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CLINICAL TRIAL REPORT

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Feasibility trial of high-dose 7-day continuous-infusion ifosfamide given on an outpatient basis

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Abstract High-dose ifosfamide (HD-IFX) has shown significant antitumor activity in advanced sarcoma and breast carcinoma. The use of uroprotective agents and the availability of ambulatory continuous-infusion pumps has allowed dose escalation in the administration of ifosfamide (IFX) on an outpatient schedule. We report the results of a phase II trial of IFX given at high doses to heavily pretreated patients. IFX was infused at 2 g/m^2 per day for a total of 7 days through a central venous access, with cycles being repeated every 21 days. Mesna was given concomitantly at equimolar doses. No hematopoietic support was used. A total of 27 heavily pretreated patients whose disease had progressed during conventional-dose chemotherapy were included (14 sarcomas, 10 breast carcinomas, and 3 bladder carcinomas). Reversible neutropenia and gastrointestinal toxicity were the most frequently encountered toxicities. Only two patients developed transient renal failure, and two others developed central nervous system toxicity. No treatment-related death was observed. Of 22 patients who were evaluable for response, 6 (27%) showed an objective response (OR), all ORs being partial responses (PRs) with a median duration of 6 months, and 12 patients had stable disease (SD; 55%) with a median duration of 3.5 months. The median overall survival (OS) was 6 months. Three patients underwent high-dose chemotherapy after showing a response to our IFX schedule. We conclude that continuous-infusion IFX given in an outpatient setting is a feasible and active regimen that produces, a manageable toxicity profile in heavily pretreated breast cancer and sarcoma patients. Early institution of this schedule in less advanced stages could improve the results obtained.

Key words: Ifosfamide · Continuous infusion · Sarcoma · Breast carcinoma · Bladder cancer

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Introduction

Ifosfamide (IFX) is an oxazaphosphorine nitrogen mustard whose chemical structure is minimally modified from that of cyclophosphamide. In tissue culture and in laboratory animals, IFX is more active and less toxic than cyclophosphamide [11], with an improved therapeutic/toxicity ratio being achieved with a fractionated dose schedule [5]. Hemorrhagic cystitis occurs more frequently in patients receiving IFX [10] limiting its safe administration. The development of uroprotective agents has allowed the use of larger IFX doses since such agents protect the genitourinary tract from the action of toxic IFX metabolites [7].

It has been shown that some chemotherapy regimens given by continuous infusion may have different toxicity profiles and different degrees of therapeutic efficacy as compared with bolus administration [2, 8, 9, 13, 16]. The potential therapeutic benefits of continuous-infusion chemotherapy, the steep dose-response curve produced by alkylating agents, and the advantages of outpatient administration with a portable infusion pump led us to design a phase II trial of high-dose continuous-infusion IFX given on an outpatient basis. The principal aim of this study was to investigate the feasibility and tolerability of this schedule without hematopoietic support in heavily pretreated patients with advanced cancer whose disease had progressed during conventional chemotherapy. A second aim was to determine the antineoplastic activity of this regimen.

Our results show that IFX can be given at a total dose of 14 g/m^2 as a 7-day continuous infusion without hematologic support as an ambulatory regimen, consistently improves the patients' quality of life by decreasing the hospital stay, and provides promising antitumoral activity in some advanced cancer patients.

Patients and methods

Patients

Eligible patients had histologically proven metastatic or advanced tumoral disease refractory to at least one conventional chemotherapy regimen, a minimum of one measurable target lesion in a not previously radiated area, a Karnofsky performance status (KPS) of greater than 60 in association with a projected life expectancy of more than 2 months, and prior adequate bone marrow, liver, and renal function. Informed consent was obtained from all patients.

