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Phase I study of oxaliplatin in patients with advanced cancer

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Summary. Oxaliplatin, or trans-1-diaminocyclohexane-platinum, was tested in a phase I study. A total of 44 patients received 116 courses with dose escalation from 45 to 200 mg/m^2. Neither renal nor hematologic toxicities were observed at doses up to 200 mg/m^2. Gastrointestinal toxicity was practically constant and often of grade 3–4 on the WHO scale (53% of patients). The dose-limiting toxicity was a peculiar sensory neuropathy; the first neurologic phenomena appeared at a dose of 135 mg/m^2 and continued thereafter, occurring after 75% of the courses with mild to moderate intensity (WHO grade 1–2 after 67% of the courses). Neurotoxicity was cumulative and six patients developed grade 3 disabling neuropathy after a cumulative dose of 500 mg/m^2, with walking and handwriting difficulties being slowly regressive in three cases. A peculiar symptom was the influence of temperature, with exacerbation of paresthesias when patients touched cold surfaces. Nerve-conduction studies carried out in six cases showed a predominantly sensory neuropathy with axonal degeneration. No other toxicities were observed, although audiograms were not systematically done. We observed four partial responses that lasted 6–13 months in patients with oesophageal (2 cases), lung (1), and urothelial cancer (1); two of these patients had been pretreated with cisplatin. Since neurologic side effects occur very frequently and may produce a long-lasting sensory neuropathy, for phase II studies we recommend a starting dose of 135 mg/m^2, with a careful neurologic survey.

Introduction

Cisplatin (CDDP) has demonstrated significant antitumor activity against animal and human malignancies. It is one of the best available cytotoxic drugs against testicular, ovarian, and head and neck cancers [1, 16, 26]. However, its use is limited by renal toxicity, severe nausea and vomiting, and, after large cumulative doses, occasional neurotoxicity.

With the aim of avoiding or reducing these deleterious side effects, numerous analogs of CDDP have been developed [3] and studied to obtain other active but less toxic compounds. Among them, carboplatin has reached phase III studies, demonstrating a similar antitumor activity in ovarian cancer [25]. Carboplatin produces moderate nausea and vomiting but no renal toxicity or ototoxicity; however, its major dose-limiting toxic effect is myelosuppression, and carboplatin doses have to be reduced when it is given with other myelotoxic agents.

Platinum complexes of diaminocyclohexane (DACH) isomers have been extensively studied in L1210 and P388 mouse leukemias, ascitic sarcoma 180, and murine solid tumors [9–11]. The trans-1 isomer called 1-OHP (trans-1-diaminocyclohexane platinum) appears to produce the maximal treated/control values in L1210 leukemia. A comparison of 1-OHP and CDDP [14] in these models gave similar results for the two compounds, but no nephrotoxicity was observed with 1-OHP as opposed to CDDP.

A phase I study was first conducted by Mathe et al. [15] in advanced cancer patients, with intrapatient dose escalation. The starting dose was $^1/_{10}$ of the maximally effective dose in mice, and a dose of 45 mg/m^2 was reached without limiting toxicity. Interestingly, four partial responses were observed among the 22 patients. To determine the maximal tolerated dose and dose-limiting toxicities, we undertook a new phase I study using a starting dose of 45 mg/m^2.

Patients and methods

To be eligible for this study, patients had to fulfill the following criteria: histologic proof of a malignant disease that had failed to respond to conventional chemotherapy or for which no such therapy existed, a minimal interval of 4 weeks since prior chemotherapy or radiotherapy, a minimal life expectancy of 8 weeks, and a WHO performance status of <4. All patients showed evidence of adequate bone marrow function (WBC count of $>3\times10^9$/l and platelet count of $>100\times10^9$/l), adequate liver function (bilirubin levels of <32 μmol/l), and adequate renal function (creatinine values of <200 mmol/l). All patients were informed of the investigational nature of this treatment.

