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A Phase I and Pharmacokinetic Study of Diamminecyclobutane-dicarboxylatoplatinum (NSC 241240)

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ABSTRACT

Carboplatin (CBDCA; NSC 241240) is a second-generation platinum coordination compound which in preclinical testing was found to be less nephrotoxic and emetogenic than *cis*-diamminedichloroplatinum (CDDP), while retaining a broad spectrum of antitumor activity. We have conducted a Phase I trial of CBDCA in 38 patients with advanced carcinoma. The drug was given without hydration as a 24-hr constant i.v. infusion on Day 1 of a 28-day cycle. Seventy-five cycles of CBDCA were administered in eight dose levels ranging from 20 to 320 mg/sq m. Dose-limiting toxicity was myelosuppression, primarily thrombocytopenia, occurring between Days 14 and 28 of the cycle. Myelosuppression was first observed at a dose of 240 mg/sq m and became dose-limiting at 320 mg/sq m, which is the recommended dose for Phase II trial. Other toxicities included nausea and vomiting and reversible renal failure seen in two patients with low normal pretreatment creatinine clearances. No consistent changes were seen on serial audiograms. Plasma concentrations of total and ultrafilterable platinum were measured by flameless atomic absorption spectrophotometry. Following cessation of the infusion, a half-life of 170 ± 34 min (S.D.) was found for CBDCA-derived ultrafilterable platinum. *In vitro* clonogenic assay of a CDDP-sensitive human ovarian cancer cell line using clinically achievable drug concentrations suggests that prolonged infusions of CBDCA may be more cytotoxic than bolus administration. In this study, minimal responses were seen in two patients with ovarian carcinoma who had failed previous combination chemotherapy including CDDP. In addition, three patients with refractory metastatic breast cancer responded to CBDCA (two minimal responses and one partial response) with remission durations averaging 3 months. CBDCA behaves as predicted by preclinical studies with different toxicities from CDDP and apparent activity in breast cancer.

INTRODUCTION

The platinum coordination compound, CDDP,[2] has shown excellent clinical activity against germinal neoplasms of the testes, ovarian carcinoma, carcinoma of the bladder, and squamous cell cancer of the head and neck (3, 8, 15, 18, 19). Preliminary reports also suggest activity in thyroid carcinoma and carcinoma of the cervix (13, 16). Although treatment with CDDP results in severe nausea and vomiting, peripheral neuropathy, ototoxicity, and myelosuppression, the major dose-limiting toxicity is renal tubular damage resulting in renal insufficiency or acute renal failure (4, 14). While careful hydration and diuresis have reduced renal toxicity and allowed administration of higher CDDP doses, other side effects, including ototoxicity, persist even with diuresis (7).

CBDCA (Chart 1) is one of a group of new second-generation platinum compounds which retain antitumor activity with apparently less host toxicity (6, 11, 17, 20). In preclinical studies, CBDCA demonstrated activity against the B16 melanoma, the colon 26 tumor, P388 and L1210 murine leukemias, and xenografts of both human and murine breast carcinoma (2). Of interest was the finding that CBDCA demonstrated significantly less emetogenic potential than did CDDP; the lowest emetic dose in dogs was 624 mg/sq m for CBDCA and 9 mg/sq m for CDDP (2). We report the results of a Phase I trial of CBDCA and include pharmacokinetic data as well as *in vitro* cytotoxicity studies using a CDDP-sensitive human ovarian cancer cell line.

