Investigational New Drugs
The Journal of New Anticancer Agents

10.1007/s10637-005-3669-3

Original Article

A Phase I/II study of docetaxel, etoposide, and carboplatin before concurrent chemoradiotherapy with cisplatin and etoposide in limited-stage small cell lung cancer

Patrapim Sunpaweravong[1, 2], Lyn Magree[1], Rachel Rabinovitch[3], Paul Bunn[1] and

Karen Kelly[1]

(1) Division of Medical Oncology, University of Colorado Cancer Center, Aurora, Colorado 80010, USA

(2) Prince of Songkla University, Songkla, Thailand 90110

(3) Department of Radiation Oncology, University of Colorado Cancer Center, Aurora, Colorado 80010, USA

(4) University of Colorado Health Sciences Center, P.O. Box 6511, Campus Box 8117, Aurora, CO 80045, USA

Karen Kelly
Email: karen.kelly@uchsc.edu

Published online: 20 September 2005

Summary Limited stage small cell lung cancer (LS-SCLC) is an infrequent but aggressive tumor. No major advances in the treatment of this disease have been achieved in recent years. This study was conducted to determine the maximum-tolerated dose (MTD) and efficacy of docetaxel, etoposide, and carboplatin (DEC) given before definitive chest radiotherapy with concurrent cisplatin and etoposide. Seventeen untreated LS-SCLC patients received docetaxel 50 mg/m^2, etoposide 50–80 mg/m^2, and carboplatin AUC = 5–6, intravenously on day 1 followed by etoposide 100–160 mg/m^2 orally on days 2 and 3 every 21 days for two cycles followed by once daily radiotherapy to a total dose of 50 Gy given concurrently with cisplatin (60 mg/m^2, d1) and etoposide (120 mg/m^2, d1 and 240 mg/m^2 day 2–3) for 2 cycles. All patients were assessable for toxicity and 15 for response. The most frequent toxicity was grade 3 and 4 neutropenia in 41% of patients during DEC and in 57% with chemoradiation. The MTD for DEC was docetaxel 50 mg/m^2 plus carboplatin AUC = 5 and etoposide 50/100 mg/m^2 with growth factor support. Significant nonhematologic toxicities were primarily radiation-related esophagitis (43%). One patient (6%) died from toxicity. The overall response rate was 82% with 10 patients (59%) achieving a complete response. The median survival was 12.1 months (95% CI, 6.4–17.8 months) and the 1-year survival rate was 47%. This novel approach produced similar efficacy results to current two drug regimens but was associated with significant neutropenia. Alternative strategies to increase complete response rates and survival are needed.

Key words: docetaxel - triple drug chemotherapy - limited stage small cell lung cancer - clinical trial

Introduction

Small cell lung cancer (SCLC) is an aggressive and lethal malignancy. In the year 2004, approximately 27,000 new cases will be diagnosed in the United States and majority of these patients will die from their disease [*1*]. One-third of SCLC patients will present with limited-stage disease (LS-SCLC) for which combination chemotherapy and thoracic irradiation is the standard of care. Two meta-analyses of randomized trials comparing chest radiotherapy plus chemotherapy to chemotherapy alone demonstrated a modest but significant survival advantage for patients receiving bimodality therapy [*2*, *3*]. In the United States concurrent cisplatin and etoposide (PE) with thoracic radiotherapy is the most frequently used regimen producing objective response rates of about 87%, median survival times of approximately 20 months and a 2 year survival rate of 44% [*4*]. Despite high initial responses to this therapy disease relapse is frequent with only 23% of patients surviving beyond 5 years. Clearly, strategies to improve the cure rate are needed.

While concurrent chemoradiotherapy is routinely administered, controversy surrounds the optimal chemotherapy regimen, its dose intensity and schedule, as well as the optimal dose, volume and timing of thoracic radiotherapy (TRT). All of these issues are under active investigation. Since the majority of patients relapse systemically, evaluation of novel cytoxic agents alone and in combination with TRT is important. Among the various novel chemotherapeutic compounds investigated in SCLC, docetaxel has shown considerable anti-tumor activity [*5*]. Thirty-four previously treated SCLC patients received 100 mg/m^2 of docetaxel as a single agent intravenously (i.v.) over 1 h every 21 days. The overall response rate was 25% and the median duration of response was 4.7 months. Grade 3 and 4 toxicities were neutropenia (85%), leukopenia (65%), and fatigue (21%) [*6*]. Two studies were conducted in chemotherapy-na◉ve patients with extensive-stage SCLC (ES-SCLC) [*7*, *8*]. The Canadian group administered docetaxel at 75 mg/m^2 every 3 weeks. In this small study of 12 evaluable patients, one patient (8%) achieved a partial response. Median survival was 10.4 months and grade 4 neutropenia was observed in 42% [*7*]. In the Southwest Oncology Group (SWOG) phase II study, docetaxel 100 mg/m^2, was infused every 21 days. Forty-three patients were evaluable and 10 patients (23%) achieved a partial response. The median progression-free survival was 3 months and the overall survival was 9 months. Grade 4 neutropenia developed in 58% of patients [*8*]. The modest activity of docetaxel in these studies suggests this agent should be integrated with other agents for further evaluation in SCLC.

