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

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CHAPTER 8

The future of isolated hepatic perfusion for isolated liver metastases

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Introduction

Worldwide colorectal cancer is the third most common cause of cancer related deaths with approximately 639000 deaths each year (WHO fact sheet 297). In approximately 30% of colorectal cancer patients the liver is the only site of metastatic disease [1, 2]. Complete surgical resection is considered the best treatment with 5-year survival rates ranging from 25-51%. Unfortunately, surgical resection is only possible in less than 10 percent of patients due to the number, location or size of the metastases [3-5]. Recently, neoadjuvant chemotherapy has been introduced, rendering another 10 to 30 % of patients resectable [6]. The management of irresectable colorectal liver metastases, on the other hand, remains a challenge for all cancer specialists. Recent studies have shown improved survival with the introduction of oxaliplatin, irinotecan, bevacizumab and cetuximab in the systemic treatment of colorectal metastases [7-12]. Regional treatment options however, can offer the potential benefit of both aggressive local treatment and limited systemic toxicity. Several regional therapies have been developed including isolated hepatic perfusion (IHP). IHP, a technique which involves complete vascular isolation of the liver, allows for high local drug exposure. Phase II studies involving IHP in colorectal cancer patients have shown hepatic response rates up to 74% with a median time to hepatic progression up to 14.5 months, a median overall survival of 27 months and 5 year survival of 9%[13-17].

Advancing role of systemic treatment

When IHP was first introduced, 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 [18]. Recently, several new agents have become available including oxaliplatin, irinotecan and the monoclonal antibodies bevacizumab and panitumumab/cetuximab [8-12, 19-21]. The introduction of irinotecan and oxaliplatin combined with 5-FU/leucovorin or capecitabine has increased median progression free surivival and overall survival from approximately 5 and 12 months to approximately 9 and 17 months, respectively [9, 11, 22-26]. If both treatment schedules are combined even better results have been reported. 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 after both treatments of 21.5 months [12]. Koopman *et al* showed that both combination treatment and sequential treatment with capecitabine, irinotecan and oxaliplatin yields similar results [27]. Even more recently, the monoclonal antibodies have been introduced for the treatment of colorectal cancer. Hurwitz *et al* reported that the

addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to bolus irinotecan and 5-FU/leucovorin as a first-line treatment resulted in increase of progression free survival to 10.6 months and overall survival to 20.3 months [10]. Similarly, panitumumab/cetuximab, monoclonal antibodies against epidermal growth factor receptor (EGRF), have also improved survival in combination with either irinotecan or oxaliplatin, especially in patients without K-ras mutations [19, 21]. At the moment the combination of fluoropyrimidine-based chemotherapy with oxaliplatin and bevacizumab is considered standard first-line treatment in metastatic colorectal cancer, while irinotecan schould be reserved for second-line treatment and panitumumab or cetuximab for third-line treatment for patients with wild type K-ras [28, 29].

Most treatment schedules described above can be given safely prior to and after IHP without increasing the toxicity of IHP (**Chapter 4)**, rendering IHP both a possible first-line or second- and even third-line treatment option after systemic treatment. The question remains whether systemic treatment alone can achieve similar or even better results in the selected group of patients with liver metastases only, eligible for IHP. We compared IHP in 99 patients with 105 patients who received a combination of capecitabine, oxaliplatin and irinotecan **(Chapter 5)**. There was no significant difference in overall survival between IHP and systemic treatment (25.0 months vs. 21.7 months; p=0.29). However, this study was complicated by several drawbacks. Overall survival was calculated from the date of randomization for systemic treatment and date of surgery for IHP, but not from the date of diagnosis of liver metastases. Contrary to the systemic treatment patients, the IHP patients were allowed to receive systemic treatment prior to the start of the study treatment. Therefore, it is likely the IHP patients suffered from a relative survival disadvantage as compared to the systemic treatment patients. We attempted to exclude some of this disadvantage by performing a subgroup analysis of the IHP patients who received IHP as first-line treatment. Although overall survival increased to 28.9 months, still no significant difference in survival could be demonstrated. Probably, the lack of a statistically different survival advantage can be mainly attributed to the high mortality in the first few months after IHP.

