Cancer Chemother Pharmacol (1984) 12: 101–103

Cancer Chemotherapy and Pharmacology

Phase-II trial of 1,2-diaminocyclohexane (4-carboxyphthalato) platinum (II) (DACCP) in non-small cell lung cancer

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Summary. *A phase-II trial of the second-generation platinum analog 1,2-diaminocyclohexane (4-carboxyphalato) platinum (II) (DACCP) was performed in 33 patients with non-small cell lung cancer. The compound was studied because of its lack of cross resistance in vitro and decreased nephrotoxicity in both preclinical testing and in a phase-I trial. The starting dose was 640 mg/m² IV every 3 weeks, with escalations to 720 mg/m² in the absence of toxicity. Myelosuppression and nephrotoxicity were uncommon. Allergic reactions and neurotoxicity were seen in five and three patients, respectively. Of 28 patients evaluable for response, one partial remission of 3 months' duration was noted in a patient who had previously responded but subsequently progressed during cisplatin and vindesine medication. No responses were seen in 11 adequately treated patients who had received no prior therapy. DACCP has only minimal activity in non-small cell lung cancer. No further studies are planned in this disease.*

Introduction

1,2-Diaminocyclohexane (4-carboxyphthalato) platinum (II) (DACCP) is a second-generation platinum analog that was selected for clinical trial due to (1) lack of in vitro cross resistance with cisplatin-resistant P388 and L1210 cell lines [1]; (2) decreased nephrotoxicity in preclinical screening systems; and (3) enhanced solubility relative to other platinum analogs [8, 10, 13]. A phase-I trial at MSKCC demonstrated good patient tolerance with acceptable toxicity. The maximum tolerated dose was 800 mg/m²; thrombocytopenia was dose-limiting. Nephrotoxicity was uncommon. Therapeutic activity was noted in several patients, including one with non-small cell lung cancer who had progressed during cisplatin medication and some previously untreated patients. Responses were also seen in tumors for which cisplatin has demonstrated minimal activity [7].

Cisplatin has modest antitumor activity in non-small cell lung cancer, with an overall response rate (complete plus partial remissions) of 15%–20%. The cumulative toxicity of this agent frequently limits the total dosage, even in responding patients [2]. A phase-II trial of DACCP in non-small cell lung cancer was undertaken in hopes of observing enhanced therapeutic activity with less toxicity. Patients who had previously received cisplatin were included in the study to see whether a lack of in vivo cross resistance could be demonstrated.

Materials and methods

All patients had non-small cell lung cancer (epidermoid, large cell, and adenocarcinoma) with the diagnosis confirmed by the Department of Pathology, MSKCC. Prior to entrance into the study, all patients underwent a complete history and physical examination. Laboratory evaluation included a complete blood and platelet count, 12-channel screening profile, serum creatinine, creatinine clearance, chest roentgenograms, urinalysis, and electrocardiogram. Radionuclide scans, computerized tomograms, and audiograms were obtained when clinically indicated. Entry requirements included a PS (Karnofsky) of greater than 50%, WBC greater than 4,000 cells/mm³, platelets greater than 100,000 cells/mm³, bilirubin less than 1.5 mg%, creatinine less than 1.5 mg%, and creatinine clearance greater than 65 ml/min. The presence of either measurable or evaluable disease was required.

During the initial phase of the study, an ABC (automated blood count) and platelet count were obtained on days 7 and 10 after each dose of the drug. Prior to each cycle of DACCP, the above laboratory studies were repeated.

The drug was supplied by the Johnson-Matthey Corporation as a lyophilized powder and prepared immediately prior to administration by dissolving DACCP (10 mg/ml) in an 8.4% solution of sodium bicarbonate (USP) with 5% dextrose in water at a ratio of 1 : 9. The solution was then filtered and the sterile solution added to 50 ml 5% dextrose in water, placed on ice, and taken to the patient's bedside. The drug was administered as an IV infusion over 15–20 min. In the initial phase of the trial, hydration consisted of 1,000 cm³ $D_5\,^1/_2$ normal saline before and after therapy, infused over 1 h. No additional hydration was given. To standardize a schedule amenable to outpatient administration, subsequent patients were given 500 cm³ $D_5\,^1/_2$ normal saline before and after treatment. Most patients had creatinine determinations performed 24 h after the drug. Informed consent was obtained from all patients.

The starting dose was 640 mg/m² IV every 3 weeks. If no myelosuppression (WBC less than 2,500 cells/mm³, platelets less than 100,000 cells/mm³) or nephrotoxicity (peak serum

Supported in part by Public Health Service Grants CA-05826 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and the Bristol-Myers Corporation

Dr. Howard Scher is a recipient of an Untermeyer Fellowship, Memorial Sloan-Kettering Cancer Center

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creatinine greater than 1.5 mg% or decrease in creatinine clearance below 65 cm^3/min) was seen the dose was increased to 720 mg/m^2. All patients treated at the 720 mg/m^2 dose level received 1,000 cm^3 $D_{5\,1/2}$ normal saline before and after therapy.

