

A Phase I Study of Paclitaxel, Etoposide, and Cisplatin in Extensive Stage Small Cell Lung Cancer¹

Karen Kelly,² Zhaoxing Pan, Marie E. Wood, James Murphy, and Paul A. Bunn, Jr.

Division of Medical Oncology and the Lung Cancer Program [K. K., M. E. W., P. A. B.] and Department of Preventive Medicine and Biostatistics [Z. P., J. M.], University of Colorado Cancer Center, Denver, Colorado 80262

ABSTRACT

This Phase I study was designed to determine the maximally tolerated dose (MTD) of paclitaxel with standard doses of cisplatin and etoposide for patients with untreated extensive stage small cell lung cancer (SCLC). Secondary objectives were to determine the toxicities, response rate, response duration, and overall survival in this cohort. Twenty-eight SCLC patients were enrolled into four dose levels. All patients received a fixed dose of cisplatin at 80 mg/m², i.v., day 1. The first group received etoposide 50 mg/m², i.v. day 1 and 100 mg/m² p.o., days 2–3, whereas all subsequent groups received etoposide 80 mg/m², i.v., day 1 and 160 mg/m² p.o., days 2–3. The paclitaxel starting dose was 135 mg/m², i.v., over a 3-h period and was escalated to 175 and 200 mg/m². Cycles were repeated every 21 days for a maximum of six cycles. Granulocyte-colony stimulating factor was not given prophylactically but was allowed in subsequent cycles according to the American Society of Clinical Oncologists guidelines. All 28 SCLC patients were evaluable for toxicity, and 23 patients were evaluable for response. Myelosuppression was the major toxicity, with grade 4 neutropenia occurring in 23 of 28 patients (82%), but febrile neutropenia was uncommon and developed in 4 patients (14%). Grade 4 thrombocytopenia and anemia were rare, occurring as isolated events in one patient each. Dose-limiting peripheral neuropathy was observed at a paclitaxel dose of 200 mg/m². Grade 4 nausea/vomiting and diarrhea were also noted at this dose level. Five patients had complete responses (22%), and 14 patients had partial responses (61%). The overall response rate was 83% with a median time to progression of 7.5 months, a median survival of 10 months, and a 1-year survival rate of 39%. This three-drug combination of paclitaxel with cisplatin and etoposide is

active with acceptable toxicity. Neurotoxicity was dose limiting at 200 mg/m² of paclitaxel. Neutropenia was frequent but not associated with significant morbidity. The recommended doses for future clinical trials are 175 mg/m² paclitaxel, i.v., over a 3-h period on day 1 with 80 mg/m² cisplatin, i.v., on day 1 and 80 mg/m² etoposide, i.v., on day 1 and 160 mg/m² p.o. on days 2 and 3 with growth factor support. The Southwestern Oncology Group has instituted a Phase II study with this dose schedule.

INTRODUCTION

SCLC³ is one of the most aggressive and lethal cancers in humans (1). In 1999, ~40,000 new cases of SCLC will be diagnosed in the United States (2). Combination chemotherapy is the cornerstone of treatment for these patients, which results in high initial response rates of 65–85% with 50% complete responses in limited stage and 10% complete response rates in extensive stage. Despite high response rates, relapse and progression develop in the majority of patients, and median survival is <1 year for patients with extensive stage disease, which represents about two-thirds of the cases (1). Failure to achieve durable remission rates in this chemosensitive tumor is believed to be attributable to the development of multiple drug resistance (1). Attempts to overcome this problem with the use of alternating non-cross-resistant drugs, dose-intense regimens, or drugs to block resistance have not been successful; therefore, continued focus on the development of new effective agents remains crucial (3–5).

Paclitaxel, a novel plant product that inhibits cell replication by stabilization of microtubules, has shown antitumor activity in several solid tumors including SCLCs (6, 7). Two single-agent trials with paclitaxel in SCLCs have been completed. The Eastern Oncology Cooperative Group administered paclitaxel at 250 mg/m² over a 24-h period every 3 weeks to 32 patients with untreated extensive stage disease (8). Because of the limited supply of paclitaxel, patients received a maximum of four cycles of paclitaxel. Patients with progressive disease, stable disease, or a partial response received subsequent chemotherapy with PE. The confirmed response rate to paclitaxel was 34% (11 of 32 patients), and the overall response rate was 53% (17 of 32 patients). Confirmed responses required patients to have a 50% decrease in tumor measurements on two successive X-rays at least 4 weeks apart while on paclitaxel therapy. Patients who responded to paclitaxel on one X-ray but were switched to PE with a persisting response after 4 weeks were scored as “unconfirmed responses.” The estimated median survival duration was 43 weeks. A similar trial, conducted by the

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² To whom requests for reprints should be addressed, at Division of Medical Oncology B171, University of Colorado Cancer Center, 4200 East Ninth Avenue, Denver, CO 80262.

