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A Phase I Study of Cisplatin, Etoposide, and Paclitaxel in Small Cell Lung Cancer: A University of Colorado Cancer Center Study

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The University of Colorado Cancer Center is conducting a phase I study of the three-drug PET combination of cisplatin, etoposide, and paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) in patients with advanced (stage IV or IIIB with pleural effusion) small cell lung cancer. The primary study goal was to define the maximally tolerated doses given on an outpatient basis. Secondary goals were to determine toxicities, response rate, response duration, and survival. Paclitaxel was given as a 3-hour intravenous (IV) infusion prior to cisplatin and etoposide. The starting doses were paclitaxel 135 mg/m² day 1, cisplatin 80 mg/m² IV day 1, and etoposide 50 mg/m² IV day 1, and 100 mg/m² orally days 2 and 3, every 3 weeks. In the second group, the etoposide was increased to 80 mg/m² IV day 1 and 160 mg/m² orally days 2 and 3. In the third group, paclitaxel was increased to 175 mg/m² IV day 1. Granulocyte colony-stimulating factor was not given on the first cycle, but was given on subsequent cycles if grade 4 neutropenia developed. So far, 13 patients have been entered on the study; all are evaluable for toxicity and nine are evaluable for response. The major toxicity was neutropenia, with no other grade 4 toxicities observed. All patients received the full six cycles of therapy. Thus far, partial responses have been observed in four patients (44%) and complete responses in five patients (56%), for an overall response rate of 100%. This ongoing study has shown that full doses of each of these three active drugs can be administered safely on an outpatient basis. The encouraging early results should lead to a multicenter phase II evaluation of the PET combination.

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THIS PHASE I study was designed to determine the maximally tolerated doses (MTDs) of the PET combination (cisplatin/etoposide/paclitaxel [Taxol; Bristol-Myers Squibb Company, Princeton, NJ]) given on an outpatient basis without routine growth factor support as treatment for

patients with extensive-stage small cell lung cancer (SCLC). Paclitaxel was given as an intravenous (IV) infusion over 3 hours followed by 30- and 60-minute infusions of etoposide and cisplatin, respectively. Secondary objectives were to determine the response rates at each dose level, the toxicities at each dose level, and the overall survival.

The rationale for the study was based on previous experience with cisplatin, etoposide, and paclitaxel in SCLC. Several randomized trials had compared the PE combination (cisplatin/etoposide) with CAV (cyclophosphamide/doxorubicin/vincristine) and with alternating CAV/PE when given to patients with advanced SCLC.^{1,2} These studies showed equivalent efficacy for the regimens, but less toxicity in the PE arms. In addition, four cycles of PE had equivalent activity to six cycles of CAV or CAV/PE in one of these studies.¹ The efficacy of paclitaxel in SCLC was established in two phase II trials.^{3,4} In an Eastern Cooperative Oncology Group study³ in which paclitaxel was given as a 24-hour infusion at 250 mg/m² and restricted to two cycles because of limited supply, the response rate was 53% (17 of 32 patients). In a confirmatory study from the North Central Cancer Treatment Group, paclitaxel (250 mg/m² over 24 hours) produced a response rate of 68% among 37 patients with advanced SCLC.⁴

Subsequent studies involving patients with ovarian carcinoma and other cancers showed that

Table 1. PET Regimens for Three Study Arms in Patients With Small Cell Lung Cancer

Group	Drug Doses (mg/m ²)			Days
	Paclitaxel	Cisplatin	Etoposide	
1	135	80	50 IV 100 orally	1 2, 3
2	135	80	80 IV 160 orally	1 2, 3
3	175	80	80 IV 160 orally	1 2, 3

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the more convenient 1- and 3-hour infusion schedules of paclitaxel produced similar efficacy but less myelosuppression compared with the 24-hour infusion.^{5,6} Thus, this study was designed to determine the optimal outpatient doses of this three-drug PET regimen.

MATERIALS AND METHODS

Patient Eligibility

Patients were required to have histologic confirmation of extensive-stage SCLC, to be older than 18 years, to have a

performance status of 0 through 2, and to have received no previous chemotherapy. Patients were eligible if they had measurable or evaluable disease. Patients with brain metastases were excluded. Patients were required to have adequate renal (creatinine <2 mg/dL), hepatic (bilirubin <2 mg/dL), marrow (white blood cell count >4,000/ μ L, platelet count >150,000/ μ L, and hemoglobin >10 mg/dL), cardiac (no angina, congestive heart failure, myocardial infarction, or conduction disturbances), hearing, neurologic, and pulmonary function. Patients were required to provide written informed consent for this study, which was approved by the Colorado Combined Institutional Review Board.

