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Safe and Effective two-hour Outpatient Regimen of Hydration and Diuresis for the Administration of *Cis*-Diamminedichloroplatinum (II)*†

STEVEN E. VOGL,‡|| THEODORE ZARAVINOS,‡ BARRY H. KAPLAN‡ and DAVID WOLLNER§

‡*Division of Medical Oncology, Albert Einstein College of Medicine*, 1300 *Morris Park Ave., Bronx, NY* 10461, *and* §*Department of Oncology, Montefiore Hospital and Medical Center, Bronx, NY* 10461, *U.S.A.*

Abstract—*Two hundred and forty-two patients received* 1200 *doses of* cis-*diamminedichloroplatinum* (II), *generally out of the hospital, at* 50 mg/m^2 *every* 3–4 *weeks. Furosemide and mannitol were given to assure a brisk diuresis when drug was administered, and* 2 litres *of* 0.45% *saline–*5% *dextrose were given over two hours to assure hydration. Azotemia developed after* 15 *courses* (1.3%) *in eleven patients* (4.5%). *Peak serum creatinine was* >2 mg/dl *in only four patients, and azotemia lasted* >12 weeks *in only one episode. Incidence of azotemia did not increase with increasing cumulative dose. Two patients had allergic reactions, one died suddenly during drug administration, three had clinically evident hearing loss, and nearly all patients had moderately severe vomiting. Peripheral neuropathy occurred in only* 1 *of* 155 *patients not given concomitant hexamethylmelamine.*

INTRODUCTION

Cis-DIAMMINEDICHLOROPLATINUM(II) (DDP, *Cis*-Platin) is one of the major advances in cancer treatment achieved in the 1970s. Substantial activity as a single agent has been demonstrated in carcinomas of the testis, bladder, ovary, head and neck and uterine cervix, as well as lymphoma [1, 2]. DDP has contributed, in combination regimens, to the cure of a majority of patients with testicular cancer [1], and to very high response rates in the treatment of advanced cancer of the ovary [3], head and neck [4] and uterine cervix [5].

The dose limiting toxicity of DDP in phase I trials was renal [6, 7]. Renal failure is a uniform and often irreversible complication at doses of 100 mg/m^2, and occurs in approximately 20% patients treated at 50–75 mg/m^2 every three weeks [8, 9]. The demonstration that hydration and diuresis prevent nephrotoxicity has allowed the administration of single doses of 100–120 mg/m^2 with acceptable risk [10–13]. With hydration and diuresis, dose limiting myelosuppression has been observed at a dose of 60 mg/m^2 given twice a week [14]. However, experience with the administration of DDP at 100 mg/m^2 every few weeks has shown that, while hydration and diuresis remarkably ameliorate nephrotoxicity, the programs required to prevent the nephrotoxicity, and the nausea and vomiting induced by the DDP, necessitate hospitalization for safe treatment [10–13].

The present series represents a summary of our experience with a DDP regimen designed

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||Reprint requests to: Steven E. Vogl, Division of Medical Oncology, Dept. of Medicine, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461, U.S.A.

for out-patient use. It is our assumption that an out-patient regimen is required for DDP to have wide application in the treatment of large numbers of patients with advanced cancer.

Our regimen was designed to reliably induce a diuresis at the time the renal tubular epithelium is exposed to peak levels of DDP. Our hypothesis is that it is the diuresis, not some remote effect of hydration on volume receptors or plasma hormone levels, that is protective against nephrotoxicity. This hypothesis is supported by a rat model in which mercuric chloride-induced renal failure is prevented by the induction of a diuresis [15]. This protection is afforded whether the diuresis is induced by saline preloading alone or by diuretics such as furosemide or acetazolamide [15]. Furosemide pretreatment ameliorates DDP-induced nephrotoxicity in the rat [16] without substantially affecting the pattern of DDP excretion [17, 18] or the efficacy of DDP [19].

