

Isolated Hepatic Perfusion with 200 mg Melphalan for Advanced Noncolorectal Liver Metastases

Liselot B. J. van Iersel, MD,¹ Ellen J. Hoekman,¹ Hans Gelderblom, MD, PhD,¹ Alexander L. Vahrmeijer, MD, PhD,² Els L. van Persijn van Meerten, MD,³ Fred G. J. Tijl,⁴ Henk H. Hartgrink, MD, PhD,² Peter J. K. Kuppen, PhD,² Johan W. R. Nortier, MD, PhD,¹ Rob A. E. M. Tollenaar, MD, PhD,² and Cornelis J. H. van de Velde, MD, PhD²

¹Department of Clinical Oncology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

²Department of Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

³Department of Radiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

⁴Extra Corporal Circulation, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Purpose: The liver is one of the most common sites for metastatic solid tumors. If the liver is the only site of metastatic disease, regional treatment options can offer the benefit of high local exposure with limited systemic toxicity, especially for patients without (further) systemic treatment options. We report the results of our experience with isolated hepatic perfusion (IHP) in patients with isolated liver metastases from a variety of primary tumors.

Patients and Methods: Nineteen patients with isolated unresectable liver metastases from a variety of tumors (13 uveal melanomas, 2 neuroendocrine carcinomas, 2 gastrointestinal stromal tumors, 1 hepatocellular carcinoma, and 1 high-grade sarcoma) were treated with a 60-min IHP using 200 mg melphalan. Patients were monitored for toxicity, response according to response evaluation criteria in solid tumors (RECIST) criteria, and survival.

Results: One melanoma patient was not perfused due to insufficient isolation of the liver. There was no treatment-related mortality. Reversible grade 3 or 4 hepatotoxicity occurred in 10 (56%) patients, while veno-occlusive disease occurred in 4 (22%) patients. Of the 12 uveal melanoma patients who were perfused, 4 (33%) patients had a partial hepatic response, 6 (50%) patients had stable hepatic disease, and 2 (17%) patients were immediately progressive. Median disease-free survival was 6.6 months with a median overall survival of 10.0 months. Fifty percent of other primary tumors showed at least partial remission, including one complete remission in a high-grade sarcoma patient.

Conclusion: IHP with melphalan shows activity in patients with liver metastases from a variety of primary tumors, but other or additional drugs may improve therapeutic outcome.

Key Words: Isolated hepatic perfusion—Liver metastases—Melphalan—Uveal melanoma.

The liver is one of the most common sites for metastatic disease and is involved in approximately 40% of adult patients with primary extrahepatic malignant disease who undergo an autopsy. The most

common origin of hepatic metastasis confined to the liver is colorectal cancer. Neuroendocrine tumors and uveal melanomas, although rare, are the second most common origin of metastases confined to the liver.¹ Gastrointestinal neuroendocrine tumors are predominantly carcinoids (55%), consisting mainly of midgut carcinoids (50–70%) which have the greatest potential for metastasizing to the liver.^{2,3} Uveal melanoma is the most common primary intraocular tumor in

Published online May 10, 2008.

Address correspondence and reprint requests to: Liselot B. J. van Iersel, MD; E-mail: l.b.j.van_iersel@lumc.nl

Published by Springer Science+Business Media, LLC © 2008 The Society of Surgical Oncology, Inc.

adults, with an incidence of 5–7 per 1 million per year in the Western population.⁴ Up to nearly 50% of patients will ultimately develop metastases, of which more than 60% is confined to the liver.^{5,6} Other primary tumors that may initially metastasize exclusively to the liver include gastrointestinal stromal tumors (GIST) and even more rarely renal cell carcinoma, Wilms' tumor, and breast cancer. Although liver metastases from primary tumors such as cancers of the lung, breast, stomach, and cutaneous melanoma may occur more frequently, dissemination usually occurs simultaneously to other visceral locations.

