Anti-Cancer Drugs 1999, **10**, pp. 453–456

Report

Phase II study of oral trofosfamide as palliative therapy in pretreated patients with metastatic soft-tissue sarcoma

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This phase II study investigated the activity of continuously administered oral trofosfamide in chemotherapy-pretreated patients with metastatic soft-tissue sarcoma (STS). Trosfosfamide is an oxazaphosphorine with ifosfamide as the predominant metabolite. Eighteen patients with a median age of 60 years were treated with trofosfamide given as continuous oral treatment. Starting dose was 300 mg/day for 7 days and subsequently 150 mg/day. All patients had previously received at least one chemotherapy regimen including doxorubicin and ifosfamide. Three patients achieved partial responses (18%) and nine a disease stabilization (53%) for an overall response rate of 18% (95% CI: 0.5–35%). Median progression-free interval was 4 months (0–17 months) and median overall survival was 10 months (4–39+) months. Toxicity was generally mild. Only one WHO grade III nausea, but no other non-hematologic WHO grade III/IV toxicity occurred. Leukopenia WHO grade III/IV was observed in four patients (22%). No thrombocytopenia <50 000/μl and no neutropenic infection was seen. Continuously administered oral trofosfamide is a well-tolerated palliative treatment in anthracycline/oxazaphosphorin-pretreated patients with advanced STS achieving responses and/or disease stabilization in up to 70% of patients. [© 1999 Lippincott Williams & Wilkins.]

Key words: Metastatic soft-tissue sarcoma, oral trofosfamide.

Supported, in part, by DCS Innovative Diagnostik Systeme, Hamburg, Germany, and BATLE LE Inc., Ft Lauderdale, FL, USA.

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Introduction

The results of chemotherapy treatment in patients with metastatic soft-tissue sarcoma (STS) remain unsatisfactory.[1] The two most active single agents are doxorubicin and ifosfamide, both showing response rates of 20–30%.[2] However, complete remissions or long-term disease-free survival are very rare and almost all patients who have responded to first-line chemotherapy will ultimately relapse.[1] To date, no well-established second-line therapy is available for symptomatic patients. Thus, decisions regarding second-line therapy should be primarily based on the anticipated net benefit in quality of life and, less firmly, on the remote possibility of prolonging survival.

Trosfosfamide (Ixoten®; Asta-Werke) belongs to the group of oxazaphosphorin derivatives. It is well absorbed following oral administration and acts as a DNA-alkylating agent.[3] Its predominant active metabolite is ifosfamide.[4] Trofosfamide was reported to cause little toxicity when administered as continuous low-dose treatment.[5,6] Activity has been observed in patients with non-Hodgkin's lymphoma, breast cancer[8] and other solid tumors.[9]

The present phase II study was performed in order to determine the efficacy of trofosfamide as a palliative treatment for patients with advanced soft-tissue sarcoma.

Patients and methods

This phase II study accrued patients with chemotherapy-pretreated, metastatic STS from February 1996 through December 1997. Primary objectives of this

study were to determine the overall (complete and partial) response rates, the median progression-free survival (PFS), the overall survival (OS) and the toxicity of patients treated on this protocol. Eligibility criteria included histologically proven STS, measurable disease (either on CT scan, chest X-ray or ultrasound) and relapse or progression following at least one doxorubicin/ifosfamide-containing chemotherapy regimen. Adequate hematologic (leukocyte count > 2000/μl and platelet count > 75 000 μl), renal (serum creatinine < 2.5 mg/dl) and hepatic function (bilirubin < 3 × normal value) were required, as was witnessed, signed informed consent from all patients. No concurrent anti-tumor therapy was allowed.

Trofosfamide was given as continuous oral treatment on an outpatient basis. The starting dose was 300 mg/day administered in three doses for 7 days and subsequently 50 mg 3 times daily for a total daily dose of 150 mg. Signs of toxicity, complete blood count and routine laboratory tests were evaluated once weekly. Metoclopramide was administered for the prevention of nausea and vomiting, if necessary. Cycles were delayed by 1 week if the leukocyte count dropped to < 2000/μl and/or the thrombocyte count to < 50 000/μl. Following hematologic recovery, a dose reduction to 50 mg twice daily was allowed. Patients whose hematologic recovery was delayed more than 3 weeks were taken off study. All patients who completed at least 4 weeks of therapy were evaluable for response. WHO criteria were applied in order to assess response and toxicity. Staging procedures were performed bimonthly. Treatment was continued if the patient showed a remission or stable disease. Responses and survival times were calculated from beginning with the patient's first day of trofosfamide treatment.

The study was approved by the ethics committee of the University of Tübingen.

Results

A total of 18 patients pretreated with at least one doxorubicin/ifosfamide-based regimen were enrolled in this trial. Patient characteristics are listed in Table 1 All patients were fully evaluable for toxicity and 17 patients for response.