Treatment program

IFX was given at 2 g/m^2 by continuous infusion for 24 h daily for a total of 7 days (total dose 14 g/m^2), with cycles being repeated every 21 days, the drug being delivered through a central venous port by an ambulatory pump together with mesna at equimolar doses in the same solution. Patients received antiemetic treatment with ondansetron given at 8 mg/8 h by the oral route. Intravenous administration of ondansetron (16 mg) was used whenever the patient came to refill the pump (every 48–72 h). In addition, patients were given supplemental oral sodium bicarbonate at 30 mEq/day and were instructed to have an adequate oral fluid intake of at least 2 l/day throughout the treatment. Urinalysis was also performed daily during the infusion period to predict the need for additional bicarbonate replacement (a urinary pH of <6 mandated and additional oral dose of bicarbonate at 20 mEq/8 h) and permitted the monitoring of hematuria. If microscopic hematuria [<20 red blood cells (RBC) per high-power field (HPF)] occurred, an oral supplement of mesna at double the dose delivered by the i.v. route was given every 4 h without discontinuation of the infusion and until resolution of the microhematuria. Gross (20–100 RBC/HPF) or macroscopic hematuria mandated discontinuation of the infusion, with energetic hydration (i.v. administration of saline serum at 125 ml/h) and double the equimolar concentration of mesna being given by the i.v. route until recovery from the hematuria. The IFX dose was reduced by 25% if the serum creatinine level was >2.0 mg/dl, and IFX was withheld when this value was >2.5 mg/dl. The treatment was discontinued if grade ≥ 3 encephalopathy occurred. Treatment was delayed for up to 2 weeks to allow recovery to an absolute neutrophil count of $>1{,}500$/mm^3 and to a platelet count of $>100{,}000$/mm^3 on the day of treatment. Dose reductions were not scheduled for any episode of granulocytopenic fever or necessity for packed red cell transfusion. A 25% dose reduction was scheduled when thrombocytopenia reached a level of $<25{,}000$ platelets/mm^3 or if thrombopenic bleeding appeared. Growth factors were not given for hematopoietic support.

Patients were assessed for response every two cycles. They continued on treatment for up to six cycles, until documentation of progressive disease, a decrease of two levels in KPS, or unacceptable toxicity. All toxicities were reported according to standard WHO criteria [20].

Results

Between February 1991 and December 1994, 27 adults with refractory malignancies entered the study. All were available for toxicity assessment, and 22 were assessable for response and survival. Five patients were excluded from the efficacy analysis since they had received only one course of treatment (three cases of early progression, two cases of reversible grade II nephrotoxicity). The median age of the group was 43 years. In all, 10 cases of advanced breast cancer, 14 cases of metastatic soft-tissue and bone sarcoma, and 3 cases of advanced transitional-cell carcinoma of the bladder were included. The median number of chemotherapy regimens previously received was 3 (range 1–5). All patients had undergone doxorubicin-based chemotherapy, 20 had received cyclophosphamide-containing regimens, and 4 had previously received IFX at conventional doses.

Table 1 Response to the present regimen by histology (*CR* Complete response, *PR* partial response, *SD* stable disease, *DP* disease progression, *SB* sarcoma of the bone, *STS* soft-tissue sarcoma)

Tumor	Number of responses				
	Number of patients	CR	PR	SD	DP
Breast cancer	8	0	2	5	1
Sarcoma:	12	0	4	6	2
Ewing's	4	0	1	3	0
SB	3	0	2	1	0
STS	5	0	1	2	2
Bladder	2	0	0	1	1
Total (%)	22	0	6 (27)	12 (55)	4 (18)

Response and survival

Of 22 patients available for response, 6 patients experienced a partial response (response rate 27%, 95% CI 9–45%) with a median duration of 6 months (range 5–8 months; Table 1). The histopathologic diagnoses of responders included two breast cancers and four sarcomas [two osteogenic sarcomas (OS), one Ewing's sarcoma (ES), and one malignant fibrous histiocytoma (MFH)]. In all, 12 patients had stable disease (SD; 55%, 95% CI 34–75%) with a median time to progression of 3.5 months. The OS duration was 6 months (range 1–22 months). Three patients experienced a significant partial response (PR) ($>90\%$ reduction) and underwent treatment with high-dose chemotherapy with peripheral stem-cell support. A breast cancer patient with liver metastasis in PR achieved a complete response (CR) after high-dose chemotherapy and is now alive and disease-free at 10+ months. Two ES patients obtained a CR after consolidation, but their disease later recurred at 8 and 5 months, respectively.

