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ORIGINAL ARTICLE

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A phase II study of CI-973 [SP-4-3(*R*)]- [1, 1-cyclobutane-dicarboxylato (2-)] (2-methyl-1,4-butanediamine-*N, N′*) platinum in patients with refractory advanced breast cancer

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Abstract CI-973 is a water-soluble platinum diamine complex whose antitumor activity is greater than that of cisplatin in some murine tumors. It has shown activity against cisplatin-resistant tumors. This phase II trial had the objectives of determining the therapeutic efficacy of CI-973 in patients with metastatic breast cancer who had been treated with one prior chemotherapy regimen, and of further defining the toxicity of the agent and the reversibility of its toxicity. CI-973 was administered as an intravenous infusion over 30 min with no prehydration or antiemetic programs. Treatment cycles were repeated at 21-day intervals. Patients with histologically confirmed metastatic breast cancer, measurable disease, and good performance status who had received only one prior chemotherapy regimen for metastatic disease were eligible for treatment. Adequate hematologic, renal, and hepatic function were required. A total of 26 patients received a median of two courses of CI-973 (range, 1–18 courses). Hematologic toxicity was severe: nearly all patients experienced granulocytopenia with granulocyte counts of 0 at all dose levels. Nevertheless, neutropenic fever and documented systemic infection were uncommon, and there were no hospitalizations for neutropenic fever or infection. Visceral disease dominated in this patient group. Of the 26 patients, 14 had visceral disease, 6 had bone or bone marrow disease, and 6 had skin, soft-tissue, or lymph-node disease. Of the 26 patients treated, 25 were evaluable for response. There were two partial remissions, one in liver and one in bone, and three minor responses, for a response rate of 8%. Nonhematologic toxic effects were mild and consisted of nausea and vomiting, fatigue, minimum peripheral paresthesia, and hypomagnesemia. Further study of CI-973 at the dose and schedule used in this study is not warranted. Because this agent had no significant extramedullary toxicity, intensification of the dose of CI-973 with concomitant administration of colony-stimulating factors has the potential to improve response in this patient population.

Key words CI-973 · Breast cancer

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Introduction

The experimental drug [SP-4–3(*R*)]-[1, 1-cyclobutane-dicarboxylato (2-)] (2-methyl-1,4-butane diamine-N,N^1) platinum (CI-973) is a water-soluble platinum diamine complex that has exhibited antitumor activity equal to or greater than that of cisplatin against murine tumors and has shown activity against cisplatin-resistant tumors [1, 2]. In phase I trials, CI-973 was associated with a low incidence of nausea and vomiting, little or no disruption of renal function, and no significant ototoxicity or peripheral neuropathy. The dose-limiting toxic effect in a single-infusion schedule was noted to be neutropenia. The maximum tolerated dose of 290 mg/m^2 was administered as a 30-min intravenous infusion every 3 weeks [3]. A daily times five administration schedule also resulted in dose-limiting neutropenia at doses of 40 and 50 mg/m^2/ per day [4]. Neutropenia, although profound, was rapidly reversible and did not result in delays in drug administration. Thrombocytopenia and anemia were not dose-limiting, and thrombocytopenia was particularly uncommon.

The lack of nephrotoxicity, ototoxicity, and neurotoxicity and the preclinical data suggesting antitumor activity in cisplatin-resistant cell lines prompted this phase II trial of CI-973 in patients with refractory metastatic breast cancer. The study objectives were to determine the antitumor activity of CI-973 in patients with metastatic breast cancer who had already been

treated with one chemotherapy regimen, and to characterize the type, incidence, severity, and reversibility of CI-973 toxicity.

Patients and methods

Patients with histologic proof of breast cancer and measurable evidence of metastatic disease were eligible for this study. Patients with a Zubrod performance status of 2 or less [5], adequate hematologic function (absolute granulocyte count over 1500/ μl and platelet count over 100 000/μl), adequate liver function (SGPT less than twice normal and bilirubin under 2 mg/dl), and adequate renal function, with a predicted creatinine clearance ≥ 60 ml/min, as determined by the modified methods of Cockcroft and Gault [6], were eligible for treatment. No antitumor therapy was administered during the 4 weeks prior to study drug administration, or during the previous 6 weeks for patients who had received nitrosourea or mitomycin C. Patients were not to have received more than one other cancer chemotherapy regimen for metastatic disease. Patients with hypersensitivity to platinum were not eligible for enrollment. One patient had been exposued to two doses of cisplatin in prior treatment. Patients who had undergone prior high-dose chemotherapy programs requiring stem cell support were not enrolled. Written informed consent was obtained from each patient. The study was approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center.

Treatment consisted of intravenous administration of 230 mg/m^2 of CI-973 as a single dose on day 1 of the 21-day treatment cycle. The dose was administered in 1000 ml 5% dextrose and water as a 30-min infusion. There was no routine prehydration or antiemetic program. The treatment was administered only if the patient had sufficiently recovered from the previous treatment, that is, provided the absolute granulocyte count had returned to > 1500/μl and the platelet count to $> 100\,000$/μl. In addition, all toxic effects of grade 2 or greater severity had to return to grade 0 or 1, and the estimated creatinine clearance had to be more than 40 ml/min, for treatment to continue.

The initial dose-modification criteria called for reduction of the dose by 25% if the absolute granulocyte count nadir had been less than 500/μl in the preceding course or the absolute platelet count had been less than 50 000/μl. Because granulocyte counts did go below 500/μl in nearly all patients treated at the 230 mg/m^2 dose, but none of the patients developed neutropenic fever or documented infection, the protocol was amended to provide for dosage reduction by 20% if the absolute granulocyte nadir was below 500/μl and there was associated fever or documented infection. Dose escalation by 25% was allowed for those in whom the nadir granulocyte count remained at least at 1500/μl and no thrombocytopenia was documented. Response criteria were those of the World Health Organization [7] and of Hayward et al. [8].

