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Phase II study of hepatic artery infusion with 5-fluorouracil, adriamycin, and mitomycin C (FAM) in liver metastases from colorectal carcinoma*

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Summary. *Twenty-seven patients with liver metastases from colorectal carcinoma were treated with 5-fluorouracil, adriamycin, and mitomycin C (FAM) by hepatic artery infusion (HAI) every 2–3 months for a maximum of eight courses. Median survival for all patients was 22 months. Toxicity was acceptable and consisted in severe myelosuppression (8%), duodenal ulceration (8%), moderate nausea and vomiting (50%), and alopecia (100%). HAI with FAM is feasible and may have an impact on survival. Further studies are needed to determine the role of HAI, which may be of potential benefit to a substantial number of patients with metastatic colorectal carcinoma.*

Introduction

The liver is probably the predominant organ of involvement in more than 50% of patients with colorectal carcinoma who develop metastatic disease. Once colorectal carcinoma metastasizes to the liver the prognosis becomes ominous. The median survival for untreated patients can be expected to be about 6 months [8, 12, 15], and it has been stated that the length of survival depends on the extent of hepatic metastases even if bones, lungs, and liver are all involved [8]. Systemic 5-fluorouracil (5-FU) is of limited value, median survival with this drug being approximately 8 months [14]. Because hepatic metastases receive their main blood supply from the hepatic artery, one approach to treatment has been ligation of the hepatic artery. In nonrandomized studies a median survival of about 11 months has been reported with this technique [1, 10]. Another treatment modality has been the infusion of cytostatic drugs into the hepatic artery. 5-FU (F), 5-fluoro-deoxyuridine (FUDR), and mitomycin C (M) are extracted by the liver, and hence intra-arterial administration of these drugs allows for a greater concentration into the tumor-bearing organ with less systemic toxicity. It has also been shown that the systemic adriamycin (A) level during hepatic artery infusion (HAI) is 25% lower than the corresponding systemic level with peripheral venous infusion, while hepatic venous anthracycline levels, which are one measure of the intrahepatic drug concentration in the hepatic and tumor capillary bed, are consistently higher when the drug is given by the hepatic artery route [5]. The FAM combination given systemically has given a response rate of only 17% in one study of measurable advanced colorectal carcinoma [7]. HAI with a combination of five drugs including FAM yielded a response rate of 56% in patients with liver metastases from colorectal carcinoma [2]. In a pilot feasibility study in our institution 27 patients with liver metastases from colorectal carcinoma were treated with FAM by HAI. In this report the results after a median follow-up of 24 months are summarized.

Materials and methods

Twenty-seven consecutive patients with liver metastases from histologically proven colorectal carcinoma not amenable to surgery were treated from January 1979 to May 1983. The eligibility criteria were: age < 75 years; Karnofsky index $\geq 70\%$; primary excised; no (74%) or minor (26%) extrahepatic disease; bilirubin < 30 µmol/l; no previous treatment with radiotherapy or chemotherapy. A catheter was introduced into the femoral artery and placed selectively into the common or proper hepatic artery. Drugs were infused over 76 h. Dosages were: adriamycin 70 mg/m^2 during 24 h, mitomycin C 10 mg/m^2 during 4 h, and 5-FU 1,500 mg/m^2 during 48 h. Courses were repeated every 10 weeks for a maximum of eight courses. This time interval was chosen because each treatment cycle required at least 5 days of hospitalization and it was thought that a shorter cycle would seriously impair the patients' quality of life. Liver involvement was judged by the surgeon during laparotomy (51%) or by angiography if metastases were detected after resection of the primary (49%). Stage I disease implied less than 30% involvement; stage II, 30%–60%; and stage III, more than 60% invasion of the liver.

A complete response was defined as a complete disappearance of all signs of tumor confirmed by CT- scan. A partial response was defined as a $\geq 50\%$ reduction in tumor mass, judged by angiography by the sum of the products of the two longest perpendicular diameters of the lesions, in combination with a $\geq 50\%$ decrease in CEA if elevated, an amelioration of liver function tests, and subjective improvement in symptomatic patients. Stable disease was noted when lesions were unchanged ($< 50\%$ decrease or $< 25\%$ increase) for at least 2 months. Responses were evaluated after the first infusion, at the start of the second one, and subsequently at each cycle, and had to be agreed upon by all three of the present authors. Survival was measured from the start of the first infusion.

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Results

In 23 of the 27 patients (85%) the catheter could be placed correctly into the common or proper hepatic artery. In four patients this was not possible for anatomical reasons. In these four cases only one liver lobe could be infused or parts of the gastrointestinal tract or the spleen also in the infused area. In one patient a thrombosis of the hepatic artery occurred after the first infusion; this patient was considered not evaluable. Table 1 lists the patients characteristics of the remaining 26 patients, 15 of whom were symptomatic (pain, anorexia, malaise, or weight loss). In 3 patients no angiography was performed at the start of the second infusion so that they were not evaluable for response but only for survival.

Table 2 shows the response rate in 23 evaluable patients. There were two complete responders and six partial responders. Stage of the disease had no significant influence upon response rate (2 patients stage I; 4 patients stage II; 2 patients stage III). All responses were noted after the first course and in all responders further regression was noted after successive courses. One of the complete responders died of lung metastases, while the other one is alive with no evidence of disease at 46+ months. After a median follow-up of 24 months, median survival for all patients was 22 months (Fig. 1). Table 3 shows the survival data for subgroups of patients. There was a trend in survival benefit for stage I and II and for asymptomatic patients. Differences are not significant, however, probably due to the relatively small number of patients. Median time to progression for all patients was 19 months (responders 29 months; stable disease 16 months), which is only slightly less than median survival. In 68% of the patients, including all patients who had minor extrahepatic disease at the start of treatment, the main site of progression was extrahepatic and 32% had primary progression of the hepatic metastases. Once progression occurred, this was rapidly followed by death. In some patients secondary treatment was given (systemic chemotherapy or embolization of the hepatic artery) but in none of them was a response noted.