³ The abbreviations used are: SCLC, small cell lung cancer; PE, cisplatin and etoposide; PET, PE and paclitaxel; G-CSF, granulocyte-colony stimulating factor.

Table 1 Dose levels of PET

Level	No. of patients	No. of eligible patients	Paclitaxel (mg/m ²)	Cisplatin (mg/m ²)	Etoposide (mg/m ²)
1	5	3	135	80	50 (day 1) 100 p.o. (days 2 and 3)
2	5	4	135	80	80 (day 1) 160 p.o. (days 2 and 3)
3	10	9	175	80	80 (day 1) 160 p.o. (days 2 and 3)
4	8	7	200	80	80 (day 1) 160 p.o. (days 2 and 3)

North Central Treatment Group, gave 250 mg/m² over a 24-h period every 3 weeks with growth factor support (9). Partial responses were observed in 68% (25 of 37 patients). The median survival in this study was 29 weeks. Leukopenia was the major toxicity observed in both trials.

The single agent activity of paclitaxel in SCLC warrants combination with other active agents, and several regimens are presently being explored. Our approach was to add escalating doses of paclitaxel to PE, which is the most commonly used regimen to treat SCLC and produces grade 4 hematological toxicity in <5% of extensive stage SCLC cases at standard doses (3, 10, 11). With recent evidence suggesting that shorter paclitaxel infusion times were more convenient, produced less hematological toxicity, and were equally efficacious as the 24-h schedule, we designed the treatment to be given on an outpatient basis with a 3-h paclitaxel infusion plus PE, i.v., on day 1 and oral etoposide on days 2 and 3 (12). The primary objective of this trial was to determine the maximally tolerated dose of paclitaxel in combination with standard doses of PE (PET therapy). Secondary objectives were to determine the response rate, response duration, overall survival, and the toxicity profile at each dose level.

PATIENTS AND METHODS

Eligibility. Adult patients (>18 years) with histologically or cytologically confirmed extensive stage SCLC were eligible to participate in this trial if they had measurable or evaluable disease. Patients with brain metastases were excluded. All patients were required to have normal organ function according to protocol guidelines, a performance status of <2, and an expected survival of >3 months. Patients with any evidence of a cardiac conduction abnormality were ineligible, as were patients receiving β blockers, calcium channel blockers, digoxin, or antiarrhythmic medications. Patients with clinically evident hearing loss or symptomatic peripheral neuropathy were ineligible. Patients with a prior history of malignancy other than nonmelanoma skin cancer or cervical carcinoma *in situ* were excluded if their disease-free interval was <5 years. Patients could not have received prior chemotherapy, but previous surgery or radiotherapy was allowed. All patients were required to give written informed consent.

Treatment Plan. The patients received chemotherapy with PET (Bristol Myers Squibb, Princeton, NJ), according to the dose escalation schedule shown in Table 1. A minimum of five patients were entered per dose level. All patients were premedicated with oral or i.v. dexamethasone (20–40 mg),

Table 2 Patient characteristics

	All patients (n = 28)	Eligible patients (n = 23)
Median age	60	61
Age range	43–77	43–77
Male:Female	16:12	13:10
PS ^a 0–1:2	23:5	19:4
Race W/B/H/NA	21:1:5:1	17:1:4:1

^a PS, performance status; W, white; B, black; H, hispanic; NA, Native American.

cimetidine (300 mg, i.v.), and benadryl (50 mg, i.v.). Paclitaxel was given i.v. over a 3-h period, followed by PE with mannitol over a 1-h period. Additional posthydration was infused over a 2-h period. Cycles were repeated every 21 days for a total of six cycles, unless the patient had progressive disease or intolerable toxicity. The antiemetic regimen was dictated by the treating physician. G-CSF was not given prophylactically but was allowed for patients who developed grade 4 leukopenia, febrile neutropenia, or failure to recover their neutrophil count by day 28 of a cycle. If a patient on G-CSF developed grade 4 leukopenia or neutropenia, prolonged neutropenia, or febrile neutropenia, a dose reduction of all three drugs was required, as stipulated in the protocol. For other grade 4 hematological or nonhematological toxicities, dose modifications were executed per the protocol guidelines. Treatment toxicity was graded according to the Southwest Oncology Group criteria (13). Dose escalation was not allowed.