Follow-up evaluation included weekly complete blood count with differential and platelet counts, biochemical profile, and serum electrolytes including serum magnesium prior to each treatment course. Disease assessment, as well as a creatinine clearance estimate was required prior to each study drug infusion. Pre- and posttreatment audiograms were obtained. All disease sites were radiographically and clinically assessed after two courses of treatment. All patients who received at least one complete cycle of therapy were evaluated for drug efficacy. The duration of response was calculated from the date of onset of response until the date of documented disease progression. Measurable disease and disease response were reviewed and confirmed by at least three physicians from the section of Breast Medical Oncology, including the principal investigator. The statistical plan called for enrollment of 14 eligible patients, and if one response was documented the enrollment of a second cohort of 16 eligible patients. The total study population was expected to be 30.

Results

The characteristics of the 26 patients enrolled in this phase II trial are shown in Table 1. All were evaluable for toxicity and response. The median number of courses of CI-973 administered was two (range 1–18). The dominant disease sites were visceral in 14 patients, bone or bone marrow in 6 patients, and skin, soft tissue or lymph nodes in 6 patients. The median number of sites per patient was two (range 1–8). The predominant toxic effect in this treatment program was granulocytopenia with a median nadir granulocyte count at dose level 0 of 700/μl (range 0–4.2). Granulocytopenia necessitated a dose reduction from the starting dose in 13 patients, and two patients required two dose reductions, to dose level -1, 172.5 mg/m^2, and to dose level -2, 115 mg/m^2.

Hematologic toxicity by dose level is shown in Table 2. No patient was treated with granulocyte colony-stimulating factor during this trial. No patient was hospitalized with neutropenic fever or documented systemic

Table 1 Patient characteristics

Number entered			26	
Evaluable for response & toxicity			26 (100.0%)	all patients
Age median (range) (years)			52 (31–69)	
Performance status				
0			13 (50.0%)	
1			11 (42.3%)	
2			2 (7.7%)	
Histologic type				
Duct carcinoma, invasive			26 (100.0%)	
Prior therapy				
	Total	Adjuvant	Metastatic	Prior doxorubicin
Chemotherapy	26	20	21	19
Hormones			18 (69.2%)	
Immunotherapy			3 (11.5%)	
Radiotherapy			16 (61.5%)	
Surgical treatment			22 (84.6%)	
Median number of courses CI-973 (range)			2 (1–18)	

Table 2 Hematologic toxicity. Values are median radio count per microliter × 1000

Dose (mg/m^2)	Courses	Granulocytes (day) (range)	Platelets (day) (range)
115 (-2)	19	1.2 (15) (0.0–3.3)	253 (18) (193–358)
172.5 (-1)	19	0.6 (15.5) (0.0–4.2)	207 (11) (89–485)
230 (0)	52	0.7 (15) (0.0–4.2)	187.5 (14) (67–407)

Table 3 Nonhematologic toxic effects. The number of patients experiencing each effect is shown in relation to the dose and the grade of toxicity

Dose (mg/m^2)	No.of patients	No.of courses	Grade	Nausea	Vomiting	Fatigue	Hypomagnesemia	Infection	Sensory paresthesia
115	2	19	1	1	1	1			1
			2	1	1				—
172.5	13	19	1	4	3	2			1
			2	6	4	1			—
230	26	50	1	9	1	2	2	3	3
			2	16	16	6	1	4	—
			3	4	4	3			—

infection. Pre-and posttreatment audiograms indicated no significant hearing deficit in any patient. Other toxic effects by dose level, number of patients, number of courses, and grade are shown in Table 3. Treatment was associated with two partial remissions (8%; 95% CI 1–26) and three minor responses. Partial remissions were of 5 and 6 months duration, with times to progression of 11 and 13 months, respectively. The partial responses occurred in lytic bone and liver metastases. With the advent of studies with paclitaxel, this trial was discontinued after enrollment of 26 patients.

Discussion

Cisplatin is one of the most active agents available for the treatment of malignant neoplasms. It has demonstrated a broad spectrum of activity against a variety of solid tumors. Because of its toxicity profile (nausea and vomiting, renal failure, and neurotoxicity) there has been an extensive search for equally active but less toxic platinum analogues. A number of such agents have been tested in clinical trials, including carboplatin and iproplatin. Iproplatin has shown limited activity in patients who have undergone extensive prior therapy for metastatic breast disease [9 –11]. Carboplatin has been shown to have an antitumor effect. Martin et al. reported a 35% rate of response to carboplatin in chemotherapy-naive patients [12], while Kolaric and Vukas reported responses in 4 of 20 patients treated with carboplatin on a 3-week schedule at a dose of 400 mg/m^2 [13].

In the present study, the observation of partial remissions in patients who had undergone previous systemic c hemotherapy for visceral or bone metastatic disease is encouraging. The predominant myelotoxicity of this agent demonstrated in this and previous phase I studies suggests the possibility of increasing the dose-intensity by coadministering colony-stimulating factors. The dose intensity of this program was limited by the initial protocol criteria, which required dose reduction for granulocyte counts less than 500/μl, irrespective of the presence of neutropenic fever or documented infection. The limited duration of granulocytopenia, the lack of significant infection, and the absence of significant anemia or thrombocytopenia suggests that the addition of colony-stimulating factors to a more dose-intensive regimen of CI-973 may increase the frequency of response.

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