Table 2. Tests Performed to Assess Treatment Response and Toxicity

Required Studies	Prestudy	Week																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Registration	X																			
Physical																				
History and physical	X				X			X			X			X			X			X
Performance status	X				X			X			X			X			X			X
Toxicity notation			X		X	X		X	X		X	X		X	X		X	X		X
Laboratory																				
CBC/differential/ platelets*	X		X		X	X		X	X		X	X		X	X		X	X		X
Electrolytes (Na, K, Mg, Ca)	X		X		X	X		X	X		X	X		X	X		X	X		X
Serum creatinine	X		X		X	X		X	X		X	X		X	X		X	X		X
Calculated creatinine clearance†	X				X‡			X‡			X‡			X‡			X‡			X‡
Alkaline phosphatase	X							X			X			X			X			X
Bilirubin	X							X			X			X			X			X
AST/ALT/LDH	X							X			X			X			X			X
Urinalysis	X																			
ECG	X				X§			X§			X§			X§			X§			
X-rays and scans																				
Chest x-ray	X				X			X			X			X			X			X
Thoracic CT with contrast	X							X						X						X
Liver and upper abdominal CT	X							X						X						X
Brain CT or MRI	X§																			
Bone scan	X¶																			X¶
Treatment#																				
Cisplatin		X			X			X			X			X			X			
Etoposide		X			X			X			X			X			X			
Paclitaxel		X			X			X			X			X			X			

Abbreviations: CBC, complete blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ECG, electrocardiogram; CT, computed tomography; MRI, magnetic resonance imaging.

* CBC should be obtained weekly while patient is on chemotherapy and twice a week while receiving G-CSF.

† Calculated CaCl unless <60, then 24-hr creatinine clearance.

‡ Repeat only if clearance reduced <60 or if creatinine increases.

§ Only if clinically indicated.

|| If using for tumor measurement, should be repeated every two cycles.

¶ Only if clinically indicated, but if positive must be repeated after cycle 6.

See Table 1.

Table 3. Patient Demographics

Group	Gender		Median Age (yr)	Performance Status		Race		
	M	F		0-1	2	White	Black	Other
1	4	1	60	3	2	4	0	1
2	2	3	57	5	0	4	0	1
3	0	3	53	3	0	2	1	0
Total	6	7	57	11	2	10	1	2

Drug Therapy

Paclitaxel was given as a 3-hour IV infusion mixed in normal saline or 5% dextrose. All patients received a routine premedication regimen consisting of diphenhydramine (50 mg IV 30 minutes prior to paclitaxel), dexamethasone (20 mg orally or IV 12 and 6 hours prior to paclitaxel), and cimetidine (300 mg IV 30 minutes prior to paclitaxel) to prevent allergic reactions. Cisplatin was given in 12.5 g mannitol and 500 mL normal saline over 1 hour. At least 1,000 mL normal saline was given prior to and after cisplatin administration. Etoposide was given with the cisplatin infusion IV over 30 minutes following the paclitaxel infusion. This order of drug administration was based on previous studies of cisplatin and paclitaxel in which considerably less toxicity occurred when paclitaxel administration preceded cisplatin, compared with the reverse order.⁷

The study was designed to evaluate a variety of doses of each agent, with five patients studied at each dose level. The study arms are outlined in Table 1. Prophylactic growth factor support was not given during the first cycle. If a patient developed grade 4 neutropenia during one cycle or if the cycle had to be prolonged because of persistent neutropenia for more than 28 days, he or she continued in the study at the same dose level with granulocyte colony-stimulating factor (G-CSF) support. Patients who had grade 4 hematologic toxicity in cycles supported by G-CSF had chemotherapy doses reduced by one dose level (25 mg/m² for paclitaxel, 10 mg/m² for IV etoposide, 20 mg/m² for oral etoposide, and 15 mg/m² for cisplatin).

Study Parameters

Disease staging was assessed by chest roentgenograms and computed tomography scans of the chest and upper abdomen. Computed tomography scans of the head, bone scans, and bone marrow biopsy specimens were obtained when indicated clinically. Table 2 shows the tests performed to assess treatment response and toxicity.