The maximally tolerated dose was defined as one dose level below the level in which two of five patients developed grade 4 leukopenia, neutropenia, febrile neutropenia, or a prolonged neutrophil recovery >28 days while receiving G-CSF, or grade 4 anemia or thrombocytopenia, or grade 3 nonhematological toxicity. If 0–1 patient met these criteria at a given dose level, accrual continued to the next higher level.

Patients with measurable or evaluable disease were assessable for response to therapy. Clinical response was determined according to Southwest Oncology Group criteria (13).

Statistical Analysis. Time to progression curves and the Kaplan-Meier survival curves were produced in SAS 6.10 using Proc Lifetest. Time to progression was calculated from the time of diagnosis to progressive disease, relapse, death, or last follow-up evaluation. Overall survival was calculated from the time of death or last follow-up evaluation as of June 1, 1998.

Table 3 Hematological toxicity (n = 28)

Level	No. of patients							
	Gr 4 PMN	Feb Neu -G-CSF	Gr 4 PMN	Feb Neu +G-CSF	Platelets Gr 3/Gr 4		Hematocrit Gr 3/Gr 4	
1	2/5	0/0	0/0	0/0	0/5	0/5	0/5	0/5
2	5/5	0/5	2/3	0/3	1/5	0/5	1/5	0/5
3	9/10	3/10	2/6	0/6	0/10	0/10	2/10	1/10
4	7/8	1/8	1/4	1/4	0/8	1/8	1/8	0/8

Gr 4 PMN, grade 4 polymorphic neutrophils; Feb Neu, febrile neutropenia, -G-CSF, without G-CSF; +G-CSF, with G-CSF.

RESULTS

Twenty-eight patients were enrolled into this trial between July 1993 and January 1997 from 12 participating institutions (see "Appendix"). Five patients were ineligible, three patients had limited disease, one patient was on a β blocker, and one patient had incomplete radiographs. Patient characteristics for all patients and the 23 eligible patients are listed in Table 2. The majority of patients were white men, 60 years of age, with a performance status of 0-1.

All 28 patients received one or more cycles of chemotherapy. The mean number of chemotherapy cycles for the eligible patients was 5.3. Patients on level 1 received 6 cycles, patients on level 2 received 5.5 cycles, patients on level 3 received 5.2 cycles, and patients on level 4 received 4.7 cycles. Two patients on level 3 and four patients on level 4 discontinued treatment because of toxicity. One patient on level 4 died from toxicity and tumor progression during cycle 2. One patient on level 3 was lost to follow up. The median follow-up time for all patients was 14.3 months and 12.3 months for the eligible patients.

Hematological Toxicity. All patients were evaluated for toxicity. The most frequent grade 4 toxicity was neutropenia, which occurred in 23 of 28 patients (82%) as shown in Table 3. The neutropenia was observed in cycles 4 and 5 on dose level 1 but gradually appeared with earlier cycles at the higher dose levels. On dose level 4, seven of eight patients developed neutropenia in cycle 1. Febrile neutropenia occurred in 4 of 23 patients (14%). The addition of G-CSF greatly reduced the incidence of grade 4 neutropenia and febrile neutropenia. All patients recovered uneventfully. Other significant hematological toxicities were uncommon.

Nonhematological Toxicity. Nonhematological toxicities occurred rarely in patients on levels 1 and 2 but increased with levels 3 and 4, as shown in Table 4. Dose-limiting peripheral neuropathy was seen at level 4. Three patients developed grade 3 peripheral neuropathy, one during cycle 3 and two with cycle 5. All three patients were removed from study. No patient had a predisposing condition for neuropathy. Grade 4 diarrhea developed in two patients on level 4 during cycle 1. The severe diarrhea was associated with fever and neutropenia in both cases. Grade 4 nausea and vomiting occurred in four patients on level 4, and grade 3 nausea and vomiting developed in two patients on level 3. Other nonhematological toxicities were infrequent.

