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Phase-II Study with Cis-dichlorodiammineplatinum (II) in Small Cell Anaplastic Bronchogenic Carcinoma*

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Abstract—*Twenty-four patients with small cell cancer of the lung were treated with cisplatin. The drug was given at a dose of* 80 mg/m^2 *in a* 6-hr *infusion repeated every* 3 weeks. *All but* 1 *patient had received extensive prior therapy. Of* 23 *patients evaluable for response,* 5 *achieved partial remission. A minor response was noted in* 3 *additional patients. Nausea and vomiting were prominent. Mild to moderate myelosuppression and nephrotoxicity were commonly encountered. There was one, probably drug-related, death with renal impairment after apparently optimal forced diuresis. These data warrant the incorporation of cisplatin in combination chemotherapy for this disease.*

INTRODUCTION

CIS-DICHLORODIAMMINEPLATINUM (II) (DDP) has shown a striking activity against testicular cancer. This new drug is also effective in a wide variety of other tumor types, particularly ovarian, bladder and head and neck cancers [1, 2]. The role of DDP in the treatment of lung cancer remains to be ascertained. Detailed information on its single agent activity by cell types is scanty [3–5]. However, various cisplatin-containing combination chemotherapy regimens have been studied with interesting results [1]. Thus, a combination of DDP and VP-16-213 has been reported to yield a 48% complete and a 96% overall response rate in patients with previously untreated small cell cancer of the lung [6]. These provocative figures prompted us to initiate a disease-oriented phase II clinical trial with DDP in small cell cancer of the lung.

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MATERIALS AND METHODS

Between May 1978 and May 1979, 24 patients with histologically or cytologically proven small cell lung cancer were included in the trial. All but one patient, who was entered by mistake in this study, had received prior treatment with at least one combination chemotherapy (Table 1). Initial work-up included physical examination, blood chemistries, chest X-rays and bone marrow biopsy. Bone and liver scans were performed when indicated. Patients with proven or suspected involvement of the central nervous system were excluded from the trial. All patients had absolute granulocyte counts $>2000/mm^3$ and platelet counts $>100{,}000/mm^3$ unless bone marrow impairment was clearly disease-related. Patients also had serum creatinine levels <1.5 mg/dl, a creatinine clearance $>75\%$ of the predicted value, a total serum bilirubin <2 mg/dl and SGOT <120 IU.

DDP was given at a dose of 80 mg/m^2 in a 6-hr infusion with saline. Treatments were repeated every 3 weeks. Patients were hydrated with 3–6 l of dextrose 5%. If urine output was less than 150 cm^3/hr for two consecutive hours with this program, furosemide (20–40 mg i.v.) and/or mannitol (15–35 g i.v. bolus) were added.

Table 1. Pretreatment patient characteristics

No. of patients	24
Median age (range)	60 (42–75)
Sex	
women	3
men	21
ECOG performance score	
0–1	6
2	13
3	5
Previous therapy	
none	1
radiotherapy and chemotherapy	2
chemotherapy only	21
—1 combination	11
—2 or more combinations	10
Stage of disease at entry in the protocol	
limited	10
extensive	14
Median time interval (months) since diagnosis (range)	10,5 (1–30)

Subsequent courses of DDP were administered if renal function tests were, or had returned to normal and if the nadir of the blood cell counts had been reached and the bone marrow was recovering. Drug doses were adjusted according to hematologic values at the scheduled time of retreatment. Doses were reduced by 50% if the WBC count was 3000–3999/mm^3 and/or the platelet count was 75,000–99,999/mm^3. They were reduced by 75% if the corresponding counts were 2000–2999/mm^3 and/or 50,000–74,999/mm^3 respectively. Treatment was postponed with lower blood cell counts. Nine patients received 1 course, 6 patients 2 courses, 8 patients 3 courses, 1 patient 5 courses of DDP.

Patients were to receive at least 2 courses of DDP, unless disease progression was life-threatening and required other or additional anticancer therapy.

Effect of therapy was classified as complete remission (CR), partial remission (PR), minor responses (MR), no change (NC) or progressive disease (PD). PR indicated a decrease by 50% of the product of the two largest perpendicular diameters of all indicator lesions. MR was defined as a greater than 50% tumor shrinkage of at least one measurable lesion, whereas other indicator lesions remained unchanged.

RESULTS

Twenty-three patients who received at least 1 course of therapy are evaluable for response (Table 2). One patient died within 1 week of initiation of the first course. The only previously untreated patient (case 1, Table 2) experienced a greater than 90% tumor shrinkage. After 3 courses of DDP, radiotherapy was given to the primary and the patient attained a CR. He is still in CR for 10+ months with no further therapy.