PE is a standard regimen for patients with LS-SCLC, carboplatin plus etoposide (CE) has shown comparable efficacy with lesser toxicity than PE in a randomized trial involving 143 patients with both limited and extensive stage SCLC [*9*]. At the time this trial was designed, the addition of a third agent to a standard platinum doublets was a popular strategy in both non-small cell and small cell lung cancers. A preliminary report from our phase I study of paclitaxel plus PE (PET) revealed the triplet was active and safe in patients with extensive stage SCLC [*10*]. Another pilot trial with paclitaxel, carboplatin and etoposide also demonstrated similar results [*11*]. This data suggested that a triplet regimen may be feasible and warranted evaluation with thoracic radiation in patients with limited stage disease. Pilot trials with paclitaxel-based triplets regimens were ongoing therefore we elected to explore an alternative design using docetaxel with CE (DEC) as an induction and consolidation regimen surrounding standard thoracic radiotherapy plus PE chemotherapy to determine if this novel triple drug regimen could be safely integrated into a standard treatment plan. Docetaxel was not added to the chemoradiation regimen because the dose and schedule of docetaxel in combination with chest radiotherapy was undefined. Oral etoposide was substituted for intravenous etoposide on day 2 and 3 of the DEC regimen as part of an ongoing program to evaluate convenient triple drug regimens in both extensive and limited stage SCLC. This study was designed to determine the maximum-tolerated dose (MTD) of DEC chemotherapy before and after standard concurrent chemo-radiotherapy. Once the MTD was determined additional patients were treated to evaluate for efficacy.

Patients and methods

Eligibility criteria

All patients had histologically or cytologically confirmed LS-SCLC. LS disease was defined as disease that could be entirely encompassed within a tolerable, single radiation port. Patients with extrathoracic metastases, pleural effusions or severe emphysema defined as an FEV 1 < 1.0 liters were excluded. Patients had to have measurable or evaluable disease, a performance status (PS) of 0–2, and adequate bone marrow, renal, cardiac, and liver function. Patients could not have received prior chemotherapy or biological therapy. All patients gave written informed consent in accordance with institutional and federal regulations.

Treatment plan

Induction DEC began at a dose level of docetaxel 50 mg/m^2, carboplatin AUC = 6, and etoposide 80 mg/m^2 i.v. day 1 followed by etoposide 160 mg/m^2 orally on days 2 and 3. The oral etoposide dose was rounded to the nearest 50 mg dose. Two cycles were administered every 21 days.

All patients were premedicated with dexamethasone (8 mg po twice a day" 3 days starting the day prior to DEC). Docetaxel was given i.v. over 60 min, followed by etoposide i.v. over 60 min, then carboplatin i.v. over 30 min on day 1 of each cycle. Carboplatin AUC dosing was calculated using the Calvert formula: Carboplatin dose (mg) = Target AUC" (GFR + 25) [*12*]. The GFR was calculated using the Cockcroft-Gault formula:

After completion of DEC, nonprogressing patients received (TRT) with concurrent PE chemotherapy. TRT commenced on day 1 of PE chemotherapy. Radiotherapy was delivered in 2 Gy fractions once daily on week days. The initial 44 Gy was delivered to the pre-chemotherapy primary tumor and involved LNs (defined as any LN >2 cm) along with elective irradiation of ipsilateral radiographically uninvolved hilar and mediastinal LNs. An additional 6 Gy was delivered as a cone down only to the primary tumor and involved LNs via an off-cord technique. Any lymph nodes ≥2 cm radiographically was considered pathologic, and received 50 Gy. PE chemotherapy consisted of cisplatin 60 mg/m^2 i.v. and etoposide 120 mg/m^2 i.v. on day 1 followed by etoposide 240 mg/m^2 orally on day 2 and 3. Two cycles were administered during radiotherapy.

Upon completion of the chemoradiotherapy phase, patients received an 2 additional consolidation cycles of DEC in concordance with the above schedule. The use of prophylactic cranial radiation (PCI) in responding patients was recommended but not mandated.

