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

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CHAPTER 3

Hepatic artery infusion of high-dose melphalan at reduced flow during isolated hepatic perfusion for the treatment of colorectal metastases confined to the liver: A clinical and pharmacologic evaluation

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Abstract

Isolated hepatic perfusion (IHP) offers the advantage of high local drug exposure with limited systemic toxicity. To increase local drug exposure, we administered melphalan at a reduced flow in the hepatic artery during IHP (Hepatic artery Infusion, Hepatic artery-Portal vein Perfusion, HI-HPP).

Between December 2001 and December 2004, 30 patients with colorectal cancer liver metastases underwent HI-HPP with 200mg melphalan. Samples of the perfusate were taken for pharmacokinetic analysis. Patients were monitored for response, toxicity and survival.

Perfusion was aborted prematurely in 2 patients due to leakage. During melphalan administration in the hepatic inflow cannula a mean flow rate of 121.3 mL/min and mean pressure of 62.5 mm Hg was achieved. One patient died within 30 days after HI-HPP. Four patients developed veno-occlusive disease (VOD), while 2 patients showed signs of VOD. Twelve patients showed hepatic response, with a median duration of response of 11.5 months, according to WHO criteria.

Although HI-HPP results in high perfusate melphalan concentration levels, it is associated with a relatively high level of hepatotoxicity and a limited response rate. We believe the low flow and pressure rates found in this study can result in reduced drug penetration of the tumour and thus limited tumour response.

Introduction

Liver metastases are diagnosed in 10-25% of colorectal cancer patients at the time of resection of their primary tumour and eventually up to 70 % of patients with colorectal cancer develop liver metastases [1]. In approximately 30% of the patients the liver is the only site of metastatic disease [2, 3]. Hepatic resection is considered the treatment of choice for colorectal cancer liver metastases with 5-year survival rates ranging from 25-51%, while 5-year survival after systemic treatment alone remains <1%, emphasizing the importance of aggressive liver-directed treatment [4-6]. Unfortunately curative resection of liver metastases is only possible in less than 10 percent of patients due to the number, location or size of the metastases [4], warranting the necessity for other liver-directed therapies. Although 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 can offer the potential benefit of both aggressive local treatment and limited systemic toxicity. Several regional therapies have been developed including radiofrequency ablation, hepatic artery infusion (HAI) and isolated hepatic perfusion (IHP). In both HAI and IHP high drug concentrations can be achieved at the tumour site with relatively low systemic drug exposure. HAI is based on the principle that liver metastases derive most of their blood supply from the hepatic artery. As a result high drug concentrations can be achieved at the tumour site, while the liver parenchyma is relatively spared [13, 14]. The systemic exposure in HAI mainly depends on the rate of hepatic extraction and metabolization. IHP, on the other hand, involves complete vascular isolation of the liver, which allows the use of high dosages that would cause fatal complications if delivered systemically. Marinelli *et al*. showed that in a rat model bolus administration of the maximally tolerated doses of melphalan in HAI (6 mg kg-1) and IHP (12 mg kg-1) resulted in four times higher concentrations in both liver and tumour tissue of the IHP treated rats [15]. Furthermore, effective anti-tumour compounds which can not be administered systemically due to their toxicity, such as tumour necrosis factor alpha (TNF-α), can be used in IHP. At our institution a phase I/II trial was performed in 73 colorectal cancer patients with bolus administration high dose melphalan, achieving an overall response rate of 59%, with a median progression-free survival of 7.7 months and a median overall survival of 28.8 months, similar to the results at other institutions [16-19]. Pharmacokinetic analysis of these patients showed that the concentration of bolus administered melphalan rapidly declines in the first 5-10 minutes of circulation [20]. Theoretically, infusing melphalan directly into the hepatic artery over a certain period would lead to more selective tumour exposure and prolonged exposure of the tumour to high concentrations of melphalan, which can be expected to improve antitumour efficacy of IHP. Based on the above we developed a Hepatic artery Infusion, Hepatic artery-Portal vein perfusion (HI-HPP). In this report, we present the results of

30 colorectal cancer patients with irresectable liver metastases treated with isolated hepatic perfusion with a 20 minute infusion of melphalan.