Response and Survival. Twenty-two of the 23 eligible patients received one or more cycles of chemotherapy and were evaluable for response as shown in Table 5. The one inevaluable

Table 4 Nonhematological toxicity (n = 28)

Toxicity	n = 5		n = 5		n = 10		n = 8	
	Level 1	Level 2	Level 3	Level 4	Level 3	Level 4	Level 3	Level 4
Cardiac	0	0	0	0	1	1	0	0
Diarrhea	0	0	0	0	1	0	0	2
Dizziness	0	0	0	0	0	0	1	0
Fatigue	0	0	0	0	0	0	1	0
Hypocalcemia	0	0	0	0	1	0	0	0
Hypomagnesemia	0	0	0	0	1	0	0	0
Hyponatremia	0	0	0	0	0	1	0	0
Hypotension	0	0	0	0	0	0	1	0
Infection	0	0	0	0	0	0	1	0
Nausea/Vomiting	0	0	0	0	2	0	0	4
Neuropathy	1	0	0	0	1	0	3	0
Ototoxicity	0	0	1	0	0	0	0	0
Renal	0	0	1	0	0	0	0	0
Retinopathy	0	0	0	0	0	0	1	0
Stomatitis	0	0	0	0	0	0	1	0

^a Gr, grade.

patient came off treatment during cycle 2 because of toxicity and was not fully reevaluated. Five patients had a complete response (22%), and 14 patients (61%) had partial responses, for an overall response rate of 83%. In the five ineligible patients, one patient had a complete response, two patients had a partial response, one patient had stable disease, and one patient was inevaluable. Response did not correlate with paclitaxel dose.

The intent-to-treat analysis revealed that the median time to progression was 7.5 months, with a median survival of 11 months. The 1- and 2-year survival rates were 46 and 14%, respectively. For the eligible patients, the time to progression was 7.5 months, with a median survival of 10 months. The 1- and 2-year survival rates were 39 and 6%. Fig. 1 shows the overall survival for all patients and for the eligible patients. All patients have since died.

Sites of Relapse. The sites of first relapse could be determined in 19 patients, whereas four patients were not assessable: two responding patients were removed from study because of toxicity and switched to an alternative regimen, one patient refused a work-up at the time of progression, and one patient died during cycle 2. Four patients relapsed in the brain. Three additional patients had brain metastases as their first site of relapse but did not undergo evaluation to determine other sites of involvement. Six patients relapsed locally, and six patients relapsed at distant sites.

Table 5 Objective response rate (n = 23)^a

Level	#Pts ^b	CR	PR	SD	PD	NE
1	3	2	1	0	0	0
2	4	1	2	0	1	0
3	9	1	7	0	0	1
4	7	1	4	2	0	0
Total	23	5 (22%) ^c	14 (61%)	2 (9%)	1 (4%)	1 (4%)

^a Responses in the five ineligible patients: 1 complete response (CR), 2 partial responses (PRs), 1 stable disease (SD), and 1 not evaluable (NE).

^b #Pts, number of patients; PD, progressive disease.

^c Numbers in parentheses, percentages.

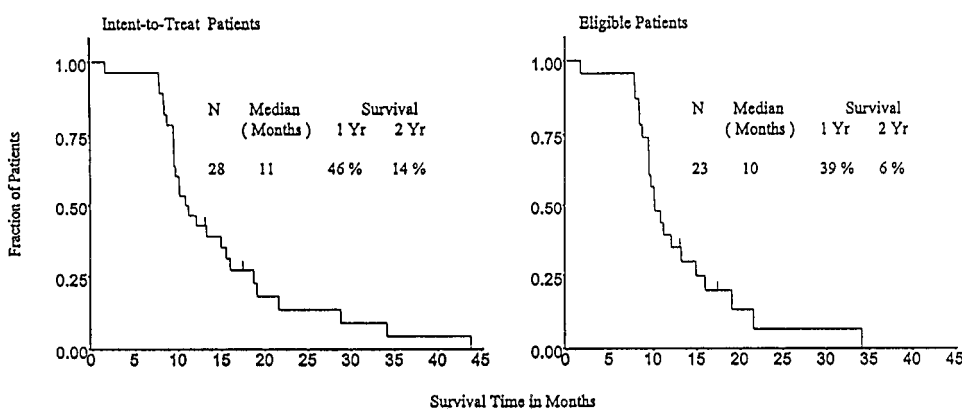


Fig. 1 Kaplan-Meier curve of overall survival for all patients and for the eligible patients.

