Paclitaxel, Carboplatin, and Extended Schedule Etoposide in the Treatment of Small Cell Lung Carcinoma

John D. Hainsworth, M.D.
Steven L. Stroup, M.D.
F. Anthony Greco, M.D.

Sarah Cannon-Minnie Pearl Cancer Center, Centennial Medical Center, Nashville, Tennessee.

Supported in part by a grant from Bristol-Myers Squibb.

Address for reprints: John D. Hainsworth, M.D., Sarah Cannon-Minnie Pearl Cancer Center, 250 25th Avenue North, Suite 412, Nashville, TN 37203.

Received January 18, 1996; accepted February 20, 1996.

BACKGROUND. Paclitaxel is an active agent in the initial treatment of patients with small cell lung carcinoma. The authors evaluated the toxicity and efficacy of paclitaxel (1-hour infusion) added to a standard combination regimen of carboplatin and etoposide in a Phase II trial for the treatment of patients with small cell lung carcinoma.

METHODS. Thirty-eight patients with previously untreated small cell lung carcinoma were treated with a combination regimen including paclitaxel, 135 mg/m^2 by 1-hour intravenous (i.v.) infusion, on Day 1; carboplatin at AUC 5, on Day 1; and oral etoposide, 100 mg alternated with 50 mg, on Days 1–10. Prior to availability of reimbursement for oral etoposide, 13 patients received etoposide, 25 mg/m^2 i.v. on Days 1–5 and 8–12. Treatment courses were repeated every 21 days for a total of 4 courses. Patients with limited stage disease received radiation therapy (4500 centrigray in 25 fractions) concurrently with the last 2 courses of chemotherapy.

RESULTS. This combination chemotherapy regimen was easily tolerated. Eleven episodes of Grade 3 or 4 leukopenia occurred in 9 patients (8% of courses); Grade 3 and 4 thrombocytopenia and anemia were also infrequent. Fifteen patients were hospitalized for treatment of fever associated with leukopenia. Concurrent treatment with chemotherapy and radiation therapy was also tolerable, but was more toxic; 6 of 15 patients (40%) developed esophagitis (Grade 3 in 5 patients, Grade 4 in 1 patient), and 45% of all episodes of Grade 3/4 leukopenia occurred during concurrent therapy. Other nonhematologic toxicity was uncommon. Twenty-nine of 38 patients (76%) achieved a partial or complete response to treatment (limited stage, 14 of 15 patients, 93%; extensive stage, 15 of 23 patients, 65%). The complete response rate was 26% (limited stage disease, 40% versus extensive stage disease, 17%). Median actuarial overall survival was 7 months for patients with extensive stage disease, and 17 months for patients with limited stage disease. Prophylactic whole brain irradiation was not used, and seven patients developed brain metastases as their initial site of relapse.

CONCLUSIONS. The combination of paclitaxel, administered by 1-hour infusion, carboplatin, and extended schedule etoposide is feasible and well tolerated in the doses administered in this Phase II trial. This regimen was highly active with treatment results comparable to other standard regimens. Increased doses of both paclitaxel and carboplatin could probably be tolerated and are currently being evaluated. Precise definition of the role of paclitaxel in the treatment of small cell lung carcinoma awaits the results of randomized studies. *Cancer* **1996; 77:2458–63.** © *1996 American Cancer Society.*

KEYWORDS: paclitaxel, carboplatin, etoposide, small cell lung carcinoma, limited stage, extensive stage.

Small cell lung carcinoma accounts for 20–25% of all lung cancer cases, and is initially highly responsive to combination chemother-

apy.[1] However, long term remissions are not achieved in most patients, and resistance to chemotherapy develops rapidly. The combination of cisplatin and etoposide has been a standard first-line treatment for several years, producing median survivals of 7–12 months and 18–24 months in patients with extensive and limited stage disease, respectively.[2,3] The substitution of carboplatin for cisplatin has shown similar efficacy, and may have advantages with respect to toxicity.[4,5]

Paclitaxel is the first highly active drug with a unique mechanism of cytotoxicity introduced in the last several years. In Phase II trials, this drug was active when used as a single agent in the treatment of small cell lung carcinoma.[6,7] In patients with previously untreated extensive stage small cell lung carcinoma, single agent paclitaxel produced response rates of 34% and 68% in trials by the Eastern Cooperative Oncology Group (ECOG) and the North Central Cancer Treatment Group, respectively.[6,7] Both of these Phase II studies used a high dose of paclitaxel (250 mg/m^2) administered by 24-hour infusion.