Patients and methods

Patient Eligibility

Between December 2001 and December 2004, 30 patients with colorectal cancer confined to the liver were treated with HI-HPP with 200mg melphalan. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center and informed consent was obtained from all patients. All patients had measurable, irresectable colorectal metastases confined to the liver. Liver metastases were deemed irresectable based on number, size and localization. Standard staging studies were performed including CT scan of the chest and abdomen. Additional MRI or PET scans were performed if clinically indicated. Eligibility criteria included a WHO performance status of 0 or 1, leukocyte count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, maximum serum creatinine level 135 µmol/L, maximum bilirubin level 17 µmol/L and minimum albumin level 40 g/L. Exclusion criteria were age over 70 years, life expectancy of less than 4 months, more than 60 per cent hepatic replacement by tumour tissue as estimated from the preoperative abdominal CT scan, coagulation disorders and evidence of extrahepatic metastatic disease. The interval between resection of the primary colorectal tumour and perfusion had to be at least 6 weeks.

IHP technique

All patients were treated with HI-HPP, consisting of an extracorporeal venovenous bypass (see figure 1), as described previously [17]. Briefly, the liver was mobilized from the diaphragm through a transverse abdominal incision. The common hepatic artery (8-Fr 77008 one-piece pediatric arterial cannula; Medtronic, Minneapolis, Minnesota, USA) and the portal vein (12-Fr perfex perfusion catheter CH12; B. Braun Medical, Oss, The Netherlands) were cannulated and connected to a heart-lung machine which consisted of two independent roller pumps (model 10-30-00; Cobe/Stöckert, Munich, Germany). The inferior vena cava (IVC) was cross-clamped above the hepatic veins and cannulated proximal of the renal veins (Polystan 36 Fr, straight, A/S, Värlöse, Denmark) to allow undisturbed blood flow from the hepatic veins through the IVC towards the heart-lung machine. To isolate the hepatic circuit, tourniquets were secured around the hepatic artery, portal vein and IVC.

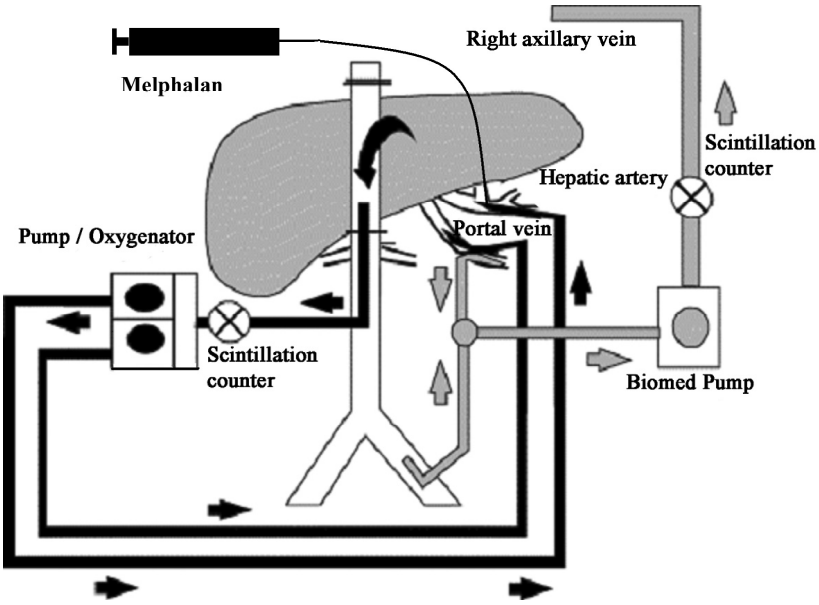

Figure 1. Isolated hepatic perfusion circuit with infusion of melphalan in the hepatic artery (HI-HPP).

