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Phase II study of 5-day continuous infusion of *cis*-diamminedichloroplatinum(II) in the treatment of non-small-cell lung cancer

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Summary. *cis*-Diamminedichloroplatinum(II) (CDDP) was given as a single agent at a dose of 25 mg/m^2 daily for 5 days by continuous infusion; treatment was repeated every 4 weeks in 30 previously untreated patients with advanced non-small-cell lung cancer (NSCLC). The median age of the patients was 61 years; 13 patients had limited disease and 17, extensive disease. The overall response rate was 40% (12/30; 95% confidence limits, 23–58%), with a median survival of 8 months. Vomiting was observed in 37% of patients; elevated serum creatinine levels (>1.5 mg/dl), in 7%; leukopenia (<3,000/mm^3), in 39%; thrombocytopenia (<70,000/mm^3), in 26%; and anemia (hemoglobin <9.5 g/dl), in 60% of patients. In all cases, these toxicities were mild and transient, requiring no dose modification. The exposure to filterable platinum, determined from the area under the concentration-time curve, was 9.08 ± 3.21 μg h ml^{-1}. We conclude that CDDP given by 5-day continuous i.v. infusion is safe and effective for treatment of NSCLC.

Introduction

Combination chemotherapy containing *cis*-diamminedichloroplatinum (II) (CDDP) has been widely used in the treatment of inoperable non-small-cell lung cancer (NSCLC), and an improved therapeutic effect has been achieved [2, 12, 13]. In recent years, however, both the response rate and survival appear to have reached their limits. To push these limits further, new and more effective anticancer agents are obviously needed; however, in the meantime it is important that the optimal therapeutic schedule for administration of existing drugs be determined. In clinical trials, the most common method of CDDP administration is a short-term push infusion.

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Drewinko et al. [5] observed that CDDP cytotoxicity to asynchronous human lymphoma cells in culture was enhanced by prolonged low-dose exposure to this drug. Belliveau et al. [1] reported that the area under the concentration-time curve achieved for non-protein-bound CDDP was 2 times higher after continuous infusion than that observed when an equivalent dose of CDDP was given by i.v. push. These results promoted the evaluation of CDDP given by continuous i.v. infusion to determine whether it is possible to modulate the therapeutic selectivity of this agent in patients with NSCLC. In phase I studies [9, 11], it was concluded that continuous infusion of CDDP at a dose of 25–30 mg/m^2 daily could be carried out safely for 5 days. Therefore, we conducted a phase II study of 5-day continuous infusion of CDDP at a daily dose of 25 mg/m^2 in patients with advanced NSCLC.

Patients and methods

From October 1987 to July 1989, 30 patients with histologically proven advanced NSCLC were entered in this phase II protocol. Eligibility criteria included the presence of measurable lesions, an Eastern Cooperative Oncology Group (ECOG) performance score of ≦3, a white blood count (WBC) of ≧4,000/mm^3, a platelet count of ≧100000/mm^3, total bilirubin levels of <2 mg/dl, SGOT and SGPT values of less than twice the normal range, serum creatinine levels of <1.5 mg/dl, and creatinine clearance of >40 ml/min; patients had to be <80 years old and could not have received prior chemotherapy, radiotherapy, or surgery.

Pretreatment evaluation included a medical history, physical examination, and complete blood count (CBC), determination of urinary creatinine clearance, relevant laboratory tests, a chest roentgenogram, an ECG, complete urinalysis, and a bone marrow examination. All patients underwent bronchofiberscopy, a radionuclide bone scan, a computerized tomographic (CT) scan of the brain and thorax, and an abdominal ultrasound examination or CT scan. Physical examinations, CBCs, and chest roentgenograms were obtained weekly, as were biochemical tests and serum electrolyte determinations. A chest CT scan and determination of creatinine clearance were done before each course of CDDP.

The disease was defined as limited if the tumor was confined by all clinical measurements to one hemithorax, including the mediastinal or ipsilateral supraclavicular nodes; disease occurring beyond these confines was classified as extensive.