MATERIALS AND METHODS

Patient Selection. Patient characteristics are shown in Table 1. Thirty-eight patients, 9 men and 29 women, ranging in age from 24 to 80 years, were entered into study. All patients had pathological confirmation of cancer, and all but 2 had received prior therapy. Prior to beginning therapy, each patient underwent a comprehensive evaluation including: complete history and physical examination with attention to signs or symptoms of peripheral neuropathy, audiogram, and evaluation of measurable disease by appropriate modality (physical examination, X-ray, or scan). Pretreatment evaluation also included complete blood count, with WBC differential, urinalysis, stool guaiac, 24-hr urine for electrolytes, magnesium, calcium phosphorus, glucose, and creatinine clearance, and serum chemistries including serum magnesium. Complete blood counts were followed weekly while the patient was on study, and other parameters were repeated on Day 1 of each cycle with the exception of audiograms which were repeated every other cycle unless clinically indicated. All patients had adequate pretreatment renal function as defined by a creatinine clearance of 60 ml/min or greater and serum creatinine less than 1.8 mg/dl, normal hemogram with WBC >3,000/cu mm, platelet count >100,000/cu mm (except in documented cases of metastatic involvement of bone marrow), normal hepatic function with bilirubin less than 2 mg/d, and serum glutamic-oxialoacetic transaminase less than 100 units/dl (except in cases of documented metastatic involvement of liver). All patients gave written informed consent prior to therapy.

Drug Formulation and Dosage. CBDCA was supplied by the Investigational Drug Branch, National Cancer Institute, Bethedsa, Md., in 20-ml amber vials containing 150 mg of drug as a white lyophilized powder with 150 mg of mannitol. When reconstituted with 9.8 ml of Sterile Water for Injection United States Pharmacopeia, each ml contained 15 mg of CBDCA and 15 mg of mannitol at pH 4.5 to 7.0. The prescribed dose was further diluted in 500 ml of 5% dextrose and water for administration by constant infusion. When reconstituted as directed, the solution of CBDCA exhibits no decomposition under these conditions for at least

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[2] The abbreviations used are: CDDP, *cis*-diamminedichloroplatinum; CBDCA, diamminecyclobutanedicarboxylatoplatinum; T-Pt, total platinum; UF-Pt, ultrafilterable platinum; MTD, maximally tolerated dose; MR, minimal response.

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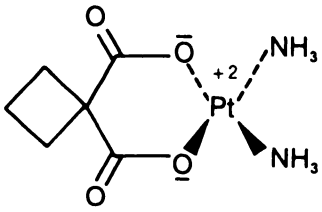

Chart 1. Structure of carboplatin (CBDCA; NSC241240).

Table 1
Patient characteristics

No. of patients in study (eligible/evaluable)	38 (38 of 32)
Men	9
Women	29
Median age (yr)	51 (24–80)[a]
Median Karnofsky performance status	70 (40–100)
Prior therapy	
Chemotherapy	22
Chemotherapy and radiotherapy	14
None	2
Tumor types	
Breast	12
Lymphoma	7
Ovarian	5
Sarcoma	4
Glioma	3
Renal cell	3
Non-small cell lung	1
Cervical	1
Melanoma	1
Adenocarcinoma, unknown primary	1

[a] Numbers in parentheses, range.

24 hr at room temperature.

The starting dose of CBDCA was 20 mg/sq m administered by constant infusion over 24 hr; approximately 5% of the dose causing 10% lethality in mice. Dose escalation was performed using a modified Fibonacci search scheme (20, 40, 66, 100, 140, 180, 240, and 320 mg/sq m) with 3 patients entered at each dose level before escalation was performed. No dose escalation was performed in individual patients. Treatment was continued for at least 2 cycles unless contraindicated by progressive disease or unacceptable toxicity.

Pharmacological Studies. CBDCA plasma pharmacokinetics were determined in selected patients using flameless atomic absorption spectrophotometry. Samples of venous blood were drawn into 10-ml heparinized tubes prior to therapy and at 1, 6, 12, 18, and 24 hr after beginning treatment. Following cessation of the infusion, samples were drawn at 1, 2, 6, 12, and 24 hr. Upon collection, blood samples were iced and immediately centrifuged for 10 min at 2200 rpm. Plasma was decanted, and an aliquot was separated for determination of T-Pt. The remaining plasma was processed for UF-Pt by centrifugation at 3000 rpm through membrane cones (Amicon Centriflo ultrafiltration membrane cones, CF-25; Amicon Corp., Lexington, Mass.). Samples were frozen at −70° until Pt analysis. Determination of Pt metal concentration was performed by flameless atomic absorption spectrophotometry as described previously with some modifications (10). A Perkin-Elmer 5000 spectrophotometer, equipped with an HGA graphite furnace, a ramping facility, and an autosampler, was used. The furnace settings were: dry at 96° for 60 sec (ramp, 30 sec); char at 1400° for 40 sec (ramp, 20 sec); and atomize at 2700° for 7 sec. Sample size was 10 μl using pyrolyzed tubes. UF-Pt was determined without sample alteration, but 1:1 dilution of the plasma with a solution of 0.25% Triton-X was necessary to give reproducible results for T-Pt. Standard curves were obtained by adding known amounts of CBDCA to either plasma or ultrafiltrate. All samples were performed at least in duplicate. Lower limits of detectability were between 0.03 and 0.06 μg platinum per ml. This analysis determined concentration at steady state of UF-Pt and T-Pt, as well as the kinetics of disappearance of UF-Pt after cessation of the 24-hr infusion. Total body clearance of UF-Pt was calculated as dose rate divided by concentration at steady state.