MTD and dose-limiting toxicity (DLT)

The MTD was defined as one dose level below the DLT. DLT was defined as 2/6 patients developing grade 4 leukopenia or neutropenia lasting more than 5 days, grade 4 thrombocytopenia, grade 3–4 febrile neutropenia, or any grade 3 nonhematologic toxicity except for alopecia and nausea/vomiting during cycle 1. At least 3 patients were enrolled at each dose level. If DLT was observed in 1 patient, 3 additional patients were accrued at this dose level. If DLT was observed in 2 or more of the initial patients, patient accrual was discontinued and the dose level was considered as the MTD. Once the MTD was determined, the recommended dose level for the phase II study was one dose level below the MTD. The phase II portion of the study was terminated early due to slow accrual.

Dose modifications

Patients received DEC chemotherapy according to the schedule in Table 1. After 3 initial patients were treated on dose level 1, grade 4 neutropenia was observed during cycle 1 in all patients and a 20% dose reduction for DEC was required for the subsequent cycles. Thus, all newly enrolled patients, were treated at the −1 dose level consisting of docetaxel 50 mg/m^2, carboplatin AUC = 5, and etoposide 50 mg/m^2 i.v. followed by 100 mg/m^2 orally. At the −1 dose level, all 3 patients developed grade 4 neutropenia. Instead of reducing the drug doses further and jeopardizing adequate drug delivery of all agents, we declared dose level −1 as the MTD and modified the protocol to give G-CSF as primary prophylaxis beginning with

patient #7. G-CSF 5 mg/kg was administered subcutaneously on day 4 and continued until the white blood cell was greater than 10,000 ul. After 5 patients received consolidation DEC it was omitted due to significant neutropenia. No further dose modifications were allowed for carboplatin or etoposide. Docetaxel could be reduced by 25% for grade IV neutropenia, febrile neutropenia or grade III or IV thrombocytopenia, or any grade III or IV non-hematological toxicity.

Table 1 Dose levels of docetaxel, carboplatin, and etoposide (DEC).

Group	Dose level	Patients	Docetaxel[a] (mg/m^2)	Carboplatin[a] (AUC)	Etoposide (mg/m^2) IV[a]/PO[b]	Patients with DLT
1	1	3	50	6	80/160	3
2a	−1	3	50	5	50/100	3
2b[c]	−1	11	50	5	50/100	1

[a]Day 1.
[b]Days 2 and 3.
[c]G-CSF was given as primary prophylaxis for leukopenia/neutropenia DLT, dose-limiting toxicity.

During chemoradiation, TRT was held for grade IV hematological toxicity and grade III nonhematological toxicity until the toxicity was ≤ grade 2 within 2 weeks. PE chemotherapy was reduced to 50 mg/m^2 of cisplatin and 100/120 mg/m^2 of etoposide if the patient had a delay in treatment of 1–2 weeks due to a WBC <3000/ul, ANC of <1000/ul and/or a platelet count <100,000/ul. A 50% dose reduction of cisplatin was required if the serum creatinine was ≥1.6–2.0 with a creatinine clearance of ≥50 cc/min and no treatment was given if the creatinine clearance was ≤50 cc/min.

Assessment

Before enrollment, all patients underwent a history and physical examination, SWOG performance status, complete blood counts, electrolytes, renal and liver function tests, urinalysis, and an electrocardiogram. Required radiographs included a baseline chest X-ray, computed tomography (CT) of the chest and upper abdomen, CT or magnetic resonance imaging of the brain and a bone scan. Bone marrow biopsy and aspiration were optional. History and physical examinations were required before every cycle. Complete blood counts were drawn weekly. Renal and liver function tests were obtained before each cycle. Radiographs for tumor assessment were obtained after every two cycles.

Standard SWOG criteria was used for response determination [*13*]. Toxicity grading was performed according to the Common Toxicity Criteria, version 2.0. Criteria for removal of patients from the study included progression of disease, unacceptable toxicity a delay in treatment greater than 2 weeks, or patient refusal.

Statistical analysis

Selecting the MTD as one dose level below DLT offers protection such that 95% of the time the dose selected will have average toxicity less than 80% with a modal value below 40%. Increasing the sample size by 20 patients at the MTD provides a 95% confidence interval of at least ±0.2 for efficacy estimations.

Time to disease progression was calculated from the date of treatment to the date the patient was assessed as having progressive disease. Overall survival was calculated from the start time of treatment until death. Time to disease progression and Kaplan-Meier survival curves were produced in SPSS version 10.0. Patients who died without progression or who had not progressed were censored at the death or last follow-up. Living patients were censored at the date of last follow-up.

