HIGH DOSE CIS-PLATINUM DIAMMINE DICHLORIDE

Amelioration of Renal Toxicity by Mannitol Diuresis

DANIEL M. HAYES, MD,* ESTEBAN CVITKOVIC, MD† ROBERT B. GOLBEY, MD,‡
ELLEN SCHEINER, MD,§ LAWRENCE HELSON, MD, ‖ IRWIN H. KRAKOFF, MD¶

A clinical trial was undertaken to improve the therapeutic index of cis-platinum diammine dichloride with a concomitantly administered mannitol induced diuresis. Sixty patients, heavily pretreated, were entered; fifty-one are evaluable. The technique of concomitant osmotic diuresis and CPDD administration is described in detail. Doses ranged from 3 mg/kg to 5 mg/kg. At 5 mg/kg, dose-limiting renal, marrow and ototoxicity were seen, and resulted in one drug death. Marrow toxicity was moderate. Renal toxicity was limited to transient elevations in serum creatinine levels, except in some patients who had renal impairment prior to CPDD treatment. These patients had moderate renal toxicity. Serial treatments as frequently as once every 3 weeks were used to maintain responses. Serial high dose CPDD produced only mild renal dysfunction. Ototoxicity, usually subclinical, was quantitated audiometrically, and found to be dose related, but not clinically prohibitive at 4 mg/kg or less. The overall response rate (PR/MR) was 42%. Clinically significant responses in epidermoid carcinoma of the head and neck, adenocarcinoma of the ovary, and germ cell tumors of the testis were seen. All six responding patients with germ cell tumor of the testis, had been resistant to low dose (1mg/kg) CPDD. Two responding patients with ovarian adenocarcinoma had been resistant to alkylating agents.

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CIS-PLATINUM DIAMMINE DICHLORIDE (NSC 119875), (CPDD), is the first of a group of platinum coordination complexes with known anti-neoplastic activity and the only one of the complexes extensively studied in humans. Despite significant anti-neoplastic activity in a variety of animal tumor models,[2] as well as proven effectiveness in the treatment of some human cancers, nephrotoxicity has prevented extensive use of CPDD in the treatment of cancer.[1,2,7,10,15,19,21] Consequently, consistent standardized dose administration and scheduling has never been established. There have been many attempts to increase the therapeutic index of this drug, using a variety of dose schedules, and concurrently administered drugs to alter renal function.[10,19]

Animal studies[4] have shown that pre-hydration, and a concomitant osmotic diuresis can prevent serious nephrotoxicity from CPDD that was given at doses greater than the conventionally used 1 mg/kg dosage. In the light of this encouraging work, a new trial of CPDD was undertaken. The aims of this trial were to achieve an increase in therapeutic index, to redefine the toxicity of CPDD used at these higher doses, to establish a better dose schedule of CPDD, and to fully define the activity of CPDD against a variety of tumors.

From the Memorial Sloan-Kettering Cancer Center, New York, NY.

* Clinical Fellow in Medical Oncology, Solid Tumor Service.

† Clinical Fellow in Medical Oncology, Solid Tumor Service.

‡ Attending Physician, Chief, Solid Tumor Service.

§ Attending Physician, Clinical Physiology Service.

‖ Attending Physician, Pediatric Service.

¶ Attending Physician, Chief, Clinical Chemotherapy Service.

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Address for reprints: E. Cvitkovic, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

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METHODS

Patients who could meet the following criteria were selected for entry into this study: histologic diagnosis of malignancy, disease that was measureable but not controlled by conventional therapeutic means, adequate marrow reserves, adequate renal function defined by a creatinine clearance of greater than 50 cc/min., and a performance status greater than 20%. Fully informed consent was obtained. All patients were treated as in-patients. Patients with serious cardiac or pulmonary disease were excluded. Baseline studies included complete history and physical, CBC, platelet count, SMA 12, urinalysis, 24 hour urine, creatinine clearance, IVP, chest x-ray, audiogram, and radionucleotide scanning when indicated to measure extent of disease.