Median interval between the end of the last ifosfamide-containing chemotherapy cycle and trofosfamide treatment was 1 month (0–12 months). The median number of prior chemotherapy regimens was 1 (1–4 regimens). No complete remissions, but three cases of partial remission (18%) and nine cases of stable disease (53%) were observed, resulting in an overall remission rate of 18% (95% CI: 0.5–35%). Median duration of treatment with trofosfamide was 4 months (0–17 months) (Table 2). One patient, diagnosed with a metastatic malignant fibrous histiocytoma, grading 2, showed a complete remission of his lung metastases and a partial remission of his bone metastases following trofosfamide therapy. He had previously progressed after three cycles of doxorubicin/ifosfamide che-

Table 1. Patient characteristics (*n*=18)

	n (%)
Sex	
male	11 (61)
female	7 (39)
Age (years)	
median	60
range	35–71
Histology	
liposarcoma	4 (22)
malignant fibrous histiocytoma	5 (27)
malignant schwannoma	2 (11)
leiomyosarcoma	4 (22)
synovial sarcoma	1 (6)
hemangioperiyctoma	1 (6)
undifferentiated	1 (6)
Grading	
1	4 (22)
2	3 (17)
3/4	10 (55)
not known	1 (6)
Tumor localization	
lung metastases	10 (55)
liver metastases	5 (27)
lymph nodes	3 (17)
abdominal cavity (liver metastases excluded)	6 (34)
soft tissues	7 (39)
bone metastases	2 (11)
Prior therapy	
doxorubicin/ifosfamide-containing regimen	18 (100)
radiation therapy	9 (50)
surgery (primary tumor)	15 (83)
Prior chemotherapy regimens	
1	12 (66)
2	4 (22)
3	1 (6)
4	1 (6)

Table 2. Treatment results

CR	0
PR	3 (18%)
SD	9 (53%)
PD	5 (29%)
Median PFS	4 months (0–17 months)
Median OS	10 months (4–39+ months)

CR = complete remission; PR = partial remission; SD = stable disease; PD = progressive disease; PFS = progression-free survival; OS = overall survival

motherapy. The remission lasted for 17 months. At this point in time he progressed with a bone metastasis and received radiation therapy. Trofosfamide therapy was continued after the end of radiation therapy and the patient remained in complete remission with his lung metastases for a further 18 months. The second and third patients suffered from liposarcoma, grading 3, and synovial sarcoma, grading 2, respectively. Both showed a partial remission of 6 months duration of their lung metastases. These two patients had been pretreated with doxorubicin/ifosfamide-based chemotherapy which had resulted in a stable disease of 4 months in one and a partial response of 6 months duration in the other patient. Following trofosfamide the second patient progressed with his bone and lung metastases, and the third patient developed liver metastases. Five patients (29.4%) progressed within the first 4 weeks of therapy. Overall, median time to progression was 4 months (0–17 months).

Four patients are alive and 14 patients are dead after a median follow-up of 10 months (4–39+ months). Median overall survival is 10 months (4–39+ months).

Toxicity was generally mild and tolerable. WHO grade III nausea occurred in one patient 2 weeks after initiation of therapy. This patient subsequently refused further treatment and was therefore not evaluable for response. No other non-hematologic WHO grade III or IV toxicity was observed. Leukopenia WHO grade III/IV occurred in four patients (22.2%) and resulted in an 1 week delay in therapy; no neutropenic infection developed in these patients. No thrombocytopenia with platelet counts $<50\ 000/\mu l$ was seen.

Discussion

This study was conducted in patients with metastatic STS who had received at least one prior doxorubicin/ifosfamide-containing chemotherapy regimen. Effective and well-tolerated palliative treatment is urgently needed, since many of these patients exhibit a good performance status and expressly request further treatment. Trofosfamide is available in an oral formulation and has been reported to be a relatively non-toxic treatment,[5–8] which can be administered on an outpatient basis. These factors make trofosfamide an interesting agent for palliative therapy in patients with advanced cancer.

In our study, a daily dose of 150 mg of continuously administered trofosfamide administered in three doses was associated with mild side-effects. The observed toxicity was almost exclusively hematological. Only one patient complained about intractable nausea and refused further treatment. All patients in whom treatment was delayed due to leukopenia were able to continue therapy after 1 week of delay and without dose reduction. No gastrointestinal or renal toxicity was seen and no hair loss was reported.

A partial response rate of 18% and a disease stabilization rate of 53% for a median duration of 4 months demonstrate the palliative effect of oral trofosfamide. All partial responses occurred in the lung, lasting for 6 months in a patient with liposarcoma as well as in a patient suffering from synovial sarcoma and for 17 months in a patient with malignant fibrous histiocytoma. Our results appear to correspond with the 13% response rate and the 26% disease stabilization rate reported in the only published study examining trofosfamide therapy in patients with metastatic STS.[6] However, the three responding patients in this study had received trofosfamide as first-line therapy.

All patients in the present study had previously received anthracyclines and ifosfamide-based therapy with ifosfamide given as continuous 18–24 h infusion at a dose of 4–5 g/m^2. It is known that the use of high-dose ifosfamide may circumvent resistance to previously administered standard-dose ifosfamide treatment.[10,11] The median treatment-free interval between the last ifosfamide-containing therapy and the start of trofosfamide treatment was only 1 month (0–12 months). Thus, our results might indicate that a continuous oral administration of low-dose trofosfamide may be effective in some patients progressing after standard-dose doxorubicine/ifosfamide therapy.

Conclusion

In summary, daily oral trofosfamide application appears to be a reasonable palliative treatment option in patients with advanced STS progressing after anthracycline/oxazaphosphorine-based therapy. It can be safely administered on an outpatient basis.

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(Received 14 January 1999; revised form accepted 11 February 1999)