Table 1. Patients' characteristics and therapeutic response[a]

Total	30	(12)
Sex:		
Men	24	(9)
Women	6	(3)
Median age (range)	61	(38–79) years
ECOG performance status:		
0	12	(6)
1	9	(2)
2	4	(3)
3	5	(1)
Extent of disease:		
Limited	11	(6)
Extensive	19	(6)
Weight loss (≧10% body weight):		
Yes	5	(1)
No	23	(11)
Unclear	2	
Histology:		
Squamous-cell carcinoma	6	(5)
Adenocarcinoma	21	(7)
Large-cell carcinoma	3	
Response:		
CR	0	
PR	12	
Stable disease	12	
Progressive disease	6	

[a] Unless specified otherwise, values represent the number of patients; values shown in parentheses represent the number of patients who achieved a PR

CDDP was reconstituted with 0.9% NaCl solution immediately before its use and was infused by constant pump infusion for 5 consecutive days at a dose of 25 mg/m^2 daily. In practice, one-third of the daily dose was infused continuously every 8 h with 20 mEq of KCl and 1 mg/kg metoclopramide in 800 ml 0.9% NaCl solution. Moreover, for nausea and vomiting, methylprednisolone (125 mg) was given intravenously over 30 min simultaneously with the start of CDDP administration and thereafter every 8 h for 5 consecutive days. Therapy was repeated every 4 weeks.

Patients were evaluated for response after completion of one or two cycles. A complete response (CR) was defined as the complete disappearance of all known disease as indicated by examinations done at least 4 weeks apart. A partial response (PR) was defined as a reduction of ≧50% in the product of the longest perpendicular diameters of all measurable lesions for ≧4 weeks, without the appearance of new lesions. Stable disease (SD) was defined as either a reduction of <50% or an increase of <25% in the product of the longest perpendicular diameters of the measurable lesions, without the occurrence of new lesions for ≧4 weeks. Progressive disease (PD) was defined as an increase of ≧25% in the tumor area or the appearance of new lesions. The duration of response was defined as the time from the start of chemotherapy until the appearance of the first sign of progressive disease. Survival curves from day 1 of treatment until death were calculated by the method of Kaplan and Meier [7]. Toxicity criteria was used as recommended by the World Health Organization (WHO) [10].

Therapy was discontinued if disease progression occurred after the first course of treatment or if SD was observed after the second course. In patients showing a PR or CR, treatment was continued for a total of four courses (4 months). Responding patients with limited disease received chest radiation therapy (RT) (50–60 Gy) after this treatment. Patients who were resistant to chemotherapy or who relapsed received CDDP at 25 mg/m^2 daily for 1–5 days by continuous infusion, plus 3 mg/m^2 vindesine (VDS) on days 1 and 8 every 4 weeks as second-line chemotherapy, depending on the patient's clinical condition.

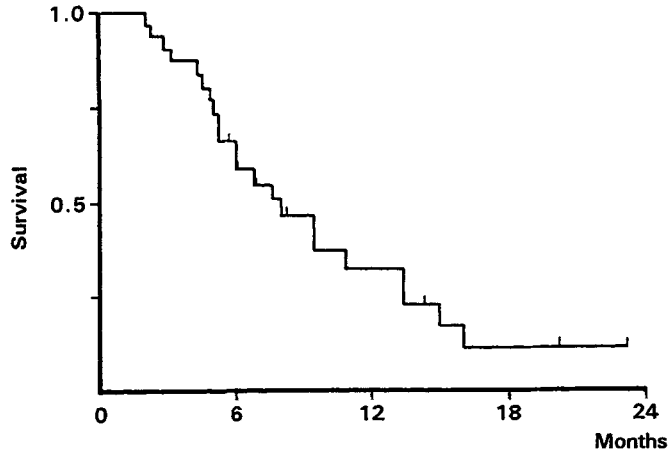

Fig. 1. Actuarial survival curve for 30 patients with NSCLC who were treated with a 5-day continuous infusion of CDDP