The toxicities observed are listed in Table 2. The main common toxicity was myelosuppression, which was usually

Table 2 Toxicity of the present regimen (*CNS* Central nervous system)

	Grade			
	1–2		3–4	
Toxicity	Number	%	Number	%
Neutropenia	14	52	13	48
Thrombocytopenia	15	55	3	11
Anemia	11	41	3	11
Emesis	16	59	11	41
Alopecia	6	22	21	82
Renal	2	7	0	0
CNS	1	4	1	4

brief and reversible. The treatment had to be discontinued due to unacceptable toxicity only in two bladder cancer patients who developed grade 4 myelosuppression and grade 3 CNS toxicity after two cycles, respectively. No treatment-related death was seen.

Discussion

There is evidence that repeated administration of IFX produces an increase in its metabolism by an enzime-induction pathway, resulting in the production of higher levels of active metabolites. We could thus expect a higher level of antitumoral activity from a continuous infusion [9, 13] as opposed to a bolus infusion [17]. IFX at conventional doses (6–9 g/m^2) has been established as an effective second-line therapy for germ-cell carcinoma [18, 21], sarcoma [1, 2 19], ovarian carcinoma [26], breast cancer [3, 14, 25], lymphoma [23], lung cancer [6], and bladder cancer [27]. IFX has produced response rates of over 15–20% against advanced breast cancer and of up to 30% in patients who have had no prior exposure to chemotherapy [3]. Studies of single-agent IFX in patients with sarcoma report overall responses of 18–46% in a highly heterogeneous group of patients [4, 19].

In a phase I trial in patients with advanced cancer, Elias et al. [9] used escalating doses of IFX with mesna uroprotection to a maximum tolerated dose of 16 g/m^2 without the need of hematological rescue. In this study, renal insufficiency was the dose-limiting toxicity. In the present trial we attempted a longer infusion period. We chose a dose lower than the maximum tolerated dose of IFX in a schedule that had successfully been used by one group of investigators in 13 patients with metastatic synovial sarcoma [24].

In general, toxicities in the current trial were substantial, although reversible. Neutropenia was the most significant acute toxicity but was usually of brief duration and was infrequently associated with infection. Acute nausea and vomiting were frequently observed even with administration of the new 5-hydroxytryptamine$_3$ (5-HT3) antagonists. Two bladder cancer patients developed transient grade II nephrotoxicity related to previous cisplatin-based treatment, resulting in a renal toxicity rate lower than those obtained in other studies that used the same total dose of IFX [22]. It is well known that patients more frequently develop encephalopathy [12] during short-term IFX infusions (6–24 h) than during longer infusions. In our trial the use of a 7-day continuous-infusion schedule may have helped to avoid the predictable neurotoxicity of HD-IFX (only one bladder cancer patient who had previously been treated with a platinum-based regimen developed grade III CNS toxicity). Interestingly, we did not see any grade 3 or 4 cardiac toxicity, which has sometimes been described in patients who have previously received anthracycline-containing regimens [15].

Apart from its manageable toxicity, this outpatient schedule proved to be active in a heterogeneous group of patients with advanced cancer (33% response rate in heavily pretreated sarcomas, 25% response rate in anthracycline-resistant breast cancers). Four of six responses occurred in patients who had previously been treated with IFX or cyclophosphamide at a conventional dose level, suggesting a partial lack of cross-resistance between these two drugs and a dose-response effect related to IFX. No response was seen in the three patients with advanced bladder cancer. It is remarkable that half of the ES patients (1 PR, 1 minor response) whose disease had progressed after treatment with all conventional active schedules responded to HD-IFX. Among the five available patients with soft-tissue sarcoma, only one patient with a MFH responded to treatment.

Although only two responses (response rate 25%) were obtained in breast cancer patients, one of those patients achieved a 90% reduction in her measurable liver metastases. One of the most important potential applications of this regimen could be to test chemosensitivity in cancer patients with demonstrated refractoriness to conventional treatment. Three heavily pretreated patients (two ES patients and one breast cancer patient) were considered to be further eligible for inclusion in an intensive high-dose chemotherapy program.

In conclusion, the results obtained in this study with high-dose outpatient administration of IFX demonstrate that this schedule is active and produces a manageable toxicity profile in a heavily pretreated population of breast cancer and sarcoma patients. The addition of hematopoietic growth factors and adequate antiemetic support could reduce the toxicity of this regimen. Early institution of this schedule in less advanced stages could also improve the results obtained. This regimen could be useful as a definitive test of chemoresponsiveness before further chemotherapy dose intensification in patients with potentially responsive tumors that do not show a response to conventional salvage regimens.

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