Results

Patient characteristics

Seventeen patients were enrolled in this study between July 1997 and October 2001. All patients were assessable for toxicity and 15 patients were evaluable for response. Patient characteristics are shown in Table 2. The patients were between 44 and 69 years of age, with a median age of 58 years. Sixty-five percent were men, and 35% were females. Nearly all patients had a SWOG PS of 0–1 (94%), and 6% had a PS of 2.

Table 2 Patient characteristics.

Total no. of patients	17
Age, years	
Median	58
Range	44–69
Gender	
Male	11 (65%)
Female	6 (35%)
SWOG PS	
0	8 (47%)
1	3 (18%)
2	6 (35%)

Determination of MTD

At least one cycle of DEC chemotherapy was administered to all 17 patients. The number of patients who developed DLT is listed in Table 1. DLT occurred in all three patients at dose level 1. These DLTs were grade 4 neutropenia in 3 patients, grade 4 leukopenia in 2, grade 3 and 4 febrile neutropenia in 2 patients, and grade 3 diarrhea and dehydration in 1 patient each. A dose de-escalation of carboplatin and etoposide was instituted. All 3 patients treated at the −1 dose level also developed grade 4 neutropenia. Dose level −1 was determined to be the MTD because further dose reductions would lead to insufficient drug delivery. The protocol was amended to allow for prophylactic G-CSF. Eleven additional patients were treated without major hematological toxicity.

Toxicity

All 17 patients were assessable for toxicity. Grade 3 and 4 toxicities are shown in Table 3. In the induction DEC phase, the major toxicities were grade 4 neutropenia and leukopenia, which developed in 7 (41%) and 4 patients (23%), respectively. After prophylactic G-CSF was given, only 1 patient developed grade 4 neutropenia with DEC but this progressed to sepsis and death. Two patients (12%) had grade 4 dehydration-related hypotension. Grade 3 hematological events included: leukopenia—2 patients (12%) febrile neutropenia—1 patient (6%) and thrombocytopenia 1 patient (6%). Other grade 3 toxicities were infrequent and included fatigue in 2 patients (12%) and diarrhea, tachycardia, myalgias, nausea, mucositis and electrolyte wasting in 1 patient each (6%).

Table 3 ≥Grade 3 toxicity (n = 17).

	Induction (n = 17)			**TRT[a]/Chemo (n = 14)**	
Toxicity grade	**3**	**4**	**5**	**3**	**4**
Hematological					
Leukopenia	2	4		6	1
Neutropenia	1	7		3	5
Febrile neutropenia	1	0	1	2	0
Anemia	0	0		1	0
Thrombocytopenia	1	0		1	0
Nonhematological					

	Induction (n = 17)			TRT[a]/Chemo (n = 14)	
Toxicity grade	**3**	**4**	**5**	**3**	**4**
Diarrhea	1	0		1	0
Cardiovascular	1	2[b]		0	0
Myalgia	1	0		0	0
Fatigue	2	0		2	0
Nausea	1	0		2	0
Vomiting	0	0		2	0
Anorexia	0	0		1	0
XRT esophagitis	0	0		4	2
XRT pneumonitis	0	0		1	1
Mucositis	1	0		0	0
Dermatitis	0	0		1	0
Urinary electrolyte wasting	1	0		0	0

[a]TRT, thoracic radiotherapy.
[b]Hypotension secondary to dehydration.

Fourteen patients (82%) underwent concurrent chemoradiotherapy. Three patients did not proceed to this phase, one because of disease progression, one due to the discovery of a second primary cancer and one patient died from neutropenic sepsis. An additional patient erroneously received thoracic radiation with DEC chemotherapy and was taken off of the study but is included in this toxicity analysis. Grade 4 neutropenia was documented in 5 patients (36%), and radiation esophagitis and pneumonitis in 2 patients (14%) and 1 patient (7%), respectively (Table 3). The most frequent grade 3 hematological toxicity was leukopenia which developed in 6 patients (43%) and was associated with neutropenia in 3 patients (21%). In 2 patients the neutropenia was complicated by fever (14%). Grade 3 non-hematological toxicity was predominantly esophagitis in 29% of patients (N = 4).

Five patients (29%) received consolidation DEC and three patients (60%) developed grade 4 neutropenia. Grade 3 and 4 leukopenia were observed in 3 (60%) and 1 (20%) patients, respectively. No grade 3 or 4 anemia was seen and 1 patient developed grade 3 thrombocytopenia. No patient had grade 3 or 4 nonhematological toxicity during the DEC consolidation.

