Pharmacologic and clinical aspects of isolated hepatic perfusion (IHP) of liver metastases of solid tumours

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CHAPTER 1

General introduction

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Silberman & Silberman, Principles and Practice of Surgical Oncology, Second edition 2009; Ch. 48: p882-p891: Liver Tumors: Multi-modality treatment of hepatic metastases

Multimodality treatment of colorectal liver metastases

The most common origin of hepatic metastasis is colorectal cancer. Liver metastases are diagnosed in 10-25% of patients at the time of resection of their primary colorectal tumour and eventually up to 70 % of patients with colorectal cancer will develop liver metastases [1]. In approximately 30% of the patients the liver is the only site of metastatic disease [2, 3] . If the metastases are confined to the liver there are several locoregional treatment options, including partial hepatic resection, local ablative therapy, administration of chemotherapy by hepatic artery infusion (HAI) and isolated hepatic perfusion (IHP) with high dose chemotherapy. Curative resection of colorectal cancer liver metastases is possible in less than 10 percent of patients due to the number, location or size of the metastases [4, 5]. After neoadjuvant treatment with modern systemic chemotherapy regimens another 12-14% of colorectal cancer patients with liver metastases are suitable for hepatic resection [6]. If patients are ineligible for hepatic resection, palliative systemic chemotherapy is often the only treatment option for liver metastases. The role of locoregional treatment options other than resection is currently subject to much debate.

Local ablative therapy

Several local ablative techniques are available for the treatment of liver metastases. Radiofrequency ablation (RFA) is most often applied. Other less frequently applied therapies include cryotherapy, hepatic artery embolization (HAE), percutaneous alcohol injection (PAI), microwave coagulation therapy (MCT), laser induced thermotherapy (LITT), photodynamic therapy (PTD) and radiotherapy. Local ablative therapies provide the possibility of local disease control without systemic toxicity.

Radiofrequency ablation

The major advantage of RFA is the selective destruction of tumour tissue without significant damage to normal liver tissue. In RFA, the needle electrodes cause hyperthermia, through the delivery of a high frequency alternating current, resulting in the destruction of proteins and cell membranes, inducing coagulative necrosis. Under optimal conditions current RFA devices can provide spherical lesions of up to 7cm in diameter [7]. RFA can be applied alone or in combination with surgical resection if surgical resection criteria are not fulfilled, widening the applicability of surgical resection. Most studies on RFA focus around colorectal liver metastases, neuroendocrine tumours and breast cancer. Results are often difficult to interpretate, because reports include different tumour types, treated with a variety of techniques and additional treatments such as chemotherapy obscure the primary effect of RFA treatment.

In colorectal cancer liver metastases, RFA has resulted in complete response rates of 52-95%, with a median survival time of approximately 30-34 months after diagnosis of liver metastases. Local recurrence rates (lesion-based) vary between 2.0-39% depending on which method is applied [8-18]. Several studies have shown local recurrence rates to be less if an open or laparoscopic technique is applied as compared to the percutaneous method [19, 20]. Over 90% of the recurrent disease occurs outside the treated area both intra- and extrahepatically, emphasizing the local nature of the treatment. Optimal results in RFA are achieved in an experienced centre, using an open technique, on 3 or less liver metastases, not located near any large vascular structures and less than 5cm in diameter [18, 21, 22].

The possibility of curation and the large percentage of extrahepatic recurrences after RFA have resulted in the common practice of combining systemic treatment with RFA, even though the benefits of combining both treatments have not been thoroughly examined. The true value of RFA remains to be seen.

Other ablative treatment modalities

Cryoablation results in tumour destruction through the formation of intra- and extracellular ice crystals by repeated freezing and thawing, caused by inserting a probe with circulating liquid nitrogen. Cryoablation is most frequently applied in the treatment of hepatocellular carcinoma (HCC) and to a lesser extent in colorectal cancer liver metastases. In colorectal cancer patients a median survival of around 26 months after cryoablation has been published [23-26]. Cryotherapy has been replaced by other ablative treatment modalities, due to the high rates of local recurrences and complications [27, 28].

Hepatic arterial ligation and (chemo)embolization are based on the principle that, liver metastases derive most of their blood supply from the hepatic artery, while healthy liver tissue is mainly supplied by the portal vein [29, 30]. Although ligation and embolization were considered promising treatments at introduction several decades ago, no studies have shown substantial benefit in the treatment of liver metastases [31]. Therefore many centres have abandoned this technique.

Percutaneous alcohol injection (PAI) is mainly applied in the treatment of HCC with tumour response rates up to 80%, but its role in the treatment of liver metastases seems limited [32]. As shown by the poor results of PAI in colorectal liver metastases, with no necrosis induced in a series of 22 colorectal tumours, the more solid aspect of colorectal liver metastases, can impair the adequate injection of sufficient volumes of alcohol in the tumour [33].