Thus, furosemide diuresis was employed to reliably increase the rate of urine flow in our patients, and intravenous hydration was given to replace the fluids lost. The composition of the intravenous fluids was chosen to mimic that of the hypotonic saline diuresis and kaliuresis induced by furosemide. Since we desired the regimen to be suitable for clinics and office hours organized in half-day periods, we chose a 2-hr period of hydration, administering 2 liters in 2 hr, since the administration of greater amounts of fluid would be very difficult in many patients whose only accessible veins are small and peripheral. To doubly ensure the presence of a brisk diuresis at the time of administration of DDP, a bolus of mannitol was administered just prior to the DDP.

MATERIAL AND METHODS

DDP was given as a intravenous bolus 30 min after starting a 2-hr infusion of 2 liters of 5% dextrose in 0.45% saline with 10 mEq of KCl per liter. Furosemide (40 mg) was given intravenously at the start of the infusion, and 12.5 g mannitol was given intravenously just prior to DDP. If a brisk diuresis was not produced by the initial dose of furosemide, patients were given more furosemide together with mannitol to produce a minimal diuresis of 250 ml in the 30 min prior to DDP administration.

Two hundred and forty-two patients were treated with *cis*-platin between July 1976 and April 1979. These are all the patients given *cis*-platin at our institution at a dose of 50 mg/m^2 who were followed for 2 weeks or more. Patients not eligible for protocol study because of poor performance status or lack of measurable disease are included in this report, since the primary purpose of the present paper is an analysis of toxicity. The total dose for all the patients was 85,788 mg given in 1200 separate doses. The mean number of doses per patient was 4.9. The median cumulative dose per patient was 175 mg/m^2, with a mean cumulative dose per patient of 219 mg/m^2.

Seven patients received 30 mg/m^2 of DDP intravenously with this program of hydration and diuresis on days 1, 3 and 5 of 3-week cycles early in their treatment. None of these courses resulted in azotemia. Because of the inconvenience of the schedule and the prolonged period of nausea and vomiting induced, these patients all reverted to 50 mg/m^2 i.v. every 3 weeks after the second course, and they are included in the analysis with patients similarly treated at 50 mg/m^2 every three weeks.

One hundred and seventy-nine patients received 1–6 doses of DDP, 52 received 7–12 doses, and 11 received more than 12 doses. The median age of the patients was 58, with a range of 24–84 years. One hundred and sixty patients were female. DDP was given in combination regimens in all but two instances (see Table 1).

DDP was to be withheld whenever azotemia (defined as serum creatinine >1.5 mg/dl) occurred. Doses were modified for mild leukopenia (white blood count 3000–4000/μl) or thrombocytopenia (platelet count 75,000–100,000/μl) by 33–50%, and treatment was withheld in the presence of more severe myelosuppression. Serum creatinine was checked four days after DDP administration on the MBD, BAMP and mito-MBD regimens, and 14 days after DDP on the CHAD, HD, HAD and mito-BOP regimens. Since the patients were followed out of the hospital, routine creatinine clearance determinations were not made. Audiograms were not performed in the absence of clinically apparent hearing loss. Table 1 defines the patient population by primary site and treatment regimen.

RESULTS

There were only 15 episodes of nephrotoxicity in 11 patients. Thus, azotemia was observed in 4.5% of patients, and after 1.3%

Table 1. *Combination chemotherapy regimens using* cis-*platinum*

Other drugs	Frequency of DDP	Number of patients	Primary site	Response rate‡	Reference
Methotrexate + bleomycin* (MBD)	q3 week	58	Head and neck	63%	[4]
		13	Cervix	89%	[5]
		9	Esophagus	50%	[22]
		2	Vulva	‡	
		1	Lung	‡	
		1	Unknown		
Methotrexate + bleomycin + adriamycin* (BAMP)	q3 week	20	Lung	45%	[23]
Methotrexate + bleomycin + mitomycin* (MitoMBD)	q3 week	15	Head and neck	70%	[24]
Mitomycin + bleomycin + vincristine (MitoBOP)†	q3 week	8	Cervix	78%	[25]
Hexamethylmelamine (HD)†	q3 week	7	Ovary	38%	[3]
Hexamethylmelamine + adriamycin (CHAD)†	q3 week	34	Ovary	58%	[3]
Hexamethylmelamine + adriamycin + cyclophosphamide (CHAD)†	q4 week	40	Ovary	93%	[3]
Miscellaneous	q3–4 week	25	Miscellaneous		

*DDP given 3 days after methotrexate and bleomycin, and serum urea nitrogen and creatinine checked 4 days after DDP.