If the metastases are confined to the liver several locoregional treatment options can be considered, including partial hepatic resection, radiofrequency ablation (RFA), administration of chemotherapy by hepatic artery infusion (HAI), and isolated hepatic perfusion (IHP) with high-dose chemotherapy. Curative resection is possible in only a small fraction of patients due to the number, location or size of the metastases.^{7,8} RFA is mainly suitable for patients with a limited number of liver metastases that are not located near any large vascular structures and less than 5 cm in diameter.^{9–11} Compared to HAI, IHP offers the benefits of high local drug exposure with limited systemic toxicity.¹² Various studies have been published on IHP for colorectal liver metastases,^{13–15} but only a few studies have been reported on IHP for liver metastases from other primary tumors.^{16–20}

In this study we present our experience with 19 patients with a variety of primary tumors other than colorectal cancer, including uveal melanoma, high-grade sarcoma, and GIST, who underwent IHP at the Leiden University Medical Center.

PATIENTS AND METHODS

Patient Eligibility

Between May 1995 and May 2006, 19 patients with liver metastases of uveal melanoma (13), GIST (2), hepatocellular carcinoma (1), neuroendocrine carcinoma (2), and high-grade sarcoma (1) were treated with IHP with 200 mg melphalan according to a study protocol approved by the local ethics committee. Using the same melphalan dose, during the accrual period, IHP was performed in 105 patients with colorectal cancer hepatic metastases (13, 15 and van Iersel, *Annals of Oncology*, in press 2008), indicating feasibility and our experience with this procedure. Informed consent was obtained from all patients. The tumour response of eight uveal melanoma patients

has been previously reported.²¹ 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 $\mu\text{mol/L}$, maximum bilirubin level 17 $\mu\text{mol/L}$, and minimum albumin level 40 g/L. Exclusion criteria were age over 70 years, life expectancy of less than 4 months, more than 60% hepatic replacement by tumor tissue as estimated from the preoperative abdominal computed tomography (CT) scan, coagulation disorders, and evidence of extrahepatic metastatic disease. All patients had a preoperative chest and abdominal computer tomography (CT), full blood count, liver function tests, and determination of lactate dehydrogenase, albumin and creatinine, and electrolytes.

IHP Technique

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). For 14 patients both the hepatic artery and portal vein were used for inflow of melphalan in the isolated circuit, because this technique was used in our previously reported phase I¹⁵ and II¹³ study. Although there is no established benefit from drug delivery by using the portal vein during our IHP procedure oxygenated blood is perfused through the portal vein and this may possibly prevent hypoxia-induced damage to the liver. Moreover, by using our technique, the MTD of melphalan is much higher than reported by other groups who only used the hepatic artery for drug delivery. For five patients we used hepatic artery infusion at reduced flow as reported in a recent publication.²² 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, Värlose, 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.

For the extracorporeal venovenous bypass, the right femoral vein (22-Fr cannula DIITF022L; Edwards Lifesciences, Irvine, California, USA) and the portal vein (17-Fr perfex perfusion catheter CH17; B. Braun) (proximal to the tourniquet) were cannu-

lated 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 liters. 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 three patients who were oxygenated using a different oxygenator (Dideco D901, SORIN group Italia, Mirandola, Italy). After perfusion, the liver was flushed for approximately 10 min with 3 liters Gelofusine®. All cannula and clamps were removed, and the incisions were closed. To prevent possible melphalan induced 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 as a bolus in the isolated hepatic circuit^{13,15} and in the last five patients through 20-min infusion using an infusion pump (Pilote Anesthésie; Fresenius, Brezins, France) connected to the hepatic artery line of the isolated hepatic circuit.²²

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.^{23,24} If no leakage was detected, melphalan was administered: If leakage was calculated to exceed 10% during the perfusion period, the procedure was stopped and the liver was flushed just before this level was reached.

