 175 mg/m^2 IV 3 hr day 1	100	25	NR	NR	73†	0
		Routine growth factor use; not otherwise specified						
Hainsworth and Niell[16]	22	C (AUC = 6) IV day 1*						
		E 80-100 mg/m^2 IV days 1-3						
		T 175-200 mg/m^2 IV 3 hr day 1	91	18	NR	NR	41†	7§
		G-CSF 5 μg/kg SC days 14-18						
Glisson et al‡	41	P 75 mg/m^2 IV day 1						
		E 80 mg/m^2 IV days 1-3						
		T 130 mg/m^2 IV 3 hr day 1	90	16	11	10	47	5

Abbreviations: alt, alternating; AUC, area under the concentration-time curve; C, carboplatin; E, etoposide; G-CSF, granulocyte colony-stimulating factor; I, Ifosfamide; NR, not reported; P, cisplatin; SC, subcutaneously; T, paclitaxel.

*Phase I study with multiple dose levels.

†Reported as percentage of patients.

‡Current study.

§Two deaths in a total of 29 patients with non-SCLC and SCLC.

contribution of paclitaxel to the outcome of treatment with etoposide and cisplatin or carboplatin for patients with extensive SCLC. Two such trials are under way.

Hainsworth et al are continuing to explore their regimen in a study being run through the Minnie Pearl Cancer Research Network. The standard arm, consisting of etoposide 120 mg/m^2 IV on days 1 to 3 and a carboplatin area under the concentration-time curve of 6 on day 1, is being compared with the high-dose regimen from their phase II trial in patients with both extensive and limited SCLC, both regimens being administered without growth factor support. Cancer and Leukemia Group B 9732, which is being run through the intergroup mechanism, compares standard etoposide (80 mg/m^2 IV on days 1 to 3) and cisplatin (80 mg/m^2 IV on day 1) with the addition of paclitaxel (175 mg/ m^2 IV over 3 hours on day 1) to the same doses of etoposide and cisplatin in patients with extensive disease. Routine use of granulocyte colony-stimulating factor is included in the experimental arm. The results of these two trials hopefully will clarify the role of paclitaxel in the initial treatment of SCLC and may also shed light on the contribution of routine growth factor support in this setting.

Table 7. Recent Prior Phase II Trials in Extensive SCLC at The University of Texas M.D. Anderson Cancer Center

Study	No. of Patients	Dose/Schedule	Overall Response (%)	Complete Response (%)	Median Survival (months)	2-Year Survival (%)	Grade 4 Neutropenia (% courses)	Treatment-Related Death (%)
Glisson et al[17]	33	P 20 mg/m^2 IV days 1-3						
		I 1,500 mg/m^2 IV days 1-3	93	17	12	9	24	0
		E 50 mg/m^2 orally days 4-17						
Khuri et al[18]	40	P 25 mg/m^2 IV days 1-3						
		E 100 mg/m^2 IV days 1-3	89	10	11	6	24	0
		IFN 5 × 10^6 μ/m^2 SC days 1-3						

Abbreviations: E, etoposide; I, ifosfamide; IFN, interferon alfa; P, cisplatin; SC, subcutaneously.

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