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Clinical Trials Summaries

A Phase II Trial of Ifosfamide/Mesna with Doxorubicin for Malignant Mesothelioma

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INTRODUCTION

MESOTHELIOMA is generally considered poorly responsive to therapy, although modest activity has been observed using single agent chemotherapy [1]. Doxorubicin is considered the most active single agent with a response rate of 44% [1], with alkylating agents also shown to have activity, although conflicting results were observed in a randomized study where no responses were seen in 30 patients treated with doxorubicin or cyclophosphamide [2].

Ifosfamide is an oxazaphosphorine similar in structure to cyclophosphamide. Bladder toxicity is the dose limiting toxicity with less myelosuppression observed than with cyclophosphamide. Ifosfamide has been shown to be active in many tumour types as a single agent and was recently shown to have activity in mesothelioma [3]. It has been shown to be active in combination with Adriamycin® for patients with soft tissue sarcoma [4]. In this study a combination of ifosfamide with mesna and doxorubicin was used in patients with malignant mesothelioma.

MATERIALS AND METHODS

Seventeen patients with histologically proven malignant mesothelioma and assessable disease were studied, with clinical details shown in Table 1. Patients were generally of good performance status, the majority having pleural disease. Treatment consisted of ifosfamide with mesna as a uroprotector and doxorubicin at a dose of 40 mg/m^2, given every 3 weeks.

Ifosfamide (5 g/m^2) was given as a 24 h infusion in 3 l of dextrose saline, with frusemide 40 mg given immediately prior to treatment. Mesna 1 g was given immediately prior to ifosfamide, with mesna 4 g/m^2 then given by continuous infusion over 32 h. All patients received oral dexamethasone 4 mg q.d.s. for 1 day and oral domperidone 60 mg q.d.s. for 2 days or longer as anti-emetics, with additional anti-emetics given as necessary.

Investigations prior to each course comprised: full blood count, urea and electrolytes, liver function tests and creatinine clearance. Clinical response and toxicity were assessed following each course of chemotherapy, using WHO criteria.

RESULTS

Sixteen patients were evaluable and two patients (12.5%) had partial responses (95% confidence limits 1.5–38.3%), one of whom was previously untreated. One partial response was observed in the pleura and the other in a needle track recurrence. Response duration was disappointingly short (8 weeks and 16 weeks), with median survival 34 weeks for all patients. Details of chemotherapy courses and toxicity are shown in Table 1, with only two patients receiving more than three courses of chemotherapy. Treatment was discontinued in the majority because of progressive disease. Gastrointestinal toxicity was common and frequently severe, although myelosuppression was minimal. Encephalopathy, in the form of mild confusion, was observed in one patient but this was fully reversible. Pneumo-

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Table 1. *Details of treatment courses and toxicity*

Number of patients treated		17
M:F		14:3
Mean age (range)		56 (43–71)
Previous chemotherapy		13
Performance status (ECOG)	0	3
	1	6
	2	6
	3	2
Disease sites	Pleura	16
	Peritoneum	2
	Liver	2
	Needle track	2
Courses of chemotherapy	1	4
	2	4
	3	7
	4+	2
Dose reductions (70% of predicted)		3
Toxicity:		
Early death		1
Alopecia	Grades 2–4	16 (100%)
Nausea and vomiting	Grade 3	11 (65%)
	Grade 4	5 (29%)
Neutropenia	Grade 3	1 (7%)
Mucositis	Grade 2	1 (7%)
Encephalopathy		1 (7%)
Pneumothorax		1 (7%)

thoraces have previously been described with this chemotherapy in responding patients with large pulmonary deposits [5], and although one patient in this study had a spontaneously resolving pneumothorax following treatment, there was no evidence of tumour response. There was one treatment related death, with the patient dying 4 days after the first chemotherapy course. Unfortunately the exact cause of death was not determined as an autopsy was not performed.

DISCUSSION

Our results are disappointing particularly in view of the reported response rates to doxorubicin, cyclophosphamide and ifosfamide as single agents [1, 3]. However, as the majority of these patients had previously received chemotherapy, this may have accounted for the low response rate. Alternatively, ifosfamide was given over 24 h in this study, and it is feasible that larger doses given on a 5 day schedule are move active [3].

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