Standard phase-II response criteria were employed. Complete remission (CR) was defined as complete disappearance of all measurable, radiologic, and biochemical abnormalities; partial remission (PR), as a greater than 50% decrease in the summed products of the longest perpendicular diameters of all measurable soft tissue lesions by physical examination or by CT scan for greater than 1 month, or a greater than 50% decrease in the sum of all available measurments of the liver by physical examination; stabilization of disease (STAB), as a less than 25% decrease or an increase in tumor size. Progression (PROG) was defined as a greater than 25% increase in tumor size. An adequate trial was one course with active progression of disease and 3 week's survival.

Patient characteristics. Thirty-three patients, 28 males and five females, were entered into this trial. Histologic diagnoses were adenocarcinoma in 20, epidermoid carcinoma in 11, and large cell carcinoma in two. The median age was 55 years (range 34–74), and median PS (Karnofsky) 70 (range 50–100). Prior therapy included chemotherapy and radiation therapy in 11 patients, and chemotherapy alone in 10. Eighteen had received prior cisplatin. Twelve patients had received no prior therapy. Primary indicator lesions were pulmonary (outside of previously radiated areas) in 22 cases; in lymph nodes in seven, liver in two and subcutaneous masses in two.

Results

Twenty-eight patients were considered to have an adequate trial. Two patients were lost to follow-up and could not be evaluated for response; two developed allergic reactions and did not complete drug infusions; and one died of disseminated disease 10 days after receiving DACCP. The median number of courses was 1 (range 1–4). Thirty patients were entered at 640 mg/m^2 and for four the dose was escalated to 720 mg/m^2. Three were entered at 720 mg/m^2. Overall, one PR in a supraclavicular lymph node (SCLN) of 3 months' duration was observed among 17 adequately treated patients who had received prior chemotherapy, including cisplatin in 14. This patient had previously responded but subsequently progressed while receiving a combination of cisplatin and vindesine. A second patient had stable disease after four doses of therapy but DACCP was discontinued because of a severe peripheral neuropathy. Three patients who progressed during DACCP medication subsequently responded to chemotherapy; – two achieved a PR in pulmonary nodules with a combination of cisplatin and vinblastine, while the third patient, who had obtained a CR with cisplatin and vinblastine and subsequently relapsed, progressed during DACCP therapy and subsequently achieved a PR with mitomycin C. A fourth patient responded to local radiation therapy after failing DACCP.

Toxicity was similar to that observed in the phase I trial. Nausea and vomiting were observed in 75% of patients treated, but were quantitatively less than with cisplatin, and allowed a number patients to be treated as outpatients. Metaclopromide (2 mg/kg IV every 2 h for three doses beginning 30 min prior to DACCP) ameliorated the nausea and vomiting in approximately four of six (66%) patients treated. Diarrhea was observed in 30% and fever in 12%. Anorexia for 2–3 days after treatment was noted in approximately 20% of patients treated. Alopecia was not seen. A slight decreased in auditory function was noted in two patients, one of whom had received three prior courses of cisplatin.

Allergic reactions were observed in five patients. Two, one of whom had not received prior cisplatin, developed hives, and urticaria during drug administration, and did not complete the infusion. Three other patients who developed hives were treated with diphenhydramine and corticosteroids and safely completed infusions. Subsequent therapy was given following premedication with the same agents without difficulty.

Hematologic toxicity was minimal at all dose levels, with a median WBC nadir of 6,800 cell/mm^3 (range 1,900–13,000), platelet nadir 214,000 cells/mm^3 (range 94,000–516,000) at the 640 mg/m^2 dose level and 4,800 cells/mm^3 (range 3,900–12,000) and 202,000 cells/mm^3 (range 65,000–285,000) for six of seven patients who received doses of 720 mg/m^2. In all, two of 29 (7%) had WBC nadirs below 3,000 cells/mm^3 and three of 29 (11%) had platelet nadirs below 125,000 cells/mm^3 (Table 1). Nephrotoxicity was likewise minimal, with 1/11 patients who had received no prior chemotherapy and 5/21 who had received prior chemotherapy developing peak creatinine levels above 1.5 mg%. Of patients receiving 720 mg/m^2, two of seven developed creatinine levels above 1.5 mg%. Two patients were noted to have increases in their baseline creatinine levels without a change in clearance, and a third developed a peak creatinine of 2.5 mg% after the fourth dose, with a decrease in creatinine clearance from 78 to 62 cm^3/min (Table 2).