For the extracorporeal venovenous bypass, the right femoral vein (22-Fr cannula DI-ITF022L; Edwards Lifesciences, Irvine, California, USA) and the portal vein (17-Fr perfex perfusion catheter CH17; B. Braun) (proximal to the tourniquet) were cannulated and connected to the right axillary vein (18-Fr 7326 perfusion cannula; Lifestream International, The Woodlands, Texas, USA). The venovenous bypass was supported by a centrifugal pump (Medtronic BIO-Medicus, Eden Prairie, Minnesota, USA) and primed with 700 mL 0.9 % saline. The perfusion medium consisted of intrahepatically trapped blood and 1250 mL Gelofusine® (Vifor Medical, Sempach, Switzerland) plus 2500 units heparin (Leo Pharma, Breda, The Netherlands) to yield a final volume of approximately 2 litres. Throughout the 1-h perfusion interval, the perfusate was kept at a temperature of 39·5 °C by a heat exchanger and oxygenated using an oxygenator (Cobe VPCML; Cobe Cardiovascular, Arvada, Colorado, USA) except for the last patient who was oxygenated using a different oxygenator (Dideco D901, SORIN group Italia, Mirandola, Italy). After perfusion, the liver was flushed for approximately 10 minutes with 3 liters Gelofusine®. All cannulas and clamps were removed, and the incisions were closed. To prevent possible postoperative cholecystitis, cholecystectomy was performed.

Melphalan

Melphalan 200mg (Alkeran®, GlaxoSmithKline, Zeist, The Netherlands) was first dissolved in 40 mL Wellcome Diluent (a 60/40 (v/v) mixture of proylene glycol containing 5.2%

(v/v) ethanol and 0·068 mol/l sodium citrate), which was subsequently diluted with 60 mL sterile saline. Melphalan was administered through 20 minute infusion using an infusionpump (Pilote Anesthesie; Fresenius, Brezins, France) connected to the hepatic artery line of the isolated hepatic circuit.

Leakage Detection

Leakage of perfusate into the systemic circuit was monitored by adding 10 MBq ^{99m}Tc-pertechnetate to the isolated circuit with subsequent measurement of the level of radioactivity in both the systemic and isolated circuit, as described previously [21, 22]. If no leakage was detected, melphalan was administered; however, if leakage exceeded 10% during the perfusion period, the procedure was immediately aborted and the liver flushed.

Postoperative Care

All patients received a daily subcutaneous dose of 480 µg granulocyte colony-stimulating factor (G-CSF) (Filgrastim/Neupogen®; Amgen, Breda, The Netherlands) starting the day after the operation until the nadir in leukocyte count was reached and the count had risen to more than 1.0×10^9/L. Patients were monitored in the intensive care unit for at least 1 day after IHP. Liver and renal function tests and full blood counts were carried out daily in the first week and henceforth as indicated by their respective levels. Antibiotics in a combination of cefuroxim and metronidazol were given to all patients for 5 days after IHP.

Toxicity

Systemic and regional toxicity were graded according to the National Cancer Institute Common Toxicicity Criteria version 2.0. Hepatic toxicities were considered melphalan related if elevations in liver function persisted beyond 7 days after perfusion, as previously suggested [18]. Nonhepatic toxicities were defined as all toxicities that are not reversed within 24 hours after perfusion.

Melphalan levels

Heparinized samples of four patients were taken from the perfusion medium at the inflow of the hepatic artery and at the outflow of the inferior caval vein, at 10 different time intervals (t=0, 5, 10, 15, 20, 25, 30, 40, 50, 60 minutes). Samples were stored at -80 °C until analysis. All samples were analyzed by a HPLC assay as previously described [23]. The

areas under the concentration-time curves (AUC) were calculated with the trapezoidal rule.

