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Treatment of Colorectal Cancer Metastases Confined to the Liver

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Hepatic metastases are a major cause of death in patients with disseminated colorectal cancer. The prognosis of patients with hepatic metastases is very poor and mainly determined by the extent of hepatic disease at presentation. In these patients, the goal of any treatment is to obtain a complete tumour remission in the liver; this is the only way to obtain a significant survival benefit. In this overview, we summarise data from (i) studies comparing survival of patients after primary resection of liver metastases with survival after repeat liver resections, (ii) studies comparing hepatic arterial infusion of fluoropyrimidines with systemic delivery of these anticancer drugs, and (iii) phase I/II studies on isolated liver perfusion (ILP) with alkylating compounds. Furthermore, we discuss alternative strategies to combat liver metastases, including those taking advantage of an ILP setting.

Key words: hepatic artery infusion, liver metastases, colorectal cancer, isolated liver perfusion, drug resistance
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INTRODUCTION

DURING THE past decades, knowledge about colorectal cancer has much increased, but little progress has been made in improvement of patient survival. Approximately half of the patients presenting with advanced colon cancer have disseminated disease and the prospects of these patients are invariably poor. Because the liver is the first major vascular bed in which disseminating colorectal tumour cells are trapped, it is not surprising that no less than 20% of patients undergoing resection of their primary tumour show liver involvement [1]. Moreover, 60% of patients who die from colorectal cancer show evidence of hepatic metastases and in the majority of cases, liver failure is reported to be the actual cause of death [2]. After radical resection of the primary tumour, median survival of patients who do not obtain further treatment of their liver metastases is expressed in months rather than years [3, 4]. Evidently, to improve patient prognosis in terms of morbidity and mortality, reduction of tumour load in the liver is a primary goal, but options for curative treatment are limited; for patients in whom metastases are confined to the liver, resection is the only hope for prolonged survival. Selection criteria for this type of surgery are that no primary cancer is left, that no extrahepatic metastases are detectable, and that liver metastases are resectable with tumour-free margins. As a consequence, the vast majority of patients have to be excluded from further surgical treatment.

Unfortunately, systemic treatment with available anticancer drugs has led to tumour responses in at the most 15% of patients [5]. Clearly, much higher drug concentrations are required to have a significant impact on liver metastases and an obvious strategy to increase maximally tolerable doses is some form of regional treatment. This has encouraged attempts to infuse drugs directly into the liver circulation or to isolate the liver totally from the systemic blood circulation and perform a recirculating perfusion.

SURGERY

The first attempts to cure patients by resection of their hepatic metastases were made more than 30 years ago, and in the 1970s it became clear that this type of surgery could increase patient survival. Surgical methods gradually improved, and currently the consensus is that, with an acceptable risk of mortality due to the surgical intervention, the 5-year overall survival rate is approximately 25% [6–14] (Table 1).

The following factors were found to be important with respect

Table 1. Resection of colorectal cancer liver metastases: results from different studies

Reference	No. of patients	Mortality rate (%)	Morbidity rate (%)	5-year actuarial survival (%)
Nordlinger [6]	80	5	13	25
Hughes [7]	859	-	-	33
van Ooijen [8]	118	8	35	21
Scheele [9]	226	5	-	31
Ringe [10]	157	5	10	23
Adson [11]	141	2.8	-	23
Ekberg [12]	72	5.6	15	16
Doci [13]	100	5	39	30
Nordlinger [15]	1818	2.4	24	26
van de Velde*	54/6	5	15	23/0

*Unpublished data; 5-year actuarial survival of 23% for patients (54) with tumour-free margins > 10 mm, compared to 0% in patients (6) with tumour-free margins < 10 mm.

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to patient prognosis: stage of the primary tumour, duration of disease-free interval between primary tumour removal and resection of hepatic metastases, presence of extra-hepatic metastases, type of resection (wedge, anatomical), size and number of liver metastases, and the extent of tumour-free margins of surrounding liver tissue [7]. The importance of the latter factor seems to be supported by preliminary data showing that of 6 patients with tumour-free margins less than 1 cm, none were alive 5 years after surgery (Table 1).

Considering the importance of Dukes' stage of the primary tumour on patient survival after curative removal of hepatic metastases, it was found that median survival for patients with Dukes' A and B tumours was dramatically longer than for patients with Dukes' C tumours (125 versus 28.6 months, respectively). However, in patients with a similar Dukes' stage, no difference in survival was found whether or not liver metastases were detected and curatively resected (R0) in the further course of their disease [15].