As shown in Fig. 1, patients were prehydrated intraveneously with 2 l of 5% glucose in one-half normal saline during the night before Cis-platinum therapy. Patients were weighed before and after the treatment procedure. A Foley catheter was inserted on the morning of therapy, and urine volumes were measured accurately. The CPDD was reconstituted within one hour of therapy, with 1 ml of sterile water added for each milligram of CPDD. Immediately prior to infusion of the platinum compound, 12.5 g (50 ml of 25% mannitol) of mannitol solution was given in an intravenous bolus. The CPDD was infused as rapidly as possible over a 10–15 minute interval. A continuous infusion of mannitol, at the rate of 10 g (50 ml of 20% mannitol) per hour, was given intravenously for the next 6 hours. In order to replace the copious diuresis, one-half normal saline was infused at the rate of

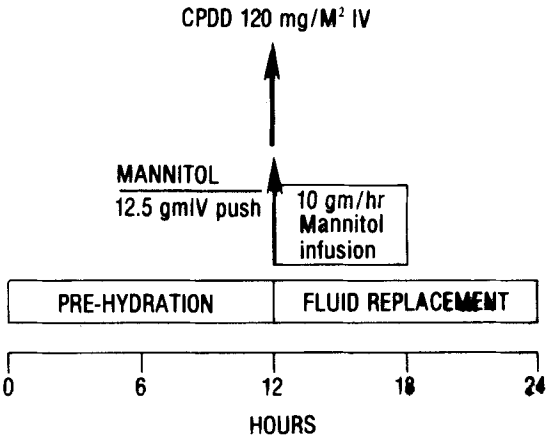

FIG. 1. Procedure of administration of high dose Cis-Platinum.

200 cc/hr during that 6 hours immediately after the CPDD administration. Regulation of the intravenous flow, as well as accurate recordings of urine output, was monitored at the bedside by the chemotherapy nurse. At the end of 6 hours, the diuresis was discontinued, and total fluid output (urine plus emesis) was replaced "cc for cc" every 2 hours until the next morning. Serum electrolytes, glucose, magnesium and urine electrolytes were monitored on the evening of the therapy; and intravenous infusions were thereafter adjusted accordingly. On the day after CPDD therapy, the Foley catheter was discontinued. Adequate hydration was maintained with further intravenous therapy if nausea and vomiting persisted for more than 18 hours after therapy. After the CPDD treatment, marrow function, renal function and fluid-electrolyte metabolism were observed daily for a week. Creatinine clearance and an audiogram were repeated within one week after therapy.

RESULTS

This study was begun on May 21, 1975, and ended on January 21, 1976. Encouraging results have subsequently mandated high dose CPDD clinical trials in head and neck cancer,[6] and also the incorporation of high dose CPDD into combination chemotherapy for the treatment of disseminated germ cell tumor.[5]

TABLE 1. High Dose Cis-Platinum Dose Groups

	mg/kg					Multiple
	3.0	3.5	4.0	4.5	5.0	doses
Total entered	19	10	3	3	5	20
Inadequate	3	4	0	1	1	0
Adequate courses	16	6	3	2	4	20
Drug deaths	0	0	0	0	1	0

Table 1 displays the dose groups studied. The dose of CPDD was periodically escalated by 0.5 mg./kg. The initial study dose was 3mg/kg (represented on Fig. 1 as 120 mg/m²), and maximal dose was 5mg/kg, one at which prohibitive toxicity occurred. Patients were given a second course of CPDD, (usually the same dose but occasionally lower), unless drug toxicity or disease progression prevented the second course. Patients, in whom antitumor effect with their initial CPDD treatment was documented, were given further courses at 4–6 week intervals. In these cases subsequent doses were always lowered to 3mg/kg, irrespective of the initial dose.

