Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1271–1276, 1995
Elsevier Science Ltd
Printed in Great Britain
0959-8049/95 $9.50+0.00

0959-8049(95)00162-X

Regional Chemotherapy of Colorectal Cancer

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Hepatic metastases are a major cause of mortality in patients with colorectal carcinoma. The rationale for hepatic arterial chemotherapy has an anatomical and pharmacological basis as presented below. The randomised studies are reviewed and demonstrate a significantly higher response rate with hepatic arterial therapy versus systemic therapy. Survival information is difficult to evaluate because some of the studies are small, and some had a crossover design, but two studies demonstrate a significant improvement in 2-year survival after hepatic arterial therapy compared with systemic therapy. New combinations of 5-fluoro-2-deoxyuridine with dexamethasone and/or leucovorin have produced response rates as high as 72%, median survivals of 22–27 months, and a 2-year survival of 66%. More recent studies on patients who have failed previous systemic chemotherapy have produced response rates around 50%. Hepatic toxicity, especially biliary sclerosis, is the dose limiting toxicity, occurring in 6–25% of patients. To truly define the role of regional therapy, a more accurate randomised study will have to be conducted, to determine if hepatic arterial infusion improves the quality of life and, or survival in patients with hepatic metastases from colorectal cancer.
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1271–1276, 1995

INTRODUCTION

THE LIVER is frequently involved with metastatic cancer. Metastases can reach the liver from any organ, but the direct passage of blood from the gastrointestinal tract to the liver via the portal circulation plays a critical role in explaining the high rate of liver metastases in patients with colorectal cancer.

The rationale for hepatic arterial chemotherapy has an anatomical and pharmacological basis:

(1) Liver metastases are perfused almost exclusively by the hepatic artery, while normal hepatocytes derive their blood supply from the portal vein and a minimal supply from the hepatic artery [1].
(2) The liver is often the first and only site of metastatic disease. A theory of the stepwise pattern of metastatic progression [2, 3] states that spread occurs first via the portal vein to the liver, and then to the lungs, or other organs. Thus, aggressive treatment of metastases confined to the liver (resection and/or hepatic infusion) may yield prolonged survival for some patients.
(3) Some drugs have a high hepatic extraction resulting in high local concentrations of drug with minimal systemic toxicity. Ensminger and associates [4] demonstrated that 94–99% of 5-fluoro-2-deoxyuridine (FUDR) is extracted by the liver during the first pass, compared with 19–55% of 5-fluorouracil (5FU). The pharmacological advantage of various chemotherapeutic agents for hepatic arterial infusion (HAI) is summarised in Table 1 [5].
(4) Drugs with a steep dose–response curve will be more useful when administered via the intrahepatic route, since a large dose can be given regionally.
(5) Drugs with a high total body clearance are more useful for hepatic infusion.

If a drug is not rapidly cleared, recirculation through the systemic circulation diminishes the advantage of hepatic arterial delivery [6].

Regional hepatic arterial therapy can be performed by using either an hepatic arterial port or a percutaneously placed catheter connected to an external pump, or a totally implantable pump. Early studies with percutaneously placed hepatic artery catheters produced high response rates, but clotting of the catheters and the hepatic artery as well as bleeding led physicians to abandon this method [7]. The development of a totally implantable pump allowed long-term HAI with good patency of the catheter and the hepatic artery and a low incidence of infection [8]. A number of trials using the implantable pump produced high response rates with good survivals (Table 2).

RANDOMISED STUDIES

The impact of hepatic infusional therapy on the natural history of patients with hepatic metastases has been addressed in randomised studies where patients were stratified for parameters known to affect response and survival. The strong influence of the per cent of liver involvement on survival has been shown by many investigators. At the Memorial Sloan-Kettering Cancer Center, U.S.A. (MSKCC), the median survival for patients with less than 20% involvement (assessed medically or surgically) was greater than 29 months, while it was only 6 months for those with greater than 60% involvement [19]. Certain laboratory parameters also influence tumour response and patient survival. In one study, patients whose initial lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA) levels were normal had a median length of survival of 32 months, versus only 8 months for those who originally had abnormal values [20].

There are a few completed randomised studies (Table 3) in

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Table 1. Drugs for hepatic arterial infusion (HAI)

Drug	Half-life (min)	Estimated increased exposure by HAI
5-Fluorouracil (5FU)	10	5–10-fold
5-Fluoro-2-deoxyuridine (FUDR)	<10	100–400-fold
Bischlorethylnitrosourea (BCNU)	<5	6–7-fold
Mitomycin C	<10	6–8-fold
Cisplatin	20–30	4–7-fold

Table 2. Hepatic arterial FUDR infusion with internal pump: responses

Reference	No. of patients	% Prior Chemo	% PR	% Decrease in CEA	Median survival (months)
Niederhuber [9]	70	45	83	91	25
Balch [10]	40	–	83	26	
Kemeny [11]	41	43	42	51	12
Shepard [12]	42	32	–	17	
Cohen [13]	36	51	–	–	
Weiss [14]	85	29	57	13	
Schwartz [15]	23	–	15	75	18
Johnson [16]	–	47	–	12	
Kemeny [17]	31	50	52	–	22
Lorenz [18]	–	52	–	16	

PR, Partial response; CEA; carcinoembryonic antigen.

