

## Hepatic Arterial Infusion of Oxaliplatin and L-Folinic Acid-modulated 5-Fluorouracil for Colorectal Cancer Liver Metastases

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**Abstract.** *Background:* Despite the progress made in the treatment of metastatic colorectal cancer (CRC), the results of second-line chemotherapy remain poor. *Patients and Methods:* The feasibility of hepatic arterial infusion (HAI) of oxaliplatin (100 mg/m<sup>2</sup> over 6 h) followed by l-folinic acid (L-FA) (400 mg over 2 h i.v.)-modulated continuous HAI of 5-Fluorouracil (5-FU) (60 mg/kg over 42 h; q2w) as second-line chemotherapy for metastatic CRC limited to the liver was investigated. *Results:* A median of 9 treatment cycles were administered (range 4-14). Treatment-limiting toxicity consisted of: abdominal pain (3 patients), elevated liver enzymes accompanied by fatigue (3), elevated bilirubin (2), neutropenia (2), thrombocytopenia (3) and hypersensitivity to oxaliplatin (1). Normalization for >4 weeks of the carcinoembryonic antigen (CEA) level was documented in 3 patients and a decline of >50% for >4 weeks in 5 patients. A confirmed partial response (PR) was documented in 5, stable disease (SD) in 1 and progressive disease (PD) in 3 patients. In the latter 3 patients, lung metastases developed while a PR was observed in the liver metastases. A pathological complete response (CR) was documented in 2 patients. The median time to progression was 7.2 months (95% CI 1.3-13) and the median overall survival 18.3 months (95% CI 16.3-20.3). *Conclusion:* HAI of oxaliplatin plus CI5-FU/LV is feasible and merits further evaluation.

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In the European Union, colorectal cancer (CRC) has an annual incidence of about 372,000 cases. It is the second most important cause of cancer-related death in the Western world. About half of all patients with CRC are cured by surgery, radiotherapy and adjuvant chemotherapy. Systemic chemotherapy is considered the standard treatment for patients with metastatic disease, because it is more effective than best supportive care at prolonging survival and improving quality of life. The most active chemotherapeutic regimens available combine the topoisomerase I inhibitor irinotecan (CPT-11) or the third-generation platinum analog oxaliplatin with the folinic acid-modulated administration of infusional 5-Fluorouracil (ci5-FU/L-FA). The outcome of patients treated with chemotherapy has recently been improved by the addition of targeted therapeutics, such as the anti-VEGF and anti-EGFR monoclonal antibodies bevacizumab and cetuximab (1-3). Metastatic CRC is only rarely curable, but patients with resectable liver metastasis have a 25-30% chance of 5-year survival following hepatectomy (4, 5). The median survival of patients with metastatic CRC, who are not candidates for hepatectomy, is limited to 18-20 months (6-9).

Colorectal cancer has a marked predisposition to metastasize to the liver. At the time of diagnosis, approximately 30% of patients have liver metastases and in 30-40% of patients with stage IV disease the metastases seem to be limited to the liver. Only in about 10% of all metastatic CRC patients will the liver metastases be limited to one anatomical half of the liver and be amenable to hepatectomy with curative intent. Recently, a small number of dedicated centers have provided evidence that patients in whom liver metastases become resectable after regression under chemotherapy have a chance of long-term survival that is comparable to patients with initially resectable liver metastasis. However, the majority of CRC patients who

present with unresectable liver metastasis will not be candidates for surgical resection, even after regression of their liver metastasis under systemic chemotherapy.

At present, hepato-biliary toxicity is not the limiting factor for active chemotherapy regimens for CRC. Intensified treatment directed towards the liver might be rewarding for patients in whom liver metastases determine survival. Hepatic arterial chemotherapy is considered to be an attractive alternative treatment to systemic intravenous administration because the blood supply to liver metastases is more dependent on the hepatic artery than is the case in normal liver parenchyma. In addition, higher concentrations of chemotherapeutic drugs can be obtained within liver metastases by direct infusion of these drugs into the hepatic artery (10).