Response evaluation

Objective tumour response measurements were obtained by follow up CT scans of the liver and remaining abdomen at 3-month intervals after treatment and at 6-month interval after 1 year. Additional imaging was performed if clinically indicated. Both WHO and RECIST criteria were used to determine response rates. Hepatic response and overall response were measured separately, in view of the local nature of the treatment. According to the WHO criteria the size of all measurable lesions was determined, complete response was defined as disappearance of all known disease, partial response as a reduction in the sum of the product of maximal diameter x longest perpendicular diameter of all measurable metastases of ≥50%, stable disease as a reduction of <50% or an increase of <25% and progressive disease as an increase of ≥25% or the appearance of new intra- or extrahepatic lesions [24]. For the RECIST criteria lesions were only considered measurable if ≥10mm, complete response was defined as disappearance of all known disease, partial response as a reduction in the sum of maximal diameters of ≥30%, stable disease as a reduction of <30% or an increase of <20% and progressive disease as an increase of ≥20% or the appearance of new intra- or extrahepatic lesions [25]. Metastases were localized according to the Bismuth classification [26].

Serum carcinoembryonic antigen (CEA) levels were determined prior to treatment and at all follow-up visits.

Statistics

All data were analyzed using SPSS (version 12.0) software and presented as mean +/- SD or median followed by the range. All survival and disease progression analysis was performed by using Kaplan-Meier statistics.

Results

Patient and treatment characteristics

Demographics and tumour characteristics of the patient population are listed in Table 1. In total, 30 colorectal cancer patients with unresectable liver disease and no evidence of extrahepatic disease were treated with HI-HPP: 8 women and 22 men with a mean

Table 1 Patient and tumor characteristics

Characteristic	n
No. of patients	30
Sex ratio (F:M)	8 : 22
Mean age (years), [range]	55 [36-67]
Liver metastases synchronous : metachronous	 17 :13
Median no. of metastases [range]	9 [2-20]
Pretreatment CEA level Normal (≤3.0 µg/mL) Raised (>3.0 µg/mL) Unknown	 6 23 1
Chemotherapy prior to IHP, directed at: Primary tumor Liver metastases	 5 16

age of 56 years (range 37 to 69 years). Seventeen patients presented with synchronous liver metastases, whereas 13 had metachronous liver metastases. Median time between diagnosis of liver metastases and perfusion was 5 months (range 1.5 to 19.8 months). Nineteen patients received treatment directed at their liver metastases prior to enrolment in this trial, including systemic chemotherapy in 16 patients, chemoembolization in 2 patients and metastasectomy in 1 patient. Seven of the 16 patients who received chemotherapy prior to IHP showed progressive disease under therapy. Tumour burden varied among patients, the median number of metastatic lesions was 9, but ranged from 2 to more than 20 lesions. The lesions ranged in size as measured by greatest diameter from 2mm to 131mm with a mean diameter of 22mm. The estimated percentage of hepatic replacement ranged from 5% to 40% with a mean replacement of 14%. Carcinoembryonic antigen (CEA) levels were elevated (> 3.0 µg/mL) in 23 patients prior to perfusion.

Treatment parameters are shown in Table 2. All 30 patients underwent HI-HPP. In two patients the HI-HPP was prematurely aborted (after 25 and 30 minutes respectively), because the calculated maximum tolerated leakage for the entire procedure of 10% would be exceeded. Median operative time was 8.8 hours (range 7.0 to 12.8 hours) with a median blood and fluid loss of 4.0 L (range 1.3 to 14.0 L). Median hospital stay was 10 days (range 7 to 27 days). Mean flow rate in the hepatic artery during the 20-minute melphalan infusion was 121.3 mL/min (range 100.0 to 290.0 mL/min) and climbed to 270.7 mL/min (range 100.0 to 400.0 mL/min) after melphalan administration. Corresponding pressures in the hepatic artery during infusion ranged from 33.0 to 140.0 mm Hg (mean

Table 2 Isolated hepatic perfusion parameters HI-HPP

	HI-HPP during infusion (20min)	HI-HPP during perfusion (40min)
flow rate hepatic artery (mL/min)	121 ± 41	270 ± 95
flow rate portal vein (mL/min)	246 ± 56	253 ± 52
pressure hepatic artery (mm/Hg)	64 ± 32	93 ± 30
pressure portal vein (mm/Hg)	34 ± 8	35 ± 8
Mean % leakage during perfusion (range)	1.2 (0-7)	

Values are mean ± s.d.

