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Treatment of non-small-cell lung cancer with vinblastine and very high-dose cisplatin. A Southwest Oncology Group study*

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Summary. Suggestions of a dose-response effect for cisplatin in non-small-cell lung cancer have contributed to the development of very high-dose cisplatin regimens (200 mg/m^2 per cycle). We treated 53 eligible patients with metastatic or recurrent non-small-cell lung cancer with a combination of 100 mg/m^2 cisplatin and 4 mg/m^2 vinblastine, each given on days 1 and 8 of a 28-day cycle. We observed no complete response and 4 partial responses (8%). Median survival was 6 months. Toxicities of grade III or greater included leukopenia (11 cases), nausea/vomiting (6 cases), thrombocytopenia (2 cases), anemia (2 cases), and elevation of transaminase (1 case). Neurotoxicity has been reported to be a major problem in several other very high-dose cisplatin regimens. The low level of neurotoxicity observed in this study may be attributable to the median cumulative cisplatin dose of <600 mg/m^2. This vinblastine/very high-dose cisplatin regimen showed minor activity against non-small-cell lung cancer. The level of activity did not surpass that of standard-dose (100 mg/m^2 per cycle) cisplatin-containing regimens.

Introduction

Escalation of cisplatin dosing beyond standard high-dose regimens (120 mg/m^2) has been limited by both hematologic and non-hematologic toxicities. When a monthly cisplatin dose of 200 mg/m^2 is given at 40 mg/m^2 per day $\times 5$, severe peripheral neuropathy is the dose-limiting toxicity [8]. However, Gandara et al. [3] used a similar total monthly cisplatin dose given at 100 mg/m^2 on days 1 and 8 and reported a marked decrease in the incidence of neuropathy. It was postulated that the reduction in neurotoxicity could be attributable to the lower accumulation of unbound platinum on the intermittent-dose schedule as compared with the daily-dose regimen.

The question of a cisplatin dose response has been actively investigated in the treatment of non-small-cell lung cancer. Gralla et al. [5] reported an increase in the duration of response and survival of responding patients on a vindesine/cisplatin combination when the cisplatin dose was increased from 60 to 120 mg/m^2. Exploratory studies by Gandara et al. [3, 4] of very high-dose cisplatin (100 mg/m^2 on days 1 and 8) were also conducted in non-small-cell lung cancer and resulted in response rates of 47% and 31% in series of 17 and 92 patients, respectively. Since vinblastine/cisplatin exhibits activity comparable with that of vindesine/cisplatin [9], we chose to modify a vinblastine/cisplatin combination by adding a very high-dose cisplatin schedule to create a vinblastine/very high-dose cisplatin regimen for investigation in non-small-cell lung cancer.

Patients and methods

Eligible patients had measurable or evaluable recurrent or metastatic non-small-cell lung cancer and had received no prior chemotherapy. Full recovery from prior surgery or radiotherapy was required, with previous radiotherapy fields having measured <225 cm^2 in total area. Adequate performance status (Southwest Oncology Group 0–2), hematologic reserve (granulocyte count, $\geq$2,000/μl; platelet count, $\geq$100,000/μl; hemoglobin, $\geq$9 gm%), hepatic reserve (bilirubin $\leq$2 mg%), and renal reserve (estimated creatinine clearance, $\geq$60 ml/min) were also required. Patients were ineligible if they showed a history of brain metastases or had a serious intercurrent illness requiring immediate therapy. Pregnant subjects were excluded from the investigation. All patients were informed of the investigational nature of this study and signed a written informed consent form. The study was approved by the Southwest Oncology Group and by the institutional review boards of the participating institutions. All flowsheets were reviewed by the Southwest

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Table 1. Description of patients

Number entered	54	
Number eligible	53	
Men/Women	37/16	(70%/30%)
Median age (range)	57	(40–78 years)
Histology:		
Adenocarcinoma	25	(47%)
Squamous	17	(32%)
Large-cell	10	(19%)
Adenosquamous	1	(2%)
Cycles received[a]:		
0.5	9	(17%)
1	10	(19%)
1.5	3	(6%)
2	12	(23%)
2.5	5	(9%)
3	14	(26%)

[a] One cycle requires treatment on both day 1 and day 8

Oncology Group Statistical Center and by the study coordinator (S. M. G.).