†DDP given on same day as other intravenous medications and serum urea nitrogen and creatinine checked 14 days after DDP.

‡Response rates are those given in published references based only on patients evaluable for response.

of courses. Among the azotemic patients, the highest serum creatinine was between 1.6 and 2.0 ml/dl in 7 patients, between 2.1 and 3.0 in 2 patients, and between 3.1 and 4.1 in 2 patients. Azotemia was fully reversible in less than 4 weeks for 10 episodes in 9 patients, in 4–12 weeks for 4 episodes in 2 patients, and lasted more than 12 weeks for only a single episode. The latter patient continued DDP chemotherapy for ovarian cancer for 5 months while her creatinine level remained 1.9–2.5 mg/dl.

Table 2 details the incidence of nephrotoxicity per cycle according to the number of cycles of DDP administered. The right-hand column lists the incidence of new nephrotoxicity per patient. The risk of nephrotoxicity per dose is 1.2% with doses 1–5 (based on 843 doses), 0.75% for doses 6–10 (based on 261 doses) and 3.8% per dose for doses beyond the 10th (based on 78 doses). The cumulative risk of experiencing one or more episodes of azotemia was 3.45% after two doses, 4.37% after five doses, 5.48% after six doses, and 6.98% after seven or more doses. No patient became azotemic after the 7th dose who had not been azotemic previously and recovered. Six patients received more DDP after recovering from their first episodes of azotemia.

Table 2. *Incidence of nephrotoxicity by cycle*

Cycle	No. of patients treated	Nephrotoxic episodes	Newly nephrotoxic patients
1	242	6	6
2	206	3	2
5	105	1	1
6	86	1	1
7	63	1	1
12	18	2	
15	6	1	

There were two allergic reactions to DDP. A 24-year-old man with testicular cancer developed cutaneous burning and erythema as well as cough after his sixth DDP dose, and a 61-year-old woman with pulmonary metastases of a squamous cancer from an unknown primary site developed hypotension and bronchoplasm after her eighth dose. Both responded to intravenous hydrocortisone and diphenyhdramine, and neither was given further DDP. A 64-year-old male had a cardiac arrest and died after 4 mg of his second dose of DDP for bladder cancer. There were no premonitory signs of allergy, though he did complain of mild burning at the injection site, which was changed just before he died.

An occasional patient escaped vomiting after the first or second dose of DDP, but thereafter nausea and vomiting were universal. Vomiting was moderately severe, generally lasting 3–24 hr. Only one patient required hospitalization for complications related to nausea and vomiting. Three patients, all women, complained of hearing loss. Two were on CHAD (5th and 8th cycles) and one on MBD (8th cycle).

Neurologic toxicity without concomitant hexamethylmelamine administration was observed in this series in only one patient. This patient developed severe paresthesias and some limb weakness in the eighth month of combination chemotherapy with methotrexate, bleomycin and DDP for advanced cancer of the uterine cervix. The incidence of neurotoxicity seen with combination hexamethylmelamine and platinum was higher with the CHAD regimen (25%) than the HAD and HD regimens (12%), probably because the median duration of therapy in the patients without prior chemotherapy given CHAD was more than twice as long as for the alkylating agent failures given HAD.

The extent of myelosuppression from DDP cannot be accurately estimated for most of the patients treated in this series, since concurrent myelosuppressive chemotherapy was administered.