***In Vitro* Cytotoxicity Studies.** The effect of duration of drug exposure upon cytotoxicity was examined in a human ovarian cancer cell line, NCI-H 2780, kindly provided for us by Dr. Stuart Aaronson, National Cancer Institute. The cell line grows as a monolayer in Roswell Park Memorial Institute 1640 media with 10% fetal calf serum (HEM Research, Inc., Rockville, Md.). Cell suspensions in logarithmic growth phase were exposed to drug concentrations of 0.1 to 10 μg CBDCA/ml (0.27 to 27 nmol/ml) or CDDP (0.33 to 33 nmol/ml) for 1 hr, were washed, and were plated in a double-layer agar system. After 7 days of incubation in a 5% CO_2-humidified atmosphere, the number of colonies in triplicate culture from drug-exposed cells was compared to untreated controls. Additional cultures were exposed to CBDCA or CDDP (drug concentrations, 0.01 to 1.0 μg/ml) for 24 hr before being washed and plated in agar. The cytotoxicity effects on triplicate cultures were compared as described above.

RESULTS

Toxicity. Thirty-eight patients were treated with CBDCA during this study with a total of 75 cycles of therapy. Six patients died with progressive disease prior to completion of one full cycle and cannot be considered evaluable. The remaining 32 patients received 69 cycles of treatment. There were no drug-related deaths.

Dose-limiting toxicity consisted of reversible myelosuppression (Table 2), predominantly thrombocytopenia, which was first observed at a dose of 240 mg/sq m. At the MTD of 320 mg/sq m, 12 of 14 patients developed thrombocytopenia (<100,000/cu mm). In 6 of these patients, the platelet count at nadir was less than 20,000/cu mm. Of interest, thrombocytopenia was delayed, occurring between Days 14 and 28 of treatment. Neutropenia was less marked, with a mean WBC at nadir of 3000/cu mm. One patient developed culture-negative fever in association with a WBC of 900/cu mm, requiring hospitalization and support with i.v. antibiotics. In all cases, myelosuppression was reversible, and there was no evidence for cumulative toxicity. Five patients treated at the MTD received multiple cycles (mean, 5.2); one patient who received 10 cycles of treatment developed anemia requiring transfusion.

Other toxicities included acute reversible renal failure seen in 2 patients with low pretreatment creatinine clearances. The first patient was a 52-year-old woman with retroperitoneal sarcoma with ascites and Adriamycin-induced cardiomyopathy requiring

Table 2
Hematological toxicity of CBDCA

Dose (mg/sq m)	Median nadir (× 10^3/cu mm) WBC	Platelets
20	4.5 (4.2–4.9)[a]	224 (209–249)
40	3.7 (3.2–4.3)	208 (192–223)
66	6.6 (3.9–9.9)	216 (153–268)
100	3.9 (3.3–4.5)	158 (148–168)
140	5.0 (4.3–5.6)	222 (195–252)
180	3.6 (2.1–5.2)	132 (95–190)
240	4.8 (2.8–8.7)	88 (20–175)
320	3.0 (0.9–8.4)	63 (2–256)[b]

[a] Numbers in parentheses, range.
[b] Platelet nadir less than 100,000 in 12 of 14 patients; less than 20,000 in 6 of 14 patients.