DISCUSSION

Despite attempts to improve survival in SCLC by modifying the doses and schedule of drugs available previously, no major survival advantage has been achieved in the last 20 years. Recently, six new chemotherapy agents were reported to have activity SCLC, including two taxanes (paclitaxel and docetaxel), two topoisomerase I inhibitors (irinotecan and topotecan), gemcitabine, and vinorelbine (5). How to incorporate these new agents into more effective regimens is a dilemma. One strategy is to add a new drug to an established active regimen.

Paclitaxel, a promising new active agent in SCLC, is well tolerated, making it an ideal candidate to combine with PE (8, 9). This Phase I trial revealed the maximally tolerated dose of paclitaxel combined with standard doses of PE was 175 mg/m². At paclitaxel doses of 200 mg/m², dose-limiting peripheral neuropathy occurred. The PET regimen was well tolerated and active with a complete response rate of 23%, an overall response rate of 83%, and a 1-year survival rate of 39%.

Not surprisingly, neutropenia was the most common toxicity, but it was not dose limiting because it was uncommonly associated with fever of long duration or recurrent if G-CSF was used after an episode of grade 4 neutropenia. Although 82% of patients developed grade 4 neutropenia, only four patients (14%) developed an episode of febrile neutropenia. These patients subsequently received growth factor support, and febrile neutropenia reoccurred in only one patient. The neutropenia was frequently observed in cycle 1 or 2 but was abolished by the administration of G-CSF, and no patient died from complications of neutropenia. Paclitaxel did not significantly increase the occurrence of grade 4

thrombocytopenia or anemia, with only one episode of each (5%) reported.

A similar pilot trial using the PET regimen has been completed by Glisson *et al.* (14) at the M. D. Anderson Cancer Center. Grade 3 or 4 neutropenia occurred in five of six patients during cycle 1, with one patient developing febrile neutropenia when paclitaxel was administered at 130 mg/m² over a 3-h period on day 1, with cisplatin 75 mg/m² on day 2, and etoposide 80 mg/m² on days 2–4. A total of 26 patients were treated on this regimen, with the majority of patients receiving paclitaxel doses of 105–130 mg/m². Grade 4 neutropenia was reported in 48% of the 142 courses administered. Six percent of these courses were associated with febrile neutropenia. G-CSF was not administered. When carboplatin was substituted for cisplatin in this regimen without cytokine support, Hainsworth *et al.* (15) reported an incidence of grade 3/4 leukopenia in 8% of patients treated with paclitaxel at 135 mg/m² with carboplatin at an AUC of 5 with etoposide 50/100 mg p.o., alternating days 1–10, which increased to 38% when the dose of paclitaxel was increased to 200 mg/m² with an increased carboplatin dose to an AUC of 6. Significant thrombocytopenia and anemia were not seen in any study.

Dose-limiting peripheral neuropathy was observed with this triple drug combination. Neurotoxicity has been reported by other investigators evaluating paclitaxel with cisplatin or carboplatin. Nair *et al.* (16) conducted a pilot trial of paclitaxel plus cisplatin in extensive stage SCLC and observed neurotoxicity in 1 of 45 patients treated on the high-dose arm (175 mg/m² of paclitaxel over a 3-h period with 75 mg/m² of cisplatin, but no report of peripheral neuropathy was mentioned by Glisson *et al.*

