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Phase I clinical evaluation of [SP-4-3(R)]-[1,1-cyclobutanedicarboxylato(2-)](2-methyl-1,4-butanediamine-*N*,*N*[1]) platinum in patients with metastatic solid tumors

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Summary. The development of clinically useful drugs is a priority of clinical cancer research. CI-973, [SP-4-3(R)]-[1,1-cyclobutanedicarboxylato(2-)](2-methyl-1,4-butanediamine-*N*,*N*[1]) platinum, has been shown in preclinical murine and human tumor models to have activity equivalent or superior to that of cisplatin and carboplatin and to exert activity against cisplatin-resistant cell lines. In addition, preclinical testing suggests a reduced toxicity profile for CI-973 as compared with currently available drugs, especially decreased nephrotoxicity, ototoxicity, and gastrointestinal toxicity. A total of 29 (28 evaluable) patients with solid tumors were treated with intravenous CI-973 given over 30 min every 4 weeks. No routine pre- or post-treatment hydration or antiemetic program was used. The CI-973 doses given were 75, 150, 170, 188, 230, and 290 mg/m^2. The dose-limiting toxicity was granulocytopenia. Nausea and vomiting occurred in the majority of patients but was mild to moderate in severity. No renal or auditory toxicity was seen. The maximum tolerated dose (MTD) for patients who had a good performance status, had not received prior radiation therapy to bone marrow, and had not previously been exposed to platinum or stem-cell toxin was 290 mg/m^2. For those who had received prior radiation therapy, had a performance status of 2 or worse, or had previously been exposed to platinum or stem-cell toxin, the MTD was 230 mg/m^2. The recommended phase II starting doses for these groups of patients are 230 and 190 mg/m^2, respectively. No clinical tumor response was seen in this phase I study.

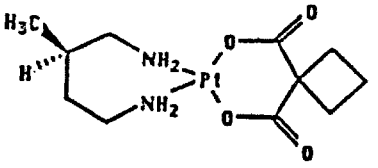

Fig. 1. Chemical structure of CI-973

Introduction

CI-973, [SP-4-3(R)]-[1,1-cyclobutanedicarboxylato(2-)]-(2-methyl-1,4-butanediamine-*N*,*N*[1]) platinum, is a water-soluble platinum diamine complex having the *cis* configuration (Fig. 1). CI-973 has been shown to demonstrate activity superior or equivalent to that of cisplatin in a number of in vitro and in vivo murine and human tumor systems. Especially noteworthy is its activity in cisplatin-resistant cell lines [4].

In acute toxicity studies performed in mice, rats, and dogs, myelosuppression, including both leukopenia and thrombocytopenia, was the primary toxicity encountered. Gastrointestinal toxicity was also noted. In repeated-dose studies in rats and dogs, hematologic toxicity was dose-limiting. Gastrointestinal toxicity, including diminished food intake, diarrhea, and, in dogs, emesis, was reported. Testicular and renal toxicity were also noted; however, renal toxicity, which occurred in 4 of 22 treated dogs, was observed only at lethal doses. A phase I study using a single-dose, 30-min intravenous infusion of CI-973 was conducted in Japan [2]. In this trial, involving 40 patients with solid tumors, leukopenia was dose-limiting, and the maximum tolerated dose, based on grade 3 or 4 leukopenia, was 360 mg/m^2. The recommended starting dose for phase II study was 300 mg/m^2. Thrombocytopenia was infrequent, occurring in less than 10% of patients, and generally mild in severity, even at higher dose levels. Mild to

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Table 1. Patients' characteristics

Number of patients entered		29
Evaluability status:		
	Nonevaluable	1
	Response and toxicity	28
Median age (years)		
Performance status:		
	0	7
	1	13
	2	8
Sex (F/M):		
	F	15
	M	13
Primary disease site (evaluable patients):		
	Breast	8
	Lung	4
	Colorectal	9
	Head and neck	2
	Melanoma	1
	Gastric	1
	Esophagus	1
	Pancreas	1
	Neurofibrosarcoma	1

moderate anemia was relatively common. Nausea and vomiting, loss of appetite, and fatigue were the most common nonhematologic toxicities; these were usually mild (grade 1) in severity and occurred in 41%, 44%, and 19% of evaluable patients, respectively. Headache, stomatitis, elevated transaminase levels, and elevations of blood urea nitrogen (BUN) and creatinine values were infrequent, occurring in less than 6% of patients. Because of the apparent lack of in vivo cross-resistance with cisplatin and carboplatin and due to the potential for reduced renal toxicity, the present phase I clinical evaluation of CI-973 in patients with solid tumors at M. D. Anderson Cancer Center was completed.

