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CLINICAL TRIAL REPORT

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Oral trofosfamide: an active drug in the treatment of soft-tissue sarcoma

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Abstract A total of 23 patients with metastatic sarcomas were treated with continuous oral trofosfamide, an alkylating agent structurally related to cyclophosphamide and ifosfamide. In all, 12 of the patients were chemotherapy–naive. Doses were escalated every 3rd week until the development of leukopenia of WHO grade 2. The treatment was well tolerated and produced little subjective toxicity. Leukopenia was the dose-limiting toxicity. The daily dose that produced grade 2 leukopenia was 200–250 mg in 65% of the patients. Three patients responded, all of whom had been treated with trofosfamide as first-line treatment.

Key words Soft-tissue sarcoma · Chemotherapy
Trofosfamide

Introduction

Combination chemotherapy yields objective responses in less than 50% of patients, and the toxicity is considerable [1–3]. Many patients are aged and tolerate these treatment regimens poorly. In a large Finnish population–based study the mean age at diagnosis of soft-tissue sarcoma was 52 years, and 20% of the patients were older than 70 years [4]. During the last decade, ifosfamide has emerged as one of the most effective drugs for the treatment of soft-tissue sarcoma [2,5]. Trofosfamide is an oxazaphosphorine with a structure related to that of ifosfamide. In fact, one of the main metabolites of trofosfamide is ifosfamide [6]. Trofosfamide is available only in oral formulation and causes little subjective toxicity when given as continuous low-dose treatment [7,8]. It has previously shown activity in the treatment of non–Hodgkin's lymphomas and chronic lymphatic leukemia [8–10].

This trial was started to determine the activity and toxicity of oral trofosfamide in the treatment of patients with advanced sarcomas who were not considered for intravenous combination chemotherapy. Two categories of patients were included: patients with a poor performance status (usually elderly; first–line therapy) and patients who had progressed on previous chemotherapy.

Patients and methods

A total of 23 patients were treated between April 1991 and September 1993. Of these, 12 received the treatment as first-line therapy. Seven of the pretreated patients were given second-line therapy, and the rest had received two to four previous treatment regimens. All pretreated patients had received doxorubicin or epirubicin and ifosfamide or cyclophosphamide. The patients' characteristics and tumor histology are summarized in Table 1.

Trofosfamide was given as continuous oral treatment starting at a daily dose of 150 mg, which was escalated by 50 mg every 3rd week until achievement of the maximum tolerated dose (MTD), defined as leukopenia of grade 2 (leukocyte count, $2.0–3.0 \times 10^9$/l). The dose was decreased by 50 mg daily if the leukocyte count decreased below 2.5×10^9/l. In case of leukopenia of WHO grade 3 (leukocytes, $< 2.0 \times 10^9$/l), treatment was discontinued until leukocyte recovery above 2.5×10^9/l. Hemoglobin, leukocyte, and platelet counts were recorded weekly. Clinical investigation and chest radiographs (if the patient had lung metastases) were performed monthly. Computerized tomography (CT), magnetic resonance imaging (MRI), or ultrasound was performed every 3rd month if needed for response evaluation. The response was defined according to WHO criteria [11]. For stable disease a minimum period of 3 months without progression was required. The study was approved by the local ethics committee.

Results

A summary of the hematological toxicity encountered is shown in Table 2. Three patients suffered from macroscopic hematuria: all three, however, had other

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Table 1 Pretreatment characteristics (*DFI* Disease-free interval, *MFH* malignant fibrous histiocytoma, *NOS* not otherwise specified)

	All ($n = 23$)	First-line ($n = 12$)
Median DFI, months (range)	9 (0–67)	4 (0–31)
Mean age, years (range)	56 (21–79)	69 (22–79)
Metastatic sites, median (range)	1 (1– 3)	1 (1– 2)
Lung	6	5
Liver	2	2
Abdominal cavity	5	2
Lung and soft tissue	5	2
Lung and abdominal cavity	1	1
Lung and pleura	1	
Lung, brain	1	
Lung, bone, lymph nodes	1	
Lung, pericardium, pleura	1	
Histology:		
Leiomyosarcoma	9	7
MFH	3	2
Liposarcoma	2	
Ewing's sarcoma[a]	3	
Synovial sarcoma	2	
Sarcoma NOS	3	2
Malignant giant-cell tumor[a]	1	1
Grade II	7	3
Grade III	6	3
Grade IV	10	6

[a]Bone primaries

Table 2 Hematological toxicity expressed in numbers of patients affected

	WHO grade				
Toxicity	0	I	II	III	IV
Overall[a]	1 (4%)	2 (9%)	13 (56%)	7 (30%)	
Leukopenia	1 (4%)	3 (13%)	13 (56%)	6 (26%)	
Anemia	6 26%)	9 (39%)	6 (26%)	2 (9%)	
Thrombocytopenia	7 (71%)	2 (10%)	3 (14%)	1 (5%)	
Overall hemotological toxicity					
First-line	1 (8%)	2 (17%)	7 (58%)	2 (17%)	