(14) in their preliminary analysis with low-dose paclitaxel, cisplatin and etoposide. Hainsworth *et al.* (15) reported two cases of significant peripheral neuropathy treated with 200 mg/m² of paclitaxel with carboplatin and etoposide. The low frequency of neuropathy in this study may be attributable to the majority of patients receiving only four cycles of therapy. In previous studies of paclitaxel plus cisplatin in non-SCLC, dose-limiting peripheral neuropathy was reported by Chaudry *et al.* (17) at 300 mg/m² of paclitaxel infused over a 24-h period with 75 mg/m² of cisplatin in non-SCLC. At <250/75 mg/m² paclitaxel/cisplatin dose levels, no grade 3 or greater neuropathy occurred. Consistent with these results are those from Sculier and Klastersky (18), who reported only grade 1–2 peripheral neuropathy in five of seven patients receiving 200 mg/m² paclitaxel over a 3-h period with 100 mg/m² cisplatin in their dose escalation trial. The degree of neurotoxicity seen in this study appears to be higher than predicted and suggests that the dose of paclitaxel as well as the number of cycles of therapy are important factors contributing to neurotoxicity. Another possibility is that etoposide may be enhancing the neurotoxicity. Nonhematological toxicities were infrequent in all studies.

The overall response rate in this Phase I trial was 83% with a median survival of 10 months, which compares favorably to previous regimens. This small trial did not show a dose-response effect with paclitaxel, but other investigators have observed a difference in favor of higher doses. Hainsworth *et al.* (15) reported a response rate of 65% versus 84% with 135 mg/m² versus 200 mg/m², which translated into a survival advantage for the high dose arm with a median survival of 7 versus 10 months with the low versus high dose of paclitaxel. Nair *et al.* (16) reported a dose response in their Phase II trial of paclitaxel plus cisplatin in extensive stage SCLC. Fifteen of 21 patients (71%) receiving 135 mg/m² of paclitaxel responded as compared with 39 of 44 patients (89%) receiving 175 mg/m² of paclitaxel. Median survival was prolonged for the patients in the high-dose paclitaxel arm, with a median survival of 7.7 and 8.6 months, respectively. In contrast, Glisson *et al.* (14) reported an impressive median survival time of 15.5 months with their low-dose PET regimen.

Two issues regarding this study deserve comment: (a) the accrual time on this study was lengthy and most likely attributable to competing protocols within our network, because all sites are members of cooperative groups; and (b) the ineligibility rate was 18% (five patients). Three of these patients were originally thought to have extensive stage disease. All three cases were difficult; it was only after reevaluation upon receiving PET treatment, for which they all were responding, that the treating physicians felt it was in the best interest of their patients to receive radiotherapy. One patient mistakenly did not reveal that she was on a β blocker. She received all six cycles of therapy and had a complete response. The last patient had only a noncontrast brain scan, although he was capable of having a contrast brain scan. This patient received one cycle of treatment but refused further therapy and reevaluation. All five patients received treatment and were included in the toxicity analysis. If these patients were included in the response analysis, the response rate was similar at 79%. Survival was also similar in the intent-to-treat group as compared with the eligible group.

In conclusion, PET is active with acceptable toxicity and

deserves further investigation at the doses determined by this study. On the basis of these data, the Southwest Oncology Group instituted a Phase II trial of 175 mg/m² paclitaxel with 80 mg/m² cisplatin and 80/160 mg/m² etoposide with growth factor support in patients with extensive stage SCLC.

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APPENDIX

Participating Institutions

Investigator	Institution
David Faragher	Aurora Presbyterian Hospital, Aurora, CO
David H. Garfield	Rocky Mountain Cancer Center, Denver, CO
Douglas J. Kemme	North Colorado Medical Center, Greeley, CO
Stuart A. Merl	St. Elizabeth's Hospital, Dayton, OH
Eduard Pajon	Aurora Presbyterian Hospital, Aurora, CO
Robert N. Raju	St. Elizabeth's Hospital, Dayton, OH
Mark A. Sitarik	Boulder Valley Oncology, Boulder, CO
Mark W. Stutz	Deaconess Health System, St. Louis, MO
Daniel T. Tell	Memorial Hospital, Colorado Springs, CO