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 $1.0 \times 10^9/L$. 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 data were collected prospectively and graded retrospectively according to the National Cancer Institute Common Toxicity Criteria version 2.0. Hepatic toxicities were considered melphalan related if elevations in liver function persisted beyond 7 days after perfusion, as previously suggested.²⁵

Response Evaluation

Objective tumor 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 intervals after 1 year. Additional imaging was performed if clinically indicated. All Ct scans were revised using RECIST criteria to determine response rates. For the response evaluation criteria in solid tumors (RECIST) criteria lesions were only considered measurable if ≥ 10 mm, complete response was defined as disappearance of all known disease, partial response as a reduction in the sum of maximal diameters of $\geq 30\%$, stable disease as a reduction of $<30\%$ or an increase of $<20\%$ and progressive disease as an increase of $\geq 20\%$ or the appearance of new intra- or extrahepatic lesions.²⁶ Disease-free survival was calculated from the date of IHP until the date of local and/or systemic recurrence or death from any cause.

Statistical Analysis

All data were analyzed with SPSS statistical software (version 14.0. for Windows, SPSS, Chicago, IL, USA). The analyses of time to progression and survival were carried out by the Kaplan–Meier method. If patients died before hepatic progression had occurred, date of death was taken as date of progression.

TABLE 1. Patient and tumor characteristics

Characteristic	n (%)
No. of patients	19
Sex	
Male	6 (32)
Female	13 (68)
Primary tumor	
Uveal melanoma	13
Neuroendocrine tumor	2
GIST	2
HCC	1
High-grade sarcoma	1
Median age in years (range)	51.4 (29–69)
Liver metastases	
Synchronous	3 (15.8)
Metachronous	16 (84.2)
Mean hepatic replacement, % (range)	23.4 (5–50)
Median no. of metastases (range)	12 (1 to >100)
Median time of diagnoses of hepatic metastases to IHP	2 (0.7–13.7)

RESULTS

Patient and Treatment Characteristics

Patient and tumor characteristics are listed in Table 1. A total of 19 patients with unresectable liver disease and no evidence of extrahepatic disease were considered eligible for IHP. Thirteen patients presented with uveal melanoma as primary tumor, two patients with a GIST, two patients with neuroendocrine carcinoma, one patient with hepatocellular carcinoma (HCC), and one patient with high-grade sarcoma. Sixteen patients presented with metachronous liver metastases. The mean number of liver metastases was 24 (range 1 to >100) with a mean estimated hepatic replacement of 23% (range 5–50%). Mean time from diagnosis of liver metastases to IHP was 4.3 months (range 0.7–13.7 months). Five patients received chemotherapy prior to IHP.

All 19 patients underwent IHP, but in 1 patient the procedure failed due to failure to obtain sufficient isolation of the liver and this patient was excluded from further analyses. Treatment characteristics of the remaining 18 patients are similar to our previous experience with colorectal cancer patients and are listed in Table 2.¹³ Median operating time was 8 hours 7 min, with a median blood loss of 3.5 liters (range 1–8 liters). Median hospital stay was 11 days (range 7–25 days). Median follow-up was 74 months (range 4–137 months).

Toxicity and Complications

Ten patients experienced grade 3 or 4 toxicity of one or more liver enzymes 1 week after IHP, as

TABLE 2. Treatment parameters

Parameter	Mean \pm SD
Flow rate hepatic artery (mL/min)	290.4 \pm 100
Flow rate portal vein (mL/min)	230.8 \pm 97.3
Pressure hepatic artery (mm/Hg)	118.1 \pm 24.6
Pressure portal vein (mm/Hg)	36.5 \pm 9.3
Percentage leakage during perfusion	2.6 \pm 4.9
Blood loss (L)	3.9 \pm 2
Operative time (h)	8.9 \pm 1.3
Hospital stay (days)	12.7 \pm 4.8

shown in Table 3. This hepatotoxicity was transient and only persisted in the four patients that developed veno-occlusive disease (VOD). Major complications occurred in five patients; as previously mentioned, four patients developed signs of VOD and one other patient experienced a lung embolism. Neutropenia was rare and no neutropenic infections occurred. Given the low leakage rate G-CSF, which was common practice since early development of this procedure in phase I, is deemed unnecessary in future patients. All patients left the hospital within 4 weeks.