The initial experience with hepatic arterial infusion (HAI) of chemotherapy drugs was acquired with fluorodeoxyuridine (FUdR), an analog of 5-FU. This drug is 95% absorbed by the liver ("first pass effect") when administered by HAI, which results in an important reduction of the systemic exposure (and systemic toxicity). 5-FU, in contrast, undergoes only a 50-60% first pass extraction when administered as a bolus and the systemic exposure to 5-FU by HAI is comparable to that observed after intravenous (*i.v.*) infusion (11). This makes the HAI of 5-FU more attractive than FUdR, since high local drug concentrations are achieved without the loss of systemic drug exposure, that might favor disease progression outside the liver (12, 13).

Initial clinical trials and 2 meta-analyses of comparative trials with HAI FUdR demonstrated a significantly higher response rate, but no overall survival advantage (14, 15). This was also observed in a 3-arm study that compared *i.v.* ci5-FU/FA with the HAI of FUdR and ci5-FU/FA (16). This German randomized phase II study demonstrated a more favorable tumor response in patients treated by HAI ci5-FU/FA as opposed to *i.v.* administration. Extra-hepatic progression at 6 months was similar in patients treated with *i.v.* vs. HAI ci5-FU/FA (12% vs. 13%). A British phase III study failed to demonstrate a statistically significant survival advantage in favor of HAI of ci5-FU/FA (17). However, a significant percentage of patients in this study failed to receive the planned treatment by HAI because of early dysfunction of the hepatic artery port. Newer, less invasive, techniques, such as placement by laparoscopy or a permanent percutaneous catheter, may reduce the morbidity of hepatic arterial catheter placement and circumvent the problems of early catheter dysfunction.

Administration of both irinotecan and oxaliplatin by HAI has been the subject of a small number of phase I/II studies. An increased metabolic ratio is seen upon the HAI of irinotecan, without evidence of enhanced activity (18, 19). In contrast, encouraging activity has been observed in the

second-line setting throughout a number of studies that have evaluated the HAI of oxaliplatin, with or without intravenous ci5-FU/FA (objective response rate of 46-68%) (20-25). The pharmacokinetics of oxaliplatin showed a slightly reduced systemic availability by HAI as compared to *i.v.* administration. A particular toxicity associated with the HAI of oxaliplatin is the occurrence of HAI-related abdominal pain. In a small number of patients this pain can be acute and severe and has been reported to occur on the first administration. Although this pain syndrome can be treatment-limiting, it has not been related to tissue damage and is not considered to be of life-threatening potential.

We performed a feasibility study of the HAI of oxaliplatin followed by L-folinic acid (L-FA)-modulated continuous HAI of 5-FU as second-line chemotherapy for patients with stage IV CRC limited to the liver.

## Patients and Methods

*Study design, objectives and patient numbers.* The primary objective of this study was to demonstrate the feasibility and document the toxicity of oxaliplatin and 5-FU, administered by HAI, at a dosage comparable to that commonly used for the systemic treatment of patients with metastatic CRC. We planned to recruit a maximum of 12 patients for this study. The secondary objective was to document the antitumor activity and survival.

*Patient selection criteria.* Patients were eligible for study participation if they had a histologically- or cytologically- documented colorectal adenocarcinoma with predominant metastasis to the liver that could not be resected with curative intent, or patients who refused such surgery. Asymptomatic extra-hepatic disease localizations were allowed on the condition that the extent of the metastatic disease in the liver represented the bulk of the metastatic disease. Patients were required to have measurable disease in the liver, defined as lesions measuring  $\geq 1$  cm in largest diameter on spiral-computed tomography (CT) or magnetic resonance imaging (MRI); a performance status according to the WHO criteria of  $\leq 2$ ; and a life expectancy of  $\geq 3$  months. One non-oxaliplatin-containing systemic chemotherapy regimen for metastatic CRC was allowed. The anatomy of the hepatic arteries had to allow for the placement of one catheter in such a way that the liver was selectively perfused. In case of aberrant collateral arterial branches, these had to be obliterated prior to the first HAI of chemotherapy. The required laboratory values were: ANC count  $\geq 1,500$  /mm<sup>3</sup>, platelets  $\geq 100,000$  /mm<sup>3</sup>, PTT  $\geq 60\%$ , serum creatinine  $\leq 2.0$  mg/dl with creatinine clearance  $\geq 60$  ml/min (as calculated by the Cockcroft-Gault formula) and serum bilirubin  $< 2.0$  mg/dl.