Blood samples were obtained at 0, 3, 6, 24, 48, 72, 96, and 120 h during infusion and at 30, 60, and 180 min and 6, 12, 24, 48, and 72 h postinfusion. Blood was collected in a heparin-containing syringe, and plasma was immediately separated by centrifugation at 600 *g* for 10 min. Part of the plasma was immediately passed through an Amicon MPS-3 filter (Amicon Corporation, Danvers, Mass., USA) by centrifugation at 2,000 *g* for 20 min at 4° C for the removal of protein. Both the ultrafiltered, protein-free plasma and whole plasma were stored at –70° C until analysis. Platinum concentrations in plasma (total platinum) and plasma ultrafiltrate (free platinum) were measured using an electro-thermal atomic absorption spectrophotometer (Spectra AA-40, Varian Techtron, Australia), with monitoring of the 265.9-nm line at 6 mA and 0.2 nm. For the preparation of samples for total platinum measurement, 200 µl plasma was diluted with 2 vol. 0.2% Triton X solution. For determination of ultrafilterable platinum, samples were first centrifuged as described above. The area under the curve (AUC) for platinum in plasma ultrafiltrate was determined during infusion and up to 24 h postinfusion by the linear trapezoidal method.

Results

All of the 30 patients entered in this study were evaluable for therapeutic response and toxicity; patients' characteristics and therapeutic responses are summarized in Table 1. A median of 3 treatment cycles were completed (range, 1–4 cycles).

No CR was observed; however, 12 patients achieved a PR, for an overall response rate of 40 % (12/30; 95% confidence limits, 23–58%). PRs were achieved by 5 of 6 patients with squamous-cell carcinoma and by 7 of 21 patients with adenocarcinoma, but 3 patients with large-cell carcinoma failed to respond to chemotherapy. The median duration of response for all patients who achieved a PR was 3.5 months (range, 2.6–10.4 months). The median survival for all patients was 8 months (Fig.1). Overall, 6 patients received chest RT; 8 of the 18 patients who had failed 5-day continuous infusion of CDDP received second-line chemotherapy with CDDP plus VDS, and a PR was noted in 2 cases. Of the 12 responding patients, 11 relapsed; 5 of them received second-line chemotherapy but none responded.

Table 2. Toxicity

	Maximum toxicity according to WHO grade: No. of patients				
	0	1	2	3	4
Leukopenia	14	4	8	4	0
Thrombocytopenia	22	3	4	1	0
Anemia	7	5	14	4	0
Fatigue	4	11	14	1	0
Nausea, vomiting	3	16	11	0	0
Diarrhea	29	0	1	0	0
Alopecia	21	9	0	0	0
Neurotoxicity (peripheral)	27	3	0	0	0
Elevated SGOT/SGPT	29	0	1	0	0
Elevated serum creatinine	28	2	0	0	0

Table 2 outlines the toxicity observed. Hematologic toxicity was generally mild. The median leukocyte count nadir for all patients was 3,400/mm^3 (range, 1,000–6,500/mm^3); 4 patients (13%) had WHO grade 3 leukopenia (1,000–1,900/mm^3). The median platelet count nadir was 138,000/mm^3 (range, 37,000–265,000/mm^3); only 1 patient (3%) experienced WHO grade 3 thrombocytopenia (25,000–50,000/mm^3), and no platelet transfusions were required. The median hemoglobin nadir was 9.5 g/dl (range, 6.8–13.7 g/dl). Four patients (13%) showed WHO grade 3 anemia (6.5–7.9 g/dl) and were given blood transfusions. WHO grade 1–2 fatigue was frequent, but it disappeared within 1 week after drug administration. In all, 53% of all patients experienced nausea, and transient vomiting occurred in 37%; 10% of patients reported no nausea or vomiting. Creatinine elevations (WHO grade 1) were observed in two patients (7%) but returned to levels of <1.5 mg/dl within 1 week. There were no treatment delays, refusals of further treatment due to toxicity, or treatment-related deaths.