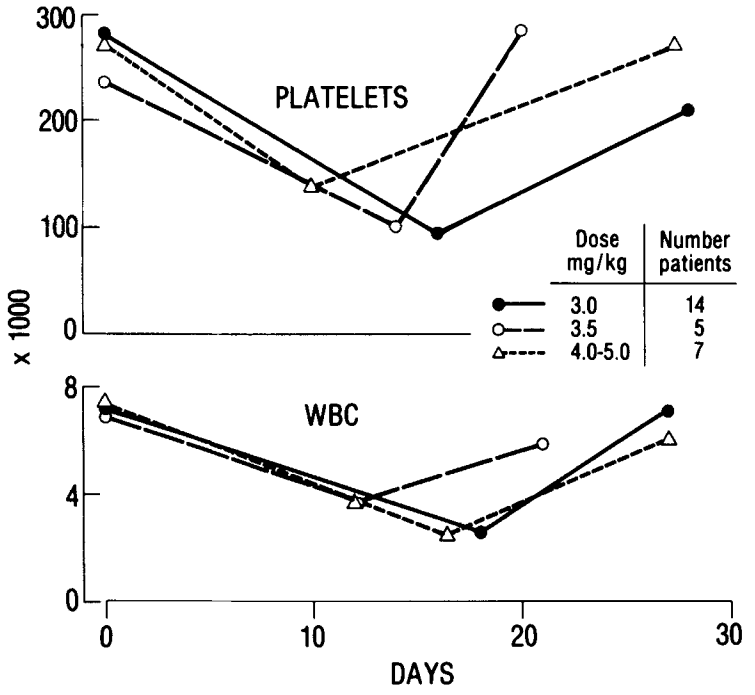

FIG. 2. Effect of high-dose Cis-Platinum, in single treatment courses, upon WBC and Platelets.

Sixty patients were entered into this study. Of these, fifty-one were evaluable for anti-tumor effect, with one drug death and eight premature, non-drug deaths accounting for the unevaluable patients. Table 1 displays these patients in the various dose groups used in the study.

Figure 2 displays the effect on blood counts of the patients treated with single courses of high dose Cis-platinum and mannitol. The data are arranged in dose groups. Because the numbers are small in the higher dose, single treatment groups, three patients are included who received doses greater than 4.0 mg/kg as the first course in their sequential, multiple course treatment. These data reveal that at doses greater than 4.0 mg/kg, there is no significant increase in the rapidity of count depression nor significant increase in the recovery time over that seen in the 3.0 mg/kg dose group. Although it prevented nephrotoxicity, mannitol diuresis did not prevent myelosuppression. The nadir of the blood counts was earlier, and recovery of marrow function was protracted, in patients who experienced severe renal insult. Of the 60 patients treated throughout the study there were 13 who had serious myelosuppression, defined as a white count of less than 2.0 or platelet count of less than 50,000. Associated with the leukopenia, there were five cases of sepsis, all successfully treated with antibiotics until white blood cells returned. There were six patients who required platelet transfusions.

There were seven patients who received therapeutic doses of corticosteroids during and after receiving high dose Cis-platinum therapy. Cortico-steroids did not alter, prevent or ameliorate the effect of CPDD or white blood count or platelets.

Renal function in 52 patients can be evaluated. Table 2 displays the renal toxicity, defined as the peak, post treatment serum creatinine level. Toxicity was limited to transient elevation of serum creatinine in most patients. Of the 10 patients who showed peak elevations of serum creatinine greater than 2.0 mg/100 ml, nine had significant renal abnormalities (ascites,

TABLE 2. High Dose Cis-Platinum Renal Toxicity

Dose mg/kg	Number patients	Serum Creatinine mg/100 ml < 2.0	2.0–3.0	3.0
3.0	17	13	2	2
3.5	6	6	—	—
4.0	3	2	—	1
4.5	2	1	—	1
5.0	4	3	—	1
Multiple dose	20	17	3	—

anasarca, creatinine clearances between 50 and 70 cc/min., hydronephrosis, one functioning kidney, or bilateral renal metastases) prior to CPDD treatment. The other remaining patient was one who received 5.0 mg/kg of CPDD, and who died of renal and marrow failure. The renal failure produced by CPDD in the nine patients that had pre-existing renal abnormalities was dose dependent and reversible. Figure 3 graphs serum creatinine levels against time in days for patients who were treated with single courses of CPDD, and who experienced no renal insult. The curve, fitted by means of polynomial regression analysis, depicts the transient rise and fall of the serum creatinine during high dose CPDD treatment. No consistent abnormality of urinalysis was seen after high dose CPDD treatment.

Figure 4 displays the serial creatinine clearances of 11 of those patients who received multiple courses of high dose CPDD. The recovery clearance represents the best return of creatinine clearance following the last CPDD treatment. None of the 20 patients in the multiple treatment group suffered serious renal toxicity.

Except for the one patient who died from drug toxicity (5mg/kg) all patients exhibited reversibility of CPDD-induced renal toxicity. One patient was markedly oliguric for 6 days before renal function slowly returned. All cases of acute nephrotoxicity were medically managed without dialysis.