The treatment plan consisted of 4 mg/m^2 vinblastine and 100 mg/m^2 cisplatin, each given intravenously on days 1 and 8 of a 28-day schedule for a maximum of three cycles. Grounds for removal from study included grade 3 neurotoxicity, a reduction in estimated creatinine clearance to <50 ml/min, or progressive disease. Dose adjustments were made for significant myelosuppression, nephrotoxicity or neuropathy. Patients were reevaluated for tumor response or progression every 28 days during therapy. Subjects continued to be followed after completion of treatment for determination of survival.

Results

Patients' characteristics

Between September 1, 1987, and June 1, 1989, 54 patients were entered in this study (Table 1). One subject was found to be ineligible due to a change in diagnosis from non-small-cell lung cancer to breast cancer metastatic to the lung. The study population comprised 37 men and 16 women with a median age of 57 years. Adenocarcinoma was the most common histologic diagnosis and accounted for 47% of the cases. A median of 2 full cycles of vinblastine/high-dose cisplatin were given; 44 patients (83%) received at least 1 full cycle (delivery of chemotherapy on both day 1 and 8), and 14 subjects (26%) received all 3 complete cycles.

Response

No complete response was seen in this study. Four patients (8%; 95% confidence interval, 2%–18%) achieved a partial response. Exclusion of the 9 subjects who received <1 full cycle and thus did not receive very high-dose cisplatin results in 4/44 patients' (9%) achieving a partial response. Of the 53 patients entered in and eligible for this study, 48 have since died; the median survival was 6 months (Fig. 1).

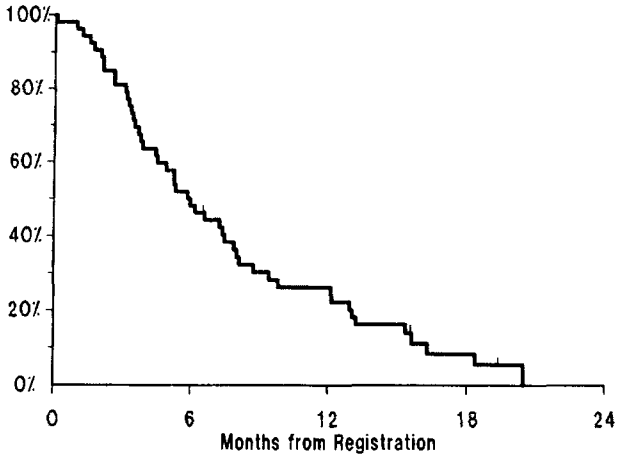

Fig. 1. Overall survival of the 53 eligible patients. The median survival was 6 months

Toxicity

The most common toxicities noted in this study were nausea/vomiting and myelosuppression (Table 2). Six patients experienced grade 3/4 nausea/vomiting. Grade 3/4 leukopenia, thrombocytopenia, or anemia were seen in 11, 2, and 2 subjects, respectively. None of our patients experienced grade 3/4 nephrotoxicity or neuropathy.

Discussion

Several studies have suggested that cisplatin is a valuable component of chemotherapeutic regimens for non-small-cell lung cancer and that escalation of the cisplatin dose might be advantageous. Rapp et al. [12] have reported a randomized trial of the National Cancer Institute of Canada Clinical Trials Group in which patients with advanced non-small-cell lung cancer who received cisplatin-based