Short infusions of paclitaxel have recently proven to be safe and less myelosuppressive than infusions of 24 hours or longer.[8,9] We recently demonstrated that paclitaxel can be administered by 1-hour infusion without severe hypersensitivity reactions and with modest myelosuppression, even at a dose of 200 mg/m^2.[9,10] The limited toxicity of paclitaxel when administered by 1-hour infusion makes this drug relatively easy to combine with other drugs. In this article, we report the results of a Phase II study in which paclitaxel by 1-hour infusion was added to a standard carboplatin/etoposide regimen in the treatment of patients with small cell lung carcinoma.

PATIENTS AND METHODS

In June 1993, we initiated a new trial to evaluate the feasibility, toxicity, and efficacy of a three-drug regimen containing paclitaxel, carboplatin, and etoposide. All patients had histologically confirmed small cell lung carcinoma, and were previously untreated with chemotherapy or radiation therapy. Patients with either limited or extensive stage small cell lung carcinoma were eligible. Additional eligibility criteria included the following: measurable or evaluable disease; ECOG performance status of 0, 1, or 2; leukocytes $\geq$4000/μL; platelets $\geq$100,000/μL; serum bilirubin $<$ 1.5 mg/dL; and serum creatinine $\leq$ 1.5 mg/dL. Patients with brain metastases were eligible, but only if they had minimal neurologic symptoms and met all other entry criteria for this study. The study was approved by our Institutional Review Board, and all patients gave written informed consent prior to participation.

All patients had complete staging for small cell lung carcinoma including a chest radiograph, chemistry profile, computerized tomography of the chest and abdomen, bone scan, and computerized tomography of the whole brain. If no distant disease was documented with these staging procedures, patients also underwent bilateral bone marrow aspiration and biopsy. All patients received initial chemotherapy with the following regimen: paclitaxel, 135 mg/m^2 intravenously on Day 1, administered by 1-hour infusion; carboplatin at a calculated AUC dose of 5 intravenously on Day 1; and etoposide, 25 mg/m^2 intravenously on Days 1–5 and 8–12. After the first 13 patients were treated, oral etoposide became routinely reimbursable; the remaining 25 patients received etoposide 50 mg alternating with 100 mg orally on Days 1–10. Prior to paclitaxel administration, all patients received premedication with dexamethasone, 20 mg orally 12 hours and 4 hours before treatment, and with dexamethasone (20 mg), diphenhydramine (50 mg), and cimetidine (300 mg) given intravenously 30 minutes prior to the paclitaxel administration. Carboplatin dose was calculated by the Calvert formula (dose = [glomerular filtration rate (GFR) + 25] $\times$ 5); the GFR was calculated by the method of Jelliffe using serum creatinine measurement.[11] Treatment was administered at 3-week intervals. Patients were reevaluated after the first two courses; responding patients and those with stable lesions received two additional courses for a maximum of four courses of treatment.

Patients with limited stage small cell lung carcinoma also received concomitant radiation therapy. The radiation therapy was administered in fractions of 180 centrigray (cGy) daily, for a total dose of 4500 cGy given over 5 weeks. The radiation therapy portal was based on the prechemotherapy tumor size, and included the primary lesion with a minimum of 2 cm and a maximum of 2.5 cm around the mass. The radiation field also included the mediastinum to encompass ipsilateral and contralateral hilar lymph nodes, as well as superior mediastinal, paratracheal, and subcarinal lymph nodes. To allow for better evaluation of the toxicity and efficacy of this novel chemotherapy regimen, patients received two courses of chemotherapy before radiation therapy was begun concurrently with the third course of chemotherapy. Radiation therapy to the brain was not routinely administered as part of this study.