No acute pulmonary edema or urinary retention was observed. The bulk of the patients were treated out of the hospital. Hospitalization was advised for elderly patients without resources at home to care for them during periods of vomiting. It was our policy to hospitalize patients for chemotherapy if they requested it, but many patients preferred to return to their homes for their periods of emesis rather than spend the night in an institutional setting.

DISCUSSION

The 4.5% incidence of mild and readily reversible nephrotoxicity makes this outpatient regimen of DDP administration suitable for widespread clinical use.

Table 3 summarizes available information on the nephrotoxicity of DDP without attention to hydration or the induction of a diuresis. Approximately 20% of patients treated at 50 or 75 mg/m^2 every three weeks develop azotemia, with an occasional death occurring from oliguric acute renal failure [8]. Notable is the very high incidence of nephrotoxicity with weekly DDP at the relatively low dose of 40 mg/m^2: 5 of 11 patients became azotemic by the fourth week of treatment [20].

Table 4 compares the results of the present study to two other out-patient regimens of DDP; one with weekly [21] and the other semi-weekly administration [14]. All seem equally effective at preventing nephrotoxicity, though the present regimen has not been extensively tested at the more frequent schedules of DDP administration. The present regimen is, however, the quickest and the most convenient of the three. The very low incidence of mild nephrotoxicity noted with 60 mg/m^2 DDP twice a week with hydration and diuresis at Roswell Park Memorial Institute [14] should be compared with the high rate (45%) of significant nephrotoxicity noted at 40 mg/m^2 weekly without hydration in the trial at Memorial Hospital [20].

The incidence of azotemia from DDP at 20 mg/m^2 daily for 5 days was reduced from 38 to 12% at Indiana University by the employment of saline hydration without any diuretics. The patients, however, were young men with testicular cancer who could be expected to promptly and reliably produce a diuresis when fluid-loaded. We believe that similar programs of fluid loading without diuretics would not be as safe or effective in sicker, more elderly patients with advanced cancer, especially those with expanded "third space" fluid compartments, such as ascites accompanying ovarian cancer.

All components of our program may not be necessary in every patient. If one is willing to closely observe individual patients continuously for urine output and signs of fluid overload or cardiac decompensation, use of potent diuretics could probably be avoided in many instances.

However, the use of these diuretics is quite safe in our experience. Further, the use of these diuretics allows us to treat, in a standard and convenient manner, without very close medical supervision, very sick patients, some of whom have ascites, pleural effusions and edema. The regimen that we describe is thus suitable for broad use in a variety of settings, many of which do not include close physician supervision. The safety, convenience and standardization of the regimen described here led to its adoption for use throughout the Eastern Cooperative Oncology Group in the United States.

It remains controversial whether hydration of diuresis are absolutely necessary with doses of DDP in the 50–75 mg/m^2 range. Available

Table 3. Cis-*platinum without attention to hydration and diuresis*

	Number of patients	Dose	Frequency	% with creatinine peaks above 1.5	2	4 mg/dl
Higsby & Rossoff [6,7]*	45	50–75/mg/m^2	Q2–3 week	33		
Vogl [8]†	48	50 mg/m^2	Q3 week	19		
Rossoff [9]	122	75 mg/m^2	Q3 week	40‡	19	11
Randolph [20]	11	40 mg/m^2	Q1 week	45		

*Phase I.
†Regimen including adriamycin.
‡ > 1.2 mg/dl.

Table 4. Cis-*platinum with hydration and diuresis*

	Number of patients	Dose (mg/m^2)	Frequency	Volume of fluid	Infusion period	Diuretics*	% of Pts with peak Creatinine above 1.5	2	4 mg/dl
Chary [13]	23	60	Q$\frac{1}{2}$ week	3l	6–8 hr	M + F		4	
Corder [17]	46	40–60	Q1 week	3$\frac{1}{4}$l	7 hr	M	2		
Present series	242	50	Q3 week	2l	2 hr	M + F	4.5	1.5	0.6

*Abbreviations: M for mannitol, F for furosemide.

data suggest that the induction of a diuresis substantially reduces the risk of renal damage (from 20% [8, 9] to 5% in our hands), and that the renal damage that is observed is much milder when hydration and diuresis are employed. Since the programs in use, such as the one described here, are non-toxic, inexpensive, and relatively convenient, we see no reason to sacrifice the renal function of 15–20% of our patients by not employing them.

