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Current Controversies in Cancer

Is Intra-arterial Chemotherapy Worthwhile in the Treatment of Patients with Unresectable Hepatic Colorectal Cancer Metastases?

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THE USE of drugs with short half-lives, which are rapidly cleared from the bloodstream, have a pharmacokinetic advantage when given by regional infusion [1]. Primary and secondary hepatic tumours greater than 3 mm in size obtain most of their blood supply from the hepatic artery, while the normal hepatocytes derive their blood supply mostly from the portal circulation [2]. Chemotherapeutic drugs that would be most attractive for regional infusion are substantially extracted by the liver during the first pass, thus producing lower peripheral drug levels and systemic toxicity [3]. These are the three major theoretical benefits for hepatic artery infusion (HAI) chemotherapy, as long as the appropriate chemotherapy drugs are utilised. For perspective, the regression rate for systemic chemotherapy with 5-fluorouracil/leucovorin (5-FU/LV), generally the standard regimen at this time, is 20–40% [4–6]. One might argue that all patients with hepatic metastases eventually develop disseminated cancer. However, autopsy data reported by Weiss indicate that 46% of patients dying of colorectal cancer hepatic metastases have disease limited to their liver [7]. In addition, disseminated disease is frequently a late phenomenon, with cancer death related to liver failure or associated inanition. As with surgical resection, a regional strategy may produce only a modest improvement in median survival, but a significant 'tail on the curve' with prolonged survival of a subset of patients.

Ensminger and colleagues [8] measured drug levels from hepatic venous catheters, and demonstrated that the hepatic extraction of 5-fluorodeoxyuridase (FUdR) was 4-fold higher after hepatic arterial injection compared to systemic injection. The ability to administer a higher dose locally exposes tumours to a higher drug concentration than can be achieved with systemic therapy. Since most drugs have a steep dose–response curve, their antineoplastic efficacy should be increased by HAI.

Initial clinical trials of hepatic artery chemotherapy used percutaneous systems. The initial report of a study using an implantable pump and continuous FUdR therapy indicated an 83% response rate [9]. Despite the fact that other investigators using this technique and drug could not reproduce such high responses, the mean response rate of 44% in 10 trials (where 42% of the patients were previously treated) was higher than the mean response rate obtained with systemic chemotherapy at that time.

RANDOMISED TRIALS OF HEPATIC ARTERY FUdR CHEMOTHERAPY (TABLE 1)

To understand the impact of HAI therapy on the natural history of patients with hepatic metastases, randomised studies were initiated where patients were stratified for parameters known to affect response and survival. The major trials that justify HAI chemotherapy will be discussed.

The Memorial Sloan-Kettering Cancer Center study compared HAI to systemic (Sys) infusion, applying the same chemotherapeutic agent (FUdR), drug schedule and method of administration [10]. The only difference was that the dose of FUdR was 0.3 mg/kg a day for 14 days in the HAI group, and 0.125 mg/kg a day for 14 days in the Sys group. These were equitoxic doses. All patients underwent exploratory laparotomy to assess the per cent of liver involvement and to rule out extrahepatic disease. Both groups generally had hepatic artery catheters placed through the ligated gastroduodenal artery. Patients randomised to the systemic group had the hepatic artery catheter connected to a subcutaneous access port and the infusion pump connected to an additional catheter placed in the cephalic vein. This allowed a crossover to intrahepatic therapy by a minor

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Table 1. Randomised trials of hepatic artery for chemotherapy

Study [Ref.]	Number of patients	Response rate (%) HAI	Response rate (%) Systemic	% Alive (HAI/systemic)* 1 year	% Alive (HAI/systemic)* 2 years
Memorial Sloan-Ketering Cancer Center [10]	163	50	20	60/50	35/18
Northern California Oncology Group [11]	142	42	10	60/42	30/30
National Cancer Institute [121]	64	62	17	85/60	44/13
Mayo Clinic [13]	74	48	21	60/42	18/10
France [14]	168	43	9	61/44	22/10

*HAI, hepatic artery FUdR (floxuridine). Systemic: FUdR or 5-fluorouracil.

surgical procedure in the event of tumour progression on systemic therapy.

This study demonstrated a 50% response rate (> 50% reduction in measurable disease) with HAI therapy compared with 20% for systemic infusion ($P = 0.001$). 31 of the systemic patients crossed over to HAI therapy after tumour progression. Twenty-five per cent had a partial response, 22% stabilisation of disease, and 50% a reduction in DEA (carcinoembryonic antigen) on intrahepatic therapy. The toxicity was quite different between the two groups. In the HAI group, the most frequent side-effect was hepatic enzyme elevation. In 4 patients (8%), there were changes in the bile ducts which resembled biliary sclerosis. In 3 of 4 patients, the jaundice was reversed by discontinuing regional chemotherapy. The most frequent toxicity from systemic therapy was diarrhoea, occurring in 70% of patients and requiring admission for intravenous hydration in 9%.