Study Definitions

Complete response was defined as complete resolution of all evidence of measurable and evaluable disease lasting for at least 4 weeks. Partial response was defined as a 50% decrease in the sum of the perpendicular diameters of measurable lesions or a greater than 50% decrease in the estimated area of evaluable but nonmeasurable lesions (agreed on by two independent observers) lasting for at least 4 weeks. Tumor progression was defined as either a 50% increase in the sum of the products of measurable lesions over the smallest sum observed, the reappearance of any lesion that had disappeared, clear worsening of any evaluable disease, the appearance of any new lesion, or failure to return for evaluation due to cancer-related deteriorating condition. The MTD was established if two of five patients developed a nonneutropenic grade 4 toxicity during the first cycle, at which time the next lower dose level was defined as the MTD. For neutropenia, the MTD was defined by the occurrence of grade 4 neutropenia in two of five patients receiv-

Table 4. Number of Patients With Hematologic Toxicity by Study Group

Group	No. of Patients	Neutrophils		Platelets	
		Grade 3	Grade 4	Grade 3	Grade 4
1 (cycle no.)	5	1 (c3)	2 (5, 4)*	0	0
2 (cycle no.)	5	0	5 (1, 3, 1, 4, 1)†	1 (c4)	0
3 (cycle no.)	3	0	3 (c1, 1, 1)‡	0	0

* One patient received G-CSF.
† Three patients received G-CSF.
‡ Two patients received G-CSF.

ing G-CSF or two of five patients developing febrile neutropenia with or without G-CSF.

RESULTS

Thirteen patients (six males and seven females) have been entered into the first three study groups to date (February 28, 1995). Patient demographics are shown in Table 3. The median age was 57 years. All patients had extensive-stage SCLC, and the majority were white (10 of 13). Performance status was excellent, with 11 patients classified as 0 or 1 and two patients as 2.

Overall, the PET combination has been well tolerated. Table 4 shows the hematologic toxicity by study group. One grade 3 and two grade 4 neutrophil toxicities were observed in the five patients in group 1. These all occurred in cycle 3 or later. One of these patients later received G-CSF. No patients had grade 4 thrombocytopenia. Of the five patients in group 2, three had grade 4 neutropenia in cycle 1 and the remaining two had grade 4 neutropenia later, one during cycle 3 and one during cycle 4. The three patients with grade 4 neutropenia in cycle 1 received G-CSF in subsequent cycles without dose reductions. One patient in this group experienced a grade 3 thrombocytopenia during cycle 4, but no episodes of grade 4 thrombocytopenia occurred. In group 3, two patients had a grade 4 neutropenia in cycle 1, both of whom subsequently received G-CSF without dose reduction. No episodes of grade 3 or 4 thrombocytopenia occurred.

Nonhematologic toxicity was quite mild. Table 5 shows the incidence of grade 3 or 4 nonhematologic toxicities, which consisted of one episode each of hypomagnesemia, ototoxicity, and neurotoxicity, all occurring during the fifth cy-

Table 5. Number of Patients With Grade 3 or 4 Nonhematologic Toxicity							
Toxicity	Cycle No.						Total
	1	2	3	4	5	6	
Hypomagnesemia	0	0	0	0	1	0	1
Ototoxicity	0	0	0	0	1	0	1
Neuropathy	0	0	0	0	1	0	1
Hyponatremia	0	1*	0	1*	0	0	1
* Same patient.							

Table 6. Best Response by Group

Group	No. Evaluable	No. of Patients (%)		No. of Cycles Delivered	
		CR	PR	Total	Mean
1	3	2 (67)	1 (33)	18	6
2	3	1 (33)	2 (67)	18	6
3	3	2	1 (100)	18	6
Total	9	5 (56)	4 (44)		

Abbreviations: CR, complete response; PR, partial response.

cle. In general, nausea and vomiting were mild and no patient died as a result of an adverse event.

The response by study group and the number of cycles given in each group are shown in Table 6. Among the three evaluable patients in group 1, there were two complete responses and one partial response, and the mean number of cycles was six. Among three evaluable patients in group 2, in which the mean number of cycles was also six, two patients had a partial response and one had a complete response. Three patients are evaluable in group 3; two had complete responses and one had a partial response. The mean number of cycles delivered was also six. From the combined groups 1 through 3, four (44%) of the nine evaluable patients had partial responses and five (56%) had complete responses. It is too early for a meaningful survival analysis at this time.

DISCUSSION

This ongoing study was designed to determine the maximal doses of the combination of paclitaxel, etoposide, and cisplatin when given on an outpatient basis without routine growth factor support and with paclitaxel administered as a 3-hour infusion prior to cisplatin. The MTDs have not yet been defined, but are likely to be 175 mg/m² for paclitaxel, 80 mg/m² for IV etoposide (160 mg/m² for oral etoposide), and 80 mg/m² or higher for cisplatin.

Given the results observed so far, it is likely that the dose-limiting toxicity will be neutropenia. No episodes of grade 4 thrombocytopenia have been observed to date. The preliminary results suggest

high overall and complete response rates. Whether higher doses will increase the complete response rates and the survival will be determined as this study progresses. If the high response rate is confirmed by additional follow-up in this study and by other studies, randomized trials comparing this PET combination with etoposide/cisplatin should be undertaken.

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