63.5 mm Hg) rising to 40.0 to 160.0 mm Hg (mean 93.2 mm Hg) after melphalan administration. Actual leakage ranged between 0 and 7.0%.

Toxicity and complications

One patient died perioperatively as a result of a progressive liver failure. Major complications are listed in Table 3. Veno-occlusive disease occurred in 4 patients, while 2 other patients showed clear signs of portal hypertension not present prior to therapy, including oesophageal varices on post-perfusion imaging. One of these patients died 11 months after perfusion of massive hematemesis. Despite limited leakage and postoperative administration of G-CSF, 3 patients developed a grade 3-4 leukopenia. Regional toxicity data are presented in Table 4. Grade 4 hepatoxicity was present in 5 patients and consisted of elevated levels of bilirubin in 1 patient, elevated transaminases in 1 patient, elevated gammaglutamyl transpeptidase in 2 patients and both elevated gammaglutamyl transpeptidase and bilirubin in another patient. The hepatotoxicity was transient in most patients, although some elevation persisted in the patients with either VOD or portal hypertension.

Table 3 Number of patients with major complications

Major complications	HI-HPP
Toxic hepatitis	1
Bleeding requiring re-operation	1
VOD	4
Portal hypertension	2
Infection	2
Pulmonary embolism	1
Serious delirium	1

Table 4 Toxicity according to National Cancer Institute Common Toxicity Criteria (n=30)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte nadir	20	3	4	1	2
Bilirubin	13	6	6	3	2
Alkaline phosphatase	0	7	16	7	0
GGT	0	1	8	18	3
ALAT	2	10	11	6	1
ASAT	2	16	8	3	1

Melphalan pharmacokinetics

Figure 2 shows a typical example of a drug concentration-versus-time curve of HI-HPP. During the 20-minute infusion the melphalan concentration rapidly increases to remain at a constant high level (peak concentration of 93.2µg/mL) for approximately 18 minutes. The melphalan concentration gradually increases during the first 20 minutes as a result of recirculation. After the end of the infusion the melphalan concentration declines rapidly to approximately 30 µg/mL followed by a gradual elimination of melphalan.

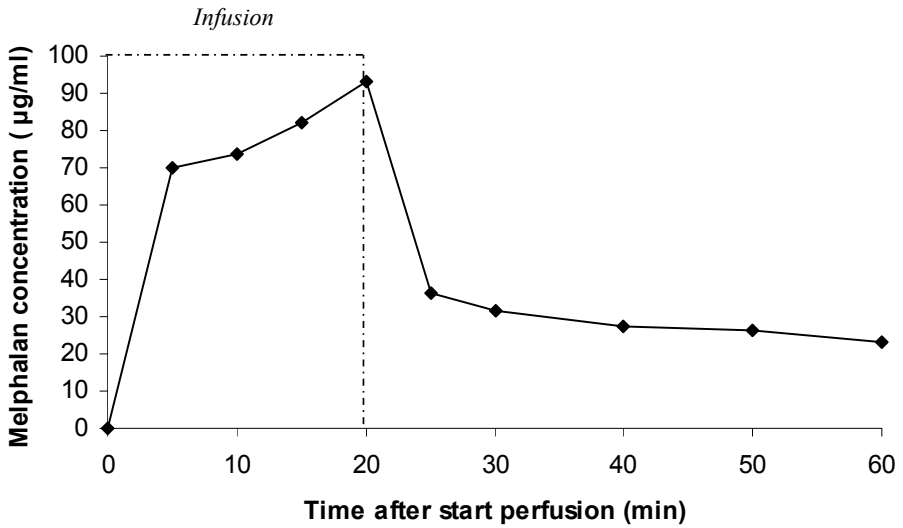

Figure 2. A typical example of a concentration-time curve of melphalan in perfusate during HI-HPP. A constant high level of melphalan is maintained for up to 20 minutes. The peak concentration of 93.2µg/mL is achieved after 20 minutes. The area under the concentration-versus-time curve (AUC) was calculated for the entire procedure: 2841,6 µg x min/mL.