REFERENCES

1. A. W. Prestayko, J. C. D'Aoust, B. F. Issell and S. T. Crooke, *Cis*-platinum (*cis*-diamminedichloroplatinum II). *Cancer Treat. Rev.* **2,** 17 (1979).
2. M. P. Corder, T. E. Elliott, L. C. Maguire, J. T. Leimert, S. K. Panther and P. A. Lachenbruch, Phase III Study of *cis*-dichlorodiammineplatinum (II) in Stage IV B Hodgkin's disease. *Cancer Treat. Rep.* **63,** 763 (1979).
3. S. E. Vogl, M. Berenzweig, B. H. Kaplan, M. Moukhtar and W. Bulkin, The CHAD and HAD regimens in advanced ovarian cancer: Combination chemotherapy including cyclophosphamide, hexamethymelamine, adriamycin, and *cis*-diamminedichloroplatinum II. *Cancer Treat. Rep.* **63,** 311 (1979).
4. S. E. Vogl and B. H. Kaplan, Chemotherapy of advanced head and neck cancer with methotrexate, bleomycin, and *cis*-diamminedichloroplatinum II in an effective out-patient schedule. *Cancer* **44,** 26 (1979).
5. S. E. Vogl, M. Moukhtar and B. H. Kaplan, Chemotherapy for advanced cervical cancer with methotrexate, bleomycin and *cis*-dichlorodiammineplatinum (II). *Cancer Treat. Rep.* **63,** 1005 (1979).
6. D. J. Higby, H. J. Wallace, D. J. Albert and J. F. Holland, Diamminedichloroplatinum: A phase I study showing responses in testicular and other tumors. *Cancer (Philad.)* **33,** 1219 (1974).
7. A. H. Rossoff, R. E. Slayton and C. P. Perlia, Preliminary clinical experience with *cis*-diamminedichloroplatinum (II) (NSC 119875, CACP). *Cancer (Philad.)* **30,** 1451 (1972).