The following criteria were regarded as exclusion criteria: prior treatment with oxaliplatin, prior radiotherapy to all areas of measurable disease, other than concurrent malignant disease, previous malignancies, except for adequately treated *in situ* carcinoma of the cervix uteri, basal or squamous cell carcinoma of the skin or any other malignancy given potentially curative treatment more than 5 years before study entry, the presence of known metastatic disease in the central nervous system, pre-existing polyneuropathy with a severity of  $>$  grade 1 in the

CTCAEv3.0 scale, patients who were at poor medical risk because of non-malignant systemic disease, as well as those with active uncontrolled infection and the concomitant use of other investigational drugs. The subjects were not allowed to participate concurrently in any other clinical trial. Female patients of childbearing age not using contraceptives or nursing mothers were not allowed to participate in the study.

The patients had to be at least 18 years old and be able to commit to regular visits for adequate follow-up. The Medical Ethical Committee of the AZ-VUB, Brussels, Belgium, approved the study protocol and all patients gave written informed consent before study entry.

**Pretreatment evaluation.** The pretreatment evaluation included a complete medical history, physical examination and laboratory studies (including complete blood count, urea, creatinine, ionogram, total bilirubin, lactate dehydrogenase, alkaline phosphatase,  $\gamma$ -GT, AST/ALT, carcinoembryonic antigen (CEA), hepatitis B, hepatitis C and HIV serology), contrast-enhanced CT or gadolinium-enhanced MRI of the abdomen and pelvis and an X-ray of the thorax. All patients underwent arteriography to evaluate the hepatic arterial blood supply before placement of the hepatic artery catheter.

**Study treatment.** The patients were premedicated with 10 mg of dexamethasone *i.v.*, a setron anti-emetic *i.v.* and 1 g CaCl plus 1 g MgCl<sub>2</sub> (in 250 ml of glucose 5%) before and after oxaliplatin. Oxaliplatin (Eloxatin<sup>R</sup>) was administered as a 6-hour HAI at a dose of 100 mg/m<sup>2</sup>. L-FA (Elvorin<sup>R</sup>) was administered as a 2-hour *i.v.* infusion during the 2 final hours of oxaliplatin HAI. On completion of the oxaliplatin and L-FA infusions, 5-FU was administered as a 42-hour HAI by a portable pump. The treatment was repeated every 2 weeks.

**Evaluation of toxicity, dose modification and treatment delay.** All toxicities were graded according to the National Cancer Institute common toxicity criteria (CTCAEv3.0). In the event of ANC < 1,500/mm<sup>3</sup> and/or platelets < 100,000/mm<sup>3</sup>, or any non-hematological toxicity (other than alopecia) not recovering to  $\leq$  grade 2 or to baseline toxicity levels on day 15 (=the planned day 1 of the following cycle), treatment had to be delayed until recovery to the stated levels. A maximum treatment delay of 2 weeks was allowed.

In the case of grade 4 neutropenia (symptomatic or not), febrile neutropenia, grade 4 thrombocytopenia or grade 3/4 thrombocytopenia accompanied by hemorrhage of grade >2 during a treatment cycle, 3 consecutive dose reductions were allowed (1=dose reduction of oxaliplatin by 25%; 2=dose reduction of oxaliplatin by 25% and 5-FU by 25%; 3=dose reduction of oxaliplatin by 50% and 5-FU by 25%).

In the case of grade 3 or 4 non-hematological toxicity (other than alopecia), 2 dose reductions (to level 2 and 3) were allowed. In the case of isolated dysesthesia associated with pain and unrelated to cold exposure lasting more than 3 days or provoking functional impairment, 2 dose reductions of oxaliplatin by 25% and 50% were allowed. If, at the allowed maximal dose reduction, unacceptable toxicity was seen again, the patient had to stop the study treatment.

In the event of severe abdominal pain during HAI, treatment had to be stopped and an angiography of the hepatic artery port and hepatic artery were required to rule out extrahepatic perfusion.