For IHP to remain a treatment option for isolated liver metastases, perioperative mortality needs to be reduced or new agents with better responses need to be introduced. Possibly, in view of the developments in systemic treatment, IHP should be abandoned completely for the treatment of colorectal liver metastases and the application of IHP in metastases from various other origins further explored.

Improving the technique, reducing the mortality

The IHP procedure, as currently performed at our center, is a difficult technique with a relatively high mortality and considerable morbidity. Several efforts have been undertaken to develop minimally invasive procedures for IHP, but with only limited success. Chemofiltration has been used to allow for high doses of intrahepatic chemotherapy without systemic toxicity [30-32]. After the drug is infused in the hepatic artery, the hepatic venous blood is bypassed to a charcoal hemoperfusion filter for extracorporeal drug elimination before it returns to the patients' systemic circulation. A phase I study using the technique described above, demonstrated that treatment with high-dose melphalan is feasible. Nevertheless, complete extraction of melphalan by charcoal hemoperfusion is not possible, limiting the maximum tolerated dose [33]. At our center, we demonstrated complete isolation of the liver using minimally invasive techniques to be technically feasible in pigs, but recently performed phase I trials at other centers have shown disappointing results [34, 35]. Savier *et al.* reported a repetitive IHP procedure, in which the first course was given at laparotomy and the next two courses with the new percutaneous technique [36]. At the initial laparotomy a catheter in the gastroduodenal artery was inserted which during subsequent percutaneous treatment was used to administer the melphalan. Although they achieved an isolated hepatic perfusion circuit, considerable leakage to the systemic circulation occurred during IHP. Another study published by van Etten *et al* reported a phase I-II study in 18 patients [37]. In the first 8 patients vascular isolation was attempted through occlusion of the portal vein with outflow through the hepatic veins into an intracaval double-balloon catheter, resulting in on average 56% leakage. The following 10 patients were treated with a different technique using retrograde outflow perfusion, with a triple balloon blocking outflow into the caval vein and allowing outflow via the portal vein. The last technique resulted in less leakage, but retrograde perfusion was still complicated by 35% leakage on average, limiting the possible applications of this technique. Recently Verhoef *et al.* published a study on an alternative simplified technique for IHP. [38]. A new technique using a retrograde hepatic flow in an isolated hypoxic hepatic perfusion was applied. In total 24 patients were treated with irresectable liver metastases of various origin. Operation time and blood loss were considerably less as compared to classical IHP and no perioperative mortality was observed. Although the method described above was open procedure not suitable for repetition it seems the most promising of the recent developments, considering the leakage control and reduction in mortality.

Introducing new agents

The past decade melphalan has been the main drug applied in IHP. The application of new agents in IHP might improve response rates and increase overall survival. Before, we examined new agents, we tried to improve efficacy by changing the administration of melphalan **(Chapter 3)**. To achieve high local concentrations, we administered 200 mg of melphalan through a 20-minute infusion in the hepatic artery, instead of the previously performed bolus administration. Although we achieved high local concentrations in 30 patients for an increased period of time, toxicity increased without improvement of survival or response rates. We concluded that while response is probably dose-dependent, toxicity is mainly concentration-dependent. Therefore we abandoned this technique and directed our efforts towards exploring new agents.

New agents for IHP have to fulfil at least three conditions. Firstly, the drug has to cause rapid tumour cell destruction, due to the 1-hour nature of the procedure. Secondly, the drug has to be a direct working agent and thirdly, ideally the agent has a steep dose-response curve. Of the drugs recently introduced for the systemic treatment of colorectal cancer, only oxaliplatin fulfils all these conditions. Zeh *et al.* published a phase I study of IHP with oxaliplatin in colorectal cancer patients [39]. Dose-limiting veno-occlusive disease was observed at 60mg/m2. In this study, however IHP was combined with HAI complicating the interpretation of both toxicity and response rates. Moreover, the perfusate consisted of oxaliplatin monotherapy, while in systemic therapy combination therapy has been shown more beneficial [40]. Therefore, we studied the combination of oxaliplatin with melphalan. In vitro results show a schedule dependent synergistic interaction between these two agents **(Chapter 6)**. Recently, we performed a phase I trial in 11 patients with IHP with escalating doses of oxaliplatin followed by 100mg melphalan **(Chapter 7)**. Dose-limiting-toxicity, consisting of sinusoidal obstruction syndrome (SOS), was achieved at only 150mg oxaliplatin combined with 100mg melphalan. Currently, the dose of oxaliplatin used in regular systemic combination treatment in colorectal cancer patients exceeds 100mg/m2 per treatment cycle. Therefore conducting a phase II IHP trial based on the MTD dose of 100mg oxaliplatin seems hardly beneficial. Moreover, HAI study protocols already apply a dose of oxaliplatin of up to 150mg/m2 and contrary to IHP the procedure is suitable for repetition [41-45]. In view of this we believe that further exploration of the application of oxaliplatin in IHP will not improve treatment results.