Tumor Response, and Progression-Free and Overall Survival

The patients with uveal melanoma and the patients with liver metastases from other primary tumors were analyzed separately. The details on tumor responses, progression-free survival and overall survival details of the six patients with primary tumors other than uveal melanoma are given in Table 4. The high-grade sarcoma patient had a complete response for 27.1 months while one neuroendocrine tumor patient had a partial response for 33.4 months and was still alive at the end of follow-up.

Of the 12 uveal melanoma patients, 4 (33%) patients had a partial hepatic response, 6 (50%) patients had prolonged stable hepatic disease, and 2 (17%) patients were immediately progressive. Progressive disease occurred in all patients during follow-up. Six (50%) patients had hepatic progression, three (25%) had extrahepatic progression, and three (25%) were both hepatic and extrahepatic progressive. Progression-free and overall survival curves for uveal melanoma patients are shown in Fig. 1. The median time to hepatic progression was 8.2 months (range 1.7–17.1 months), while median time to overall progression after IHP was 6.6 months (range 1.7–17.1 months). All but one patient died during follow-up. The median overall survival after IHP was 10 months (range 4.8–47.6 months), with median

TABLE 3. Toxicity according to National Cancer Institute Common Toxicity Criteria version 2.0 ($n = 18$)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte nadir	63.2% (12)	10.5% (2)	5.3% (1)	5.3% (1)	10.5% (2)
Bilirubin	23.3% (5)	21.1% (4)	36.8% (7)	0% (0)	10.5% (2)
Alkaline phosphatase	5.3% (1)	42.1% (8)	21.1% (4)	26.3% (5)	0% (0)
ALAT	15.8% (3)	26.3% (5)	26.3% (5)	21.1% (4)	5.3% (1)
ASAT	5.3% (1)	42.1% (8)	21.1% (4)	21.1% (4)	5.3% (2)

Aspartate transaminase, ASAT; Alanine transaminase, ALAT

TABLE 4. Treatment results of IHP with 200 mg melphalan in patients with isolated liver metastases of primary tumors other than uveal melanoma

Patient	Primary tumor	Hepatic response	Location progression	Time to progression (months)	Overall survival after IHP (months)	Survival after diagnosis of liver metastases (months)
1	Neuroendocrine tumor	Stable disease	Extrahepatic	5.9	8.9	18
2	Neuroendocrine tumor (carcinoid)	Partial remission	Extrahepatic	33.4	89.4 ^a	95.3 ^a
3	GIST	Stable disease	Extrahepatic	8	36.2	36.9
4	GIST	Stable disease	Hepatic	13	22	23.8
5	HCC	Partial remission	Hepatic	5.9	14.4	26.8
6	High-grade sarcoma	Complete remission	Both	27.1	50.2	52

^a Patient was still alive at the end of follow-up. Data is censored at the end of follow-up.

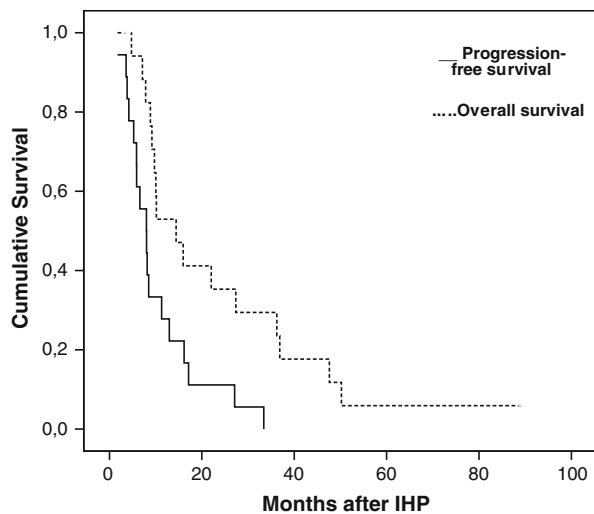


FIG. 1. Overall and progression-free survival curves for uveal melanoma patients. Of the 13 uveal melanoma patients, 12 patients were treated with IHP and included in the progression-free and overall survival analysis.

overall survival from diagnosis of liver metastasis of 12.2 months (range 8.7–49.6 months).