During the entire four courses of therapy, blood counts were monitored on a weekly basis. The Day 8 blood counts were used to modify the etoposide dose if necessary. Dose reductions based on Day 8 blood counts were as follows: leukocytes $>$ 3000/μL and platelets $>$ 100,000/μL, etoposide continued at the same dose; leukocytes 2000–3000/μL or platelets 75,000–100,000/μL, etoposide continued at a 75%

dose; leukocytes < 2000/μL or platelets < 75,000/μL, etoposide discontinued for the remainder of the course. The Day 21 blood counts were used to modify doses in the subsequent course as follows: leukocytes > 3000/μL and platelets > 100,000/μL, all drugs given at full dose; leukocytes < 3000/μL or platelets < 100,000/μL, treatment delayed 1 week or until counts rose above leukocytes 3000/μL and platelets 100,000/μL, then patients retreated with the full dose of all agents. During radiation therapy, the radiation was continued uninterrupted as long as leukocytes remained > 2,000/μL and platelets > 75,000/μL. If the counts fell below these levels, radiation therapy was interrupted for 1 week or until counts rose to leukocytes > 3000/μL and platelets > 100,000/μL, and then continued to the same total dose. Patients who were hospitalized for treatment of neutropenia and fever had 75% doses of all drugs administered during all subsequent treatment courses. Cytokines were not used prophylactically in this study.

After completion of therapy, restaging was performed by repeating all studies that were abnormal at the beginning of treatment. All patients were assigned a response category based on standard definitions. Complete remission required the total disappearance of all clinically and radiologically detectable disease for at least 4 weeks. Partial remission required at least a 50% reduction in the size of all measurable lesions as measured by the product of the greatest length and the greatest width, with no new lesions appearing. All patients not meeting criteria for complete or partial response were considered nonresponders. Toxicity was graded according to the World Health Organization common toxicity criteria.

After completion of all treatment, patients were followed at monthly intervals until tumor progression occurred. Treatment received at the time of tumor progression was at the discretion of the treating physician.

RESULTS

Between June 1993 and December 1994, 38 patients were enrolled in this study. Patient characteristics are summarized in Table 1. These patients formed a typical group of patients with small cell lung cancer, with 61% having extensive disease, and two-thirds of patients having an ECOG performance status of 1. Eight of the patients with extensive stage disease had asymptomatic brain metastases; all these patients received whole brain radiation therapy during the first month of treatment.

All 38 patients were evaluable for toxicity, and 35 received at least 2 courses of therapy and were evaluated for response. Three patients, all with extensive stage disease, received fewer than two courses of therapy. Two of these patients experienced rapid disease progression within 2 weeks of the first chemotherapy dose, and the third died of sepsis during the first course of treatment. These 3 patients are considered nonresponders; all 38 patients were included in the analysis of survival. Thirty-two patients received the planned 4 courses of therapy, and a total of 139 courses were administered. Full doses of paclitaxel and carboplatin were administered in 128 courses (92%), and full dose etoposide was administered in 116 courses (83%). In only 1 patient, and for 2 courses, was a dose reduction to < 75% required.

TABLE 1
Patient Characteristics (N = 38)

Characteristics	No. of patients
Median age (range)	61 (35–75)
Sex (male/female)	24/14
Stages	
Limited	15 (39%)
Extensive	23 (61%)
ECOG performance status	
0	0
1	25 (66%)
2	13 (34%)

ECOG: Eastern Cooperative Oncology Group.

Toxicity

Myelosuppression was the most common toxicity, but was mild to moderate in most patients. Leukopenia and thrombocytopenia occurring during each course of therapy are summarized in Table 2. Nine patients (24%) experienced 11 episodes of Grade 3 or 4 leukopenia (8% of total treatment courses). Six patients (16%) developed Grade 3 or 4 thrombocytopenia (4% of treatment courses). Five of the 11 episodes of severe leukopenia and 3 of the 6 episodes of severe thrombocytopenia occurred during the fourth course of therapy in patients with limited stage disease receiving concurrent radiation therapy. Eight patients with extensive stage disease and four patients with limited stage disease developed anemia requiring transfusions, usually during the fourth course of treatment.

Fifteen patients required hospitalization for the treatment of fever associated with leukopenia; 8 patients had Grade 3 or 4 leukopenia and 7 had Grade 2 leukopenia. Eight of these episodes occurred in extensive stage patients (four during the first course of treatment) and seven occurred in limited stage patients (four during the last course of treatment with concurrent radiation therapy). One patient with extensive stage disease had a septic death during the first course of treatment.