Oxaliplatin was supplied by Roger Bellon laboratories in vials containing 10 and 100 mg. The drug was given by i. v. infusion in 0.9% NaCl, without pre- or post-hydration. The initial duration of perfusion was 1 h, which was prolonged to 6 h for doses of >60 mg/m^2 in an effort to

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Table 1. Diagnoses

Tumor type	Patients (*n*)
Lung cancer	11
Oesophageal cancer	7
Ovarian cancer	6
Adenocarcinoma of unknown primary	4
Soft-tissue sarcoma	4
Bladder cancer	3
Colon cancer	2
Cervix cancer	2
Breast cancer	1
Kidney cancer	1
Pleural mesothelioma	1
Teratoma	1
Vulvar cancer	1

Table 2. Dose-escalation scheme

Dose (mg/m^2)	Patients (*n*)	Courses (*n*)
45	3	5
60	2	7
90	3	5
135	14	39
150	14	28
175	7	22
200	5	10

Table 3. Gastrointestinal toxicity

Dose (mg/m^2)	Patients (*n*)	WHO grade:				
		0	1	2	3	4
⩽90	8	0	2	2	3	1
135	12	0	2	2	8	0
150	11	1	2	3	4	1
175	7	1	2	1	2	1
200	5	0	1	0	3	1
Totals	43[a]	2	9	8	20	4

[a] One patient was nonevaluable

reduce gastrointestinal toxicity. The drug was given at 4-week intervals.

Antiemetics were not systematically given until the dose reached 90 mg/m^2, when gastrointestinal toxicity was universal.

A cohort of three patients was studied at the starting dose, and additional patients were entered at higher doses if no dose-limiting toxicity had occurred at the initial dose. Subsequent doses were chosen according to a modified Fibonacci scheme. There was no intrapatient escalation, but four patients received two different doses.

Serum tests were carried out on the day of therapy and weekly thereafter. These included determinations of sodium, potassium, chloride, creatinine, liver enzymes and bilirubin, WBC counts with differential counts, hemoglobin, and platelets. Monthly magnesium and phosphorus determinations as well as electrocardiograms and chest roentgenograms were carried out. Other investigations were done according to the individual patient's symptoms. Toxicities were evaluated according to WHO criteria.

Results

A total of 44 patients entered this phase I study and received 116 courses (median, 2; range, 1–6), including 28 men and 16 women with a median age of 57 years (range, 26–81 years). In all, 22 patients had a performance status of 2–3. The tumor types are described in Table 1.

Prior to this study, 38/44 subjects had received chemotherapy consisting of a median of four cytotoxic agents (range, 1–11), and 32 patients had received CDDP (median cumulative dose, 210 mg/m^2; range, 80–700 mg/m^2).

The number of patients and courses at each dose level is shown in Table 2. The cohort of subjects who received 150 and 135 mg/m^2 is important because of the limiting neurologic toxicity that appeared at these doses. No direct treatment-related death occurred in this study. All but two patients experienced nausea and vomiting, which occurred at the lower doses (Table 3). The severity of vomiting did not appear to be dose-related, and grade 3–4 emesis was noted in 24/43 cases; however, it was of short duration. Diarrhea occurred less frequently (24% of courses) and was less severe (90%, grade 1–2). Gastrointestinal toxicity was not influenced by the duration of the infusion (1 h vs 6 h).

Hematologic toxic effects secondary to oxaliplatin treatment are shown in Table 4. No severe (grade 3–4) leukopenia was observed, the nadir being 2.6×10^9 cells/l.

Table 4. Hematologic toxicity

Dose (mg/m^2)	WBC nadir ($\times 10^9$/l):		Platelet nadir ($\times 10^9$/l):		Hemoglobin nadir (g/l):	
	Median	Range	Median	Range	Median	Range
⩽90	10	3.9–17.6	277	160–360	94	70–120
135	5.9	3.4–9.7	181	50–338	101	85–120
150	4.7	2.6–7.2	140	16–221	105	80–130
175	4.2	3.0–5.5	114	63–175	107	90–126
200	4.7	2.6–6.3	124	75–220	86	77–100

Table 5. Incidence of neurologic side effects during the first course

Dose (mg/m^2)	Patients (n)	Patients with neurologic side effects:	
		(n)	(%)
135	14	7	(50%)
150	14	9	(64%)
175	7	5	(71%)
200	5	5	(100%)

Table 6. Intensity of neurotoxicity

Dose (mg/m^2)	Evaluable courses (n)	Courses with neurotoxicity (WHO grade):			
		0	1	2	3
135	39	15	19	4	1
150	28	6	14	5	3
175	22	3	12	5	2
200	10	1	6	2	1
Totals	99	25	51	16	7

Table 7. Influence of cumulative dose on neurotoxicity

Cumulative dose (mg/m^2)	Patients (n)	Patients with neurotoxicity (WHO grade):			
		0	1	2	3
<270	21	14	5	1	1
270–540	11	3	7	2	0
>540	9	0	3	1	5

Mild to moderate thrombocytopenia (grade 1–2) was observed in 14/90 evaluable courses. One severe case of thrombopenia (10×10^9 platelets/l) was observed in a women who had previously developed grade 4 thrombocytopenia after each course of CDDP. Thrombocytopenia was dose-related; it did not occur in any of the patients treated with 45–90 mg/m^2 but was seen in 13% of patients receiving 135–150 mg/m^2 and in 28.5% of those treated with 175–200 mg/m^2. No significant renal toxicity was observed. Four cases of grade 1 and one case of grade 2 renal toxicity were rapidly reversible. However, sequential creatinine clearance measurements were not systematically carried out. No significative changes were observed for magnesium, calcium and other electrolytes.

