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Clinical Trials Summaries

A Phase II Study of High Dose Ifosfamide in Metastatic Colorectal Cancer

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INTRODUCTION

IFOSFAMIDE is an alkylating agent that has shown activity in sarcomas [1], testicular cancer [2], non-small cell lung cancer [3], ovarian [4] and pancreatic cancer [5].

In vitro ifosfamide showed activity against the colon tumors 26 and 38 [6]. Clinical experience with ifosfamide in colorectal cancer is very limited. Araujo and de Marco [7] observed one complete and three partial responders in nine patients treated with a 24-h infusion, while Kemeny *et al.* [8] did not observe objective responses in 18 patients using a 5-day regimen [3].

We present the data of a phase II study of ifosfamide as a 24-h infusion every 3 weeks in metastatic colorectal cancer.

MATERIALS AND METHODS

Ifosfamide was dissolved in 3 l of dextrose/saline and administered at a dose of 5 g/m^2 by continuous 24-h infusion combined with a 36-h infusion with mesna as uroprotector at a dose of 3.6 g/m^2. Before drug administration patients were hydrated with 1 l dextrose/saline in 2 h and 200 ml of mannitol 20% starting 1 h prior to chemotherapy.

Treatment cycles were repeated every 3 weeks. Treatment was delayed until full haematologic recovery; dose reduction of 25% was made in case of a WBC nadir of $<1.5\times10^9$/l or platelet nadir of $<50\times10^9$/l.

Patients were required to have an ECOG performance status of 2 or higher, age <70 years, WBC $>4.0\times10^9$/l, platelet count $>100\times10^9$/l, serum creatinine<120 Umol/l, or creatinine clearance >60 ml/min and serum bilirubin <2.0 mg/dl.

All patients had bidimensional measurable disease and cytological proof of metastases. All had undergone surgery; two patients were pretreated with floxuridine (FUDR) via the hepatic artery, five with systemic fluorouracil and one with *N*-methylformamide. Two patients had radiotherapy to the pelvis after abdominoperineal rectum extirpation.

Response to treatment was assessed after every second cycle of chemotherapy according to the WHO criteria [9].

RESULTS

Twenty-one patients were entered in the study (Table 1); all patients were evaluable for response and toxicity.

One partial response in liver metastases was observed for a duration of 7 months. This patient had also responded to previous intra-arterial FUDR therapy. Eleven patients had stable disease with a median time until progression of 12 weeks (range 9–26 weeks) and nine had progressive disease. The

Table 1. *Patient characteristics**

Total No. of patients	21
Male : female ratio	11 : 10
Median age in years (range)	53 (39–71)
Median performance status (range)	0 (0–2)
Location of metastases:	
Liver only	6
Lung only	2
Liver + lung	3
Liver + soft tissue	4
Soft tissue only	2
Local recurrence + liver	2
Local recurrence + lung	2
Total No. of courses given	66
Median No. of courses given (range)	2 (1–6)
No. of courses with dose reduction	2

* Unless otherwise specified, values = No. of patients.

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toxicity observed during this study is shown in Table 2.

The haematological toxicity was mild and consisted mainly of granulocytopenia; only two patients required a blood transfusion. One patient had a urosepsis during granulocytopenia; one patient developed transient lethargy during ifosfamide administration. No other neurotoxicity was observed, neither renal, bladder or liver toxicity.

DISCUSSION

In this phase II study we treated 21 patients with metastatic colorectal cancer, 13 of whom had not received prior chemotherapy, with high dose ifosfamide with mesna uroprotection.

Although we observed one partial response in a pretreated patient we conclude that single agent ifosfamide in this schedule has only minimal activity. The encouraging results of Araujo and de Marco [7] could not be confirmed.

Table 2. Toxicity

Toxicity	WHO grade			
	1	2	3	4
Nausea/vomiting	6	11	2	—
Diarrhoea	1	—	—	—
WBC count nadir	—	1	—	—
Platelet nadir	3	6	10	—
Alopecia				

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