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diuretics and digoxin. Pretreatment serum creatinine was 0.9 mg/dl, and creatinine clearance was 60 ml/min. Following therapy with CBDCA at 66 mg/sq m, serum creatinine rose over 3 days to 2.5 mg/dl with subsequent reversion to pretreatment levels without specific intervention. The second patient was a 58-year-old woman with ovarian carcinoma and abdominal disease refractory to multiagent chemotherapy including CDDP. Pretreatment creatinine was 1.1 mg/dl. Following treatment with CBDCA at 320 mg/sq m, serum creatinine rose over 4 weeks to 1.3 mg/dl with a decrease in creatinine clearance from 60 to 34 ml/min. Again, renal function subsequently returned to pretreatment levels without specific intervention. All other patients tolerated therapy without evidence of nephrotoxicity including one patient with renal cell carcinoma who had previously undergone radical unilateral nephrectomy and has tolerated therapy at the MTD for 10 cycles with stable retroperitoneal disease.

Nausea and vomiting (Table 3) were first reported by patients receiving a dose of 140 mg/sq m but were never dose-limiting. At the MTD, only 2 of 14 patients suffered severe nausea which responded to antiemetic treatment with phenothiazines. Pretreatment with antiemetics was not standardized, and metoclopromide was not used.

High-tone hearing loss was seen in 2 patients treated at 100 and 140 mg/sq m. However, in the first patient, unilateral right-sided high-frequency hearing loss was associated with progression of a right temporal-parietal glioma. The second patient with high-tone hearing loss had prior treatment with vincristine. No other patients had evidence of hearing loss. No other toxicities were observed. Specifically, there was no evidence of neuropathy, allergic reactions, hepatic toxicity, or alopecia.

Pharmacokinetics. Pharmacokinetic parameters of CBDCA-derived UF-Pt are given in Table 4. Following the cessation of infusion, the disappearance of UF-Pt was monoexponential. Over the range studied, there was no evidence of dose dependency of total body clearance or $t_{1/2}$ of UF-Pt. The proportion of UF-Pt in plasma was greater than 85% at the beginning of the infusion and declined to 60% at the end of infusion (n = 6; 8.5% S.D.). Chart 2 represents the concentration-time course of mean T-Pt and UF-Pt of 3 patients during and after a 24-hr infusion of CBDCA at 320 mg/sq m.

Table 3

Gastrointestinal toxicity of CBDCA

Dose (mg/sq m)	No. of patients	Grade 1[a]	Grade 2	Grade 3
140	3	1	2	0
240	3	2	0	1
320	14	6	6	2

[a] Grade 1, nausea only; Grade 2, transient vomiting; Grade 3, vomiting requiring treatment.

Table 4

Pharmacokinetic parameters for CBDCA-derived UF-Pt

Patient	CBDCA dose (mg/sq m)	CBDCA dose (μmol)	C_{ss}[a] (nmol/ml)	$t_{1/2}$ (min)	CL_{TB}[b] (ml/min)
2	20	102	0.94		74
7	66	315	2.20	120	95
9	66	269	2.10	180	87
12	100	592	2.50	130	164
13	140	565	1.70	180	83
16	140	565	2.80		51
17	180	888	4.60		131
18	180	726	4.60		107
21	210	1030	6.30		112
29	320	1720	8.00		148
30	320	1580	10.00	210	109
31	320	1540	9.70	190	109
Mean ± S.D.				170 ± 34	106 ± 31

[a] C_{ss}, concentration achieved at steady state.
[b] CL_{TB}, apparent total body clearance.