REFERENCES

- Cook, R. M., Miller, Y. E., and Bunn, P. A., Jr. Small cell lung cancer: etiology, biology, clinical features, staging, and treatment. *Curr. Prob. Cancer*, 17: 69–144, 1993.
- Landis, S. H., Murray, T., Bolden, S., and Wing, P. A. Cancer statistics, 1999. *CA Cancer J. Clin.*, 49: 8–31, 1999.
- Ihde, D. C., and Wood, A. (eds.). Chemotherapy of lung cancer: a review article. *N. Engl. J. Med.*, 327: 825–835, 1992.
- DeVore, R. F., III, and Johnson, D. H. Chemotherapy of small cell lung cancer. *In*: H. I. Pass, J. B. Mitchell, D. H. Johnson, and A. T. Turrisi (eds.), *Lung Cancer: Principles and Practice*, pp. 825–835. Philadelphia, PA: Lippincott-Raven, 1996.
- Sandler, A. B. Current management of small cell lung cancer. *Semin. Oncol.*, 24: 463–476, 1997.
- Rowinsky, E. K., Cazenave, L. A., and Donehower, R. C. A novel investigational antimicrotubule agent. *J. Natl. Cancer Inst.*, 82: 1247–1259, 1990.
- Rowinsky, E. K., and Donehower, R. C. The clinical pharmacology and use of antimicrotubule agents in cancer chemotherapeutics. *Pharmacol. Ther.*, 52: 35–84, 1992.
- Ettinger, D. S., Finkelstein, D. M., Sarma, R., and Johnson, D. H. Phase II study of paclitaxel in patients with extensive-stage small cell lung cancer: an Eastern Cooperative Oncology Group study (SCLC). *J. Clin. Oncol.*, 13: 1430–1435, 1995.
- Kirschling, R. J., Jung, S. H., and Jett, J. R. A Phase II trial of taxol and G-CSF in previously untreated patients with extensive small cell lung cancer (SCLC). *Am. Soc. Clin. Oncol.*, 13: 326, 1994.
- Ihde, D. C., Mulshine, J. L., Kramer, B. S., Steinberg, S. M., Linnoila, R. I., Gazdar, A. F., Edison, M., Phelps, R. M., Lesar, M., Phares, J. C., Grayson, J., Minna, J. D., and Johnson, B. E. 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.*, 12: 2022–2034, 1994.

11. Roth, B. J., Johnson, D. H., Einhorn, L. H., Schacter, L. P., Cherng, N. C., Cohen, H. J., Crawford, J., Randolph, J. A., Goodlow, J. L., and Broun, G. O. Randomized study of cyclophosphamide, doxorubicin and vincristine *versus* etoposide and cisplatin *versus* alternation of these two regimens in extensive small cell lung cancer: a Phase III trial of the Southeastern Cancer Study Group. *J. Clin. Oncol.*, *10*: 282–291, 1992.
12. Eisenhauer, E. A., ten Bokkel Huinink, W. W., Swenerton, K. D., Gianni, L., Myles, J., van der Burg, M. E. L., Kerr, I., Vermorken, J. B., Buser, K., Colombo, N., Bacon, M., Santabarbara, P., Onetto, N., Winograd, B., and Canetta, R. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose *versus* low-dose and long *versus* short infusion. *J. Clin. Oncol.*, *112*: 2654–2666, 1994.
13. Green, S., and Weiss, G. R. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. *Investig. New Drugs*, *10*: 239–253, 1992.
14. Glisson, B. S., Kurie, J. M., Fox, N. J., Murphy, W. K., Winn, R. J., Perez-Soler, R., Pisters, K. M. W., Shin, D. M., and Hong, W. K. Phase I-II study of cisplatin, etoposide, and paclitaxel (PET) in patients with extensive small cell lung cancer (ESCLC). *Proc. Am. Soc. Clin. Oncol.*, *16*: 455a, 1997.
15. Hainsworth, J. D., Gray, J. R., Stroup, S. L., Kalman, L. A., Patten, J. E., Hopkins, L. G., Thomas, M., and Greco, F. A. 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.
16. Nair, S., Marschke, R., Grill, J., Sloan, J., Tazelaar, H., Drevyanko, T., Michalak, J., and Marks, R. A Phase II study of paclitaxel (Taxol) and cisplatin (CDDP) in the treatment of extensive stage small cell lung cancer (ESSCLC). *Proc. Am. Soc. Clin. Oncol.*, *16*: 454a, 1997.
17. Chaudhry, V., Rowinsky, E. K., Sartorius, S. E., Donehower, R. C., and Cornblath, D. R. Peripheral neuropathy from Taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. *Ann. Neurol.*, *35*: 304–311, 1994.
18. Sculier, J. P., and Klastersky, J. Definitive results of a Phase I study of a chemotherapy regimen using cisplatin and paclitaxel for non-small cell bronchial cancer. *Rev. Mal. Respir.*, *12*: 609–614, 1995.

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