Table 2. Toxicities observed

Toxicity	Grade					
	0	1	2	3	4	5
Myelosuppression:						
Leukopenia	31	6	5	10	1	0
Thrombocytopenia	48	2	1	1	1	0
Anemia	33	9	9	2	0	0
Gastrointestinal:						
Nausea/vomiting	18	12	16	5	1	0
Diarrhea	48	4	1	0	0	0
Constipation	52	0	1	0	0	0
Elevated transaminase	52	0	0	1	0	0
Elevated bilirubin	52	1	0	0	0	0
Mucositis	52	1	0	0	0	0
Neurologic:						
Peripheral Neuropathy	48	2	2	0	0	0
Ototoxicity	48	4	1	0	0	0
Renal	42	6	5	0	0	0

chemotherapy achieved significantly longer survival than did those who received supportive care alone. Albain et al. [1] analyzed the Southwest Oncology Group (SWOG) experience with extensive non-small-cell lung cancer from 1974 to 1988 and found treatment with a cisplatin-based regimen to be an independent, favorable predictor of survival. Gralla et al. [5] have reported an improvement in the duration of response and survival of responding patients on cisplatin combination chemotherapy when the cisplatin dose is escalated from 60 to 120 mg/m^2. Gandara et al. [3, 4] have suggested that the use of even single-agent cisplatin at very high doses (100 mg/m^2 on days 1 and 8) might further improve activity.

In view of this previous work, the therapeutic results of the present trial are disappointing. The response rate of 8% and the median survival of 6 months did not surpass those achieved in trials of standard-dose cisplatin [13]. However, the results of the present trial are consistent with those of several other recent trials of very high-dose cisplatin in the treatment of non-small-cell lung cancer. Higano et al. [7] reported a regimen in which a total cisplatin dose of 200 mg/m^2 was delivered during each 6-week cycle: 50 mg/m^2 cisplatin per week $\times 4$ was combined with 8 mg/m^2 mitomycin C (week 1), 3 mg/m^2 vinblastine (week 2), and 1,000 mg/m^2 5-fluorouracil (week 3). In all, 82 patients were entered and achieved a response rate of 26% and a median survival of 4.7 months. A randomized trial has also recently been completed that directly compared standard-dose cisplatin (50 mg/m^2 on days 1 and 8 every 4 weeks) with very high-dose cisplatin (100 mg/m^2 on days 1 and 8 every 4 weeks). No significant difference in response rate or survival between the two regimens was noted. However, very high-dose cisplatin did result in increased toxicity (D. Gandara for the SWOG, personal communication).

One striking observation for the very high-dose cisplatin regimens (100 mg/m^2 on days 1 and 8) has been the lack of severe neurotoxicity as compared with previous very high-dose (40 mg/m^2 $\times 5$) cisplatin regimens. However, in a pilot study performed at the University of Southern California prior to the present study [6], severe progressive paresthesias were noted after the cessation of therapy in patients who received up to four cycles of the same vinblastine/very high-dose cisplatin regimen. The most severe neurotoxicity was seen in subjects who were given all four cycles, attaining cumulative cisplatin doses of >600 mg/m^2. In the present study, a maximum of three cycles was allowed and strict rules for the reduction or discontinuation of cisplatin due to early neurotoxicity were established. In both single-agent series [3, 4] using the days 1 and 8 regimen for non-small-cell lung cancer, the average cumulative cisplatin dose was $\leqslant$600 mg/m^2 and eligible patients had received no prior chemotherapy. By contrast, several series using 40 mg/m^2 cisplatin per day $\times 5$ in which severe peripheral neuropathy was noted, were characterized by cumulative cisplatin doses of >600 mg/m^2 [2, 10] or by the inclusion of patients who had previously received standard-dose cisplatin [11]. The lack of severe neurotoxicity observed during the days 1 and 8 regimens may therefore be a function of lower cumulative cisplatin dose rather than a function of schedule.

The present study demonstrates that the delivery of combination chemotherapy including very high-dose cisplatin is feasible. However, a therapeutic advantage over standard-dose regimens was not found. Although the 2-fold increase in dose intensity involved in these regimens does not seem to lead to significant improvement in the treatment of non-small-cell lung cancer, greater escalations of the platinum dose intensity of the magnitude possible using autologous bone marrow rescue may be of interest. Neuropathy remains the dose-limiting toxicity when the cumulative cisplatin dose surpasses 600 mg/m^2. Carboplatin may therefore be the agent of choice for further dose escalations.

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