One patient inadvertantly received 9 l of 5% dextrose as fluid replacement for 5 days after CPDD therapy, and suffered dilutional hyponatremia (serum sodium of 123 mEq/L), which was corrected. There were no other abnormalities of water or electrolyte balance associated with CPDD given by this method in any other patient.

Normochromic normocytic anemia has been known to occur with Cis-platinum therapy.[18] Because of the general debilitation and the extensive pre-treatment with both radiotherapy and chemotherapy of this patient population, no attempts were made to define any anemia that occurred. Patients were transfused whenever the need arose.

Hyperuricemia was seen only in patients who experienced moderate to severe renal insult with high dose Cis-platinum, despite the fact that some patients had rapid lysis of a great tumor burden. Patients were not routinely premedicated with allopurinol.

Throughout the entire study, there was never any fever associated with CPDD administration. There was no phlebitis seen with intravenous administration of this drug.

CPDD is known to become concentrated in the liver.[19] One patient, with known liver metastases, experienced a transient elevation of SGOT (96 to 378 to 81 international units) over the week after CPDD therapy (5mg/kg). There was no simultaneous change of bilirubin nor alkaline phosphatase. One other patient, with no known liver disease showed similar transient SGOT elevation associated with each of his three CPDD courses. Eleven other patients, with documented hepatic metastases, showed no transient elevations of SGOT, bilirubin of alkaline phosphatase. In the other patients, without metastases in the liver, there was no transient hepatic dysfunction.

While non-specific eruptions of the skin have been seen in workers of the platinum mines, dermatologic side effects from Cis-platinum have not been reported. During the course of this study, one patient experienced an erythematous pruritic macular eruption on his hands and scalp for about 10 days. This occurred 2 weeks after his second high dose Cis-platinum treatment. The patient was receiving no medication other than Prednisone at the time. His VDRL remained negative. The eruption was treated symptomatically and disappeared.

With increasing use of Cis-platinum there have been reports of systemic allergic reactions to the drug.[3,14] One patient was entered into this

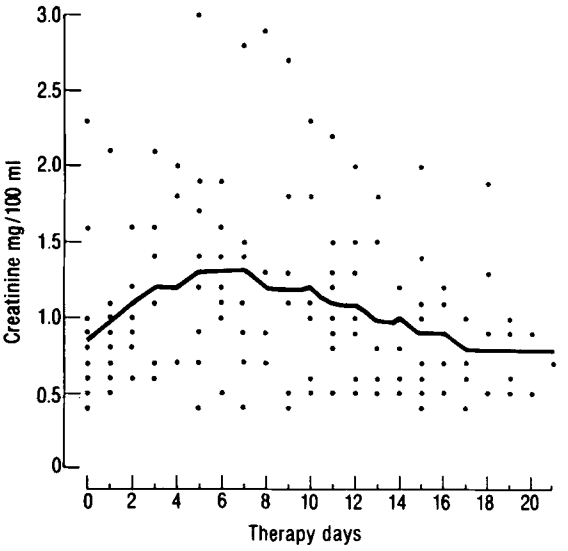

FIG. 3. Serum creatinine vs time, in patients treated with single courses of high dose Cis-Platinum. The curve represents the best fit by regression analysis of the means.

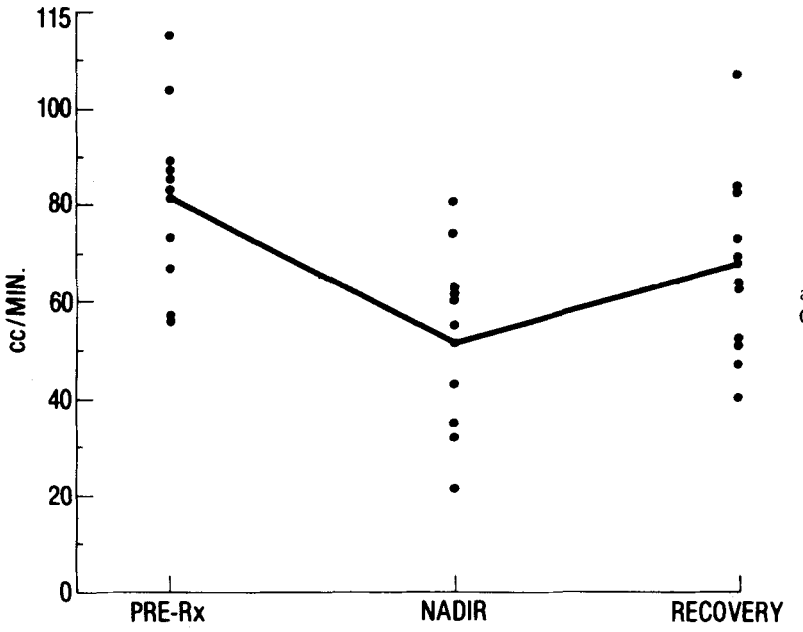

FIG. 4. Serial creatinine clearances before and after high dose CPDD, multiple treatments.