Three patients showed evidence of a sensorimotor peripheral neuropathy and one patient was removed from the study

Table 1. Hematologic toxicity

Dose (mg/m^2)	No. entered	No. adequate	WBC[c]		Platelets[c]	
			Median	Range	Median	Range
640	30	28	6.8	1.9–13	214	94–516
720	7[a]	6	4.8	3.9–13	202	65–285
	3[b]	3	4.8	3.9–13	113	65–286

[a] Includes patients escalated
[b] Patients entered at 720 mg/m^2
[c] (× 10^3 cells/mm^3)

Table 2. Nephrotoxicity

	No. entered	No. adequate	Serum creatinine (mg/dl)		
			Median	Range	No. (mg/dl)
No prior chemotherapy	12	11	1.1	0.7–1.6	1 < 1.5
Prior chemotherapy	21	21	1.1	0.7–2.3	5 < 1.6
720 mg/m^2 (only)	7	7	1.2	0.9–2.5	2 < 1.6

because of this effect. In this instance, the patient developed a major problem with manual dexterity and could not button shirts, had poor tandem gait, slow rapid alternating movements, and decreased sensation and vibration below the iliac crest. Electromyographic studies revealed distal motor neuron latency and slow nerve conduction velocities in both peroneal and posterior tibial nerves. These findings were consistent with a mixed sensorimotor polyneuropathy, predominantly sensory. Each patient who developed a neuropathy during therapy received three or more courses of DACCP and had been previously treated with cisplatin and a vinca alkaloid (either vinblastine or vindesine), but had minimal or no symptoms at the start of therapy with DACCP.

Discussion

The overall response rate of 4% (1 of 28) with 95% confidence limits 0–10%, was disappointing, but only 11 patients had not received prior chemotherapy. Although the patient population was heavily pretreated, 95% confidence limits fall within the range for cisplatin, and two patients subsequently responded to a cisplatin-containing regimen. DACCP appears to offer no advantage over the parent compound, and difficulties in formulation and administration may significantly delay further trials in this disease.

Although the drug is suitable for outpatient administration, the therapeutic index appears rather narrow. At 720 mg/m^2 two of seven patients developed increased creatinine levels and it is unclear whether higher doses could be given. It is also uncertain whether further hydration could have prevented this complication. Further, although the degree of myelosuppression was less than that observed in the phase-I trial, this may be related to the fact that the patients were not as heavily pretreated.

Most disturbing was the neurotoxicity which developed in three patients who received three or more courses of the agent, one of whom required discontinuation of the drug. A similar observation was noted in four patients treated during the phase-I trial [6]. Although the neurotoxicity can not be attributed solely to DACCP, as all patients who developed this complication had received prior cisplatin and a vinca alkaloid, all had minimal or no symptoms at the start of therapy. This side-effect has been reported with cisplatin [4, 9–11]. Differences in the configuration of the platinum may explain differences in the potency of the compound, but when platinum is corrected for on a molar basis, significantly larger amounts are given with each dose of DACCP relative to cisplatin. The neurotoxicity seen may be related to the increased quantity of platinum given with each dose. DACCP exists in two isomeric forms of the diaminocyclohexane ring, and studies by Kidani and co-workers suggest the *trans* isomer may be more active [7]. The clinical compound used in this study is approximately 70% *trans*. Further studies would be needed to assess the relative neurotoxicity of the individual isomeric forms.

Allergic reactions were seen in patients previously exposed and not exposed to cisplatin. Hypersensitivity reactions to complex metallo platinum salts have been observed following industrial exposure [11] and repeated therapeutic administration [3] and is therefore not surprising. Anaphylaxis, which occured in one instance in the phase-I trial following the fourth dose of DAACP, was not seen in this study [6]. Although two patients had the drug discontinued during the infusion with the development of hives and urticaria, subsequent patients who developed reactions were given premedication with diphenhydramine and corticosteroids, and treatments continued without difficulty. Successful retreatment following premedication with diphenhydramine has been described [12]. Skin tests, histamine release and serum IgE levels were not performed in this study, but have been reported to be normal in patients who have demonstrated hypersensitivity to cisplatin. This suggests that some reactions may be nonallergic in origin and gives further support to continuation of therapy when clinically indicated [12].

DACCP, given in the present dose and according to this schedule, has minimal activity in patients with non-small cell lung cancer. No further trials are planned in this disease.

Acknowledgements. The work described in this paper was supported in part by Public Health Service grant CA-05826 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and the Bristol-Myers Corporation.

Dr. Howard Scher is recipient of an Untermeyer Fellowship, Memorial Sloan-Kettering Cancer Center.

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Received April 5, 1983/Accepted October 21, 1983