Tumour response and patient survival

The median follow up time was 44.6 months (range 18.5 to 55.3 months). Nineteen patients of the 23 patients with previously elevated CEA levels experienced a normalization or reduction of 50% or more 1 to 3 months after perfusion with a median duration of response of 4.4 months (range 1.5 to 18.5 months).

Hepatic and overall treatment responses were measured by comparing follow-up CT scans to the pre-treatment scan, according to both WHO and RECIST criteria. As 1 patient died postoperatively, 29 patients were eligible for measurement of tumour response. Twelve patients showed hepatic response according to WHO criteria, as compared to 15 patients according to the RECIST criteria, with no complete responses. Nine patients showed stable disease according to the WHO criteria, while 6 patients showed stable disease according to the RECIST criteria. Eight patients immediately showed progressive disease for both criteria on the first follow up CT scan. The median duration of hepatic response (partial remission) was 11.5 months (range 4.4 to 48.6 months) for WHO criteria and 9.1 months (range 5.2 to 48.6 months) for RECIST criteria. In 3 patients hepatic progression has not occurred at respectively 18.5, 36.3 and 48.6 months. Two patients with hepatic stable disease and 1 patient with hepatic partial remission, according to WHO criteria, showed extrahepatic disease on the first follow up scan, resulting in an overall response in 11 patients. For the RECIST criteria, 2 patients with hepatic partial remissions and 1 patient with stable disease, showed extrahepatic disease on the first follow up scan, resulting in an overall response 13 patients. The time to overall progression (hepatic and/or extrahepatic) and overall survival curves are shown in figure 3. Progression occurred in 27 of the 29 patients, 15 of these patients showed hepatic progression, 5 patients extrahepatic and 7 patients had both hepatic and extrahepatic progression. In retrospect, two patients with extrahepatic progression had extrahepatic disease preoperatively. Median time to progression (hepatic and/or extrahepatic) was 6.6 months (range 1.4 to 43.7 months) for both WHO and RECIST criteria. The median overall survival after perfusion was 16. 9 months (range 0.9 to 52.5 months) with 7 patients still alive. The median overall survival after diagnosis of liver metastases was 27.8 months (range 5.2 to 64.6 months). Twenty-one patients received therapy after perfusion, including adjuvant systemic treatment in 1 patient, systemic treatment for metastatic disease in 19 patients and metastasectomy of pulmonary metastases in 1 patient.