study who had germ cell tumor of the testes; his prior treatment had included courses of Cis-platinum at doses of 1 mg/kg, given intravenously every 4 weeks. With low dose CPDD he had developed a hypersensitivity manifested by tachycardia, diaphoresis, dyspnea. There was no associated bronchospasm nor hypotension. This patient received two courses of high dose Cis-platinum. He was pre-medicated with anti-histamines and parental corticosteroids. With each course, a test dose of 5 mg was given intravenously one-half hour before the therapeutic dose. He tolerated both treatments without hypotension or bronchospasm but did incur diaphoresis, mild dyspnea and tachycardia. No other patient experienced any CPDD related allergic phenomenon.

Serial air conduction studies of hearing were evaluated in 31 patients. These were grouped according to age: 21–39 years (17 and 54–70 years (14). Reference audiograms prior to administration of Cis-platinum were accomplished at the patient's bedside using a portable Bletone model 12D. Pure tone thresholds were detected at the following frequenceis: 500, 1,000, 2,000, 4,000, 6,000 and 8,000 hertz. Following therapy, absolute decibel losses were calculated by comparing subsequent audiograms with the reference values.

For analysis, the thresholds at 500, 1,000 and 2,000 hertz were considered low frequency, and those at 4,000, 6,000 and 8,000 were considered high frequency. Because threshold changes following drug administration were generally bilateral, the means of the changes were calculated by averaging results from both ears. In previous studies[18] reversibility of Cis-platinum induced ototoxicity was generally relegated to low doses (1–2 mg/kg). As the magnitude of the administered dose is increased, the threshold changes become less reversible. In this study, 28/31 serial audiometric observations were accomplished within 4 weeks and were plotted against the dose without regard to the time interval following drug administration (Table 3, and Figs. 5 and 6).

Transient reversible tinnitus was frequently seen at all doses of CPDD tested. Single courses of CPDD that were less than 4.0 mg/kg produced no clinically-detectable hearing loss. Two patients who received 5.0 mg/kg were rendered

TABLE 3. High Dose Cis-Platinum: Hearing Thresholds Loss vs Frequency and Age

	Hz	500, 1000, 2000 Age		4000, 6000, 8000 Age	
CPDD mg/kg		21–39	54–70	21–39	54–70
3–4.5	db	4.6	9	19	28
5–7	db		21		35

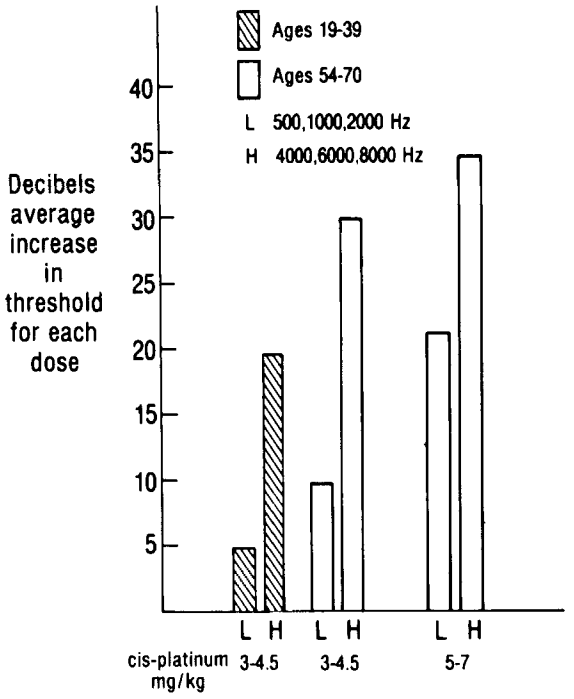

FIG. 5. Loss of hearing thresholds with high dose Cis-Platinum.

fully deaf. Three patients experienced clinically significant hearing loss after 3.0 mg/kg doses. These three patients had received a prior dose of 4.5 mg/kg. Most patients who underwent serial audiometric testing exhibited subclinical high frequency hearing loss. CPDD at doses of 3.0 mg/kg or more caused subclinical hearing losses in 90% (28/31) of the patients who were studied with serial audiometry on more than two occasions. These losses were detectable within 4 days and persisted up to 6 months in the surviving patients. Within the same dose range, older patients exhibited a greater increase in absolute hearing thresholds than younger patients. In the older patients studied, as the dosages increase, there is increasing perturbation of the lower frequencies (Figs. 5 and 6). Serial CPDD produced additive ototoxicity.