Table 3. Randomised studies of intrahepatic versus systemic chemotherapy for hepatic metastases from colorectal cancer

Group	No. of patients	Response (%)			Survival (months)		
		HAI	Systemic	*P*	HAI	Systemic	*P*
MSKCC [21]	162	52	20	0.001	18*	12	
NCOG [22]	143	42	10	0.0001	16.6	16	
NCI [23]	64	62	17	0.003	20	11	
Consortium [28]	43	58	38	–	–	–	
City of Hope [27]	41	56	0	–	–	–	
Mayo Clinic [24]	69	48	21	0.02	12.6	10.5	
France [25]	163	49	14	–	15	11	0.02
England [26]	100	50	0	0.001	13	6.3	0.03

– Not stated; * Updated.

patients with metastatic colorectal carcinoma. The study at MSKCC compared intrahepatic infusion to systemic infusion, applying the same chemotherapeutic agent (FUDR), drug schedule, and method of administration [21]. The systemic group had the hepatic artery catheter connected to an infus-a-port which allowed a crossover to intrahepatic therapy in the event of tumour progression on systemic therapy. This study demonstrated a significantly higher response rate (>50% reduction in measurable disease) with hepatic arterial therapy, 50%, versus 20% for systemic infusion ($P = 0.001$). 31 of the systemic patients crossed over to intrahepatic therapy after tumour progression. Twenty-five per cent had a partial response with a 50% reduction in CEA in 60% of patients who crossed over. The median survival for the intrahepatic and systemic groups was 17 and 12 months, respectively ($P = 0.424$). Survival information is difficult to interpret because 60% of the patients in the systemic group crossed over and received intrahepatic therapy. The patients who were unable to cross over (usually for mechanical reasons such as clotting of the infus-a-port), had a median survival of 8 months, versus 18 months for those able to undergo the crossover. A similar randomised study by the Northern California Cooperative Cancer Group also used FUDR infusion in both treatment groups. They reported a 42% partial response rate in the HAI group and 10% in the systemic FUDR infusion group [22]. The median survival was 15 months for both the hepatic arterial and systemic groups.

Though a crossover design was not built into the study, many patients received intrahepatic therapy after failing systemic therapy, and again there was a difference in median survival: 22 months for those who went on to receive intrahepatic therapy versus 12 months for those who did not receive intrahepatic therapy after systemic failure.

An NCI study [23] also compared HAI of FUDR with systemic FUDR infusion. They reported a significant increase in response rate, 62% versus 17%, respectively. If patients with positive nodes were excluded, the 2-year survival was 47% versus 13%, respectively ($P = 0.03$).

A recent Mayo Clinic [24] study compared hepatic arterial FUDR with systemic 5FU in 74 patients. They also observed a significantly higher response rate, 54%, for the intrahepatic group versus 21% for the systemic group ($P = 0.01$). The time to hepatic progression was also much longer for the intrahepatic group, 7 months versus 4 months, $P = 0.001$. The survival was 13 months versus 10.5 months for the hepatic arterial and systemic groups, respectively. However, there were not enough patients per arm to truly answer a survival question. Of the 36 patients entered in the intrahepatic group, 5 did not receive therapy, one died before treatment and 7 had extrahepatic disease, leaving 23 patients in that treatment group [11].

Two European studies demonstrated an increase in survival for the HAI groups. In a French trial [25] of 163 patients randomised to HAI of FUDR versus systemic bolus 5FU, the patients were stratified by per cent of liver involvement and baseline LDH levels. The response rates were 49% and 14% in the HAI and systemic groups, respectively. Median time to hepatic progression was 15 and 6 months, and median survival was 14 and 10 months for the HAI and systemic groups, respectively. The 2-year survival was 22% for HAI and 10% for the systemic group ($P < 0.02$). In this trial, some patients in the systemic group only received chemotherapy when they became symptomatic. In a similar study design carried out in the U.K. [26], 100 patients were randomised to HAI of FUDR versus systemic 5FU. The systemic chemotherapy was only given to symptomatic patients. Quality of life and survival were significantly improved for the HAI group. Median survival was 405 days versus 215 days for the hepatic arterial infusion and systemic groups, respectively ($P = 0.03$) (Table 3).