Nordlinger and associates reported that from a series of 1569 patients successfully resected from their liver metastases, 41% developed recurrent cancer in the liver; in 75% of these patients the liver was the only site of tumour recurrence [14]. Therefore, from all patients suffering from recurrence after resection of liver metastases, approximately one-third will have recurrent disease confined to the liver. In the above study, in 25% of patients with liver-only recurrences a second curative hepatic resection was attempted. Recently the same authors reported that survival rates of the latter patients were comparable to survival rates obtained after primary resection of the colorectal liver metastases. This was also true with respect to the operative morbidity and mortality rates [16].

One may conclude from these data that repeat liver resections are useful provided that the surgeon is experienced, but that in order to increase the number of patients who may benefit from this treatment, careful follow-up after primary resection of liver metastases is definitely required.

ADJUVANT CHEMOTHERAPY

Is adjuvant treatment after resection of liver metastases capable of eradicating small, non-detectable liver metastases? With respect to adjuvant chemotherapy of primary colon cancer, Taylor and associates reported a significant increase in overall survival in patients receiving a 7-day course of intraportally administered 5-fluorouracil (5-FU), started immediately after resection of their colorectal tumour [17]. This result has recently been confirmed by a meta-analysis of several studies on adjuvant intraportal chemotherapy (M. Buyse, personal communication). The analysis also suggests that adjuvant chemotherapy is especially beneficial to patients with Dukes' C tumours.

However, data from several randomised studies on adjuvant intraportal chemotherapy after resection of liver metastases have not provided evidence that locoregional chemotherapy can prevent recurrence of liver metastases. It should be mentioned though that these data may have been confounded by the fact that the majority of patients had been treated with adjuvant chemotherapy after removal of their primary tumour; this first exposure to anticancer drugs may have resulted in selection of tumour cell clones with enhanced resistance to adjuvant chemotherapy after liver resection. This possibility is supported by data from a recent study showing that treatment of irresectable liver metastases by administering floxuridine (FUDR) as an infusion into the hepatic artery was significantly less successful when patients had been previously treated with chemotherapy, e.g. as adjuvant to removal of their primary tumour [18].

INFUSION OF CHEMOTHERAPEUTIC DRUGS DIRECTLY INTO THE LIVER

The rationale for hepatic arterial infusion (HAI) of chemotherapeutics was based on data both from experimental tumours in rodents and from studies in human patients, indicating that hepatic metastases derive most of their blood supply from the hepatic artery [19]. With the use of an implantable pump with a cannula into the gastroduodenal artery, relatively high local drug concentrations could be achieved for prolonged periods [20]. Reported overall response rates from phase II trials of HAI of FUDR range from 32 to 83% and median survival durations from 12 to 26 months, respectively [18, 21–25] (Table 2). However, treatment was associated with considerable morbidity as a result of hepatobiliary toxicity. Biliary toxicity was better controlled in a study reported by Kemeny and colleagues who evaluated the addition of dexamethasone to a regimen of FUDR plus leucovorin via HAI; response rates were similar in both treatment arms [18].

From several randomised trials it was established that after HAI with FUDR, significantly higher response rates were achieved compared to systemic FUDR infusion [26–30] (Table 3), although these responses may have temporarily increased the quality of life of these patients, it could not be proven that HAI had any significant impact on patient survival. However it should be mentioned that possible explanations for this failure could be that a high percentage of patients were allowed to crossover to HAI after tumour progression during systemic therapy, and that most studies were performed on patients that had received adjuvant chemotherapy after removal of their primary tumour. Therefore, based on available data from the literature, it is difficult to draw straightforward conclusions on the value of HAI (with or without slow release from implantable pumps) compared to systemic infusion.

ISOLATED LIVER PERFUSION (ILP)

A totally different approach is recirculating perfusion of the vascular isolated liver. ILP was attempted clinically in the early 1980s by Aigner and associates and Skibba and colleagues using a double lumen intracaval shunt [31, 32]. However, these studies were hampered by many technical difficulties, often resulting in incomplete isolation. Subsequent preclinical studies in pigs led to a more feasible surgical technique and a reliable method of leakage detection [33]. Finally in 1990, a phase I/II study was started at our department in Leiden to evaluate mitomycin C (MMC) in an improved ILP setting. 9 patients with irresectable liver metastases confined to the liver were treated with 30 mg/m^2 MMC in ILP for 1 h. This study was not continued because of hepatotoxicity (veno-occlusive disease) in 4 of 9 patients, but it clearly demonstrated that complete vascular isolation of the liver is achievable.