The overall response rate in fifty-one (51) evaluable patients who received high dose CPDD and mannitol induced diuresis was 42%. Responses are displayed by histology and primary site in Table 4. There were nine partial responses, varying from one to six months in duration. There were fourteen minor responses seen. All responses were maintained with sequential high dose CPDD alone, until disease progression was evident.

Nine patients with germ cell carcinoma of the testes were studied. All had received extensive prior treatment, with radiation and combination chemotherapy. All but two had performance statuses, at the time of treatment, or less than 50%. All partial responses (five) were clinically beneficial, showing a 30% or greater increase in performance status. All six responders had received prior CPDD at doses of 1 mg/kg and had grown resistant to that dose. Responses were seen in pulmonary, hepatic, epidural and retroperitoneal metastases.

One patient with primary mediastinal germ cell tumor, with metastases to brain, lung and bone, failed to respond to two courses of CPDD. Two patients with disseminated trophoblastic choriocarcinoma failed to show a fall in cho-

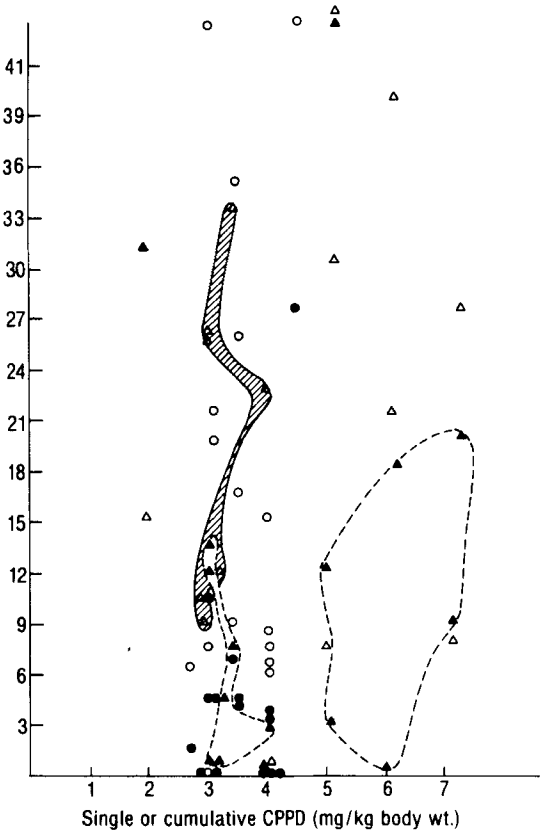

FIG. 6. Loss of hearing thresholds with high dose Cis-Platinum with key for age and frequency breakdown.

CPDD (mg/kg)		low H_z(500, 1000, 2000)		high (4000, 6000, 8000)	
	Age	21–39	54–70	21–39	54–70
		●	▲	○	△
3–4.5	Db.	4.6	9	19	28
5–7			21		35

TABLE 4. High Dose Cis-Platinum: Responses

Histology	Site	Total	Adequate	Partial Remission	Minor Response
Germ cell carcinoma	Testis	11	9	5(1-6)*	1
	Mediastinum	1	1	—	—
	Trophoblasts	2	2	—	—
	Ovary Dysgerminoma	1	1	—	1
Adenocarcinoma	Colon	6	4	—	3
	Ovary	3	2	1(3)	1
	Jejunum	1	1	—	—
	Kidney	4	4	—	1
	Gastric	1	1	—	—
	Breast	3	2	—	2
Epidermoid carcinoma	Nasopharynx	3	3	2(1+, 5)	1
	Oral Cavity	4	4	1(5+)	2
	Bladder	1	1	—	—
	Lung	4	3	—	1
Adenoid cystic	Parotid	1	1	—	—
Mesothelioma	Lung	2	1	—	—
Soft sarcoma	Mixed	6	5	—	—
Melanoma	Trunk	1	1	—	—
Lymphoma	HD	2	2	—	—
	NHL	3	3	—	1

* Durations in months

rionic gonadotrophin, (b-sub unit and urine HCG) or shrinkage of chest metastases with high dose CPDD.