[a] Maximal hematological toxicity taking into account leukopenia thrombocytopenia and anemia

predisposing factors (pelvic metastasis and radiotherapy, pyelonephritis, and anticoagulant therapy) and the hematuria was self-limited in all three cases despite continued trofosfamide treatment. One patient had *Pneumocystis carinii* pneumonia, leading to discontinuation of the drug at a leukocyte count of 1.2×10^9/l and a daily dose of 300 mg. This patient also suffered from bronchial asthma for which he used corticosteroid inhalation therapy. One patient developed septic pyelonephritis at a leukocyte count of 3.7×10^9/l. Six patients required blood transfusions for hemoglobin counts ranging between 74 and 105 g/l after a median treatment period of 9 months (range, 2–14 months). Two of the four patients treated for more than 6 months required transfusions. The MTD was reached at 100 mg (13%) in 3 patients, 150 mg (9%) in 2 patients, 200 mg in 10 patients (43%), 250 mg in 5 patients (22%), 300 mg in 2 patients (9%), and 350 mg in 1 patient (4%). There was no statistically significant difference in the MTD between patients receiving first-line treatment and those given trofosfamide as salvage therapy ($P = 0.88$, Mann-Whitney test).

Three patients responded (partial responses), all of whom had been treated with trofosfamide as first-line therapy. The overall response rate was 13% [95% confidence interval (CI), 3%–34%], and in patients receiving first-line therapy it was 25% (95% CI, 5%–57%). Six patients (26%) had stable disease. All three responders had multiple bilateral lung metastases. Two were classified as sarcoma not otherwise specified (NOS), one was classified as a malignant fibrous histiocytoma (MFH), and all three tumors were of malignancy graded 4.

The median time to progression was 3 months (range, from 2 weeks to 18 months), and the median survival was 8 months (range 1–20 + months). The times to progression in the three responding patients were 5.8, 17.9, and 8.7 + months, respectively.

Discussion

Trofosfamide is an orally administrable oxazaphosphorine that is related to cyclophosphamide and ifosfamide [7]. It is well absorbed when given by the oral route but is almost insoluble in water and, therefore, unsuitable for intravenous use. An early study of trofosfamide given as an intravenous bolus solubilized with glycerin-dimethylketal or ricin oil polyethylate found evidence of activity in hematological neoplasms and a variety of solid tumors, including one partial response in one of six sarcomas [12]. The toxicity of the intravenous formulation was high, however, with nausea, alopecia, cystitis, and phlebitis at the injection site being frequent complaints [12].

In oral formulation the drug is very well tolerated when given on a continuous low-dose daily regimen (150–300 mg/day) and produces little toxicity besides dose-related leukopenia [8, 9, 10, 13]. Previous studies have documented the activity of continuous oral trofosfamide in non-Hodgkin's lymphomas and chronic lymphatic leukemia and testicular seminoma [8, 9, 10, 13]. Single responses in breast cancer, lymphoepithelioma, and Kaposi's sarcoma have also been reported [13]. For high-dose intermittent (50 mg/kg in 48 h) oral trofosfamide, sporadic reports of activity in breast cancer, Kaposi's sarcoma, and Ewing's sarcoma have been published. [9, 13, 14]. High-dose oral treatment, however, is associated with the same toxic effects as is intravenous therapy, except for the lack of phlebitis [9, 14]. We are aware of no previous report of activity of daily continuous trofosfamide in patients with soft-tissue or bone sarcomas.

The response rate was especially encouraging in previously untreated patients, whereas there was no indication of activity in patients resistant of combination chemotherapy including doxorubicin or epirubicin and ifosfamide or cyclophosphamide. A larger phase II study should be performed to define the response rate of trofosfamide with greater accuracy.

The toxicity was almost exclusively hematological. The occurrence of anemia was noteworthy on long-term treatment. No evidence of gastrointestinal toxicity or alopecia emerged. Three patients developed hematuria; however all of them also had other predisposing factors. Since both cyclophosphamide and ifosfamide may cause hematuria [15] and high-dose oral or intravenous trofosfamide has been reported to cause cystitis [12], it is conceivable that the hematuria observed in these patients may at least partly have been attributable to trofosfamide. The MTD seemed to about 200–250 mg in most patients, although there was considerable variation in tolerance between patients, which makes individual dose adjustment necessary.

Although the true response rate of trofosfamide cannot presently be stated due to the small number of patients treated, this treatment regimen might be worthwhile for those sarcoma patients who, due to advanced age or a poor performance status, cannot tolerate conventional intravenous cytotoxic agents.

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