Median survival for the HAI and systemic groups was 17 and 12 months, respectively ($P = 0.424$). Survival data are difficult to interpret because 60% of 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 arterial catheter), had a median survival of 8 months versus 18 months for those who were able to undergo the crossover. It is unlikely these data can be explained by hepatic artery occlusion, since this is more likely to prolong survival in the 'control' group.

The Northern California Oncology Group performed a similar study with FUdR infusion in both the HAI and systemic arms of the study. They reported a 42% partial response rate in the HAI infusion group and 10% in the systemic FUdR infusion group [11]. The median survival was 16 months for both the intrahepatic and systemic groups. Though a crossover design was not built into the study, many patients received HAI therapy after failing systemic therapy, and again there was a difference in median survival: 23 months for those who went on to receive HAI therapy versus 12 months for those who did not receive such therapy after systemic failure. A National Cancer Institute study [12] also compared HAI FUdR versus systemic FUdR infusion. The study reported a significant increase in response rate: 62% versus 17%, respectively. If patients with positive portal nodes are excluded from analysis, the 2-year survival was 47% versus 13%, respectively ($P = 0.03$).

The Mayo Clinic and the North Central Cancer Treatment Group study [13] randomised patients to HAI FUdR versus systemic 5-FU without crossover. The response rates were 48% and 21%, respectively ($P = 0.02$). However, there was no significant difference in survival. Important in interpreting these data is the fact that 49% of the HAI group had either no treatment, extrahepatic disease or pump malfunctions. Extrahepatic disease (peritoneal seeding, retroperitoneal or portal nodal metastases) are considered a contra-indication for any regional (hepatic only) treatment. A large French consortium study compared intrahepatic HAI FUdR with systemic 5-FU or no treatment until patients became symptomatic. The response rate was 43% and 9% for the HAI and Sys group, respectively. There was a significant increase in survival, 23% alive at 2 years for HAI and 13% for i.v. ($P < 0.02$) [14].

NEWER REGIMENS FOR HEPATIC ARTERY CHEMOTHERAPY

A randomised trial comparing FUdR as a single agent to the three-drug regimen FUdR, BCNU and mitomycin indicated a benefit with the three-drug regimen, but with increased toxicity [15]. *In vitro*, leucovorin has a potent modulating effect on FUdR. Studies from Memorial Sloan-Kettering Cancer Center and the MD Anderson have produced response rates of 70% with this combination [16].

Prophylactic dexamethasone has been combined with the FUdR in the pump reservoir with the hypothesis that biliary sclerosis risk may be reduced. However, in a double-blind study, a marked increase in response rates with the combination therapy were obtained seemingly unrelated to the FUdR dose [17]. Based on these studies, the group at Memorial Sloan-Kettering combined FUdR, leucovorin and dexamethasone and consistently obtained response rates of 70% [18] with modest biliary sclerosis.

In summary, data from randomised clinical trials indicate a much higher response rate using the regional chemotherapy strategy in previously untreated patients. An intergroup randomised trial in previously untreated patients will be started in early 1996, comparing this regional chemotherapy programme to the widely used systemic 5-FU/LV regimen. Endpoints are overall survival, toxicity, costs and quality of life indicators. Crossover from systemic to HAI will not be allowed in order to define survival differences.

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THE IDEA of delivering chemotherapy via the hepatic artery in patients with unresectable liver metastases of colorectal cancer was developed in the 1960s [1] when the results of systemic therapy were disappointing. Indeed, the use of 5-fluorouracil (5-FU), the most active drug for this tumour, was associated with a low rate of tumour shrinkage, and any influence on the natural course of the disease was doubtful.

The rationale for intra-arterial therapy was persuasive: to deliver an antineoplastic drug with high-dose intensity via the hepatic artery, known to be the major route of blood supply for malignant tissue [2], while at the same time avoiding systemic toxic effects by a high ratio of hepatic drug extraction [3]. Additionally, the liver was considered to be the major and often first metastatic site in colorectal cancer. A step-wise pattern of metastatic spead starting in the liver and thereafter occurring in other organs has been postulated [4]. Therefore, treating the liver might not only result in tumour regression of the affected organ, but also delay extrahepatic metastasis. Even if this latter goal should not be accurate, it may be hypothesised that an effective treatment of the major tumour burden would eventually prolong patient survival.

Fluorodeoxyuridine (FUdR) appeared to be the ideal compound for intrahepatic use because approximately 95% of the drug was cleared by the liver in contrast to 5-FU with a variable hepatic extraction of 15–50% [3].

The introduction of surgically implantable intra-arterial catheters and infusion pumps [5, 6] offered a major technical advantage by reducing many of the earlier complications, such as dislocation of the catheter tip, inadequate perfusion of the liver, perfusion of upper gastro-intestinal organs, sepsis, bleeding, hepatic artery thrombosis and hospitalisation that accompanied the use of percutaneous catheters [7]. At the same time, prolonged drug delivery on an outpatient basis was possible.

Data from phase II investigations [8] revealed a high rate of objective tumour response of approximately 45% achieved by hepatic arterial infusion (HAI) of FUdR. The median patient survival of approximately 17 months indicated a possible survival advantage for patients treated with HAI compared with historical controls treated with the intravenous drug. Such favourable results have also been

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