order to optimise the dose schedule of ondansetron in this particular group of patients.

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Phase II Study of Daily Oral Miltefosine (Hexadecylphosphocholine) in Advanced Colorectal Cancer

A.S.T. Planting, G. Stoter and J. Verweij

34 patients with metastatic colorectal cancer were treated with the ether lipid miltefosine (hexadecylphosphocholine). Most patients received 3×50 mg daily, while in 11 patients the dose could be escalated to 4 × 50 mg daily. Nausea and vomiting were the most frequent side-effects occurring in all but 3 patients, nephrotoxicity was observed in 11 patients. Leucocytosis was observed in 24 and thrombocytosis in 17 patients. 28 patients are evaluable for response. 1 patient obtained a partial response of liver metastases for a duration of 8 months. 3 patients had stable disease while 24 progressed during treatment. We conclude that miltefosine in this dose and schedule has limited activity in colorectal cancer.
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INTRODUCTION

THE DISMAL outlook for patients with metastatic colorectal cancer and the lack of essential progress in chemotherapy in this common disorder is the continuous impulse to test new drugs on their activity in this disease. Miltefosine (hexadecylphosphocholine) is a synthetic phospholipid derivative with distant similarity to lecithin. The precise mode of action of miltefosine is not known but it is assumed to be related to interference with membrane functions [1, 2].

In vitro, miltefosine showed activity against the human colon carcinoma cell line Co 115 in the soft agar colony assay, and *in vivo* against DMBA- and MNU-induced breast cancer in the rat and against a transplanted KB tumour and Lewis lung carcinoma in the nude mouse.

Correspondence to A.S.T. Planting.
A.S.T. Planting, G. Stoter and J. Verweij are at the Department of Medical Oncology, Rotterdam Cancer Institute/Dr. Daniel den Hoed Kliniek, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.
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Pharmacokinetic studies in the rat revealed that orally administered miltefosine was absorbed slowly with plasma peak concentrations reached after 48 h. In rats and dogs anorexia and weight-loss were observed as the main toxicity. There were no signs of bone marrow toxicity.

In the phase I study nausea and vomiting was the dose-limiting side-effect [3]. The maximum tolerated dose was 200 mg/day with the best tolerability observed with a fractionated daily dosing. At the dose of 150 mg daily only 1 out of 6 patients had grade 3 gastro-intestinal toxicity. There were no signs of any other toxicity. For phase II studies a starting dose of 100 mg/day with dose escalation to 150 mg/day was recommended.

We performed a phase II study with oral miltefosine in patients with metastatic colorectal cancer.

PATIENTS AND METHODS

Patients were required to have histologically proven progressive metastatic colorectal cancer, a WHO performance status of 2 or better, white blood cells (WBC) $\geq 3.0 \times 10^9$/l, platelet

count $\geq 100 \times 10^9$/l, creatinine clearance ≥ 40 ml/min and serum bilirubin ≤ 20 μmol/l.

All patients had a chest X-ray and a computed tomography (CT) of the whole abdomen before start of treatment. During treatment determinations of haemoglobin, leucocytes and platelets were repeated weekly and liver and renal functions after 1 week and every 4 weeks thereafter.

Pretreatment with one cytotoxic drug was allowed.

Miltefosine (ASTA) was provided as gelatin capsules containing 50 mg of the drug. The starting dose of miltefosine was 50 mg twice daily which dose in absence of side-effects was escalated after 1 week to 50 mg thrice daily. Further dose escalation to 50 mg four times per day was allowed during the first part of the study. In cases of nausea and vomiting not controllable with standard antiemetics the dosage was reduced to 50 mg daily until nausea and vomiting were resolved or were acceptable to the patient.

Response to treatment was assessed after 8 weeks of treatment according to the WHO criteria [4]. Toxicity was evaluated weekly according to the WHO criteria; nausea and vomiting were graded as the worst grade observed during the week.

Table 1. Patients' characteristics

No. of patients entered in the study	34
Male:female	16:18
Median age in years (range)	58 (31–79)
Median performance status WHO	1 (0–2)
Previous therapy	
Surgery	34
Radiotherapy	5
Chemotherapy with 5-fluorouracil	4
Immunotherapy	4
Localisation metastases	
Liver only	16
Lung only	3
Soft tissue only	7
Adrenal only	1
Local recurrence only	1
Liver + lung	2
Liver + soft tissue	2
Liver + local recurrence	2

RESULTS

34 patients were entered in this study. 6 patients were considered not evaluable for response: 1 patient died from an unknown cause before evaluation, 2 patients refused to complete the first course of 8 weeks because of nausea and vomiting and 3 patients died due to causes not related to their cancer or to treatment. All patients are included in the toxicity analysis. The patients' characteristics are given in Table 1.

In 11 patients the miltefosine dose was escalated to 200 mg daily, 21 patients reached the dose level of 150 mg daily. Only 2 patients did not tolerate a dose higher than 100 mg. In general the 3×50 mg daily regimen was tolerated well; the higher dose of 200 mg daily however caused nausea and vomiting in most patients which improved after tapering the dose again to 150 mg daily. The 11 patients on the 200 mg dose could only tolerate this dose for a total of 29 treatment weeks. 34 patients are evaluable for toxicity. Nausea and vomiting was the most frequent occurring side-effect: grade 1 in 16 and grade 2 in 14 patients. In general, nausea and vomiting could be adequately treated with standard antiemetics. Diarrhoea grade 1 and constipation were both reported in 3 patients. Nephrotoxicity grade 1 was observed in 11 patients and grade 2 in 1 patient. This last patient also had obstructive uropathy and after de-obstruction remained nephrotoxicity grade 1. In most patients the deterioration of renal function was reversible after cessation of treatment. Bone marrow toxicity was not observed. On the contrary in most patients we observed an increase in the number of granulocytes and platelets: 24 patients developed a leucocytosis with a median WBC count during treatment of 12.2×10^9/l (range 2.7–24.4) and 17 patients a thrombocytosis with a median platelet count during treatment of 512×10^9/l (range 242–1146). A bone marrow aspiration in 4 patients with marked leucocytosis and thrombocytosis showed normal bone marrow activity.

28 patients are fully evaluable for response; we observed one partial response in liver metastases for a duration of 8 months. 3 patients had stable disease for respectively 5, 6 and 8 months; all other patients had progressive disease.

DISCUSSION

For phase II studies a daily oral dosage of miltefosine was selected because in phase I studies it had a better toxicity profile than high-dose intermittent therapy while in the long run a higher total dose of drug can be administered. Attempts to increase the dose in 11 patients failed because of gastro-intestinal side-effects. At the recommended dose of 150 mg daily, which is also used in other phase II studies, the gastro-intestinal toxicity is manageable although long-lasting often even minor nausea as well as infrequent but unexpected eruptive vomiting for several patients were a reason to stop treatment.

The observed nephrotoxicity cannot yet be explained and was not reported in the phase I studies [3]. Apart from prerenal factors related to subclinical dehydration due to chronic nausea also a renal component must exist. Renal biopsies were not performed. The observed increase in granulocytes and platelets is at least remarkable. Phase II studies in other tumour types show a similar incidence of this side-effect [5]. The cause of this effect is not elucidated yet. If related to bone marrow stimulation this effect might be advantageous in a combination with myelosuppressive drugs [6]. We observed however only one partial response in 28 evaluable patients and this lack of major activity in colorectal cancer will preclude such studies in this disease.

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