8. E. Vogl, T. Onhuma, M. Perloff and J. F. Holland, Combination chemotherapy with adriamycin and *cis*-diamminedichloroplatinum in patients with neoplastic diseases. *Cancer (Philad.)* **38,** 21 (1976).
9. A. H. Rossof, R. W. Talley, R. L. Stephens, T. Thigpen, M. K. Samson, J. S. Hewlett, J. Athens and R. Fisher, Phase II evaluation of *cis*-diamminedichloroplatinum (II) in advanced malignancies of the genitourinary and gynecologic organs. *Cancer Treat. Rep.* **63,** 1567 (1979).
10. D. M. Hayes, E. Cvitkovic, R. B. Golbey, E. Scheiner, L. Helson and I. Krakoff, High dose *cis*-platinumdiamminedichloride: Amelioration of renal toxicity by mannitol diuresis. *Cancer (Philad.)* **39,** 1372 (1977).
11. V. L. Randolph, A. Vallejo, R. H. Spiro, J. Shah, E. W. Strong, A. G. Huvos and R. E. Wittes, Combination therapy of advanced head and neck cancer: Induction of remission with diamminedichloroplatinum (II), bleomycin, and radiation therapy. *Cancer (Philad.)* **41,** 460 (1978).
12. D. P. Kelsen, E. Cvitokovic, M. Bains, M. Shils, J. Howard, S. Hopfan and R. B. Golbey, *Cis*-dichlorodiammineplatinum (II) and bleomycin in the treatment of esophageal carcinoma. *Cancer Treat. Rep.* **62,** 1041 (1978).
13. M. Hayat, M. Bayssas, G. Brule, P. Cappelaere, A. Cattan, J. Chauvergne, B. Clavel, J. Gouveia, J. Guerrin, J. Laufer, E. Pommatau, H. Szpirglas, F. Muggia and G. Mathe, *Cis*-platinum diamminedichloro (CPDD) in chemotherapy of cancers. *Biochemie* **60,** 935 (1978).
14. K. K. Chary, D. J. Higby, E. S. Henderson and K. D. Swinerton, Phase I study of high-dose *cis*-dichlorodiammineplatinum (II) with forced diuresis. *Cancer Treat. Rep.* **61,** 367 (1977).
15. G. Thiel, F. Brunner, P. Wunderlich, M. Huguenin, B. Bienko, J. Torhorst, L. Petter-Haefeli, E. J. Kirchertz and G. Peters, Protection of rat kidneys against $HgCl_2$-induced acute renal failure by induction of high urine flow without renin suppression. *Kidney Internat.* **10,** S91 (1976).
16. J. M. Ward, M. E. Grabin, A. F. LeRoy and D. M. Young, Modification of the renal toxicity of *cis*-dichlorodiammineplatinum (II) with furosemide in male F344 rats. *Cancer Treat. Rep.* **61,** 375 (1977).
17. P. A. DeSimone, R. S. Yancey, J. J. Coupal, J. D. Butts and J. D. Hoeschel, Effect of a forced diuresis on the distribution and excretion (via urine and bile) of 195m Platinum *cis*-dichlorodiammineplatinum II. *Cancer Treat. Rep.* **63,** 951 (1979).
18. M. F. Pera, B. C. Zook and H. C. Harder, Effects of mannitol or furosemide diuresis on the nephrotoxicity and physiologic disposition of *cis*-dichlorodiammineplatinum (II) in rats. *Cancer Res.* **39,** 1269 (1979).
19. M. F. Pera and H. C. Harder, Effects of mannitol or furosemide diuresis on *cis*-dichlorodiammineplatinum (II). Antitumor activity and toxicity to host-renewing cell populations in rats. *Cancer Res.* **39,** 1279 (1979).
20. V. L. Randolph and R. E. Wittes, Weekly administration of *cis*-diamminedichloroplatinum (II) without hydration or osmotic diuresis. *Europ. J. Cancer* **14,** 753 (1978).
21. M. P. Corder, T. E. Elliott and S. J. Bell, Dose limiting myelotoxicity in the absence of significant nephrotoxicity with weekly out-patient schedule of *cis*-platinum (II) diamminedichloride. *J. clin. Hematol. Oncol.* **7,** 645 (1977).
22. V. Hentek, B. Kaplan, S. Vogl and E. Greenwald, Combination chemotherapy of advanced esophageal cancer (ECa) with methotrexate (M), bleomycin (B) and diamminedichloroplatinum (D)—MBD, *Proc. Amer. Ass. Cancer Res.* **20,** 400 (1979).
23. S. Vogl, B. Kaplan and E. Greenwald, Chemotherapy of advanced squamous (SCa), adeno-(ACa) and large cell anaplastic (LCa) bronchogenic carcinoma (BCa) with a combination of *cis*-diamminedichloroplatinum (P), bleomycin (B), adriamycin (A), and methotrexate (M)—BAMP. *Proc. Amer. Ass. Cancer Res.* **20,** 103 (1979).
24. B. Kaplan, S. Vogl and H. Lerner, Head and neck cancer chemotherapy with diamminedichloroplatinum, bleomycin, methotrexate and mitomycin—mito-MDB. *Proc. Amer. Ass. Cancer Res.* **21,** 478 (1980)
25. S. Vogl, M. Moukhtar, B. Kaplan and A. Canalog, Effective combination chemotherapy of advanced cervical cancer with *cis*-platinum, bleomycin, vincristine and mitomycin. "BOMP". *Proc. Amer. Ass. Cancer Res.* **21,** 189 (1980).