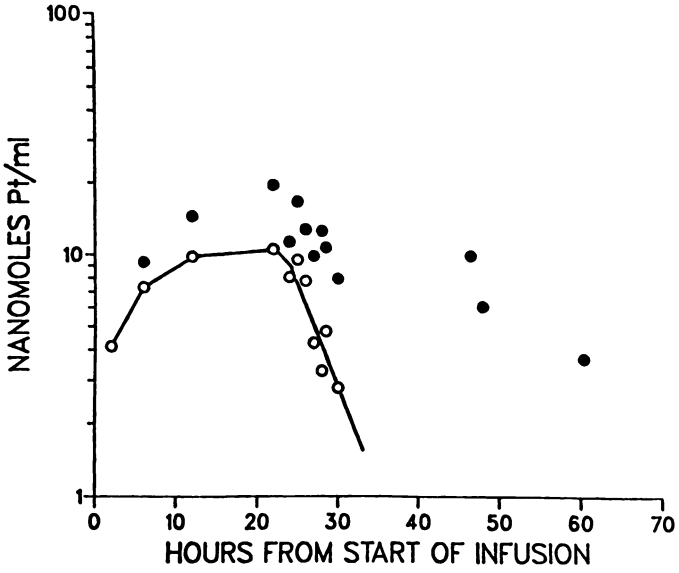

Chart 2. Concentration-time course of CBDCA-derived total (●) and ultrafilterable (○) platinum in 3 patients treated with a 24-hr drug infusion at 320 mg/sq m.

Clonogenic Assay. The human ovarian cancer cell line NCI-H2780 is sensitive to CDDP; following a 1-hr exposure to CDDP (1 μg/ml; 3.3 nmol/ml), colony survival was less than 10% control. Exposure to the same concentration of CBDCA (1 μg/ml, 2.7 nmol/ml) had little cytotoxic effect (Chart 3). However, when the period of drug exposure was lengthened to 24 hr, CBDCA showed toxicity similar to that of CDDP.

Responses. Responses were seen in 5 patients: 2 with ovarian carcinoma and 3 with breast carcinoma. The 2 responding patients with ovarian carcinoma were treated with CBDCA at 240 and 320 mg/sq m. Both had progressive abdominal disease despite treatment with CDDP. In each case, treatment with CBDCA was associated with a MR in abdominal masses (less than 50% reduction in tumor size on ultrasound) and improvement in abdominal symptoms. The 3 responding patients with breast carcinoma all had progressive disease following treatment with cyclophosphamide, Adriamycin, methotrexate, and 5-fluorouracil. One patient treated with CBDCA at 66 mg/sq m had a MR in metastatic pulmonary disease documented on chest X-ray. A second patient treated with CBDCA at 320 mg/sq m had marked improvement in bone pain and some improvement in liver function tests with serum lactate dehydrogenase decreasing from 960 to 406 units/dl and serum glutamic pyruvic transaminase from 156 to 47 units/dl. The third responding breast cancer patient, treated with CBDCA at 320 mg/sq m, had a true partial response (greater than 50% reduction in tumor size) in readily measured skin nodules and substantial improvement in local chest wall disease. Mean response duration in these 3 patients was 3 months.

DISCUSSION

CBDCA is a second-generation platinum compound selected for Phase I study because of its potential to be less emetogenic and nephrotoxic than the parent drug, CDDP. The results of this

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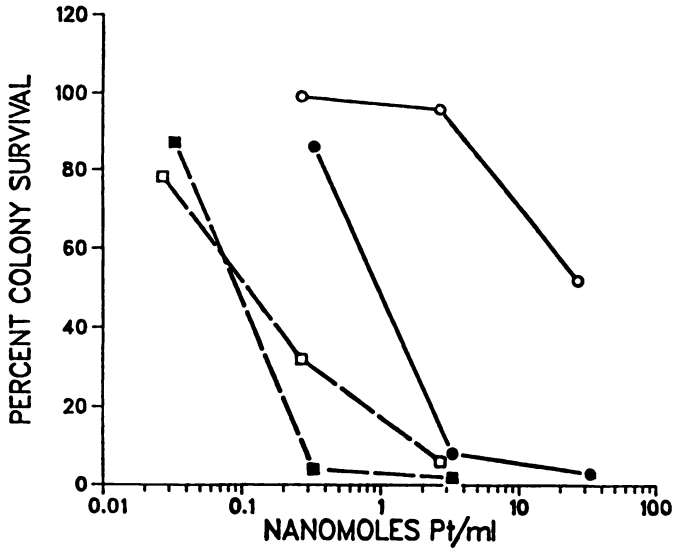

