Eur J Cancer Clin Oncol, Vol. 25, No. 12, pp. 1887–1888, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Clinical Trial Summary

Treatment of Liver Metastases from Colorectal Cancer with Continuous High Dose Intra-arterial Floxuridine (FUDR) and Systemic Fluorouracil: A Phase II Study

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INTRODUCTION

THE RESULTS of systemic cytostatic treatment of liver metastases from colorectal cancer are still very disappointing. The blood supply to liver metastases is mainly via the hepatic artery; because several cytostatics have attractive pharmacologic properties in the form of a high extraction rate by the liver, this led to a considerable interest in treating liver metastases by the intra-arterial route [1]. In most studies floxuridine (FUDR) is used because of an extraction ratio of 95%. Response rates using FUDR vary from 54–88% with a suggestion of increased survival in responding patients [2–4], but many patients relapse outside the liver.

We present the data of a phase II study of high dose FUDR via the hepatic artery combined with fluorouracil intravenously.

Accepted 5 September 1989.
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Supported in part by the Netherlands Cancer Foundation 'Koningin Wilhelmina Fonds', CKVO study 85-03.

PATIENTS AND METHODS

All patients were required to have histologically or cytologically proven liver metastases from colorectal cancer, a performance score of 2 or higher (WHO scale), a normal complete blood count and coagulation, normal serum bilirubin and renal function.

Work-up included a colonoscopy or colon X-ray, chest X-ray, a CT scan of the abdomen and an arteriography by the Seldinger technique to study the anatomy of the blood supply to the liver.

At laparotomy, if no intra-abdominal metastases were detected, a silicone catheter was placed in the gastro-duodenal artery and fixated such that the tip of the catheter was situated in the common hepatic artery. The flow through the liver was controlled by injection of methylene blue dye or crypton-81m. In case of adequate perfusion the catheter was attached to a Port-a-Cath (Pharmacia) placed on the chest wall. The cytostatic treatment was started on day 4 after surgery if scanning with Tc-labelled macro-aggregated albumin via the Port-a-Cath showed uptake in the metastases.

FUDR (floxuridine) was administered i.a. in a dose of 1 mg/kg/day on days 1–5 by a portable roller pump (Pharmacia Act-a-Pump 1000); fluorouracil

was administered intravenously on day 1 and weekly thereafter in a dose of 500 mg/m^2. A 50% dose reduction of the planned drug was prescribed if leucocytes were between 3.0 and 2.5 × 10^9/l and/or platelets between 99 and 75 × 10^9/l. Where there were lower values treatment was delayed until recovery, as also in case of mucositis grade 2 or hyperbilirubinaemia.

Evaluation of the results of treatment took place after every second course according to the EORTC WHO guidelines. In the case of response or stable disease the treatment was continued until progression.

TREATMENT RESULTS

Twenty-eight patients had full work-up for this study but 11 were ineligible because of the detection of extrahepatic intra-abdominal spread of the disease on CT scan (six patients) or at laparotomy (five patients). Seventeen patients were considered eligible for treatment, 16 of them are fully evaluable for response and toxicity. One patient never started therapy because of thrombosis of the hepatic artery after surgery. The patient characteristics and treatment results are summarized in Table 1.

One complete response was observed after two courses with only a duration of 8 weeks; in six patients we observed a partial response with a median time until progression of 30 weeks (range 24–52 weeks), giving a response rate of 44%,

In the seven responding patients disease progression occurred intrahepatically only in five, extrahepatically only in one and combined in one patient.

Toxicity data are shown in Table 2.

In general the treatment was well tolerated; hospitalization because of side-effects was only necessary in two patients because of nausea and vomiting and diarrhoea grade 3. Chemical hepatitis, cholecystitis or sclerosing cholangitis were not observed.

In three patients an occlusion of the catheter occurred; the most frequent problem reported was the flow rate of the roller pump (11 flow problems in 77 courses).

Table 1. Patient characteristics

Patients entered in the study	28
Patients eligible for treatment	17
Male:female	11:6
Median age (years + range)	53 (38–68)
Median performance status (range)	1 (0–2)
Total No. of courses	77
Median No. of courses (range)	5 (1–13)
Fully evaluable for response and toxicity	16
Not evaluable due to hepatic artery occlusion	1
Complete response	1
Partial response	6
Stable disease	3
Progressive disease	6

Table 2. Toxicity (WHO grade)

	Grade				
	0	1	2	3	4
Nausea/vomiting	5	5	5	0	0
Diarrhoea	11	3	1	2	0
Stomatitis	15	2	0	0	0
Leucopenia	13	4	0	0	0
Thrombocytopenia	14	2	1	0	0

DISCUSSION

In this phase II study we combined intra-arterial treatment with FUDR, in a high dosage, with the 'standard' systemic drug fluorouracil.

The response rate of 44% that we observed is in agreement with the response rates of more recent phase II studies and with the response rate of the intra-arterial treatment arm in Kemeny *et al.*'s randomized study [5]. The short median duration of response, however, is disappointing, although the dose of FUDR we used is higher than in other studies. This may indicate that increasing the short-term dose of FUDR is perhaps less important than a longer infusion duration. The addition of weekly bolus injections of fluorouracil seems to have no influence on the outcome of this treatment.

Before planning other studies the results of randomized studies in which regional treatment is compared with systemic treatment will be awaited.

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