Microwave coagulation therapy (MCT) and laser induced thermotherapy (LITT) resemble the RFA technique, as they are based on the generation of heat in the tumour and therefore considered thermal ablation techniques. In MCT heat is generated through a microwave-emitting needle, producing dielectric heat by stimulation of water molecules within cells. The rapid agitation of water molecules produces frictional heating and coagulative necrosis [34]. Like RFA and LITT, MCT can be performed percutaneously, laparoscopically or during an open procedure. The major drawback of MCT is it produces zones of only 10-25mm of coagulative necrosis, requiring multiple needle insertions for adequate treatment. Few studies have been performed using MCT as a treatment modality in liver metastases. In colorectal cancer liver metastases, studies have shown tumour response up to 87% with a mean survival of 27 months, but patient numbers are small [35, 36] In LITT heat is not generated by high frequency current but by a laser applicator that delivers light energy through optical fibers inserted in the target tissue, leading to tumour destruction [34]. Mack *et al* reported the largest series of 705 patients, including 57% colorectal cancer patients, 18% breast cancer patients, 5% hepatocellular carcinoma patients and 20% other patients [37-39] . The rate of clinically relevant complications such as pleural effusion, intrahepatic abscess and intra-abdominal bleeding was 1.3%. The tumour response rate was 99.3% after 3 months, with a mean survival rate in respectively colorectal cancer and breast cancer patients of 41.8 and 51.6 months.

PDT, on the other hand, uses optical fibers and laser light. The antitumor effect in PDT is caused by reactive oxygen species, generated through a photosensitizing agent, which is administered systemically and will localize in tumour tissue [40, 41]. Illumination of the tumour by light of an appropriate wavelength will cause the photosensitizer to transform to an unstable higher energy level. The absorbed energy is transformed to oxygen, leading to the formation of reactive oxygen species, which are cytotoxic and cause direct tumour cell and vascular damage[42]. Results of a phase I trial in 24 patients show PDT to be feasible and a relatively safe and effective treatment of colorectal liver metastases [43].

Application of external radiotherapy for the treatment of liver metastases has been limited by low tolerance of the normal liver parenchyma and absence of an obvious survival benefit in studies involving whole-liver irradiation [44]. Recently two alternative techniques to deliver radiation more selectively have been developed involving radioactive isotopes, i.e. SIR-spheres® and 3D planning software. In selective internal radiation therapy (SIRT) radioactive spheres are delivered selectively to the tumour through injection in the hepatic artery. Gray *et al* performed a randomized clinical trial in 74 colorectal cancer patients comparing a single administration of SIR-spheres® combined with hepatic artery infusion of FUDR with hepatic artery infusion of FUDR alone [45]. Treat-

ment with SIR-spheres® was associated with a significantly better response rate (44% vs. 17.6%, P = 0.01) and median time to progression (15.9 vs. 9.7 months, P = 0.001). Grade 3-4 treatment related toxicity was similar for both groups. In stereotactic radiotherapy improvements in positioning and 3D planning software have enabled treatment of a specific focus in the liver with a single high dose of radiotherapy with minimal damage to healthy liver tissue [34, 46]. A phase I/II trial in 60 liver tumours of various origin, show the technique is safe and local tumour control was achieved in 98% of tumours [47].

Chemotherapy

Systemic chemotherapy

Until recently, the standard treatment for metastatic colorectal cancer consisted of 5-FU based schedules, resulting in response rates around 15%, median time to progression of 5 months and overall survival of 12 months [48]. In the past decade several new agents have become available including oxaliplatin, irinotecan and the monoclonal antibodies bevacizumab and panitumumab/cetuximab [49-56]. Both irinotecan and oxaliplatin combined with 5-FU/leucovorin or capecitabine have shown an increase in terms of progression-free survival, overall survival and quality of life compared with 5-FU/leucovorin alone in first- and second-line therapy [54, 56-61]. Recently, several studies have been conducted investigating combination and sequential use of several new agents. Tournigand *et al* conducted a phase III cross-over study of first-line chemotherapy with in one arm 5-FU/leucovorin with oxaliplatin and in the other arm 5-FU/leucovorin with irinotecan resulting in maximum medium survival of 21.5 months [52]. Even more recently Koopman *et al* showed that both combination treatment and sequential treatment with capecitabine, irinotecan and oxaliplatin yields similar results [62]. The introduction of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF) has further improved treatment options in metastatic colorectal cancer. Hurwitz *et al* reported that the addition of bevacizumab to bolus irinotecan and 5-FU/leucovorin as a first-line treatment resulted in increased survival, response rate and duration of response [53]. Similarly, panitumumab/cetuximab, monoclonal antibodies against epidermal growth factor receptor (EGRF) have further improved survival in combination with either irinotecan or oxaliplatin, especially in patients without K-ras mutation [49, 55]. Now oncologists are faced with the challenge of choosing the optimal treatment schedule for advanced colorectal cancer for each individual patient. Currently, the combination of fluoropyrimidine-based chemotherapy with oxaliplatin and bevacizumab is considered standard first-line treatment in metastatic colorectal cancer. The addition of panitumumab or cetuximab to a schedule with bevacizumab increases toxicity without improving survival and thus should be reserved for second-line treatment [63, 64].