Chart 3. Clonogenic assay of a human ovarian carcinoma cell line (NCI-H2780) following exposure to CDDP for 1 hr (●) or 24 hr (■) and CBDCA for 1 hr (○) or 24 hr (□).

clinical trial and those of another recent study (1) support that hypothesis. Nausea was not dose-limiting. Although transient acute renal toxicity was seen in 2 of 32 patients, both had mildly impaired pretreatment creatinine clearances. Nephrotoxicity was not seen in other patients treated with multiple cycles at the MTD. No consistent changes in high-tone hearing were observed on serial audiography. The major dose-limiting toxicity was myelosuppression, predominantly thrombocytopenia, which was especially severe in heavily pretreated patients. Delayed thrombocytopenia may necessitate more time between treatment courses. Although 320 mg/sq m is the recommended dose for Phase II trial using this dose regimen, heavily pretreated patients should have a dose reduction to 240 mg/sq m. Using a 1-hr infusion, the MTD has been reported to range from 400 to 500 mg/sq m (1).

CBDCA differs from CDDP in its pharmacokinetics. There is evidence that CDDP reacts with plasma proteins irreversibly and, thus, of the 2 fractions in plasma, only the free fraction (*i.e.*, the UF-Pt) is active (12). For this reason, we have focused our attention on the kinetics of UF-Pt. Following the infusion, we find that CBDCA-derived UF-Pt is cleared by first order kinetics with a mean $t_{1/2}$ of 170 ± 34 min (Table 4). By comparison, CDDP-derived UF-Pt has a $t_{1/2}$ of only 30 min following a bolus infusion (9).

Furthermore, CBDCA does not react as extensively with plasma proteins as CDDP. Gullo *et al.* (5) report UF-Pt plasma concentrations less than the detection limit of 0.1 μg/ml at the end of a 20-hr CDDP infusion. Since total Pt levels were approximately 1 μg/ml, less than 10% was filterable. However, 60% of T-Pt in plasma remains filterable at the end of a 24-hr CBDCA infusion.

The clinical responses observed in this trial may be dependent on prolonged drug exposure. Using clinically achievable UF-Pt concentrations (0.27 to 27 nmol/ml; see Chart 2), CBDCA is less cytotoxic than CDDP when cells are exposed to drug for 1 hr prior to cloning in soft agar (Chart 3). More comparable cytotoxicity is seen when cells are exposed to drug for 24 hr prior to cloning. Direct comparison of cytotoxicity data using CDDP and CBDCA following a 24-hr drug exposure is difficult because of the known reactivity of CDDP with biological fluids (12). However, it appears that prolonged exposure to CBDCA increases drug cytotoxicity. This fact may explain the responses which were observed clinically including 2 MRs in patients with ovarian cancer refractory to CDDP and 2 MRs and one partial response seen in patients with heavily pretreated breast cancer.