One patient with widespread dysgerminoma of the ovary, unresponsive to radiation and other chemotherapy, had shrinkage of subcutaneous masses and stablization of large pelvic masses with CPDD.

Five patients with widespread metastatic colonic adenocarcinoma were adequately evaluated. All were heavily pretreated with nitrosurea, fluorouracil and vincristine. Three patients had minor responses to CPDD. None of the responses were associated with any unexpected prolongation of survival nor increase in performance status.

One patient with adenocarcinoma of the small bowel had no improvement in pulmonary metastases, after high dose CPDD therapy. One patient had been very heavily treated for gastric cancer, and failed to respond to CPDD. Two patients with adenocarcinoma of the ovary, in whom chlorambucil was ineffective in controlling disease, received high dose CPDD. One had marked shrinkage of pelvic masses and decrease in ascites for 3 months. The other patient developed acute renal failure and prolonged pancytopenia after CPDD treatment; but she did have considerable lessening in ascites and demonstrable shrinkage of pelvic masses which lasted for two months.

Four patients with hypernephroma were adequately evaluated. Three had undergone nephrectomy, all were pretreated with chemotherapy. One minor response was seen, with shrinkage of a skin nodule in a man who had stable pulmonary metastases, which failed to change with therapy.

One patient was entered who had bladder carcinoma, which was not controlled with cystectomy, external irradiation (6,000R) and CPDD at low (1.5 mg/kg) doses. He did not respond to high dose CPDD.

Seven patients were treated for metastatic head and neck carcinoma. All had been extensively treated with multiple surgical procedures, external irradiation, and chemotherapy. There were three partial responses. Two were clinically striking with regression of pulmonary metastases and return to functional performance status. One patient showed marked regression of huge pulmonary metastases, but died one month after therapy from complications of chronic obstructive pulmonary disease. In addition, three minor responses were seen in this group. One other patient with disseminated adenoid cystic carcinoma of the parotid failed to respond to high dose CPDD.

Four patients with non-oat cell lung cancer were treated. One patient, with epidermoid carcinoma of the lung, who did not respond to oral Cytoxan therapy, showed transient shrinkage of pulmonary masses with high dose CPDD. No response was seen in two patients with mesothe-

lioma of the lung; one was adequately evaluated, and the other died within one week of treatment, from progressive cancer.

No responses were seen in treatment of five patients with soft part sarcomas and extra-osseous osteogenic sarcoma. All had received prior treatment with Adriamycin and high dose Methotrexate. One patient with extensive subcutaneous and visceral melanoma metastases failed to respond.

Five patients with lymphoma were entered adequately. All were very heavily pretreated, and had performance statuses of less than thirty percent. One patient had shrinkage of a massive liver, which lasted less than 1 month. There were no other responses seen with high dose CPDD in lymphomas.

DISCUSSION

There are many attempts reported in the literature to increase the rather low therapeutic index of CPDD. These maneuvers vary from repeated attempts to chemically purify the compound, to the use of concurrently administered drugs such as N-acetyl-L-cysteine, spironolactone, salicylamide, or D-penicillamine.[10,19] Piel and Perlia had suggested that a different mode of administration would result in diminished hematologic and renal toxicity.[18] They refer to giving CPDD by "intravenous (IV) drip at a rate of approximately 1 mg/min. in a dilution of 1 mg/ml to well hydrated patients and followed by continuous IV hydration for a period of at least 24 hours."[18] No data were actually displayed to prove that an increase in therapeutic index was achieved. Cvitkovic *et al.*[4] have demonstrated that vigorous prehydration and a concomitant mannitol induced diuresis could increase the therapeutic index of CPDD administered in a rapid bolus to dogs. This method has now been employed in conventional phase I human studies, and an increase in therapeutic index has been demonstrated. The severe renal toxicity that CPDD can produce had been the major factor in determining the method of administration of this drug: unit dose, total dose, rate of administration, schedule or interval between courses. Gottlieb has reported on the commulative multi-institutional experience of CPDD use, the drug administration and scheduling: daily for five days, weekly; or monthly.[10] Another variable in methodology is the rate of drug infusion. Hill[12] and Peil[18] have data on CPDD given in a rate dependent fashion. Carter reports that CPDD was not found to be schedule dependent in leukemia systems.[1]