The dose-limiting side effect was a peculiar neurotoxicity. Paresthesias of fingers, hands, toes and, sometimes, lips developed with a dose-related frequency. They were not observed below 90 mg/m^2 but occurred during the first course with an incidence of 50%, 64%, 71%, and 100% at doses of 135, 150, 175, and 200 mg/m^2, respectively (Table 5). These side effects occurred in 75% of courses at doses of >90 mg/m^2, and their intensity was generally mild (51% of courses) to moderate (16%) according to WHO criteria (Table 6).

Clinically, paresthesia appeared during 1-OHP infusion, and the duration of symptoms was brief (<1 week) after the first course but tended to be longer with subsequent courses. Sensory neuropathy developed after subsequent courses, with increasing intensity (grade 3 toxicity was noted after the fourth course in 5/6 patients), with increasing duration (symptoms were permanent after the fourth course in 63% of cases vs 10% before this course). In these cases dysesthesias involved the extremities as well as the forearms, legs, mouth, and throat. Six patients developed grade 3 neurotoxicity, one of whom had a very transient laryngospasm at two consecutive courses, and five after the fourth course. Four of the latter developed marked ataxia, with difficulty in walking.

This neuropathy has slowly regressed with symptoms disappearing after 6 months. Table 7 shows the relationship between the cumulative dose and the severity of neurotoxicity.

When carried out (in six cases), electromyograms showed an axonal sensory neuropathy. No significant changes in motor nerve-conduction velocities were noted.

Table 8. Characteristics of eigth patients with a partial response or stable disease

Tumor type	Dose (mg/m^2)	Courses (n)	Response[a] (duration in months)	Prior response to CDDP[b]
Urothelial	60	5	PR (6)	NE
Oesophageal	135	5	PR (6)	+
Lung	135	6	PR (10)	NE
Oesophageal	175	6	PR (13)	–
Cervical	150	3		
	175	3	SD	+
Pleural mesothelioma	175	6	SD	NE
Teratoma	150	6	SD	+
Chondrosarcoma	175	5	SD	–

[a] PR, partial response; SD, stable disease
[b] NE, no prior exposure to CDDP; +, patients responding to CDDP; –, patients whose disease progressed during CDDP therapy

There was no clear correlation between these neurologic side effects and previous exposure to CDDP or vinca alkaloids: 59% and 42% of patients with and without prior CDDP treatment, respectively, developed neurologic side effects after receiving 1-OHP. The median cumulative doses of CDDP and 1-OHP were 270 and 845 mg/m^2, respectively, for subjects with grade 2–3 neurotoxicity, 330 and 400 mg/m^2 for those with grade 1 neurotoxicity, and 90 and 175 mg/m^2 for patients without neurologic side effects. Neither central nervous system toxicity nor ototoxicity was observed, although audiograms were not systematically done.

Other toxicities included phlebitis (one case), mild fever (three cases), and transient and mild increases in liver enzymes (six cases). Neither cardiac toxicity nor alopecia was observed in the evaluable patients.

Objective responses were observed in four subjects, with partial responses of 6–13 months' duration. Four other patients had a stabilisation of their disease, with no progression occurring for >6 months.

Of these eight patients, five had previously been treated with CDDP, two of them showing disease progression under this drug (Table 8). The first of these two patients had oesophageal cancer that had progressed on therapy consisting of CDDP, fluorouracil, and bleomycin, with the appearance of disease in the left supra-clavicular lymph node; this patient responded to 1-OHP and relapsed after 13 months. The second subject had developed progressive lung metastases of chondrosarcoma on therapy with CDDP, etoposide, and ifosfamide and experience a good stabilisation after 6 months of 1-OHP treatment. Interestingly, all partial responders had cancer of epithelial origin.

Discussion

Oxaliplatin, a new DACH-platinum analog, was evaluated in 44 patients at a dose range of 45–200 mg/m^2. Neither hematologic nor renal toxicities were dose-limiting. Gastrointestinal toxicity was practically constant and frequently severe (grade 3–4 in 24/43 cases) but not unequivocally dose-related.