Regional chemotherapy

Hepatic artery infusion (HAI) is a therapeutic option for patients with isolated liver metastases not suitable for surgical resection or local ablation. Similar to hepatic arterial ligation and embolization, HAI of chemotherapy is based on the principle that, in contrast to normal liver parenchyma, liver metastases derive most of their blood supply from the hepatic artery [29, 30]. Subsequently, high drug concentrations can be achieved at the tumour site without damage to the healthy liver tissue. HAI has mainly been applied in colorectal cancer liver metastases and hepatocellular carcinoma. Early infusion trials administered chemotherapy using percutaneously placed catheters, requiring bed rest and hospitalization during infusion of the chemotherapy. When a totally implantable pump was introduced HAI chemotherapy changed into a more convenient ambulatory treatment. All techniques require an angiogram to assess vascular anatomy before catheter placement. Most studies show around 20-40% of patients cannot receive infusion treatment due to abnormal vasculature inhibiting perfusion of the entire liver [65-67]. Catheters and pumps can be placed through laparotomy or laparoscopy. Laparotomy enables assessment of extrahepatic metastases and ligation of arterial collaterals to decrease incidence of extrahepatic perfusion and chemical gastritis or duodenitis [68, 69]. Complications associated to catheter placement include death, hepatic misperfusion, catheter obstruction and hepatic artery thrombosis, with complications rates being less for implantable pumps as compared to ports [68, 70, 71].

Fluorodeoxyuridine (FUDR) and 5-FU are the drugs most often used for hepatic arterial infusion. An ideal drug for HAI has to fulfil several criteria including a steep dose response curve, high total body clearance and minimal liver toxicity. Both FUDR and 5-FU have a steep dose response curve, but FUDR has a higher hepatic extraction rate when continuously infused (95% for FUDR vs. 19-90% for 5-FU) [72]. Although higher hepatic extraction rates lead to increased regional drug exposure, it also implies limited systemic exposure. Considering approximately 50% of patients treated with HAI have extrahepatic disease progression, some centres prefer HAI with 5-FU to obtain both local and systemic disease control [73]. Treatment-related toxicities include chemical hepatitis, biliary sclerosis and peptic ulceration. Kemeny *et al* reported an increase in response and survival rate and a decrease in hepatotoxicity if dexamethasone is added to FUDR [74]. Several randomized studies involving HAI with FUDR or 5-FU in colorectal cancer patients have reported significantly higher tumour response rates compared with systemic administration (HAI 41%, systemic 14%; $p<0.0001$) [65, 66, 75]. In 1996, two meta-analyses combining the results of 10 randomized trials appeared, comparing HAI with either systemic treatment or best supportive care [73, 76]. The Meta-Analysis Group in Cancer studied 7 randomized trials and when combining the results of the 5 trials

comparing HAI with systemic treatment, concluded that although HAI showed superior response rates compared to systemic treatment (41% vs.14%) there was no significant survival benefit and treatment-related hepatotoxicity was considerable. Harmantas *et al* studied 6 randomized trials and reported a modest survival benefit for HAI over systemic treatment. These studies have two major drawbacks. First of all, in three of the analyzed randomized trials patients were allowed to cross-over from systemic treatment to HAI possibly obscuring any survival benefit. Secondly, the drug doses and schedules varied substantially between HAI and systemic treatment groups. A recent randomized study in which 290 colorectal cancer patients were included also did not show significant differences in tumour response , progression-free survival and overall survival between patients who had received 5-FU/leucovorin either systemically or by HAI, while the HAI group reported a worse quality of life compared with the systemically treated group [77]. On the other hand Kemeny *et al* published a trial in 135 colorectal cancer patients and reported a significant survival benefit (median overall survival 24.4 vs. 20 months, P= 0.0034) and increased physical functioning in patients receiving HAI compared to systemic treatment [78].