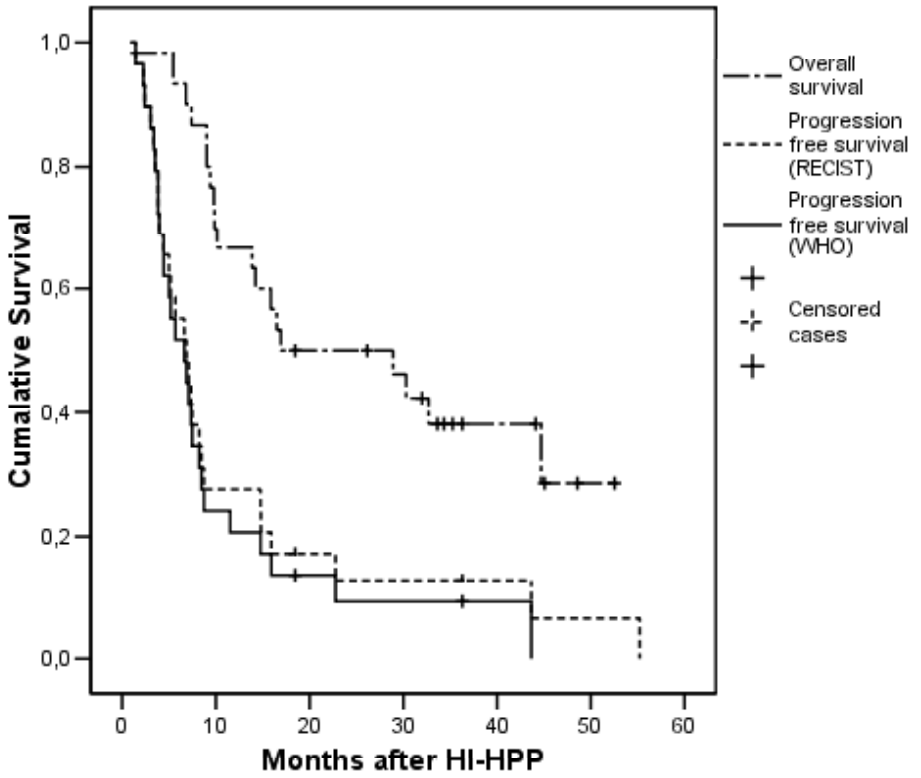

Figure 3. Overall and progression free (hepatic and/or extrahepatic) survival curves for WHO and RECIST criteria after HI-HPP. For the survival analysis all 30 patients were included. For the progression free survival (both RECIST and WHO) 29 patients were evaluable, as 1 patient died perioperatively. At a median follow up of 44.6 months 11 patients remain alive and progression has not occurred in 2 patients.

Discussion

Isolated hepatic perfusion is based on the principle of high regional drug exposure with limited systemic toxicity. By means of a 20 minute hepatic artery infusion of 200mg melphalan followed by a 40 minutes perfusion, we wanted to achieve a selective tumour exposure to an increased concentration of melphalan, as compared to conventional perfusion circuits with a drug bolus administration. Previous studies have shown a rapid decline of melphalan in the perfusate, as measured 5 tot 15 minutes after bolus administration with mean peak concentrations ranging between 18.1 to 38.6 µg/mL [17, 27]. This study in 30 colorectal cancer patients demonstrated that HI-HPP with 200mg melphalan results in high local concentrations of melphalan, with a maximum peak concentration of 93.2µg/mL, for up to 20 minutes. However, toxicity was considerable and increased selective drug exposure did not improve response rates and survival compared to previous studies [18, 27].

Veno-occlusive disease (VOD) was present in 4 patients, while 2 other patients developed portal hypertension, possibly as a result of VOD. Several other studies have reported cases of VOD after IHP, but only incidentally [18, 27-29]. A phase II trial at our institution with bolus administration of the same dose of melphalan resulted in VOD, only in 4 out of 71 patients [16]. VOD is thought to result from accumulative exposure to chemotherapeutic agents, but the patients in this study were exposed to similar amounts of chemotherapy as compared to previous studies [30]. A similar trend was observed in grade 4 biliairy toxicity, which occurred in as many as 5 out of 30 patients and 1 patient died of progressive liver failure. The toxicity data from this clinical study are in line with the results of an animal study, previously performed at our institution. In an *in vivo* rat model for liver tumours we studied the difference in tumour and liver uptake as well as an antitumour effect and hepatotoxicity of 5 and 20 minute arterial infusion of a fixed melphalan dose [31]. No difference in melphalan content of tumour/liver tissue and tumour response was found between the two infusion schedules. Hepatoxicity, on the other hand, was strongly affected by infusion duration and hence melphalan concentration. Severe cholangiofibrosis occurred in 8 of 9 rats treated with 5 minute infusion, but in only 1 of 8 rats treated with a 20 minute infusion, hence we considered a 20 minute infusion in humans to be safe. Liver toxicity appears to have a steep concentration-toxicity curve, independent of the total dose of melphalan

This study shows a hepatic response rate of 40% (according to WHO criteria) with a median duration of hepatic response of 11.5 months. Bartlett *et al* reported the results of IHP with 1.5mg/kg melphalan in 51 colorectal cancer and 1mg TNF-α in a subset of 32 patients, with a local response rate of 76% with a median duration of 10.5 months [27], similar to our own experience [16]. Contrary to toxicity, response seems to be determined by the total dose of melphalan, not by melphalan concentration levels. Although this might explain the absence of improved response it does not explain the actual reduction in response.