TABLE 2
Hematologic Toxicity

Course	1	2	3	4
		Median nadir count (range)		
Leukocytes	2600 (200–8100)	3300 (800–9500)	2500 (750–8500)	2500 (700–10,800)
Platelets	205,000 (13,000–453,000)	190,000 (81,000–299,000)	193,000 (80,000–462,000)	140,000 (11,000–246,000)
		No. of episodes Grade 3/4 toxicity (% of courses)		
Leukocytes	4 (11%)	1 (3%)	1 (3%)	5 (17%)[a]
Platelets	3 (8%)	0	0	3 (10%)[a]

[a]All episodes occurred in limited stage patients receiving concurrent radiation therapy.

TABLE 3
Treatment Results (N = 38)

	Limited	Extensive	Entire group
Complete responses	6	4	10 (26%)
Parital responses	8	11	19 (50%)
No response/early death	1	8	9
Median progression free survival, mo	10	5	7 (range, 2–28+)
Median survival, mo	17	7	10 (range, 1–28+)

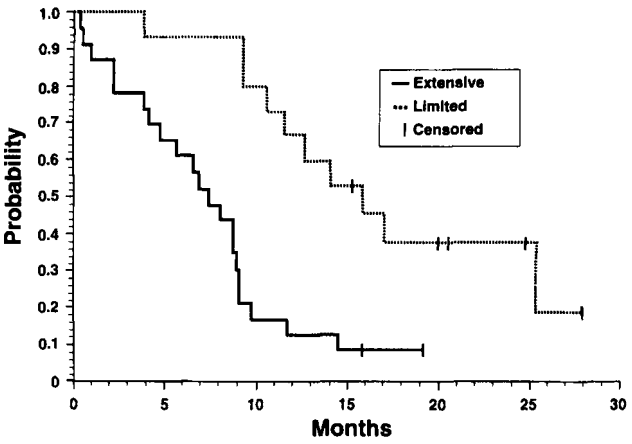

FIGURE 1. Actuarial survival curves for patients with extensive versus limited stage disease. Median survival was 7 months for extensive stage and 17 months for limited stage.

Nonhematologic toxicity was uncommon, with the exception of esophagitis in patients receiving concurrent chemotherapy and radiation therapy. Of the 15 patients who received radiation therapy, 5 developed Grade 3 esophagitis, and 1 developed Grade 4 esophagitis. Esophagitis was reversible in all patients. Other Grade 3 or 4 toxicities were uncommon, and included mucositis (one patient), diarrhea (one patient), emesis (one patient), and uncontrolled hyperglycemia (one patient).

Efficacy

Table 3 summarizes the results of treatment. As expected, this regimen was highly active, with 29 of 38 patients (76%) achieving a partial or complete response. Fourteen of 15 patients (93%) with limited stage disease had responses, versus 15 of 23 patients (65%) with extensive stage disease. Partial response was evident in 10 of 15 patients with limited stage disease after the first 2 courses of therapy (prior to radiation therapy). The overall complete response rate was 26% (40% in patients with limited stage disease and 17% in those with extensive stage disease).

The median follow-up for patients in this study is 20 months (range, 12–30 months). Median progression free survival for patients with extensive disease was 5 months, and was 10 months for those with limited stage disease. At present, 3 of 15 patients with limited stage disease remain progression free after follow-up of 21 to 28 months. Median overall survival was 7 months for patients with extensive disease, and 17 months for those with limited disease. Actuarial survival curves for limited and extensive stage patients are shown in Figure 1.

Seven patients developed brain metastases as their first site of progression. None of these patients was among the eight patients with asymptomatic brain metastases at diagnosis who received therapeutic whole brain irradiation. Six of these seven patients had limited stage disease, and four had achieved clinical complete remission. The brain was the site of first relapse in 6 of the 12 relapsing patients with limited stage disease.

DISCUSSION

In this Phase II study, we have demonstrated the feasibility of administering a three-drug combination regi-

men including paclitaxel, carboplatin, and etoposide to patients with small cell lung carcinoma. This outpatient regimen was well tolerated, producing mild to moderate myelosuppression in most patients and infrequent nonhematologic toxicity. In patients with limited stage disease, radiation therapy was administered concurrently with chemotherapy. The moderate dose of radiation (4500 cGy) used concurrently with chemotherapy in patients with limited stage disease resulted in some additional toxicity, but was well tolerated by most patients. Esophagitis was the major toxicity during combined modality therapy; one patient developed reversible Grade 4 esophagitis and five patients had Grade 3 esophagitis.