Recently several new drugs like for example oxaliplatin and irinotecan have been safely introduced in HAI [79-84]. Results of a phase I/II study on biweekly HAI with oxaliplatin combined with systemic 5-FU en leucovorin according to the de Gramont schedule were recently reported by Ducreux *et al* [85]. A total of 28 previously untreated patients with colorectal cancer with isolated liver metastases were treated with this schedule, the objective response rate was 64% and the median overall survival was 27 months. Grade 3 or 4 neutropenia occurred in 10 patients and there were two treatment related deaths. Compared to local ablative treatments HAI of chemotherapy can offer the additional benefit of both local and systemic disease control. In colorectal cancer liver metastases meta-analysis and recent randomized trials show conflicting results, but most trial designs did not allow for correct comparison of both treatment groups. Moreover, recent developments in new systemic drugs like oxaliplatin, irinotecan, bevacizumab and cetuximab/panitumumab have improved results substantially in the systemic treatment over liver metastases. If these agents have a role in HAI remains to be investigated.

Isolated hepatic perfusion

Isolated hepatic perfusion (IHP) involves complete vascular isolation of the liver to allow local treatment of the liver. During this procedure the blood circulation of the liver is temporarily isolated from the systemic circulation. Inflow catheters are inserted in the common hepatic artery and the portal vein and an outflow catheter in the infrahepatic caval vein while the suprahepatic caval vein is occluded by a surgical clamp. Subse-

quently the catheters are connected to heart-lung machine and the anticancer drug is administered in this isolated circuit. Leakage to the systemic circulation is monitored in order to prevent high systemic exposure. After perfusion of the liver with the drug for a certain period of time (1 hour in most IHP trials) the liver is flushed with clean perfusate to wash out the anticancer drug after which the natural blood circulation is restored [86].

The major advantage of IHP is the ability to treat the liver with drug levels that would be toxic when administered systemically [86]. Moreover, agents which cannot be administered systemically because of their toxicity, such as tumour necrosis factor alpha (TNF-α), can be used in IHP [87, 88]. Furthermore, hyperthermia, which is known to improve the anticancer effect of several drugs, can be applied by heating the perfusate solution [89].

Most experience with IHP has been obtained with colorectal liver metastases, but several studies have reported the treatment of uveal melanoma and neuroendocrine cancer liver metastases [87, 88, 90-94]. Various drugs have been used in IHP studies, including 5-FU, mitomycin C, cisplatin and melphalan with or without TNF-α. Usually mild hyperthermia is applied up to 40°C during IHP, although one study investigates the efficacy of hyperthermia alone (42-42.5°C). Recent clinical studies have mainly applied melphalan in IHP. Two large trials have been reported in colorectal cancer patients. Bartlett *et al* have reported IHP in 51 patients with different treatment schedules, including IHP with high doses of melphalan alone and moderately high doses of melphalan combined with TNF-α or followed by monthly hepatic intra-arterial infusion of FUDR and leucovorin [94]. Results of these studies show response rates up to 74%, a median time to progression up to 14.5months and a median survival of 27 months. Rothbarth *et al* performed a phase I/II trial in 73 colorectal cancer patients with high dose melphalan, achieving an overall response rate of 59%, median time to progression of 7.7 months and a median overall survival of 28.8 months [93]. In uveal melanoma patients, IHP has resulted in response rates of 50-62%, with a median overall survival of 9.9-12 months[87, 90, 92]. The nature and incidence of major complications was similar in all trials independent of primary origin of liver metastases. Mortality rate varied between 2-5% and major complications consisted of bleeding and hepatoxicity including veno-occlusive disease.

Melphalan has been the only agent applied in major clinical trials over the past 10 years. Over the past few years new agents like irinotecan, oxaliplatin and bevacizumab, have been introduced in the systemic treatment of colorectal metastases, increasing response rates, disease free survival and overall survival [51-53, 95]. Ideally some of the development in the systemic treatment of colorectal cancer metastases can be incorporated in isolated hepatic perfusion. Despite encouraging results in recent trials, IHP should still be considered an experimental treatment. No prospective trials have been reported

comparing IHP to either systemic treatment or local ablative treatment and little is know about the role of adjuvant systemic treatment. Whether IHP will eventually become a standard treatment option is highly depended on the introduction of new drugs in order to further increase effectiveness, as recently shown for systemic treatment, and the development of new techniques with less mortality and improved responses.

Outline of this thesis

The aim of this thesis was to study the role of IHP in the treatment of liver metastases and to evaluate possible improvements to IHP.

In chapter 2, IHP is evaluated as a treatment option for liver metastases from non-colorectal origin. In chapter 3, the safety and efficacy of a new drug administration in IHP through infusion is assessed. While in chapter 4, possible prognostic factors for IHP are identified to further improve patient selection. To establish the role of IHP, we compared IHP with systemic treatment in colorectal cancer patients with liver metastases only in chapter 5. Chapters 6 and 7 report the results of our efforts to introduce the new agent oxaliplatin as a possible drug in IHP for colorectal cancer liver metastases.

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