DISCUSSION

This study shows that IHP with 200mg melphalan shows activity in patients with liver metastases of primary tumors other than colorectal cancer. Transient grade 3 or 4 hepatotoxicity was observed in 56%

of patients, similar to the results of previous studies.^{19,27} The incidence of VOD (4/18) was relatively high compared to the results in colorectal cancer patients. VOD is thought to result from cumulative exposure to chemotherapeutic agents, but only five patients in this study received chemotherapy prior to IHP and none of them developed VOD.²⁸ The patients with VOD showed similar characteristics as compared to the patients without VOD, except for the fact that the incidence of VOD was higher (2/5) in the patients treated with hepatic artery infusion at reduced flow, a technique that was recently abandoned by us because of limited response rates and hepatotoxicity. This leaves 3 VODs out of 13 patients treated with melphalan through hepatic artery and portal vein inflow, which is considered acceptable toxicity. Of note, 5% underwent a major laparotomy, but could not be perfused: this was due to extrahepatic disease that was not observed on CT scanning. In order to reduce the incidence of unexpected extrahepatic disease on laparotomy, optimal staging with positron emission tomography (PET) scanning is being introduced for future patients. Response rates, disease-free and overall survival remain difficult to interpret due to small numbers and should be evaluated in view of the lack of other treatment options in patients with the tumors that were included in this study.

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.^{29,30} Results with immunotherapy, as for example interferon- α and interleukin-2, are equally disappointing with no or only minor responses.^{31,32} Peters et al. reported the use of HAI with fotemustine, an alkylating agent, in 101 uveal melanoma patients with liver metastases.³³ Fotemustine was infused in the hepatic artery for a 4-week induction period followed by a maintenance treatment every 3 weeks until disease progression. A median of eight infusions per patient were delivered. Catheter related complications occurred in 23% of patients. The overall response rate was 36%, with median overall survival of 15 months and 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. The difference could be explained by a difference in hepatic tumor load, but numbers estimating the tumor burden are not reported. The improved survival could also be attributed to the combination with debulking surgery in 38 patients undergoing HAI with fotemustine.

Alexander et al. reported the results of IHP with 1.5 mg/kg melphalan in 29 uveal melanoma patients. Hepatic response rate was 62% with progression-free survival of 8 months and 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 median time to progression of 6.6 months and overall survival of 10 months, similar to the results of Alexander et al. Although these results may seem disappointing as compared to IHP in other primary tumors, there is a survival benefit compared to a median survival of 2 months in uveal melanoma patients with liver metastases without antitumor treatment.³⁴ Moreover, currently we have no accepted alternative treatment options for uveal melanoma patients with unresectable isolated liver metastases.

Treatment of neuroendocrine liver metastases is aimed at improvement of the hormonal symptoms through reduction of tumor burden. Results of systemically administered agents have been disappointing in neuroendocrine cancer metastases with response rates around 6–40% for cytostatic drugs and 11% for interferon- α .^{35–38} Symptomatic improvement can be achieved in up to 70% of patients with somatostatin analogs such as octreotide, but objective tumor response occurs in less than 10% and drug resistance can develop in 3–12 months.^{39–42} Recently attention has shifted to the development of radiolabeled somatostatin