Dose intensity

Of the 17 patients treated, 3 initial patients underwent a dose reduction of DEC after cycle one for grade 4 neutropenia and leukopenia in all 3 patients. No dose reductions were required in the remaining 14 patients treated. Sixteen patients received both cycles of DEC. The remaining patient died from neutropenic sepsis in cycle 1.

Four of the 5 patients with grade IV neutropenia during definitive chemoradiation required a short radiation break. Two patients had an extended delay from radiation treatment of 8 and 15 days due to radiation esophagitis. No patient required a dose reduction of PE chemotherapy and all patients completed therapy.

Response and survival

Fifteen patients (88%) were assessable for response (Table 4). Two patients were not evaluated, 1 patient died from toxicity during cycle 1 and the other was found to have a gastric primary cancer and died after cycle 2. An overall objective response was observed in 14 of 15 evaluable patients (93%), with 10 patients (67%) achieving a complete response (CR) and 4 patients (27%) a partial response (PR). The intent to treat analysis revealed 14 patients (82%) achieved responses with a CR rate of 59%. When each phase of treatment was

evaluated, 12 of 15 assessable patients (80%) who received the induction DEC achieved objective responses, with 2 patients (13%) having a CR. Stable and progressive disease were documented in 2 (13%) and 1 (7%) patients, respectively. Thirteen of the fourteen patients (82%) underwent concurrent chemoradiotherapy (one patient was declared off protocol because he had erroneously received DEC with radiation). Eight additional patients converted to a CR for a total of 10 CRs (77%) and 3 patients had a PR (23%.) Five patients receive consolidated DEC, (four patients in CR and 1 patient in PR). The 1 patient in PR remained a PR. Eight patients received PCI.

Table 4 Treatment outcome (n = 17).

	Induction (n = 17)	**TRT[a]/Chemo (n = 13)**	**Consolidation (n = 5)**	**Overall (n = 17)**
Complete response	2	10	4	10
Partial response	10	3	1	4
Stable disease	2	0	0	0
Progression	1	0	0	1
Not evaluable	2[b]	0	0	2[b]

[a]TRT, thoracic radiotherapy.

[b]One patient had second primary cancer and died during cycle 2 and the other died from toxicity during cycle 1.

With a median follow up time of 12 months the median progression-free survival was 11.5 months (95% confidence interval (CI), 2–21 months) the median survival time was 12.1 months (95% CI, 6.4–17.8 months). The 1- and 2-year survival rates were 47% and 33%, respectively. The median survival time for the 10 complete responders was 28 months.

Discussion

This is the first pilot study to incorporate docetaxel into the treatment of limited stage SCLC. Our trial demonstrated that a modest dose of docetaxel could be added to the active regimen of carboplatin and etoposide but required prophylactic G-CSF. Dose limiting neutropenia occurred at the first dose level but with routine G-CSF administration grade IV neutropenia was rarely observed and other toxicities were infrequent.

A similar toxicity experience was seen in our phase I study evaluating the triplet regimen of paclitaxel with cisplatin and etoposide (PET) in patients with extensive stage SCLC leading us to recommend prophylactic G-CSF in phase II SWOG (Southwest Oncology Group) trial [*14*]. This trial demonstrated an encouraging median survival of 11 months in 88 patients [*15*]. Grade 4 neutropenia was documented in 40% of patients. Subsequently a randomized phase III trial was conducted by the CALGB (Cancer and Leukemia Group B) in which compared the PET regimen with G-CSF to PE [*16*]. In this large study the PET regimen was associated with higher grade 3 and 4 toxicity (84% v 77%) and grade 5 toxicities (6.7% v 2.7%) respectively. The Hellenic Oncology Cooperative Group terminated their randomized study of PET plus G-CSF versus PE due to an excessive number of deaths in the PET group (p = .001) [*17*]. The triplet regimen was also associated with more severe grade 3 and 4 toxicity than the PE regimen. Neither randomized trial showed a survival benefit for the three drug combination. The lack of efficacy and increased toxicity associated with these triplet regimens in extensive disease most likely contributed to the slow accrual on our trial.