In two patients stenosis of the hepatic artery occurred, which led to discontinuation of the treatment in one of them after three courses.

Thrombosis of the hepatic artery occurred in two other patients, in one after one course (not evaluable) and in the other after the fourth course. These events had no significant influence upon survival. In Table 4 a summary of toxicity is given. Two patients developed a granulocytopenic sepsis after the sixth course; after recovery HAI was stopped. In four patients a severe febrile reaction without granulocytopenia was seen after the first course, which was thought to be due to tumor necrosis. In two patients a duodenal ulcer was found; in both cases the gastrointestinal tract had been in the infused area. In one of these two patients, who died with progressive peritonitis carcinomatosa, the ulcer was not found until autopsy, while in the other one it was diagnosed by endoscopy and treated successfully with cimetidine. Catheter-related problems were not observed.

Table 1. Patient characteristics (26 evaluable patients)

Median age (range)	60 years (44–74)
Stage I (< 30% invasion)	6 patients
Stage II (30%–60% invasion)	10 patients
Stage III (> 60% invasion)	10 patients
Symptomatic status	
Symptomatic	15 patients
Asymptomatic	11 patients

Table 2. Response rate

Not evaluable	4/27	
Evaluable for response	23 patients	
Complete remission	2/23	35%
Partial remission	6/23	
Stable disease	12/23	
Primary progression	3/23	

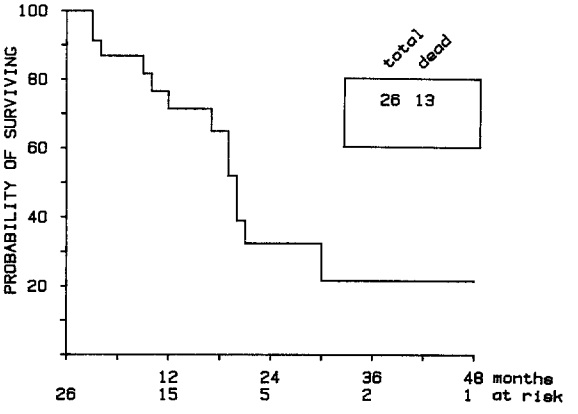

Fig. 1. Kaplan-Meier survival curve for all patients

Table 3. Median survival in subgroups

	Number of patients	Median survival (months)	
Asymptomatic	11	30	$P = 0.12$
Symptomatic	15	18	
Stage I + II	16	31	$P = 0.14$
Stage III	10	19	
Rectosigmoid	18	20	$P = 0.46$
Colon	8	30	

Table 4. Toxicity of HAI with FAM

Number of courses	119
Median number of courses per patient	4
White blood cells (day 14) grade 3/4[a]	13%
Thrombocytes (day 14) grade 3/4	5%
Nausea/Vomiting grade 1/2	50%
Alopecia grade 2/3	100%
Granulocytopenic sepsis	2 patients
Severe febrile reaction without sepsis (tumor necrosis)	4 patients
Ulcus duodeni	2 patients

[a] Gradations according to WHO criteria

Discussion

Despite lengthy experience with HAI, there has been no properly randomized study to define its place in comparison with systemic treatment. The only randomized study of HAI is inadequate in a number of critical respects. This study, conducted by the Central Oncology Group (COG), is commonly cited as demonstrating no benefit from HAI [6]. The 30 patients in this study who were randomized to receive 5-FU via HAI had either surgically or percutaneously placed catheters. In the majority of patients surgical staging of extrahepatic disease was not undertaken, so that it was not known how far the two treatment groups were comparable in the critical area of the presence of extrahepatic disease.

In recent years HAI has made a comeback, especially since the introduction of the SC-implanted infusion pump. A high response rate to continuous infusion with FUDR has been reported [3, 4], with a median survival of 24 months for patients with metastases confined to the liver at operation. Toxicity with this technique seems to be rather high, however, erosions and ulcerations of the gastrointestinal tract having been documented in 68% of cases [9]. With the Seldinger technique and infusion of a combination of drugs at regular intervals response rates of 46%–53% have been reported, median survivals ranging between 11 months (overall) and 17 months (responders) [2, 13].

In this study the median survival for all patients was 22 months, toxicity being moderate. We like to stress the importance of looking at the overall survival for the whole group of treated patients, and not mainly at the survival of responders. The comparison of responders versus nonresponders is only of limited value. The fact that responders live longer than nonresponders is all too frequently interpreted as meaning that treatment itself prolongs survival. Response to therapy, however, may simply be a feature of the fact that these patients have an inherently better prognosis. In other words, patients who respond to treatment might have done better than nonresponders even without treatment. Clear-cut evidence for survival benefit from treatment can only be obtained by comparing a treated group of patients with a matched nontreated or differently treated group, ideally in a randomized trial. Colorectal cancer patients with metastases confined to the liver may be a highly selected group with a substantially better prognosis. In such patients treated with systemic 5-FU a median survival of 11.5 months has been reported [11]. No conclusion can be drawn regarding the impact on survival of HAI as used in this study. Nevertheless we like to emphasize that half our patients were symptomatic and the majority had more than 30% liver involvement.

In conclusion, we think HAI is still an area for further therapeutic research, with potential benefit for a large number of colorectal carcinoma patients with metastases confined to the liver.

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