The dose-limiting toxicity was neurologic, with a peculiar sensory neuropathy occurring first at a dose of 135 mg/m^2 and very frequently at higher doses. Its onset was acute, cold-related, and mainly involved the extremities. Its duration and intensity were influenced by the cumulative dose, with three patients developing a disabling neuropathy that regressed slowly; these patients received a dose of >500 mg/m^2 1-OHP. Interestingly, these side effects were not influenced by prior exposure to CDDP.

Neurotoxicity is rarely dose-limiting with cytotoxic agents other than cisplatin, vinca alkaloids, and hexamethyl-melamine. Peripheral neuropathies have rather infrequently been identified with CDDP therapy, with an incidence range of 2.7% [24] to 4.3% [20]; however, these studies were retrospective, and recent, careful neurologic surveys [21] have noted a predominantly sensory peripheral neuropathy in 92% of patients receiving the compound. In the present study as well as others using CDDP [2, 7], the development of peripheral neuropathy appeared to be dose-related, with most patients receiving a cumulative dose of ⩾300 mg/m^2. With high-dose CDDP regimens (40 mg/m^2 daily ×5), disabling neurototoxicity has recently been noted, with an increased incidence ranging from 29% to 62.5% [4, 5, 12, 18, 19, 23]. Clinically, except for the effect of cold, 1-OHP-induced neuropathy mimicked that of CDDP, with predominantly sensory symptoms affecting the upper and lower extremities.

Paresthesias and dysesthesias are characteristic of this neuropathy; in severe cases, handwriting and walking difficulties are presumably related to proprioceptive abnormalities [7]. With both drugs, disabling neuropathy developed only after a high cumulative dose (300 mg/m^2 for CDDP, 500 mg/m^2 for 1-OHP); although all symptoms improved after the discontinuation of therapy, in some cases long-term deficits persisted. The main differences between 1-OHP- and CDDP-related neuropathy involve its acute onset at a dose of 135 mg/m^2 1-OHP and its temperature dependency, with exacerbation of symptoms after contact with cold surfaces or liquids.

Nerve-conduction studies and nerve biopsies have been carried out in CDDP-induced neuropathy, suggesting that the toxic mechanism involves segmental demyelinisation [2, 17] or axonal degeneration [6, 13]. Several authors [6, 8] have suggested that CDDP peripheral neuropathy might be similar to that of thallium salt toxicity. Others have suggested vitamin B12 inactivation, but this was not confirmed in a recent study [22]. More studies are needed to clarify the actual mechanisms of platinum-salt neurotoxicity. This neurotoxicity is a particularly prominent problem with oxaliplatin, but we noted that when symptoms (paresthesias) receded completely between two courses, there was no long-lasting sensory neuropathy. In contrast, when symptoms lasted until the subsequent course and the treatment was continued, severe sensory neuropathy was more likely to occur.

During this phase I study on 44 subjects, we observed four partial responses in patients with oesophageal (2), lung (1), and urothelial cancers (1). For future phase II studies, we recommend a starting dose of 135 mg/m^2 and a careful survey of neurologic side effects (nerve-conduction studies), particularly after a cumulative dose of 500 mg/m^2, when these side effects are constant and patients are at risk to develop long-lasting sensory neuropathy.

References

1. Al Kourainy K, Kish J, Ensley J (1987) Achievement of superior survival for histologically negative versus histologically positive clinically complete responders to cisplatin combination chemotherapy in patients with locally advanced head and neck cancer. Cancer 59: 233–238
2. Beecher R, Schutt P, Osieka R, Schmidt CG (1980) Peripheral neuropathy and ophthalmologic toxicity after treatment with *cis*-dichlorodiamminoplatinum (II). J Cancer Res Clin Oncol 96: 219–221
3. Bradner WT, Rose WC, Huftalen JB (1980) Antitumor activity of platinum analogs. In: Cisplatin: current status and new developments. (Prestayko, New York, pp 171–182
4. Forastiere AA, Takasugi BJ, Baker SR, Wolf GT, Kudla-Hatch V (1987) High-dose cisplatin in advanced head and neck cancer. Cancer Chemother. Pharmacol 19: 155–158
5. Gandara D, Gregorio M de, Wold H, Wilbur BJ, Kohler M, Lawrence HJ, Deissroth AB, George CB (1986) Modified dose schedule of high-dose cisplatin. Reduced toxicity and correlation with plasma pharmacokinetics. A Northern