TOXICITY OF HEPATIC ARTERIAL FUDR INFUSION

The most common problems with HAI are hepatic toxicity and ulcer disease. Myelosuppression, nausea, vomiting, and diarrhoea do not occur with HAI of FUDR. If diarrhoea does occur, shunting to the bowel should be suspected [29]. Clinically, biliary toxicity is manifested as elevations of aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin. In the early stages of toxicity, hepatic enzyme elevations will return to normal when the drug is withdrawn and the patient is given a rest period, while in more advanced cases, it does not resolve. The bile ducts derive their blood supply almost exclusively from the hepatic artery [30], and thus are undoubtedly perfused with high doses of chemotherapy.

In patients who develop jaundice, an endoscopic retrograde cholangiopancreatography (ERCP) may demonstrate lesions resembling idiopathic sclerosing cholangitis in 5–29% of patients treated by experienced clinicians [31]. Since the ducts are sclerotic and non-dilated, sonograms usually do not show dilation. The strictures may be focal and present at the hepatic duct bifurcation, and, therefore, drainage procedures either by ERCP or by transhepatic cholangiogram may be helpful. Duct obstruction from metastases should first be excluded by computed tomography (CT) of the liver.

Close monitoring of liver function tests is necessary to avoid biliary complications. If serum bilirubin becomes ≥ 3 mg/dl, no further treatment should be given until bilirubin returns to normal and then only after a long rest period, in order to prevent the development of sclerosing cholangitis.

Ulcer disease results from inadvertent perfusion of the stomach and duodenum with drug via small collateral branches from the hepatic artery, and can be prevented via careful dissection of these collaterals at the time of pump placement [32].

NEW APPROACHES TO DECREASE TOXICITY

The hepatic toxicity induced by HAI of FUDR may be related to portal triad inflammation, which could lead to ischaemia of the bile ducts. Therefore, hepatic arterial administration of dexamethasone may decrease biliary toxicity. In patients with established hepatobiliary toxicity from HAI, dexamethasone promotes resolution of the liver function abnormalities. In a randomised study of FUDR with dexamethasone (D) versus FUDR alone, there was a trend towards decreased bilirubin elevation in patients receiving FUDR + D compared with the group receiving FUDR alone (9% versus 30%, $P = 0.07$). Although the addition of dexamethasone was not associated with a significant increase in the amount of FUDR able to be administered, the response rate was 71% for the FUDR + D versus 40% for FUDR alone ($P = 0.03$). Survival was also improved: 23 months for FUDR + D versus 15 months for FUDR alone [33].

The use of circadian modification by HAI of FUDR infusion is another method of decreasing hepatic toxicity. In a non-randomised study at the University of Minnesota [34], constant (Flat) infusion was compared with a circadian modified (CM) hepatic arterial FUDR infusion in 50 patients with metastatic colorectal carcinoma. The group with circadian modification received 68% of each daily dose between 3:00 p.m. and 9:00 p.m. The patients with CM infusion tolerated almost twice the daily dose of FUDR with a decrease in hepatic toxicity compared to patients receiving flat infusions, but the study was not a prospective randomised study.

Another approach to decrease toxicity from HAI is to alternate drugs, such as HAI FUDR with hepatic arterial (HA) 5FU. Weekly HA bolus of 5FU does not cause hepatobiliary toxicity; however, it frequently produces treatment-limiting systemic toxicity or arteritis. Stagg and associates used alternating HAI of FUDR 0.1 mg/kg/day for 7 days followed by HA bolus 5FU 15 mg/kg on days 14, 21, 28 via the pump side port every 35 days [35]. The response rate was 51%, and median survival was 22.4 months. In contrast to the experience with single-agent HAI of FUDR, no patient has had treatment terminated because of drug toxicity. Since 5FU is less toxic to the biliary tract, some investigators have gone back to using external pumps connected to a surgically placed hepatic artery catheter to infuse 5FU. The dose of 5FU needed for hepatic infusion is a large dose which would not fit into a small reservoir, therefore, requiring external pumps.

Metzger and associates [36] treated 30 patients with an infusion of 5FU at 2000 mg a day for 5 days plus mitomycin-C 10 mg/m^2 on day 1; the courses were repeated every 6 weeks. The median survival was 18 months with a 57% partial response rate. No patients developed sclerosing cholangitis, but mucositis and leucopenia were seen. Catheter complications occurred in 33%, which led to premature termination of treatment in one-

Table 4. Colorectal studies survival probabilities

	No. of patients	No. of years			Median survival
		1 (%)	2 (%)	3 (%)	
HAI					
FUDR alone [20]	45	71	38	16	18
FUDR + LV early [39]	24	92	71	38	27
FUDR + LV late [39]	42	83	55	24	24
FUDR + Dec [33]	25	88	44	28	23
FUDR + LV + Dec [40]	32	91	53	41	22
Systemic					
Inf + FU [44]	37	41	16	0	10.5
PALA + FU [45]	45	60	22	6	14.9

Early and late FUDR + LV refers to different FUDR + LV schedules; three were done in an earlier group and three in a later group. Details are in ref. [39].