We observed 4 PRs among the 22 previously treated patients. All but one had limited disease and a PS of 1–2. One of these responses occurred in a patient who had had only a MR with a combination chemotherapy regimen consisting of cyclophosphamide, methotrexate, vincristine and VP-16-213 (case 4, Table 2). Responses lasted for 2.5 and 4 months in the 2 patients evaluable for response duration. The two other patients received radiotherapy after having achieved a PR status. The first one (case 2, Table 2) had two indicator lesions. One of these was a total atelectasis of the upper right lobe. Almost complete clearance was observed after 1 course of DDP. The other lesion disappeared completely. In the remaining patient (case 5, Table 2), a superior vena cava syndrome disappeared after 1 course of DDP and the measurable lesion decreased by more than 50% in size.

Three additional patients showed a clear MR for 2,2 and 3 months. All had massive liver involvement that did not respond to therapy, while the lung lesions shrank by >50%. One of these MRs died of progressive renal failure, 8 weeks after initiation of DDP. This renal failure was preceded by a hyperuricemia of 18.3 mg/dl (case 7, Table 2).

Three patients who had clearly progressive disease upon entry in the trial remained stable for a median of 1.5 months. In 12 patients, the disease was not affected by DDP therapy.

Toxicity

Nephrotoxicity proved to be manageable, with a pronounced, but transient, elevation of serum creatinine (>1.5 mg/dl) and BUN levels (>25 mg%) in 4 (17%) of the patients. One possibly drug-related death with progressive renal failure (case 7, Table 2) has already been described above.

Severe nausea and profuse vomiting, persisting for up to 24 hr, were present in almost all patients. These gastrointestinal symptoms were usually refractory to conventional antiemetics.

Haematologic toxicity was generally modest and did not correlate with bone marrow involvement. Decrease in the WBC count to <4000/mm^3 was observed in 11 patients

Table 2. Responders to DDP

Patient No.	Age (years)	Time interval since diagnosis	PS	Stage	Prior chemotherapy (response, duration)	Response to DDP	Duration of response	Indicator lesions
1	44	1	1	L	None	PR (>90%)	NE	Primary
2	70	15	1	L	(1) A (PR, 7 months) (2) C (PR, 6 months)	PR	NE	(1) total atelectasis r.u.L. (2) primary
3	50	7	1	L	B (PR, 5 months)	PR	2,5 months	primary
4	70	6	2	L	B (MR, 5 months)	PR	4 months	primary
5	55	9	2	E	A (PR, 8 months)	PR	NE	(1) superior vena cava syndrome (2) primary
6	56	9	2	E	(1) A (PR, 5 months) (2) C (PR, 3 months)	MR	3 months	(1) primary ($R>50\%$) (2) liver mets. (NC)
7	59	18	3	E	(1) A (CR, 15 months) (2) C (PD)	MR	2 months (toxic death)	(1) primary + lung mets. ($R>75\%$) (2) liver mets. (NC)
8	57	16	2	E	A (PR, 14 months)	MR	2 months	(1) primary ($R>50\%$) (2) liver mets. ($R<50\%$)

PS = performance status (ECOG scale); E = extensive; L = limited; NE = not evaluable because of radiotherapy given after having achieved PR.
Previous chemotherapy:
A = cyclophosphamide, methotrexate, vincristine, procarbazine; B = cyclophosphamide, methotrexate, vincristine, VP-16-213; C = adriamycin, VP-16-213.

(48%) with a median nadir of 3600/mm^3 and a mean nadir of 4400/mm^3 (range 1700–10,100). Platelet counts $<100{,}000$/mm^3 were observed in 6 patients (29%); the median platelet nadir was 120,000/mm^3, the mean nadir 175,000 (range 14,000–400,000). A moderate anemia with a drop in hemoglobin value >2.0 g was seen in 9 cases (39%).

DISCUSSION

Small cell lung cancer is commonly believed to be very responsive to many agents, but relatively few new drugs are being evaluated in this disease [7]. Thus, despite extensive investigation of DDP over the last 5 years, data on its effectiveness in this disease are scanty.

A phase II disease-oriented trial, was reported very recently by Dombernowsky *et al.* [4]. Among 28 patients these investigators observed only two PR (54 and 151 days) and one short-lived tumor regression (27 days). In this study, only 8 patients received DDP at doses higher than 60 mg/m^2 and only 2 of these received more than 1 course of therapy.

In our study we observed 5 PR (22%) and 3 MR (PR + MR = 35%). All but one PRs were noted in patients with limited disease and a performance status of 1–2. These favorable patient characteristics might account in part for our somewhat more encouraging results. Drug doses should also be considered when assessing the data. It has been suggested, that high doses of DDP might still achieve therapeutic effectiveness in patients resistant to lower doses [8]. At least in ovarian cancer, there is good evidence that high-dose DDP is more effective than low-dose therapy ($\leqq 60$ mg/m^2) [9]. In two ongoing phase II trial with DDP in resistant small cell lung cancer, partial remissions were reported in 3/17 [10] and 3/9 [11] patients treated once every 3 weeks with 80 and 120 mg/m^2 respectively.

The consistent finding of a definite but moderate antitumor activity of DDP in small cell lung cancer [12], could minimize the possibility of a false positive phase II study. The importance of this so-called delta error (No. of false positive/total No. of positive trials) in the assessment of cancer clinical trials has been recently stressed [13].

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