Patients and methods

Patients with solid tumors and histologically proven metastatic malignancy who were not candidates for regimens known to have higher efficacy or priority were eligible for this study. The protocol was reviewed and approved by the Institutional Review Board of M. D. Anderson Cancer Center.

The inclusion criteria included a life expectancy of 12 weeks, a performance status of at least 2 Zubrod [5], an age of between 18 and 80 years, adequate bone marrow function (an absolute granulocyte count of >1500/μl and a platelet count of >100,000/μl); adequate hepatic function (bilirubin values of <1.5 mg/100 ml and alkaline phosphatase and transaminase levels of less than twice the normal values), and adequate renal function (creatinine clearance of >60 ml/min as determined by 24-h collection). Excluded from the study were patients who had received cytotoxic chemotherapy or radiation therapy during 3 weeks prior to enrollment (6 weeks for mitomycin or nitrosoureas); those who had received more than one prior chemotherapy regimen containing a platinum compound, who had undergone major surgery within 2 weeks of study entry, or who had comorbid medical conditions; those with a clinical hearing deficit or a history of peripheral neuropathy or myopathy; those who had received aminoglycoside antibiotics within 4 weeks of enrollment; and those with brain metastases.

Pretreatment evaluation consisted of a complete history and physical examination along with a detailed neurologic examination; an audiogram; and laboratory studies, including a complete blood count (CBC) with differential and platelet count, urinanalysis, measurement of serum electrolytes, including magnesium, a biochemical profile, and determination of 24-h creatinine clearance. All patients underwent pretreatment chest radiography and electrocardiography. All patients were scheduled for twice weekly CBC with differential and platelet counts as well as for weekly biochemical profiles. Measurements of serum electrolytes, magnesium, and creatinine clearance were performed prior to each course and drug discontinuation. Disease assessment was accomplished by appropriate physical examination and clinically indicated radiography studies. Audiograms were obtained before treatment and at the conclusion of each patient's participation in the study.

CI-973 was given as a 30-min intravenous infusion using a Pancretec pump without routine pre- or posttreatment hydration or antiemetic prophylaxis. Drug administration was repeated every 28 days if adequate recovery from any toxicity was documented. Three patients were treated at each dose level and were observed for 4 weeks prior to the enrollment of additional patients or increases in the dose level. On the basis of the results of the phase I study in Japan, a starting dose of 75 mg/m^2 was selected. The starting dose was increased in 100% increments until the development of grade 1 toxicity, excluding nausea/vomiting and alopecia. Subsequent dose escalations were carried out in 25%–50% increments until the occurrence of grade 2 toxicity and then in 25% increments until the maximum tolerated dose (MTD) was established. The MTD was defined as the highest dose that did not result in grade 3 or 4 toxicity in one-half of the patients treated. Institutional toxicity criteria similar to the National Cancer Institute Common Toxicity Criteria were used [1]. Response criteria were those previously reported by Hayward et al. [3].

Results

In all, 28 of the 29 patients enrolled in this study were evaluable; 1 patient refused drug infusion after enrollment. The patients' characteristics are shown in Table 1.

Grade 4 neutropenia was unexpectedly encountered in one patient treated at the 150-mg/m^2 dose level and in two of three patients treated at the 188-mg/m^2 dose level. This was felt to be related to the type of prior treatment, including radiation therapy to bone, and to the pretreatment performance status. Therefore, criteria for poor-risk and non-poor-risk patients were defined on the basis of the characteristics of the initially treated patients. Patients were then prospectively classified for study purposes into these subgroups with the intention of defining a separate MTD for each group. Poor-risk patients were defined as those who had received prior radiation therapy to the pelvis or to greater than 30% of the axial skeleton; prior therapy with stem-cell toxins, i.e., mitomycin C or nitrosoureas; or prior platinum therapy or those who had a performance status of 2. Poor-risk patients were subsequently treated at 170, 190, and 230 mg/m^2, with the latter dose level being determined as the MTD for this subgroup. Prior chemotherapy and radiation therapy for patients treated at each dose level are shown in Table 2.

The hematologic toxicity of CI-973 according to dose and risk-subgroup classification is shown in Table 3. Nadir absolute granulocyte counts according to dose level and number of courses of CI-973 are shown in Table 4. Dose-limiting granulocytopenia, with the median duration of an absolute granulocyte count of less than 500/μl being 4.5 days, defined the MTD. The median duration of neutro-