A pharmacokinetic study was carried out in 14 patients, and the results are shown in Fig. 2. The maximal concentrations of total and ultrafilterable platinum were 2.114±0.323 μg/ml (range, 1.330–2.460 μg/ml) and 0.092±0.027 μg/ml (range, 0.049±0.126 μg/ml), respectively. The terminal half-life of ultrafilterable platinum was 126±70 min (range, 48–240 min). After the 24-h postinfusion period, the ultrafilterable platinum level dropped to or below the detection limit of 0.025 μg/ml. The AUC for ultrafilterable platinum was 9.08±3.21 μg h ml^{-1} (range, 4.59–15.66 μg h ml^{-1}).

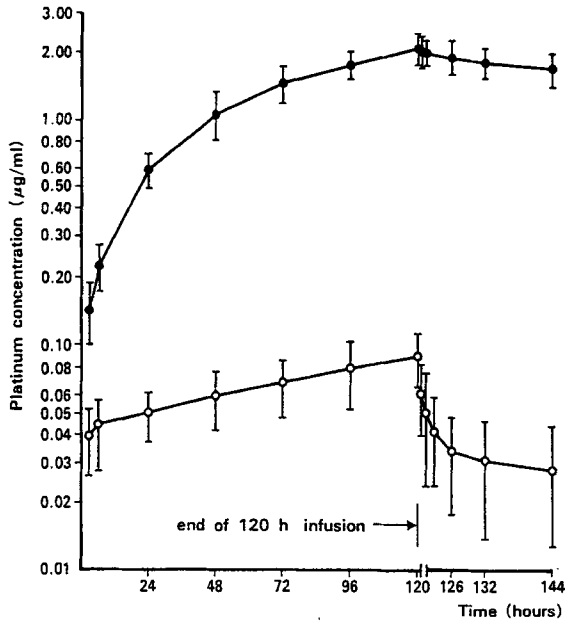

Fig. 2. Plasma level of platinum (●——●: total platinum, ○——○: filterable platinum) in 14 patients treated with 5-day continuous infusion of cisplatin. The vertical bars represent mean±SD of 14 patients

Discussion

CDDP is one of the most active agents in NSCLC patients, with a reported overall response rate of 21% [2]. Three trials carried out in previously untreated NSCLC by Casper et al. [3], De Jager et al. [4], and Klastersky et al. [8], who gave the same total CDDP dose (120 mg/m^2) by bolus administration, yielded overall response rates of 10%, 35%, and 19%, respectively. The 40% response rate reported in the present study for a single agent is both encouraging and consistent with results reported for combinations containing CDDP that were given by short-term bolus infusion to patients with NSCLC [2]. Belliveau et al. [1] reported that the AUC exposure of filterable platinum was greater after a 5-day continuous infusion (9.6 μg h ml^{-1}) at a daily dose of 25 mg/m^2 than that calculated for a short-term infusion (4.8 μg h ml^{-1}) at a similar dose level. In the present study, the AUC value was similar to that reported by Belliveau et al. [1]. This high AUC value was presumably associated with the promising response rate achieved in our study, as a study by Drewinko et al. [5] suggested that CDDP cytotoxicity to neoplastic cells was enhanced by prolonged low-dose exposure to this drug.

In spite of the high CDDP dose given (125 mg/m^2) in the present study, the toxicities were relatively mild and well tolerated. Vomiting (which poses a major obstacle to prolonged use of CDDP) of WHO grade 2 occurred in only 37% of patients. Elevated serum creatinine levels were observed in only two patients (7%), and both cases were WHO grade 1 and proved to be reversible. In comparison with data from studies in which CDDP as a single agent was infused at the same dose by short-term infusion [3, 4, 8], the incidence of vomiting and elevated serum creatinine was low in the present study. In contrast, the incidence of hematologic toxicity was slightly high. This toxicity might be more severe in association with regimens using the present infusion schedule in combination with other anticancer agents; however, it can be ameliorated by the use of recombinant human granulocyte-colony-stimulating factor [6].

This treatment modality was well tolerated and produced a response comparable with that normally observed after combination therapy, but with lower toxicity. We conclude that 5-day continuous infusion is a safe and effec-

tive method of CDDP administration in patients with NSCLC, and it provides a basis for the addition of agents for further augmentation of CDDP's therapeutic efficacy.

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