A better candidate for ILP studies was found in the alkylating compound melphalan (L-PAM). In patients given autologous bone marrow transplantation (ABMT), L-PAM could be administered at a dose five times greater than the recommended dose and this resulted in only mild, asymptomatic, and transient elevation of liver enzymes in the blood of these patients [34]. Moreover, because L-PAM shows a steep dose–response curve, a relatively small increase in intracellular concentration may translate into a significant therapeutic improvement [35]. Indeed, a surprisingly high overall response rate of 47% was

Table 2. Hepatic arterial infusion with internal pump: responses

Reference	No. of patients	Drugs	% Prior chemotherapy	% CR	% PR	Median survival (months)
Niederhuber [21]	70	FUDR	45		83	25
Balch [22]	50	FUDR	40			26
Kemeny [23]	41	FUDR	42		42	12
Shepard [24]	53	FUDR	36		32	17
Kemeny [25]	95	FUDR\FUDR + MMC + Ca	100	0	39	16.8
Kemeny [18]	29	FUDR + LV + Dec	100	0	52	13.5
	32		0	3	75	24.8

FUDR, floxuridine; MMC, mitomycin C; LV, leucovorin; Dec, dexamethasone; Ca, carmustine; CR, complete remission; PR, partial remission.

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

		Intrahepatic			Systemic			
Reference	No. of patients	Drug	% Responses	Median survival (months)	Drug	% Responses	Median survival (months)	% Crossover
Kemeny [26]	163	FUDR	50	17	FUDR	20	12	60
Hohn [27]	143	FUDR	37	17.8	FUDR	10	16.1	43
Rougier [28]	163	FUDR	43	15	5-FU	9	11	0
Chang [29]	64	FUDR	62	22	FUDR	17	12	0
Martin [30]	69	FUDR	48	12.6	5-FU	21	10.5	0

FUDR, floxuridine; 5-FU, 5-fluorouracil.

reported for patients with disseminated colon cancer after high dose L-PAM in an ABMT setting [34].

Recently, we performed a phase I/II study in a series of 24 patients with colorectal cancer confined to the liver; livers were perfused with L-PAM in doses ranging from 0.5 to 3.0 mg/kg (administered as a bolus injection into the isolated circuit). Leakage of perfusate, as monitored with ^{99m}Technetium-labelled red blood cells, ranged from 0 to 30%; the 1 h duration of ILP was compromised in no less than 35% of the cases. Because high pressures in the intracaval shunt were suspected to be a main cause of this problem, we subsequently used an external circuit with support of a centrifugal pump (Figure 1). With respect to tumour response, complete remissions were observed in 2 out of 17 evaluable patients. Data on survival are expected by the end of 1995.

FUTURE PROSPECTS OF ISOLATED LIVER PERFUSION

The surgical aspects of ILP have been improved in that, at present only very limited amounts of drug escape into the systemic circulation. As a consequence, toxicity in the liver becomes dose-limiting. From the above phase I/II study, it was established that a 1-h perfusion with 200 mg L-PAM in 2 l perfusate is close to the maximally tolerated dose. Computerised tomography scans have shown that this dose is high enough to have a significant impact on tumour growth. Could it be possible to further improve the efficacy of L-PAM, either by reducing hepatotoxicity without compromising antitumour activity (thereby allowing a higher dose to be administered), or by

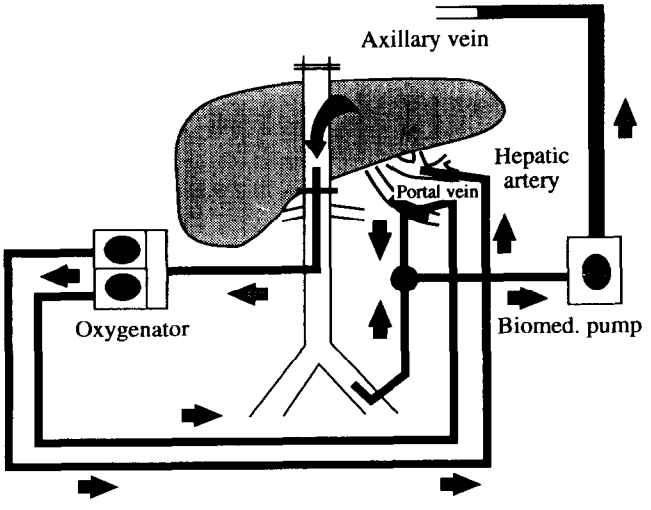

Figure 1. Perfusion circuit with extracorporeal bypass, connecting the portal vein and left femoral vein to the left axillary vein. The two inflow limbs of the isolated circuit are established by one catheter in the portal vein and another through the gastroduodenal artery into the common hepatic artery. The caval vein is temporarily clamped above and below the liver and serves as a reservoir from which the venous hepatic blood returns to the heart–lung machine.

selectively increasing the sensitivity of metastases towards L-PAM?