Table 2. Prior chemo-/radiation therapy according to risk group

CI-973 (mg/m^2)	Patient number		Poor risk	Good risk
70	1	Chemo	5FU/Dox/VCR/MTX/Vlb,5FU/M/VP-16/T	
		XRT	None	
	2	Chemo	5FU/Dox/CTX, Mito-C/5FU	
		XRT	Chest wall/lymphatics	
	3	Chemo	CDDP/5FU/VP-16, 5FU/Dox/M	
150	4	Chemo	Flox, 5FU/FA	
		XRT	None	
	5	Chemo	5FU/Dox/CTX, M/Vlb, MTX/CTX/5FU/FA, M, 5FU/FA/CDDP	
		XRT	Chest wall/lymphatics, lumbar spine, left hip	
	7	Chemo	5FU/CDDP/Bleo/MTX	
		XRT	Left neck	
177	11	Chemo	CDDP/CTX, Dox/DTIC, Ifos	
		XRT	Pelvis	
	12	Chemo	DTIC/IL-2, DTIC/CDDP,Vlb, IFN/DTIC/CDDP/VP-16	
		XRT	None	
	14	Chemo	VP-16/CDDP, M/Dox/5FU	
		XRT	Lung/mediastinum	
	15	Chemo	VP-16/CDDP/CTX	
		XRT	Lung/chest	
188	8	Chemo	5FU/MTX, CDDP/5FU, Bleo, Pira	
		XRT	Neck	
	9	Chemo	5FU/Dox/CTX/CDDP/MTX/Vlb, CTX/MTX/5FU, M/Vlb, T/MTX	
		XRT	Chest wall/lymphatics	
	10	Chemo	CDDP	
		XRT	Pelvis	
188	13	Chemo		5FU/FA, 5FU
		XRT	None	
230	16	Chemo	5FU/FA, 5FU, 5FU/IFN	
	17	Chemo	VCR/Dox/VP-16/CDDP, hydrea	
		XRT	Lung/mediastinum/brain	
	18	Chemo		5FU/IFN
		XRT	None	
	27	Chemo	5FU, 5FU, 5FU, 5FU/FA, 5FU/IFN, M, elsamatrucin	
		XRT	None	
	28	Chemo		5FU/Dox/CTX
		XRT		Chest wall/lymphatics
	29	Chemo		5FU/Dox/CTX/MTX/VCR
		XRT	None	None
290	19	Chemo	Dox/5FU/M	
		XRT	None	
	20	Chemo		5FU/FA
		XRT	None	
	21	Chemo	Dox/CTX, CTX/MTX/5FU, M/Vlb, CDDP/5FU	
		XRT	Chest wall/lymphatics	
	22	Chemo		LY186641
		XRT		None
	23	Chemo		5FU/IFN, 5FU/FA
		XRT		None
	24	Chemo		5FU/Dox/CTX, MTX/Vlb, 5FU
		XRT		Chest wall/lymphatics
	25	Chemo		5FU/FA
		XRT		None
	26	Chemo		5FU
		XRT		Esophagus

Chemo, Chemotherapy; XRT, radiation therapy; 5FU, 5-fluorouracil; Dox, doxorubicin; VCR, vincristine; MTX, methotrexate; Vlb, vinblastine; M, mitomycin C; VP-16, etoposide; T, thiotepa; CDDP, cisplatin; Flox, floxuridine; Bleo, bleomycin; DTIC, dacarbazine; Ifos, ifosfamide; IL-2, interleukin 2; IFN, interferon, Pira, pirarubicin; FA, folinic acid; CTX, Cytoxan (cyclophosphamide)

Table 3. Hematologic toxicity encountered during the first course of CI-973

CI-973 (mg/m^2)	Poor risk	Good risk
Median absolute granulocyte nadir ($\times 10^3/\mu l$):		
75	2.8 (2.7–3.5)	–
150	1.4 (0.2–3.0)	–
170	3.0 (2.7–4.5)	–
188	0.21 (0.09–0.8)	2.6
230	0.25 (0.04–0.7)	1.46 (1.16–1.9)
290	0.7 (0.05–1.5)	0.3 (0.01–1.16)
Median platelet nadir ($\times 10^3/\mu l$):		
75	227 (177–275)	–
150	278 (154–358)	–
170	324 (107–533)	–
188	299 (239–319)	300
230	297 (184–368)	285 (231–307)
290	243 (80–280)	163 (87–321)

Numbers in parentheses indicate ranges

Table 4. Median nadir absolute granulocyte count[a]

CI-973 (mg/m^2)	Courses (n)	AGC ($\times 10^3/\mu l$)
75	5	2.8 (15)
150	7	0.8 (17)
170	4	3.1 (15)
188	9	1.3 (16.5)
230	12	1.0 (15)
290	16	0.6 (15)

[a] The median duration of an absolute granulocyte count (AGC) of <500/μl was 4.5 days for all patients; CBC with differential and platelet counts were determined twice weekly. Numbers in parentheses indicate the days on which the AGC values were obtained