analogs. Valkema et al. reported the response after peptide receptor radionuclide therapy with [90Y-DOTA0, Tyr3] octreotide in 56 patients with advanced neuroendocrine tumors.⁴³ Overall, 58% of patients experienced improvement of symptoms, the median progression free survival was 29 months with a median overall survival of nearly 37 months. Several studies have been reported on the use of RFA for neuroendocrine liver metastases.^{44–46} In the largest published study the laparoscopic ablation of 234 hepatic lesions in 34 patients is reported.⁴⁷ Symptoms were relieved in 95% of the patients, with significant or complete symptom control in 80% of them for a mean duration of 10 months. New liver metastases developed in 28% of these patients, new extrahepatic disease in 25%, and local liver recurrence in 13%, at a mean follow-up of 1.6 years. Grover et al. reported an overall response rate of 50% with IHP in 13 neuroendocrine tumors with a median progression free survival of 7 months.⁴⁸ Although we treated only two patients with neuroendocrine tumors, one patient with a carcinoid showed a partial response for 33.4 months. In neuroendocrine carcinoid tumors caution should be taken to block hormone secretion, because systemic complications have been reported during RFA of carcinoids.⁴⁹

Imatinib has become the standard first-line systemic treatment for advanced GIST. GISTs have characteristic gain-of-function mutations in the KIT oncogene that results in overexpression of the KIT-protein (CD117).⁵⁰ Imatinib is a potent, specific KIT/PDGFR-small molecule tyrosine kinase inhibitor with a patient benefit rate (prolonged stable disease and response) of up to 90% and median progression-free survival of 2.5–3 years.^{51,52} Second-line treatment with sunitinib, an oral multitargeted receptor tyrosine kinase inhibitor, can add a median of 8 months in about 60% of patients.⁵³ Before the imatinib/sunitinib era no systemic treatment options existed for metastatic GIST. Hepatic arterial chemoembolization was one of the options for patients with hepatic metastasis derived from GIST resulting in a mean survival of 9.5–11.4 months.^{54,55} The addition of RFA to transcatheter arterial chemoembolization could increase survival to up to 25 months.⁵⁶ To our knowledge there have been no reports published on IHP for GIST. In our study two patients with GIST were included and showed stable disease with disease-free survival of 8 and 13 months, respectively, and overall survival of 36.2 and 22 months, respectively. Both patients were treated prior to the imatinib/sunitinib era. The aforementioned local treatment options, including IHP, can

thus be considered in patients refractory to imatinib and sunitinib with progressive liver lesions without further extrahepatic progression.

In recent studies with IHP, melphalan with or without TNF- α , has been the only chemotherapeutic agent used. Melphalan is an alkylating agent that is mainly used in the systemic treatment for multiple myeloma, isolated limb, lung, and liver perfusion. Little is known about the effectiveness of systemic melphalan treatment in the tumors described above. If IHP is considered as serious treatment option for patients with a variety of primary tumors other tumor-specific agents need to be studied to improve tumor response. Ideally, tumor-specific IHP agents should be developed. A wide range of agents is possible because, for example, IHP offers the additional advantage that, as long as agents are specific to the tissue of origin of the primary tumor, they do not have to differentiate between malignant and healthy tissue due to the local exposure in the liver.

In conclusion, IHP appears to be feasible in patients with liver metastases from a variety of primary tumors. To improve responses in IHP, the role of new agents tailored to specific tumor types needs to be assessed.