Table 5. Partial response

Study	No. of patients	Previously untreated (%)	Previously treated (%)	Biliary sclerosis (%)
FUDR [20, 38]	50	50	30	8
FUDR + Dec [33]	25	71	–	8
FUDR + LV [39]	66	62	–	12
FUDR + LV + Dec [40]	62	78	52	3
FUDR + Mit-C + Dec [41]	74	73	65	13

–, Previously treated patients were not entered.

third of patients. Schlag and Hohenberger [37] using HAI of 5FU 1000 mg/day for 5 days via a surgically placed port connected to an external pump, reported a 27% partial response in 33 patients, and a median survival of 14 months. Hepatobiliary toxicity was seen in only 5%.

METHODS TO INCREASE RESPONSE RATE

The potential benefit of multi-drug hepatic arterial therapy is now being evaluated. A randomised trial of a three-drug regimen of mitomycin-C, BCNU and FUDR versus FUDR alone [38], was conducted in 67 patients with disease progression after previous treatment with systemic chemotherapy. The overall response rate and survival were similar. The response rates in both groups were higher than would be expected with a second systemic regimen after failure of first-line treatment. For patients who were previously treated for metastatic disease rather than just receiving adjuvant therapy, the response rate was 48% for the three drugs versus 24% for FUDR alone ($P = 0.03$).

Based on success of systemic 5FU/leucovorin (LV) regimens as well as laboratory studies that suggest that LV may actually be a better modifier of FUDR than of FU, 66 patients were treated with FUDR and LV by HAI [39]. The overall response rate was 62%, but 15% of patients developed biliary sclerosis. The toxicity of the combination was higher than FUDR alone, but survival was improved: 75% of the patients were alive at 1 year, 66% at 2, 33% at 3, and 14% at 5 years [39]. More work needs to be carried out to decrease hepatic toxicity. These HAI protocols are listed in Table 4. The 1, 2 and 3 year survivals are listed and compared with survivals of systemic chemotherapy trials at MSKCC during the same time period. The response

Table 6. Is hepatic arterial therapy effective? Necessary checklist for a well-designed study

	No crossover	Good systemic chemotherapy	>100 patients	<15% extrahepatic disease
MSKCC [21]		x	x	x 0%
NCOG [22]		x	x	x 12%
Mayo [24]	x	x		19%
NCI [23]	x	x		28%
France [25]	x		x	x 6%
England [26]	x		x	NS

NS, not significant.

rates for previously untreated and those treated with systemic chemotherapy are shown in Table 5 [40, 41].

METHODS TO DECREASE EXTRAHEPATIC DISEASE

Extrahepatic disease develops in 40–70% of patients undergoing HAI. Such metastases can occur even when the patient is still responding in the liver. The use of systemic therapy plus HAI may produce a decrease in extrahepatic disease. In Safi's study of FUDR (0.2 mg/kg/day for 14 of 28 days), or a combination of intra-arterial (i.a.) FUDR (0.21 mg/kg/day) and intravenous (i.v.) FUDR (0.09 mg/kg/day), given concurrently for 14 of 28 days (i.a./i.v.), the response rates were 60% for both arms of the study. However, the incidence of extrahepatic disease was 56% in the group receiving i.a./i.v. compared with 79% in those receiving HAI alone ($P < 0.01$). However, there was no difference in survival between the two groups ($P = 0.08$) [42]. In Lorenz and associates' study [43] of 52 patients, combined HAI/i.v. did not increase survival or decrease the development of extrahepatic disease (60 and 62% for HAI/i.v. versus HAI alone, respectively). Further studies of combined systemic/arterial regimens are necessary.

CONCLUSION

There are several advantages to HAI. From a pharmacological standpoint, HAI is more effective than systemic therapy, since higher drug levels are achieved at the sites of metastatic disease. Utilising agents with high hepatic extraction results in minimal systemic toxicity.

The high response rates obtained in trials of HAI of FUDR in the treatment of colorectal cancer have not been matched by systemic therapy trials. In seven randomised trials, the response rate was higher with HAI compared to systemic therapy. The time to hepatic progression was significantly longer in the HAI groups versus the systemic groups. The randomised pump studies do not clearly evaluate the issue of survival. Table 6 lists the randomised studies and the problems related to the studies. In two large studies, a crossover design was followed. Two studies were very small and included a large number of patients with extrahepatic disease. Two of the large European studies did not use adequate systemic chemotherapy. Therefore, none of these studies were adequately designed. A large study applying all the important criteria listed in Table 6 is needed to answer the question of whether there is an increase in survival.

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