Because of the lack of schedule dependency, a wide variety of schedules have been tried in humans.[10] The use of CPDD with mannitol provides therapy that can be given with a predicatable margin of safety. The recommended dose is 3 mg/kg, or 120 mg/m^2, is not rate dependent, and can be safely scheduled every 4–6 weeks. CPDD can now be given in large bolus, comparable to other cycle non-specific agents (i.e. Cytoxan, Adriamycin, DTIC, etc.).

CPDD is a profound emetic. The "high dose" has not increased the intensity nor duration of emesis over that seen at doses of 1 to 2 mg/kg. There is a clinical suspicion that the mannitol induced diuresis may lessen the emesis, although this is an uncontrolled observation. The technique as described, certainly guards against the potential hazard of dehydration that emesis could produce.

Various qualitative and quantitative aspects of myelosuppression have been reported with CPDD use.[7,12,13,15,16,20] Each report employs one of the many variabilities in dose administration, and consequently, data on the full impact of CPDD on the marrow have been so far incomplete. The data reported here describe the type and degree of myelosuppression associated with single, large bolus doses of CPDD. We did not find the drug to be dangerously myelosuppressive. We did not find that increasing anemia was part of CPDD use. We did see cumulative toxicity of the marrow, as is seen with other comparable, intense chemotherapeutic attempts.

The experience in animal and human studies can leave no doubt that CPDD is nephrotoxic.[7,10,11,13,16] We believe that the mannitol technique prevents immediate massive platinum binding onto renal tubular proteins, and despite continuous renal exposure to that portion of the platinum which is excreted over a long half-life of 51–72 hours,[7] severe nephrotoxicity is prevented. No physiologic evidence for renal tubular leak has been seen in our experience. Gonzalez-Vitale *et al.*[9] have defined the pathologic lesions of CPDD upon the kidney to be located predominantly in the distal tubules and the collecting ducts. The exact mechanism of mannitol protection is not yet known.

Cis-platinum causes long lasting subclinical auditory changes when given in doses of 3 mg/kg or greater. The observation that older patients exhibit a greater sensitivity to CPDD remains unexplained, but may be due to presby-

acusia, previous auditory damage, or both. Younger individuals with previous auditory damage may also have increased sensitivities to Cis-platinum at all frequencies. The magnitude of the hearing loss following Cis-platinum administration is relatively predictable. We observed a 5–35 decible loss per drug administration depending upon the dose and age of the patient. By taking into account the patients' ages and previous auditory capacities, the anticipated toxicity from Cis-platinum can be gauged and the dosage determined depending upon the relative risk engendered by the patient's basic disease.

There was no hepatotoxicity associated with high dose CPDD, although there were transient minor liver function abnormalities infrequently seen with its use.

The generally low performance status (mean less than 60%) of this group of patients reflects extensive pretreatment; yet the overall response rate is encouraging. Further studies are needed to document firmly this increase in drug activity associated with the high dose technique. Results of germ cell tumors responding when low dose CPDD had become unsuccessful are supportive of this increase in drug activity.

CONCLUSION

A new "Phase I trial" of high dose CPDD has been undertaken. With prehydration and a concomitant osmotic diuresis, a greater therapeutic index has been achieved for the administration of Cis-platinum. It is now possible to give high doses of Cis-platinum, to eliminate serious dose-limiting renal toxicity, and see significant anti-tumor effect. There is now a safe, easy method of administering Cis-platinum, even in sequential courses over protracted periods of time. This technique allows the use of CPDD at doses of 3.0 mg/kg with a predictable margin of safety over serious nephrotoxicity. Any patient with a normal serum creatinine can receive "high dose CPDD" without expecting serious nephrotoxicity. Known structural or functional renal impairment will allow safe dose adjustment, without any compromise of therapy.

With encouraging responses particularly in testicular carcinoma, carcinoma of the head and neck, ovarian carcinoma, a new study using this technique with high dose CPDD will define the full anti-tumor spectrum of this compound. Repetitive high dose CPDD can now be safely used in combination chemotherapy.

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