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Clinical Trial Summary

A Phase II Study of M-Azido-pyrimethamine Ethane Sulphonate (MZPES) in Advanced, Recurrent Soft Tissue Sarcoma

An EORTC Soft Tissue and Bone Sarcoma Group Study

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INTRODUCTION

ALTHOUGH patients with soft tissue sarcoma show some response to chemotherapy, especially agents such as doxorubicin, ifosfamide and DTIC, overall response rates rarely exceed 40% and durations of remission are short. There are few, if any, long-term survivors. New compounds with significant activity are therefore sought for this disease [1].

A potentially useful group of compounds are the antifolates. The diaminopyrimidine class of antifolates do not bear a close structural similarity to folic acid and are known as the non-classical antifolates. These were first synthesized in the 1950s [2] and although the initial compounds in this group, metoprin and etoprin, showed clinical activity against leukaemia, they proved too toxic for clinical use. The classical antifolates are structurally similar to folic acid and were first used in cancer chemotherapy in 1948 by Farber *et al.* [3] who showed aminopterin to be active in acute leukaemias. The less toxic, classical antifolate methotrexate has since then become a standard agent in the treatment of malignancy.

Although methotrexate is the standard antifolate drug it has several potential disadvantages. It has little activity against most solid tumours including sarcomas, it has minimal penetration of the blood–brain barrier at lower doses since it is relatively lipid insoluble, it has a wide range of toxicities and drug resistance can develop.

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M-Azido-pyrimethamine ethane sulphonate (MZPES) is a non-classical antifolate, related to metoprin, which was developed to combine the potential advantages of lipid solubility with a relatively short half-life and the possibility of reduced toxicity [4]. The short half-life is promoted by the presence of the azido group which has the potential to be biologically transformed to the more polar, and less active, amine.

In a Phase I study, 68 patients have been treated with MZPES [5]. The dose was increased from 5.4 to 460 mg/m^2 given as a 1-h infusion with 460, 600 and 800 mg/m^2 given as a 24-h infusion. Dose-limiting toxicity was nausea and vomiting which was marked at doses above 360 mg/m^2 by 1-h infusion and 600 mg/m^2 by 24-h infusion. Above 250 mg/m^2 patients also described subjective neurological symptoms although no objective signs were apparent. Myelosuppression was not consistent at any dose level. The dose for Phase II trials was recommended to be 400 mg/m^2 three weekly.

It was therefore decided to carry out a Phase II study of MZPES to determine its activity in advanced progressive soft tissue sarcoma.

PATIENTS AND METHODS

Thirteen patients with biopsy-proven progressive soft tissue sarcoma, previously treated with chemotherapy, were entered into the study. Patients had ECOG performance status 0 or 1 and had no medical condition precluding the use of MZPES. The patient characteristics, previous treatment and sites of disease are shown in Table 1. MZPES was administered as a 60-min intravenous infusion at a

Table 1. Patient characteristics and response (12 evaluable patients)

Median age (range)
56 (21–75)

Male:female
8:4

	Number of cycles					
	1	2	3	*NC*	*Prog*	*Total*
Total	4	6	2	5	7	12
Disease						
Primary/lymph nodes	4	3	2	4	5	9
Lung	1	2	0	0	3	3
Liver	0	2	0	1	1	2
Other visceral	1	0	0	1	0	1
Previous drugs						
Adriamycin®				5	7	12
DTIC				3	3	6
Ifosfamide				3	5	8
Cyclophosphamide				1	2	3
Vincristine				1	2	3
Others				1	1	2
Number of previous drugs						
1				1	0	1
2				1	3	4
3				1	1	2
4				2	3	5

NC = no change whilst receiving protocol drug. Prog = evidence of progression whilst receiving protocol drug.

dose of 400 mg/m^2. The infusion was protected from the light during administration because of the possible risk of photodegradation of the MZPES. Courses were repeated every three weeks.

Patients should have completed a minimum of one course of treatment to be evaluable for response which was assessed using UICC criteria. WHO toxicity gradings were used.

RESULTS

Thirteen patients were eligible within the study. One patient was inevaluable because assessment was not possible at the end of the first course. Twelve patients had assessment of response made after one to three courses and were therefore evaluable for response. Five patients had no evidence of progression whilst receiving one to three cycles of treatment. The remaining seven patients had evidence of progressive disease within two courses. No responses were seen.

No myelotoxicity was seen. Nausea and vomiting was common with two patients experiencing Grade 3 toxicity on the first cycle, six Grade 2, three Grade 1 and only two Grade 0. Two patients experienced mild phlebitis at the administration site.

The major toxicity was neurotoxicity. Four patients noted mild peripheral neuropathy with paraesthesiae following treatment. Three patients had severe dizziness and headache for up to 48 h after treatment. Two patients had severe neurotoxicity with convulsions and unconsciousness during the 24 h following treatment. Neither patient had any evidence of CNS metastases. Both patients recovered full neurological function. Following the report of the second patient with severe neurotoxicity, recruitment to the trial was stopped.

DISCUSSION

On the basis of this small study MZPES appears to have no significant activity in pre-treated soft tissue sarcoma. Although the numbers recruited to the trial do not formally fulfil the criteria for demonstrating no significant activity of a drug, the lack of any perceptible response in any patient, coupled with the severe toxicity, meant that the group did not feel that this compound could be investigated further for practical and ethical reasons.

The reasons for the neurotoxicity are not fully understood. MZPES is lipophilic and probably crosses the blood–brain barrier. Methotrexate, also a dihydrofolate reductase inhibitor, can cause similar neurotoxicity in high doses, and the mechanism of action may be similar. The total lack of activity for MZPES in these pre-treated patients means that further investigation of this phenomenon is probably not justified.

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