California Oncology Group pilot study in non-small-cell lung cancer. J Clin Oncol 4: 1787–1793
6. Gastaut JL, Pellissier JF, Jean P, Tubiana N, Carcassonne Y (1982) Neuropathie périphérique au cisplatine. Une observation. Nouv Presse Med 11: 1113–1117
7. Hadley D, Herr HW (1979) Peripheral neuropathy associated with *cis*-dichlorodiammine platinum(II) treatment. Cancer 44: 2026–2028
8. Kedar A, Cohen ME, Freeman AI (1978) Peripheral neuropathy as a complication of *cis*-dichlorodiammine platinum(II) treatment: a case report Cancer Treat Rep 62: 819–821
9. Kidani Y, Inagaki K (1978) Antitumor activity of 1,2-diaminocyclohexane-platinum complexes against sarcoma-180 ascites form. J Med Chem 21: 1315–1318
10. Kidani Y, Inagaki K, Isukagoshi S (1976) Examination of antitumor activities of platinum complexes of 1,2-diaminocyclohexane isomers and their related complexes. Jpn J Cancer Res 67: 921–922
11. Kidani Y, Noji M, Tashiro T (1980) Antitumor activity of platinum(II) complexes of 1,2-diamino cyclohexane isomers. Jpn J Cancer Res 71: 637–643
12. Legha SS, Dimery IW (1985) High dose cisplatin administration without hypertonic saline: observation of disabling neurotoxicity. J Clin Oncol 3: 1373–1378
13. Manas A, Cubillo S, Alonso E (1979) Monitoring peripheral neurotoxicity from cis-platinum (DDP). Abstracts of the 5th Annual Meeting of the Medical Oncology Society, Nice, December 5–7, p 31
14. Mathe G, Kidani Y, Noji M, Maral R, Bourut C, Chenu E (1985) Antitumor activity of 1-OHP in mice. Cancer Lett 27: 135–143
15. Mathe G, Kidany Y, Triana K, Brienza S, Ribaud P, Goldschmidt E, Esctein E, Despax R, Musset M, Misset JL (1986) A phase I trial of trans-1-diaminocyclohexane oxalatoplatinum (1-OHP). Biomed Pharmacother 40: 372–376
16. Merrin CE (1979) Treatment of genitourinary tumors with *cis*-dichlorodiammine platinum(II): experience in 250 patients. Cancer Treat Rep 63: 1579–1584
17. Ostrow S, Egorin MJ, Hahn D, Markus S, Leroy A, Chang P, Klein M, Bachur NR, Wiernik PH (1980) *cis*-Dichlorodiammine platinum and Adriamycin therapy for advanced gynecological and genitourinary neoplasms. Cancer 46: 1715–1721
18. Ozols RF, Corden BJ, Jacob J, Wesley MN, Ostchega Y, Young RC (1984) High dose cisplatin in hypertonic saline. Ann Intern Med 100: 19–24
19. Ozols RF, Ostchega Y, Meyers CE, Young RC (1985) High dose cisplatin in hypertonic saline in refractory ovarian cancer. J Clin Oncol 3: 1246–1250
20. Panettiere FJ (1981) Cisplatinum toxicity: an analysis based on three SWOG studies. Proc Am Assoc Cancer Res 22: 157
21. Roelofs RI, Hrushesky W, Rogin F, Rosenberg GL (1984) Péripheral sensory neuropathy and cisplatin chemotherapy. Neurology 34: 934
22. Trugman J, Hogenkamp HPC, Roelofs R (1985) Cisplatin neurotoxicity: failure to demonstrate vitamin B12 inactivation. Cancer Treat Rep 69: 453–455
23. Trump DL, Hortvet L (1985) Etoposide and very high dose cisplatin: salvage therapy for patients with advanced germ cell neoplasms. Cancer Treat Rep 69: 259–261
24. Von Hoff DD, Reichert CM, Cuneo R, Reddick R, Gallagher M, Rozencweig M (1979) Demyelination of peripheral nerves associated with *cis*-diamminedichloroplatinum(II) (DDP) therapy. Proc Am Assoc Cancer Res ASCO 20: 91
25. Wiltshaw E (1985) Ovarian trials at the Royal Marsden. Cancer Treat Rev 12: 67–71
26. Young RC, Fuks Z, Knapp R (1985) Cancer of the ovary. In: De Vita V Jr, Hellman S, Rosenberg SA (eds) Cancer: principles and practice in oncology. Lippincott, Philadelphia, pp 1083–1117

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