The paclitaxel dose chosen in this study (135 mg/m^2) is relatively low and was based on published toxicity data using paclitaxel by 24-hour infusion. Since that time, the relative ease of administering paclitaxel by shorter infusion has been appreciated, with infusion times of either 1 or 3 hours producing mild to modest myelosuppression, even when doses of 200 mg/m^2 are used without cytokines.[8-10] Data concerning the probable dose-response relationship of paclitaxel in the treatment of patients with nonsmall cell lung carcinoma were also not available. Our experience with 1-hour infusions of paclitaxel in patients with nonsmall cell lung carcinoma have shown higher response rates with a dose of 200 mg/m^2 than with a dose of 135 mg/m^2 (31% vs. 12% respectively).[12] Because clinical trials using paclitaxel in the treatment of patients with small cell lung carcinoma have been limited, the importance of paclitaxel dose is undefined. However, because higher doses are probably more active in both nonsmall cell lung carcinoma and breast carcinoma, it seems probable that findings will be similar in patients with small cell lung carcinoma.

Accumulating data with the combination of paclitaxel and carboplatin indicate that surprisingly large doses of each drug can be safely administered.[13,14] Langer et al. have used paclitaxel, 135 mg/m^2 (24-hour infusion), and carboplatin at AUC 7.5 with easily manageable myelosuppression.[13] When cytokines are used, the paclitaxel can be increased to 215 mg/m^2. Shorter paclitaxel infusions are probably tolerated more easily when combined with carboplatin. Vafai et al. found that paclitaxel, 225 mg/m^2 (3-hour infusion), plus carboplatin at AUC 6 was well tolerated in patients with advanced nonsmall cell lung carcinoma.[14] In both studies, the incidence of thrombocytopenia seemed less than that expected with similar doses of carboplatin alone. The modest leukopenia and rare thrombocytopenia demonstrated in our study are consistent with these observations. Based on these data, it is likely that doses of both paclitaxel and carboplatin could be safely increased in our three-drug regimen.

In this regimen, the dose of etoposide was also relatively low. Chronic schedules of etoposide have been previously shown to be highly effective, with at least the efficacy of standard 3–5 day intravenous schedules.[15-17] Most reports have also shown reduced myelosuppression with chronic schedules of etoposide when similar total doses are administered. Likewise, the four courses of therapy administered in this study represent a relatively short duration of treatment. However, several randomized trials as well as several retrospective comparisons comparing brief therapy with longer durations of therapy have shown no differences in survival.[18-20]

The controversy continues regarding the role of prophylactic whole brain irradiation in the treatment of patients with small cell lung carcinoma.[21] Although this treatment has been used routinely in patients with limited stage disease achieving complete remission, definitive documentation of improved progression free or overall survival has been difficult to obtain. A recent randomized study showed a significant decrease in the incidence of isolated brain recurrences after prophylactic whole brain irradiation (19% vs. 45% in the control group), but the overall survival was unchanged.[22] In the current study, we did not administer prophylactic whole brain irradiation, and observed seven isolated brain relapses. Six of these were in patients with limited stage disease, and therefore may have adversely affected the median survival of this patient group. With the relatively small number of patients in this study, it is probable that this observation is due to change alone; however, the role of prophylactic cranial irradiation may need to be reevaluated if new regimens improve the control of systemic disease.

In summary, this Phase II study demonstrates the feasibility of adding paclitaxel to a combination regimen containing carboplatin and etoposide. This regimen can be easily administered in the outpatient setting, with mild to moderate toxicity in most patients. The role of paclitaxel in the treatment of small cell lung carcinoma remains undefined, because treatment efficacy with the regimen tested in this trial does not appear substantially different than that reported with standard combinations of cisplatin or carboplatin plus etoposide.

Based on these results, we are continuing to evaluate this three-drug regimen, but with increased doses of both paclitaxel and carboplatin. In addition, we are now giving prophylactic whole brain radiotherapy to all patients who achieve complete remission. Completion of our ongoing Phase II study will help define optimal doses for this three-drug regimen, but it seems likely that fully active doses of all three drugs can be used in combination. Definitive evaluation of the role of paclitaxel in the treatment of small cell lung carci-

noma will require a randomized trial comparing this three-drug regimen with a standard platinum/etoposide regimen.