Table 5. Nonhematologic toxicity possibly related to CI-973 administration

	Number of patients	Number of patients	
		Grades I–II	Grades III–IV
Nausea/vomiting	19	18	1
Headache	2	2	–
Malaise	2	2	–
Increased transaminases	1	1	–
Infection	4	3	1
Paresthesia	3	3	

penia for non-poor-risk patients treated at their MTD, 290 mg/m^2, was 7 days (range, 5–7 days). At both the 230- and the 188-mg/m^2 dose levels, two of three poor-risk patients experienced grade 4 neutropenia. However, both of the neutropenic patients treated at the 230-mg/m^2 dose level developed infections requiring hospitalization. The 230-mg/m^2 dose level was therefore considered to be the MTD for the poor-risk subgroup and 290 mg/m^2 was set as the MTD for the good-risk group. Cumulative myelosuppression was not apparent. Thrombocytopenia was infrequent and mild, occurring in only four patients, and was of grade 1 severity in three patients and of grade 2 severity in one patient. There was no evidence that this toxicity was dose-related. Severe thrombocytopenia did not occur, even at the highest dose level. Anemia was seen in 16 patients and included exacerbation of preexistent anemia of up to grade 4 severity; 6 patients required transfusions of packed red blood cells.

Nonhematologic toxicity was not dose-limiting (Table 5). Nausea and vomiting occurred in 19 patients after their first course of therapy and in 23 patients at some time during treatment. Only one patient experienced grade 3 nausea and vomiting. Nausea and vomiting generally began at 2–4 h after drug infusion and lasted for 8–12 h. Rash, fever, xerostomia, and diarrhea occurred in two patients each, with the maximal severity being grade 2.

Detailed neurologic examinations carried out prior to each course of CI-973 did not demonstrate detectable neurologic deficits except in one patient, who showed a loss of Achilles reflex after receiving a cumulative dose of 618 mg/m^2 CI-973. This patient had also had diabetes for 3 years and had previously been exposed to cisplatin. Six patients reported numbness or tingling in their fingers or toes; however, these complaints were inconsistent and evanescent.

Pre- and posttreatment audiograms were obtained in 13 patients. None of the posttreatment audiograms indicated significant hearing loss. None of the patients noted a clinically apparent change in hearing, although one patient complained of a decreased ability to hear the telephone ring following a total dose of 528 mg/m^2 CI-973. The median pre- and posttreatment values for creatinine clearance were 91 (range, 60–326) and 99 (range, 41–249) ml/min. The one patient who showed reduced clearance had concomitant-disease-related hypercalcemia of malignancy. Magnesium levels were monitored in all patients, but no significant hypomagnesemia developed.

Infections occurred in six patients in the absence of neutropenia and included two cases of pneumonia, which were felt not be drug-related. The other four infections included one each of grades 1–4; all were considered to be related to CI-973 administration, and all occurred during grade 4 neutropenia. Three patients required hospitalization and all recovered without sequelae.

Discussion

The development of new agents for cancer treatment is a priority of clinical research. Modification of existing compounds with known antineoplastic activity is one avenue of investigation. Two platinum compounds are currently in routine clinical use and show activity in a wide variety of solid tumors. Platinum compounds with broader activity or less toxicity are of clinical interest. CI-973 is a platinum diamine complex and is water-soluble. Preclinical studies in murine tumor systems indicate that CI-973 is superior or

equivalent to cisplatin and carboplatin and is active against cisplatin-resistant cell lines.

The toxicity profile obtained in this phase I study is generally consistent with that reported in the Japanese phase I single-dose study. Granulocytopenia was dose-limiting and of short duration and did not appear to be cumulative. The nadir of neutropenia typically occurred on study day 7, with complete hematologic recovery being noted by day 24. Of substantial importance was the absence of thrombocytopenia at doses that reliably cause granulocytopenia; this may provide an advantage for CI-973 over carboplatin. Although anemia was relatively common, it was not dose-limiting. No significant nephrotoxicity was observed.

Routine audiometry was not performed in the Japanese study. Pre- and posttreatment audiograms remained essentially normal in patients partipating in the present study. Further assessment of the potential for ototoxicity and neurotoxicity will be required in subsequent studies using higher doses and longer periods of treatment with CI-973.

Patients who had undergone prior radiation therapy, stem-cell toxin exposure, or platinum therapy seemed to be at greatest risk of developing myeloid toxicity at a given dose level. The MTD was 290 mg/m^2 for the non-poor-risk patients and 230 mg/m^2 for the poor-risk patients. The recommended phase II starting dose is 190 mg/m^2 for patients who have received prior radiation therapy to more than one-third of the bone marrow or to the pelvis, who have previously been exposed to stem-cell toxins such as mitomycin C, or who have undergone prior platinum therapy. For patients without these risk characteristics, the recommended starting dose is 230 mg/m^2. Although these doses are lower than those derived from the single-dose Japanese study, the reason for this difference is not apparent.

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