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Phase II Study of Miltefosine (Hexadecylphosphocholine) in Advanced Soft Tissue Sarcomas of the Adult— An EORTC Soft Tissue and Bone Sarcoma Group Study

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The EORTC Soft Tissue and Bone Sarcoma Group conducted a phase II study with oral miltefosine at a dose of 50 mg thrice daily in patients with metastatic soft tissue sarcomas. No responses were seen in 18 evaluable patients. Toxicity consisted mainly of nausea/vomiting. It is concluded that oral miltefosine has no activity in soft tissue sarcoma.
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INTRODUCTION

THE NUMBER of active drugs in the treatment of soft tissue sarcomas is very limited, therefore, new active drugs are urgently needed. The drugs with known activity (doxorubicin, ifosfamide and DTIC) were found also to yield activity when tested in second-line chemotherapy and thus it seems appropriate to test new drugs also in patients after failure to respond to first-line chemotherapy [1]. Hexadecylphosphocholine (miltefosine) is a new phospholipid derivative exerting antitumor activity in several *in vitro* and *in vivo* models [2]. These drugs are described as membrane-active drugs, although the mechanism of action is still unclear. Intravenous formulations of miltefosine caused haemolysis, but an oral formulation was found to be practicable. Phase I studies have shown nausea and vomiting to be the main side-effects; the recommended dose for phase II studies was 150 mg daily, divided over three daily doses [3]. We performed a phase II study with oral miltefosine given in second-line therapy to patients with soft tissue sarcomas.

MATERIALS AND METHODS

For eligibility patients were required to have a histologically confirmed diagnosis of locally advanced or metastatic progressive soft tissue sarcoma with at least one measurable lesion, WHO performance score of ≤ 2, age ≤ 75 years, white blood cells (WBC) $\geq 3.0 \times 10^9$/l, platelets count $\geq 100 \times 10^9$/l, serum creatinine ≤ 140 μmol/l and bilirubin ≤ 20 μmol/l. Previous chemotherapy was allowed.

Miltefosine (ASTA Medica AG, Frankfurt, Germany) was provided as gelatin capsules containing 50 mg of the drug. It was administered orally immediately after meals at a dose of 50 mg three times daily. Prophylactic use of antiemetics was recommended. In the case of nausea and vomiting not being adequately controllable with antiemetics, the daily dose was reduced to 100 mg. In case this reduced dose was still not tolerable, the patient was taken off the study. During treatment there was a 4-weekly assessment of haemoglobin, WBC, platelet count, and blood chemistry.

Response to treatment was assessed after 8 weeks using the common WHO criteria. Toxicity was assessed weekly and also graded according to the WHO criteria. Nausea and vomiting were graded as worst toxicity at any time during therapy.

RESULTS

23 patients were entered on the study, 1 was ineligible because she received more than one prior chemotherapy regimen and another patient was lost to follow-up. Thus 21 patients could be evaluated. Characteristics of these patients are given in Table 1. The median duration of treatment was 8 weeks (range 2–16). 3 patients required an intercurrent dose reduction to 100 mg daily

Table 1. Patients' characteristics

No. of evaluable patients	21
Sex (males/females)	12/9
Age (years)	
Median	49
Range	18–63
WHO performance	
Median	1
Range	0–2
Prior chemotherapy	21
Prior radiotherapy	8
Cell type	
Leiomyosarcoma	5
Malignant fibrous histiocytoma	4
Neurogenic sarcoma	4
Fibrosarcoma	3
Miscellaneous	5

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Table 2. Non-haematological toxicity

	WHO Grade				
Side effects	0	1	2	3	4
Nausea	9	4	5	2	1
Diarrhoea	19	2	—	—	—
Liver toxicity	18	2	—	—	1
Renal toxicity	19	2	—	—	—

after the first 4 weeks because of nausea/vomiting. All patients were considered evaluable for toxicity. There were no haematological side-effects; non-haematological side-effects are listed in Table 2. Nausea/vomiting were predominant and were present in 12 patients (57%), one of which was taken off the study because of grade 4 vomiting resistant to treatment. The other side-effects were infrequent. In 1 patient a grade 4 transaminase elevation was observed after 4 weeks, which was completely reversible after discontinuation of drug administration. The patient was taken off the study because of this toxicity. Besides these 2 patients, 1 patient was not evaluable for response because of cardiac death on day 24. Thus 18 patients were considered evaluable for response. Only 1 patient had no change for 16 weeks; all other patients progressed.

DISCUSSION

Previous studies have indicated that drugs with even moderate activity against soft tissue sarcomas can be discovered in second-line studies [1]. Miltefosine, tested in this situation, did not yield any activity. Although toxicity in the short term was manageable and apparently tolerable, the large number of patients with nausea/vomiting induced by the drug suggests that long-term treatment will be less feasible. Whether the lack of activity is related to a low bioavailability of the oral formulation in man remains to be elucidated. Miltefosine at this dose and schedule should not be tested any further in soft tissue sarcomas.

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Serum Immunoreactive and Bioactive Lactogenic Hormones in Advanced Breast Cancer Patients Treated with Bromocriptine and Octreotide

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6 patients with advanced breast cancer who had failed first and second line endocrine therapies received bromocriptine (1.25–2.5 mg twice daily *per os*) and octreotide (Sandostatin®) via a continuous subcutaneous infusion (200–400 μg/24 h) until disease progression. Pre-treatment 24-h profiles of serum lactogenic hormones and their response to standard provocative tests were established and repeated at 2 weeks, and 3 and 6 months (or at tumour progression). Immunoreactive prolactin (ir-PRL), growth hormone (ir-GH) and insulin-like growth factor I (IGF-I) were measured by radioimmunoassay and bioactive lactogenic hormone levels (BLH) were estimated using the Nb2 rat lymphoma cell bioassay. Before treatment all patients showed episodic secretion of ir-PRL, ir-GH and BLH and provocative stimuli resulted in a peak of ir-GH and BLH maximal between 60 and 90 min after injection but no change in ir-PRL. After 2 weeks of treatment, ir-PRL levels were reduced to below the limit of detection in all 6 patients. Peaks of ir-GH and BLH were still apparent, although much reduced. Immunoreactive PRL continued to be profoundly suppressed in 3 of the 4 patients who remained on treatment for 3 to 6 months. Small pulses of ir-GH were still detectable in these patients with which BLH was, again, well correlated. After 2 weeks of treatment, serum IGF-I levels were reduced by 9–54% of the pretreatment values and generally remained suppressed throughout treatment. Clinically, 4 patients did not show disease progression for periods of up to 6 months and side-effects were minimal.
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