REFERENCES

1. Ihde DC, Pass HI, Glatstein EJ. Small cell lung cancer. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. *Cancer: principles and practice of oncology.* 4th edition. Philadelphia: JB Lippincott, 1993:723–59.
2. Ihde DC, Mulshine JL, Kramer BS, Steinberg SM, Linnoila RI, Gazdar AF, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12:2022–34.
3. Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *J Clin Oncol* 1993;11:336–44.
4. Gatzemeier U, Hossfeld DK, Neuhauss R, Reck M, Achterrath W, Lenaz L. Phase II and III studies with carboplatin in small cell lung cancer. *Semin Oncol* 1992;19(Suppl 2):28–36.
5. Kosmidis PA, Samantas E, Fountzilas G, Pavlidis N, Apostolopoulou F, Skarlos D. Cisplatin/etoposide versus carboplatin/etoposide chemotherapy and irradiation in small cell lung cancer: a randomized phase III study. *Semin Oncol* 1994;21(Suppl 6):23–30.
6. Ettinger DS, Finkelstein DM, Sarma RP, Johnson DH. Phase II study of paclitaxel in patients with extensive-disease small-cell lung cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1995;13:1430–5.
7. Kirschling RJ, Jung SH, Jett JR. A phase II trial of taxol and GCSF in previously untreated patients with extensive stage small cell lung cancer [abstract]. *Proc Am Soc Clin Oncol* 1994;13:326.
8. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, Van der Burg MEL, et al. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusions. *J Clin Oncol* 1994;12:2654–66.
9. Hainsworth JD, Greco FA. Paclitaxel administered by one-hour infusion: preliminary results of a phase I/II trial comparing two schedules. *Cancer* 1994;74:1377–82.
10. Hainsworth JD, Raefsky EL, Thomas M, Greco FA. Paclitaxel administered by 1-hour infusion: phase I/II study comparing two schedules of administration. *Cancer J Sci Am* 1995;1:281–7.
11. Jelliffe RW. Creatinine clearance:bedside estimate [letter]. *Ann Intern Med* 1973;79(4):604–5.
12. Hainsworth JD, Thompson DS, Greco FA. Paclitaxel by one-hour infusion:an active drug in metastatic non-small cell lung cancer. *J Clin Oncol* 1995;13:1609–14.
13. Langer CJ, Leighton JC, Comis RL, O'Dwyer PJ, McAleer CA, Bonjo CA, et al. Paclitaxel and carboplatin in combination in the treatment of advanced non-small cell lung cancer: a phase II toxicity, response, and survival analysis. *J Clin Oncol* 1995;13:1860–70.
14. Vafai D, Israel V, Zaretsky S, Natale RB. Phase I/II trial of combination carboplatin and taxol in non-small cell lung cancer (NSCLC) [abstract]. *Proc Am Soc Clin Oncol* 1995;14:352.
15. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD. Prolonged administration of oral etoposide in patients with relapsed or refractory small cell lung cancer: a phase II trial. *J Clin Oncol* 1990;8:1613–7.
16. Clark PI, Cottier B. The activity of 10-, 14-, and 21-day schedules of single-agent etoposide in previously untreated patients with extensive small-cell lung cancer. *Semin Oncol* 1992;19(Suppl 14):36–9.
17. Carney DN, Grogan L, Smit EF, Harford P, Berendsen HH, Postmus PE. Single-agent oral etoposide for elderly small-cell lung cancer patients. *Semin Oncol* 1991;17(Suppl 2):49–53.
18. Spiro SG, Souhami RL, Geddes DM, Ash CM, Quinn H, Harper PG, et al. Duration of chemotherapy in small cell lung cancer. A Cancer Research Campaign trial. *Br J Cancer* 1989;59:578–83.
19. Splinter TAW, EORTC Lung Cancer Cooperative Group. Induction versus induction plus maintenance chemotherapy in small cell lung cancer: definitive evaluation [abstract]. *Proc Am Soc Clin Oncol* 1988;7:202.
20. Bleehan NM, Fayers PM, Girling DJ. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small cell lung cancer. *Br J Cancer* 1989;59:584–90.
21. Bunn PA Jr, Kelly K. Prophylactic cranial irradiation for patients with small-cell lung cancer. *J Natl Cancer Inst* 1985;87:161–2.
22. Arriagada R, Le Chevalier T, Borie F, Riviere A, Chomy P, Monnet I, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995;87:183–90.