OPEN ACCESS

This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

REFERENCES

- Sutcliffe R, Maguire D, Ramage J, et al. Management of neuroendocrine liver metastases. *Am J Surg* 2004; 187:39–46.
- Shebani KO, Souba WW, Finkelstein DM, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. *Ann Surg* 1999; 229:815–21.
- Moertel CG, Sauer WG, Dockerty MB, et al. Life history of the carcinoid tumor of the small intestine. *Cancer* 1961; 14:901–12.
- Egan KM, Seddon JM, Glynn RJ, et al. Epidemiologic aspects of uveal melanoma. *Surv Ophthalmol* 1988; 32:239–51.
- Rajpal S, Moore R, Karakousis CP. Survival in metastatic ocular melanoma. *Cancer* 1983; 52:334–6.
- Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol* 2001; 119:670–6.
- Ihse I, Persson B, Tibblin S. Neuroendocrine metastases of the liver. *World J Surg* 1995; 19:76–82.
- Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. *World J Surg* 1995; 19:59–71.
- Solbiati L, Livraghi T, Goldberg SN, et al. Percutaneous radiofrequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. *Radiology* 2001; 221: 159–66.
- Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. *J Clin Oncol* 2005; 23: 1358–64.
- Sutherland LM, Williams JA, Padbury RT, et al. Radiofrequency ablation of liver tumors: a systematic review. *Arch Surg* 2006; 141:181–90.
- Marinelli A, van de Velde CJ, Kuppen PJ, et al. A comparative study of isolated liver perfusion versus hepatic artery infusion with mitomycin C in rats. *Br J Cancer* 1990; 62:891–6.
- Rothbarth J, Pijl ME, Vahrmeijer AL, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of colorectal metastasis confined to the liver. *Br J Surg* 2003; 90:1391–7.
- Alexander HR, Libutti SK, Bartlett DL, et al. A phase I–II study of isolated hepatic perfusion using melphalan with or without tumor necrosis factor for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2000; 6:3062–70.
- Vahrmeijer AL, van Dierendonck JH, Keizer HJ, et al. Increased local cytostatic drug exposure by isolated hepatic perfusion: a phase I clinical and pharmacologic evaluation of treatment with high dose melphalan in patients with colorectal cancer confined to the liver. *Br J Cancer* 2000; 82:1539–46.
- Noter SL, Rothbarth J, Pijl ME, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of uveal melanoma metastases confined to the liver. *Melanoma Res* 2004; 14:67–72.
- Grover AC, Libutti SK, Pingpank JF, et al. Isolated hepatic perfusion for the treatment of patients with advanced liver metastases from pancreatic and gastrointestinal neuroendocrine neoplasms. *Surgery* 2004; 136:1176–82.
- Feldman ED, Wu PC, Beresneva T, et al. Treatment of patients with unresectable primary hepatic malignancies using hyperthermic isolated hepatic perfusion. *J Gastrointest Surg* 2004; 8:200–7.
- Alexander HR Jr, Libutti SK, Pingpank JF, et al. Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2003; 9:6343–9.
- Alexander HR, Libutti SK, Bartlett DL, et al. A phase I–II study of isolated hepatic perfusion using melphalan with or without tumor necrosis factor for patients with ocular melanoma metastatic to liver. *Clin Cancer Res* 2000; 6:3062–70.
- Noter SL, Rothbarth J, Pijl ME, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of uveal melanoma metastases confined to the liver. *Melanoma Res* 2004; 14:67–72.
- van Iersel LB, Verlaan MR, Vahrmeijer AL, et al. 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. *Eur J Surg Oncol* 2007; 33:874–81.
- Marinelli A, de Brauw LM, Beerman H, et al. Isolated liver perfusion with mitomycin C in the treatment of colorectal cancer metastases confined to the liver. *Jpn J Clin Oncol* 1996; 26:341–50.
- Runia RD, de Brauw LM, Kothuis BJ, et al. Continuous measurement of leakage during isolated liver perfusion with a radiotracer. *Int J Rad Appl Instrum B* 1987; 14:113–8.
- Alexander HR Jr, Bartlett DL, Libutti SK, et al. Isolated hepatic perfusion with tumor necrosis factor and melphalan for unresectable cancers confined to the liver. *J Clin Oncol* 1998; 16:1479–89.
- Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of

- Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205–16.
27. Grover AC, Libutti SK, Pingpank JF, et al. Isolated hepatic perfusion for the treatment of patients with advanced liver metastases from pancreatic and gastrointestinal neuroendocrine neoplasms. *Surgery* 2004; 136:1176–82.
 28. King PD, Perry MC. Hepatotoxicity of chemotherapeutic and oncologic agents. *Gastroenterol Clin North Am* 1995; 24: 969–90.
 29. Bedikian AY, Legha SS, Mavligit G, et al. Treatment of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors. *Cancer* 1995; 76:1665–70.
 30. Flaherty LE, Unger JM, Liu PY, et al. Metastatic melanoma from intraocular primary tumors: the Southwest Oncology Group experience in phase II advanced melanoma clinical trials. *Am J Clin Oncol* 1998; 21:568–72.
 31. Agarwala SS, Hellstrand K, Gehlsen K, et al. Immunotherapy with histamine and interleukin 2 in malignant melanoma with liver metastasis. *Cancer Immunol Immunother* 2004; 53:840–1.
 32. Bedikian AY. Metastatic uveal melanoma therapy: current options. *Int Ophthalmol Clin* 2006; 46:151–66.
 33. Peters S, Voelter V, Zografos L, et al. Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients. *Ann Oncol* 2006; 17: 578–83.
 34. Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. *Ophthalmology* 1991; 98:383–9.
 35. Kulke MH, Wu B, Ryan DP, et al. A phase II trial of irinotecan and cisplatin in patients with metastatic neuroendocrine tumors. *Dig Dis Sci* 2006; 51:1033–8.
 36. Moertel CG, Kvols LK, O'Connell MJ, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991; 68:227–32.
 37. Rivera E, Ajani JA. Doxorubicin, streptozocin, and 5-fluorouracil chemotherapy for patients with metastatic islet-cell carcinoma. *Am J Clin Oncol* 1998; 21:36–8.
 38. Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. *Digestion* 2000; 62(Suppl 1):92–7.
 39. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986; 315:663–6.
 40. Oberg K. Endocrine tumors of the gastrointestinal tract: systemic treatment. *Anticancer Drugs* 1994; 5:503–19.
 41. Oberg K, Norheim I, Theodorsson E. Treatment of malignant midgut carcinoid tumours with a long-acting somatostatin analogue octreotide. *Acta Oncol* 1991; 30:503–7.
 42. Vinik A, Moattari AR. Use of somatostatin analog in management of carcinoid syndrome. *Dig Dis Sci* 1989; 34(3 Suppl):14S–27S.
 43. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med* 2006; 36:147–56.
 44. Hellman P, Ladjevardi S, Skogseid B, et al. Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. *World J Surg* 2002; 26:1052–6.
 45. Henn AR, Levine EA, McNulty W, et al. Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes. *AJR Am J Roentgenol* 2003; 181:1005–10.
 46. Wessels FJ, Schell SR. Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. *J Surg Res* 2001; 95: 8–12.
 47. Berber E, Flesher N, Siperstein AE. Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. *World J Surg* 2002; 26:985–90.
 48. Grover AC, Libutti SK, Pingpank JF, et al. Isolated hepatic perfusion for the treatment of patients with advanced liver metastases from pancreatic and gastrointestinal neuroendocrine neoplasms. *Surgery* 2004; 136:1176–82.
 49. Wettstein M, Vogt C, Cohnen M, et al. Serotonin release during percutaneous radiofrequency ablation in a patient with symptomatic liver metastases of a neuroendocrine tumor. *Hepatogastroenterology* 2004; 51:830–2.
 50. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; 279:577–80.
 51. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; 347:472–80.
 52. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; 358:1421–3.
 53. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; 368:1329–38.
 54. Patel SR, Benjamin RS. Management of peritoneal and hepatic metastases from gastrointestinal stromal tumors. *Surg Oncol* 2000; 9:67–70.
 55. Tarazov PG. Transcatheter therapy of gastric cancer metastatic to the liver: preliminary results. *J Gastroenterol* 2000; 35:907–11.
 56. Bloomston M, Binitie O, Fraiji E, et al. Transcatheter arterial chemoembolization with or without radiofrequency ablation in the management of patients with advanced hepatic malignancy. *Am Surg* 2002; 68:827–31.