Finding new applications

While the application of IHP in colorectal cancer patients has been thoroughly explored, little is known about the application in liver metastases from other primary tumours. Possibly a new role can be found for IHP in isolated liver metastases from a variety of tumours. Neuroendocrine tumours and uveal melanomas, although rare, are the second most common origin of metastases confined to the liver[46].

In neuroendocrine cancer metastases results of systemically administered agents have been disappointing with response rates around 30-40% for cytostatic drugs and 11% for interferon-α [47-49]. Symptomatic relief can be achieved through somastatin analogs such as octreotide. Symptomatic improvement occurs in up to 70% of patients, but objective tumour response is less than 10% and drug resistance can develop in 3-12 months [50-53]. Grover *et al.* reported the experience with IHP in 13 neuroendocrine cancer patients with a overall response rate of 50% and median progression free survival of 7 months [54]. The nature and incidence of major complications and mortality was similar to other trials independent of primary origin of liver metastases. At our center we have only treated two patients with liver metastases from neuroendocrine carcinoma, one patients showed stable disease, while the other patient showed a partial response for 33.4 months **(Chapter2)**.

For the treatment of metastatic uveal melanoma no standard systemic agent currently exists. Several studies have reported response rates of less than 10% to conventional systemic chemotherapy [55, 56]. Results with immunotherapy, as for example interferon-α and interleukin-2, are equally disappointing with no or only minor responses [57, 58]. Alexander *et al* reported the results of IHP with 1.5mg/kg melphalan in 29 uveal melanoma patients. Hepatic response rate was 62% with a progression-free survival of 8 months and an overall survival of 12.1 months. In our patients the response rate was less; only 33%, but 50% of patients did show stable disease with a median time to progression of 6.6 months and an overall survival of 10 months similar to the results of Alexander *et al.* **(Chapter 2).** Although these results may seem disappointing as compared to IHP in other primary tumours, there is a survival benefit compared to a median survival of 2 months in uveal melanoma patients with liver metastases without antitumour treatment [59]. Moreover, we have no accepted alternative treatment options for uveal melanoma patients with irresectable isolated liver metastases. Recently, at the 2010 ASCO annual meeting Pingpank *et al.* presented a phase III study in 92 malignant melanoma patients with hepatic metastases randomly assigned to either percutaneous hepatic perfusion with melphalan or standard of care. Median hepatic progression free survival was 245 days for the perfusion group and 49 days for the standard care group ($p<0.001$). Cur-

rently we are looking into the application of new agents in IHP for uveal melanoma patients. Peters *et al* reported the use of HAI with fotemustine, an alkylating agent, in 101 uveal melanoma patients with liver metastases [60]. Fotemustine was infused in the hepatic artery for a 4-week induction period followed by a maintenance treatment every three weeks until disease progression. The overall response rate was 36%, with a median overall survival of 15 months and a 2-year survival rate of 29%. Although the response rate of fotemustine infusion is similar to our results with IHP in uveal melanoma patients, the overall survival of 15 months seems superior to our observed 10 months. Possibly, in future IHP trials fotemustine can be introduced.

Conclusion

Although IHP made a promising start in the early 90s, currently it is faced by many challenges. In view of recent developments in systemic treatment, the absence of significant improvement of the technique and the lack of new applicable agents, IHP should not be considered a standard treatment option for colorectal cancer patients with isolated liver metastases. Possibly, a role still exists for IHP in the treatment of liver metastases from non-colorectal cancer origin. Whether under these circumstances, IHP can still attract the interest of both clinical and surgical oncologists necessary for further improvements, remains the question.

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