One of the major drawbacks of HI-HPP is the low pressure and flow in the perfusion circuit. In a regular IHP setup mean flow rates ranging between 502 to 844 mL/min and associated pressures of 159 to 164 mm Hg can be achieved [17, 18]. In this study we achieved a mean flow rate of 121.3 mL/min (mean pressure 63.5 mm Hg) during infusion and 270.0 mL/min (mean pressure 93.17 mm Hg) during perfusion. Efficacy of chemotherapeutic agents in the treatment of solid tumours is, on top of the development of drug resistance of cancer cells, dependent upon the drug delivery and penetration within the tumour. Impaired transport of cytostatic agents into the tumour has been attributed to changes in the extracellular matrix, deformed tumour vasculature and pathologically increased interstitial fluid pressure (IFP) [32-34]. Less *et al* measured the IFP in colorectal

liver metastases and found a mean IFP of 10 times above the IFP of normal liver tissue [35]. In animal models, lowering of the IFP, through for example prostaglandin E1 (PGE_1), resulted in an improved drug penetration [36, 37]. It has even been argued that the increase in disease-free survival seen in phase III trials of conventional chemotherapy combined with a monoclonal antibody against vascular endothelial growth factor, is partly attributable to the IFP lowering effect of bevacizumab [38]. It seems likely that a reduction of more than 50% in flow rate and pressure during perfusion would lead to decreased melphalan penetration and hence tumour response. Healthy liver and biliary tract tissue, on the other hand, with a normal IFP is penetrated by the melphalan, resulting in the previously described toxicity. Ideally, decreased penetration of melphalan in the tumour is determined by detecting melphalan levels in liver biopsies taken during and after perfusion. However, in our experience this would increase morbidity considerably due to haemorrhage as a result of heparinization.

The current IHP technique is an expensive, demanding and technically difficult procedure with considerable morbidity and mortality, which is not amenable to repetition, therefore attention has shifted to the development of a less complicated percutaneous technique. Several phase I studies, using a variety of percutaneous approaches with variable results, have been published so far [39, 40]. Savier *et al* reported treatment of 4 patients with 3 successive courses of chemotherapy by IHP, in which the first course was given at laparotomy and the next two courses percutaneously [29]. Percutaneous isolation of the liver was achieved by placing an occlusion catheter in the portal vein according to the transhepatic Seldinger technique and a double-balloon catheter in the retrohepatic caval vein through the saphenous vein. Finally, the HA was occluded by traction of a silicon-lined nylon thread that was positioned around the common hepatic artery during previous laparotomy. Although isolated perfusion was achieved by this method, considerable leakage to the systemic circulation occurred during IHP and the flow rate was limited to 200-300mL/min. Phase II trials need to be performed for a sensible determination of response rates. Nevertheless, in view of our findings response rates could be disappointing, considering the limited flow rate due to catheter size in a percutaneous technique.

In summary, we have demonstrated that HI-HPP with 200mg melphalan results in high perfusate melphalan concentration levels, but is associated with a relatively high level of hepatotoxicity and a limited response rate. We believe that the low flow rates and pressures found in this study can result in reduced drug penetration of the tumour and thus limited tumour response. This could prove to be an important consideration in the development of future percutaneaous isolated hepatic perfusion techniques. We will abandon HI-HPP and are currently focusing on the introduction of new tumour-specific

agents in an isolated hepatic perfusion system capable of producing adequate flow and pressure rates.

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