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REFERENCES

1. Calvert, A. H., Harland, S. J., Newell, D. R., Siddik, Z. H., Jones, A. C., McElwain, T. J., Raju, S., Wiltshaw, E., Smith, I. E., Baker, J. M., Peckham, M. J., and Harrap, K. R. Early clinical studies with *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II. Cancer Chemother. Pharmacol., *9:* 140–147, 1982.
2. Cancer Therapy Evaluation Program, Clinical Brochure, CBDCA (NSC 241240), Investigational Drug Branch, National Cancer Institute, Bethesda, Md., September 1981.
3. Einhorn, L. H., and Donohue, J. *Cis*-diamminodichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann. Intern. Med., *87:* 293–298, 1977.
4. Gonzales-Vitale, J. C., Hayes, D. M., Cvitkovic, E., and Sternberg, S. S. The renal pathology of *cis*-platinum-II. Cancer (Phila.), *39:* 1372–1381, 1977.
5. Gullo, J. J., Litterst, C. L., Maguire, P. J., Sikic, B. I., Hoth, D. F., and Woolley, P. V. Pharmacokinetics and protein binding of *cis*-dichlorodiammine platinum (II) administered as a one hour or twenty hour infusion. Cancer Chemother. Pharmacol., *5:* 21–26, 1980.
6. Harrap, K. R., Jones, M., Wilkenson, C. R., Clink, H. M., Sparrow, S., Mitchley, B. C. V., Clarke, S., and Veasey, A. Antitumor, toxic, and biochemical properties of *cis*-platinum and eight other platinum analogs. *In:* A. Prestayko, S. T. Crooke, and S. K. Carter (eds.), *cis*-Platin: Current Status and New Developments, pp. 193–212. New York: Academic Press, Inc., 1980.
7. Hayes, D. M., Cvitkovic, E., Golbey, R. B., Scheiner, E., Helson, L., and Krakoff, I. H. High-dose *cis*-platinum diammine dichloride. Amelioration of renal toxicity by mannitol induced diuresis. Cancer (Phila.), *39:* 1372–1381, 1977.
8. Higby, D. J., Walker, H. J., Albert, D., and Holland J. F. Diamminedichloroplatinum in the chemotherapy of testicular tumors. J. Urol., *122:* 100–104, 1974.
9. Himmelstein, K. J., Patton, T. F., Belt, R. J., Taylor, S., Repta, A. J., and Sternson, L. A. Clinical kinetics of intact cisplatin and some related species. Clin. Pharmacol. Ther., *29:* 658–664, 1981.
10. LeRoy, A. F., Wehling, M. L., Sponseller, H. L., Friauf, W. S., Solomon, R. E., Dedrick, R. L., Litterst, C. L., Gram, T. E., Guarino, A. M., and Becker, D. A. Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem. Med., *18:* 184–191, 1977.
11. Mong, S., Huang, C. H., Prestayko, A., and Crooke, S. T. Effects of second generation platinum analogs on isolated PM-2 DNA and their cytotoxicity *in vitro* and *in vivo*. Cancer Res., *40:* 3318–3324, 1980.
12. Repta, A. J., and Long, D. F. Reactions of cisplatin with human plasma and plasma fractions. *In:* A. Prestayko, S. T. Crooke, and S. K. Carter (eds.), *cis*-Platin: Current Status and New Developments, pp. 285–304. New York: Academic Press, Inc., 1980.
13. Reyes, J., and Shimoka, K. Chemotherapy of thyroid carcinoma. Proc. Am. Assoc. Cancer Res. Am. Soc. Clin. Oncol., *16:* 332, 1978.
14. Rozenzweig, M., von Hoff, D. D., Slavik, M., and Muggia, F. M. *Cis*-diamminedichloroplatinum (II), a new anticancer drug. Ann. Intern. Med., *86:* 803–812, 1977.
15. Sternberg, J. J., Brackey, R. B., Handel, P. B., and Johnson, D. E. Combination chemotherapy for advanced urinary tract carcinoma, J. A. M. A., *238:* 2282–2287, 1977.
16. Thigpen, T., and Shingleton, H. Phase II trial of *cis*-platinum in the treatment of advanced squamous cell carcinoma of the cervix. Proc. Am. Assoc. Cancer Res., *19:* 332, 1978.
17. Wilkenson, C. R., Cox, P. J., Jones, M., and Harrap, K. R. Selection of potential second generation platinum compounds. Biochimie (Paris), *60:* 851–857, 1978.
18. Wiltshaw, F., and Kroner, T. Phase II study of *cis*-dichlorodiammineplatinum (II) in advanced carcinoma of the ovary. Cancer Treat. Rep., *60:* 55–60, 1976.
19. Wittes, R. E., Cvitkovic, E., Shah, J., Gerold, F. R., and Strong, E. W. *cis*-Dichlorodiammineplatinum II in the treatment of cancer of the head and neck. Cancer Treat. Rep., *61:* 359–366, 1977.
20. Wolpert-DeFillipes, M. K. Antitumor activity of cisplatin analogs. *In:* A. Prestayko, S. J. Crooke, and S. K. Carter (eds.), *cis*-Platin: Current Status and New Developments, pp. 183–191. New York: Academic Press, Inc., 1980.

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