In LS-SCLC, seven phase II paclitaxel-based triplet combinations have been evaluated (Table 5). The doses and schedules of all the agents varied as did the timing of TRT, nonetheless grade 3 and 4 leucopenia and neutropenia occurred frequently. Hainsworth et al., conducted sequential paclitaxel, carboplatin, etoposide trials with a low dose (135 mg/m^2) of paclitaxel plus carboplatin AUC = 5 and etoposide 50 mg alternating with 100 mg orally day 1–10 regimen and then a high dose (200 mg/m^2) paclitaxel, carboplatin AUC = 6 and the

extended schedule etopside [*18*]. Fifty-six limited stage patients were enrolled and received TRT with cycles 3 and 4. In all patients grade 3 and 4 leucopenia occurred in 24% on the low dose regimen and 71% on the high dose regimen. In Europe, two similar trials were performed but responding patients with limited disease received consolidation thoracic radiation at the end of chemotherapy. In the first study Vieitez et al. administered paclitaxel 175 mg/m^2, carboplatin AUC = 6, and etoposide 80 mg/m^2 IV d 1–3 [*19*]. Forty-seven percent of patients (n = 45) had LS disease. Grade 3 or greater neutropenia developed in 62% of all patients. Reck gave the same dose of paclitaxel with carboplatin AUC = 5 and oral etoposide 50 mg bid on day 2–8 [*20*]. Fifty six of the 84 patients had limited disease. In this study grade 3 and 4 neutropenia was modest developing in 45% of courses.

Table 5 Phase II taxane-based chemoradiation trials in limited stage SCLC.

Author	Chemotherapy regimen	TRT	No. of patients	GR 3/4 Leukopenia	ORR	CR	MS
Hainsworth et al., 1997 [*18*]	C AUC=5	45 Gy	15	24%	93%	40%	17 m
	E 50/100 mg po d1–10	Cycle 3					
	T 135 mg/m^2						
	C AUC=6	45 Gy	41	71%	98%	71%	>16 m
	E 50/100 mg po d1–10	Cycle 3					
	T 200 mg/m^2						
Vieitez et al., 2003 [*19*]	C AUC=6	After CET in responders	45	62%[a]	73%	49%	15.6 m
	E 80 mg/m^2, IV d1–3						
	T 175 mg/m^2						
Reck et al., 2003 [*20*]	C AUC = 5	50–56 Gy after CET in responders	56	45%[a]	87%	20%	20.5 m
	E 50 mg po bid, d2–8						
	T 175 mg/m^2						
Sandler et al., 2000 [*21*]	P 80 mg/m^2	63 Gy	61	59%[a,c]	64%	13%	NR
	E 80 mg/m^2 IV d1–3	Cycle 3					
	T 135[d]/170 mg/m^2						
	G-CSF Cycle 1,2						
Ettinger et al., 2000 [*22*]	P 60 mg/m^2	45 Gy	51	75%[a]	NR	78%	~ >30 m
	E 80 mg/m^2	twice daily					
	T 135[d]/175 mg/m^2	Cycle 1					
Levitan et al., 2000 [*23*]	P 60 mg/m^2	45 Gy	17	32%[a,c]	94%	29%	22 m[b]
	E 60[d]/80 mg/m^2	Cycle 1		20%[a,c]			
	T 135[d]/170 mg/m^2			(cycles)			
Bremnes et al., 2001 [*24*]	P 50 mg/m^2	42 Gy	39	49%	92%	81%	21 m
	E 100 mg/m^2 d1, 100 mg po bid, d2–5	Cycle 3					
	T 175 mg/m^2						

Author	Chemotherapy regimen	TRT	No. of patients	GR 3/4 Leukopenia	ORR	CR	MS
Edelman et al., 2004 [25]	P 50 mg/m^2, d 1,8	61 Gy	96	49%[a]	86%	33%	17 m
	E 50 mg/m^2, d 1–5	Cycle 1					
	Consolidation:						
	T 200 mg/m^2, d 1						
	C AUC = 6, d 1						

TRT: thoracic radiotherapy, C: carboplatin, E: etoposide, T: paclitaxel, P: cisplatin, m: months, NR: not reported.
[a]neutropenia.
[b]all patients phase I and Phase II *N*=28.
[c]Grade 4 only.
[d]With thoracic radiation.

Four trials using paclitaxel, cisplatin and etoposide commonly reported grade 3 and 4 neutropenia (Table 5) [*21–24*]. Sandler et al. reported a high rate of grade 4 neutropenia at 59% despite prophylactic growth factor support [*21*].