A number of studies have shown that the tripeptide, thiol glutathione (GSH), may be a key factor in tumour cell resistance towards alkylating compounds, including L-PAM. It was found that in mice, treatment with buthionine sulphoximine (BSO), a clinically applicable inhibitor of GSH synthesis, enhanced cytotoxicity of L-PAM by a factor of 2 [36]. Moreover, the kinetics of GSH depletion (and repletion) were found to differ greatly among different organs/tissue types [37]. Could it, therefore, be possible to selectively decrease tumour GSH prior to ILP with L-PAM to an extent that it would translate into a marked increase in tumour cell kill? And could we in this context take advantage of the fact that blood supply to colorectal liver metastases is mainly arterial, whereas the portal vein is largely responsible for blood supply to the liver [38]? These and other questions are addressed in ongoing preclinical studies using the CC531 colorectal carcinoma cell line in a rat model for hepatic metastases.

Many variables are involved in the role of GSH in the efficacy of anticancer drugs, and even if we could succeed in enhancing the efficacy of a drug like L-PAM in our model system, many questions at molecular, cellular and organ levels need to be resolved before GSH modulation could possibly enter the operating room.

GSH has two major functions in cellular metabolism. As a substrate for the enzyme GSH peroxidase, it is an important anti-oxidant. It has been hypothesised that oxidative stress may be a mediator of apoptotic cell death [39] and, therefore, that the sensitivity of cells to induce apoptosis in response to anticancer drugs may in part depend on the oxidant–antioxidant balance.

A second function of GSH is to conjugate to (and thereby detoxify) various drugs (including many alkylating compounds). This conjugation reaction can occur spontaneously or by the action of GSH S-transferases (GSTs). Cells contain a variety of different GST isoenzymes with different substrate specificities and a cell-type dependent level of expression. For example, colorectal cancer cells generally contain high levels of GSTπ isoenzyme and virtually no GSTα [40], the isoenzyme held responsible for GSH-L-PAM conjugation [41], whereas hepatocytes are rich in GSTα, but lack GSTπ. However, with respect to the detoxification of L-PAM, the relative contribution of GSTα-mediated conjugation is still uncertain.

An interesting development is the design of prodrugs that can be activated by specific GST isoenzymes; it is expected that anticancer drugs that are strictly activated by GSTπ would be very effective in an ILP setting. Recently, compounds have been designed and synthesised that might be very promising in this respect [42].

Another approach that may show a high tumour cell specificity when performed in an ILP setting is based on somatic gene therapy. A gene that is currently used for such an approach is the herpes simplex virus thymidine kinase (*HSV-tk*). HSV-tk protein product specifically phosphorylates the nucleoside base analogue and antiviral drug ganciclovir (GCV). Phosphorylated GCV inhibits DNA synthesis and kills the cell. Retroviral-mediated transfer of the *HSV-tk* gene was used in the treatment of rapidly growing brain tumours in rat models [43]. Currently, experiments are in progress to test whether in the afore-mentioned CC531 tumour model, viral vectors can be used in ILP to introduce *HSV-tk* exclusively in liver and tumour cells and whether subsequent systemic treatment with GCV irradicates the majority of (proliferating) tumour cells.

Clearly, ILP offers a variety of opportunities beyond that of treatment with standard chemotherapeutic compounds. Apart from the strategies outlined above, one can think of the application of biological response modifiers, such as tumour necrosis factor, or of compounds that sensitise tumour cells to the devastating action of a laser beam, new treatment modalities that are now intensively studied in proper animal models. It is hoped that these preclinical endeavours in the future may lead to protocols that can be tested in clinical trial settings. At present, however, the life of the patient depends on the knife of the surgeon.

Clinicians should realise that in treating patients with liver metastases, the only way to achieve benefit for the patient is to treat aggressively, or not at all. In other words, to phrase Shakespeare's famous line. "Diseases desperate grown, by desperate appliance are reliev'd, or not at all" (Hamlet Prince of Denmark, Act IV, scene III, line 9).

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