This degree of toxicity could be acceptable if efficacy was superior. Although the sample size was small in our study, 82% of patients achieved an objective response including 10 patients (59%) with a confirmed CR. These results were similar to those observed in the other trials listed in Table 5 with response rates ranging from 64–98% and CR rates of 13 to 71%. We were encouraged by our high CR rate but disappointed that this did not lead to prolonged survival. However, in the three studies that reported exceptionally high CR rates of 71, 78, and 81% a meaningful survival benefit was observed in only one study [*18, 22, 24*]. Our median progression-free survival was long at 11.5 months but the median overall survival of 12.3 months with the 1-year survival rate of 47% was shorter than anticipated. Most likely this was due to the small numbers of patients and the two early deaths during DEC therapy. If these 2 patients are excluded from the analysis the median survival is 21.7 months. Nonetheless, it is difficult to determine the impact that DEC may have had on outcome given the small numbers of patients. Typical prognostic clues such as a high CR rate and prolonged PFS time were modestly increased in this study but may have been influence by undefined factors and PCI. Another possibility is that the variable bioavailability of oral etoposide may have had a negative impact on efficacy and toxicity, however four trials described in Table 5 also gave oral etoposide with acceptable result [*18, 20, 24*].

Finally, we designed this trial to give two additional cycles of DEC after completion of definitive chemoradiotherapy for a total of 6 cycles of chemotherapy. Significant neutropenia occurred and the consolidation DEC was omitted. Subsequently data emerged demonstrating that 4 cycles of chemotherapy was acceptable [*4*]. In addition, the Southwest Oncology Group conducted a phase II trial of PE chemotherapy plus 61 Gy of thoracic radiation followed by 2 cycles of consolidation paclitaxel plus carboplatin, Table 5 [*25*]. They showed a similar survival rate to standard regimens, therefore is it unlikely that DEC consolidation would have had a produced a survival benefit but only added unwanted toxicity.

In conclusion, modest doses of DEC chemotherapy followed by standard PE chemoradiation has similar efficacy to PE plus thoracic radiation. The requirement of prophylactic G-CSF to prevent significant neutropenia without demonstration of superior efficacy suggests other strategies are needed to improve the cure rate in this disease.

Contribution in PDF

Acknowledgment We thank our colleagues Dr. Thomas Braun, Dr. Carolyn Collins, Dr. John Fleagle, Dr. Nicholas Napoli, Dr. Doug Rovira, Dr. Larry Schafer and Dr. George Simon for enrolling patients into this trial and Jessica Pfeifer for her administrative support. This trial was supported in part by a grant from Aventis Pharmaceuticals and the University of Colorado

Cancer Center. Conflict of interest: Paul A. Bunn Jr., and Karen Kelly, Honoraria and Consulting for Aventis.

References

1. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer Thun MJ: Cancer Statistics 2004 CA. A Cancer Journal for Clinicians 54: 8–29, 2004

2. Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RI, Brodin O, Joss RA, Kies MS, Lebeau B, et al.: A meta-analysis of thoracic radiotherapy for small cell lung cancer. New Engl J Med 327: 1618–1624, 1992

3. Warde P, Payne D: Does thoracic irradiation improve survival and local control in limited-stage small cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10: 890–895, 1992

4. Turrisi AT, Kyungmann K, Blum R, Sause WT, Livingston RB, Komaki R, Wagner H, Aisner S, Johnson DH: Twice-daily compared with once daily thoracic radiotherapy in limited small cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340: 265–271, 1999

5. Kelly K: New chemotherapy agents for small cell lung cancer. Chest 117(4 Suppl 1): 156S–62S, 2000

6. Smyth JF, Smith IE, Sessa C, Schoffski P, Wanders J, Franklin H, Kaye SB: Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer 30A(8): 1058–1060, 1994

7. Latreille J, Cormier Y, Martins H, Goss G, Fisher B, Eisenhauer EA: Phase II study of docetaxel (taxotere) in patients with previously untreated extensive small cell lung cancer. Invest New Drugs 13(4): 343–345, 1996

8. Hesketh PJ, Crowley JJ, Burris HA 3rd, Williamson SK, Balcerzak SP, Peereboom D, Goodwin JW, Gross HM, Moore DF Jr, Livington RB, Gandara DR: Evaluation of docetaxel in previously untreated extensive-stage small cell lung cancer: a Southwest Oncology Group phase II trial. Cancer J Sci Am 5(4): 237–41, 1999

9. Skarlos DV, Samantas E, Kosmidis P, Fountzilas G, Angelidou M, Palamidas P, Mylonakis N, Provata A, Papadakis E, Klouva G: Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann Oncol 5(7): 601–7, 1994

10. Bunn PA Jr, Kelly K: A phase I study of cisplatin, etoposide and paclitaxel in small cell lung cancer: A University of Colorado Cancer Center Study. Sem Oncol 22(Suppl 12):

54–58, 1995

11. Neill HB, Miller AA, Clamon GH, Perry MC, Crawford J, Green MR: A phase II study evaluating the efficacy of carboplatin, etoposide, and paclitaxel with granulocyte colony-stimulating factor in patients with stage IIIB and IV non-small cell lung cancer and extensive small cell lung cancer. Semin Oncol 24(4 Suppl 12): S12-130–S12-134, 1997

12. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E: Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7(11): 1748–1756, 1989

13. Green S, Weiss GR: Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs 10(4): 239–253, 1992

14. Kelly K, Pan Z, Wood ME, Murphy J, Bunn PA Jr: A phase I study of paclitaxel, etoposide and cisplatin in extensive stage small cell lung cancer. Clin Can Res 5: 3419–3424, 1999

15. Kelly K, Lovato L, Bunn PA Jr, Livington RB, Zangmeister J, Taylor SA, Roychodhury D, Crowley JJ, Gandara Dr: 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. Clin Can Res 2325–2329, 2001

16. Neill HB, Herndon JE II, Miller AA, Watson DM, Sanlder AB, Kelly K, Marks RS, Perry MC, Ansari RH, Otterson G, Ellerton J, Vokes EE, Green MR: Cancer and Leukemia Group: Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive stage small cell lung cancer: Cancer and Leukemia Group B Trial 9732. J Clin Oncol 23: 3752–3759, 2005

17. Mavroudis D, Papadakis E, Veslemes M, Tsiafaki X, Stavrakakis J, Kouroussis C, Kakolyris S, Bania E, Jordanoglou J, Agelidou M, Vlachonicolis J, Georgoulias V: A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. Ann Oncol 12: 463–470, 2001

18. Hainsworth JD, Gray JR, Stroup SL, Kalman LA, Patten JE, Hopkins I, Thomas M, Greco FA: Paclitaxel, carboplatin and extended schedule etoposide in the treatment of small-cell lung cancer: Comparison of sequential phase II trials using different dose intensities. J Clin Oncol 15: 3464–3470, 1997

19. Vieitez JM, Valladares M, Gracia M, Gonzalez-Baron M, Martin G, Mel JR, Rodriguez R, Constenia M, Gomez Aldavari JL, Dominguez S, Dorta J, Garcia-Giron C, Lopez R, Sevilla I, Esteban E, Anton LM, Pelaez I, Lopez E, Lacave AJ: Phase II study of carboplatin and 1-h intravenous etoposide and paclitaxel in a novel sequence as first-line treatment of patients with small cell lung cancer. Lung Cancer 39: 77–84, 2003

20. Reck M, Jagos U, Grunwald F, Kaukel E, Koschel G, von Pawel J, Hessler S, Gatzemeier U: Long-term survival in SCLC after treatment with paclitaxel, carboplatin

and etoposide---A phase II study. Lung Cancer 39: 63–69, 2003

21. Sandler A, Declerk L, Wagner H, Levitan N, DeVore R, Levitt M, Johnson D: A phase II study of cisplatin (P) plus etoposide (E) plus paclitaxel (P) (PET) and concurrent radiation therapy for previously untreated limited stage small-cell lung cancer (SCLC) (E2496) (abstr): An Eastern Cooperative Oncology Group trial. Proc Am Soc Clin Oncol 19: 491a, 2000

22. Ettinger DS, Seiferheld WF, Abrams RA, Fontanesi J, Machtay M, Duncan P, Curran W, Byhardt R: Cisplatin (P), etoposide (E), paclitaxel (P), and concurrent hyperfractionated thoracic radiotherapy (TRT) for patients (Ps) with limited disease (LD) small cell lung cancer (SCLC) (abstr): Preliminary results of RTOG 96-09. Proc Am Soc Clin Oncol 19: 490a, 2000

23. Levitan N, Dowlati A, Shina D, Craffey M, Mackay W, DeVore R, Jett J, Remick SC, Chang A, Johnson D: Multi-institutional phase I/II trial of paclitaxel, cisplatin, and etoposide with concurrent radiation for limited-stage small cell lung carcinoma. J Clin Oncol 18: 1102–1109, 2000

24. Bremnes RM, Sundstrom S, Vilsvik J, Aasebo U: Multicenter phaseII trial of paclitaxel, cisplatin, and etoposide with concurrent radiation for limited-stage small cell lung cancer. J Clin Oncol 19: 3532–3538, 2001

25. Edelman MJ, Chansky K, Gaspar LE, Leigh B, Weiss GR, Taylor SA, Crowley J, Livingston R, Gandara DR: Phase II Trial of cisplatin/Etoposide and concurrent radiotherapy followed by paclitaxel/carboplatin consolidation for limited small-cell lung cancer: Southwest Oncology Group 9713. J Clin Oncol 22: 127–132, 2004