Table I. *Characteristics of the evaluable patients.*

Number of patients (Male/Female)	9 (8/1)
Median age (range)	56 (28-71)
Performance status 0/1	3/6
Localization of primary: rectum/colon	3/6
Sites of metastasis	
Liver only	7
Liver and peritoneal cavity*	2
Preceding chemotherapy for metastatic CRC	
Irinotecan, 5-FU/L-FA	8
Irinotecan, HAI 5-FU/L-FA	1
Stereotactic radiotherapy to the liver	1

\*In one patient limited peritoneal carcinomatosis was discovered at laparoscopic surgery and a second patient had evidence of peritoneal carcinomatosis on CT, but already disposed a hepatic artery port and had previously been treated by HAI before recruitment.

**Evaluation of response.** Patients underwent blood analysis, including liver tests and CEA, every 2 weeks and contrast-enhanced CT of the abdomen (or GdMRI) every 8 weeks during the study treatment (26). The objective tumor response was assessed according to the RECIST criteria (27).

## Results

**Patient characteristics.** Eleven patients were recruited to this study. Two patients could not be evaluated for the study end-points. One patient experienced a loss of function of the hepatic artery port during the administration of the first treatment cycle. This patient had previously been treated with HAI of 5-FU/L-FA in combination with intravenous irinotecan. In his first treatment cycle, he returned to the clinic 1 hour after the end of the HAI of 5-FU. The 5-FU-containing solution had crystallized and obstructed the hepatic artery catheter. This event was not accompanied by any toxicity. This patient was treated thereafter with *i.v.* oxaliplatin and 5-FU/L-FA and responded to this treatment. A second patient died before study treatment was initiated.

The characteristics of the 9 patients that could be evaluated for the toxicity and activity of the regimen under study are listed in Table I.

**Hepatic artery access.** In 2 patients, a permanent hepatic artery catheter was inserted during laparotomy. In 1 patient this was performed at the same time as the surgical removal of the primary colon tumor; in a second patient this was done at a laparotomy with the intent of resection of the hepatic metastases (which were found to be non-resectable).

In 9 out of 11 patients, the permanent hepatic artery port was inserted by a laparoscopic procedure during which a cholecystectomy was also performed. In 2 patients with a

Table II. Treatment-related adverse events that necessitated cycle extensions and/or dose reductions and/or cessation of treatment (8/9 patients).

Initials	Adverse events (AE)	Cycle extension (cycle no.)	Dose reduction (cycle no.)	Number of cycles after which adverse events necessitated treatment cessation
HJ	Hypersensitivity to oxaliplatin			6
VDBR	Thrombocytopenia, gradual increase in $\gamma$ -GT/AP and bilirubin, asthenia	6, 9, 10	6	13 4
DLG	Thrombocytopenia	6-15	6	
	Dysfunction of hepatic artery port			14
LL	Neutropenia/asthenia	3, 6	3	
	Airway infection / ascites (non-malignant transudate)	7		
	Gradual increase in $\gamma$ -GT/AP and bilirubin, asthenia		6	8 4
VRD	Acute abdominal pain with vaso-vagal reaction, nausea/vomiting, thrombocytopenia <sup>1</sup>	2	2	
	Gradual increase in $\gamma$ -GT/AP and bilirubin, asthenia			10 4
WH	Acute abdominal pain, nausea/vomiting <sup>2</sup>		1	
	Neutropenia	2	3	
	Thrombocytopenia/ elevated ALT		6	
TA	HAI of oxaliplatin-related acute abdominal pain <sup>3</sup>	2, 5	1, 5	5
VR	Dysfunction of hepatic artery port			9

<sup>1</sup>Oxaliplatin dosing was 5% and 5-FU dosing was 25% too high in cycles 1 and 2.

<sup>2</sup>Oxaliplatin dosing was 30% too high in cycle 1.

<sup>3</sup>HAI of oxaliplatin was administered over 12 h in cycles 2-5 because of abdominal pain during infusion over 6 hours in cycle 1.

<sup>4</sup>Patient requested to stop therapy in the absence of CTCAEv3.0 grade 3/4 treatment-related toxicity.

dominant left hepatic artery, a variant right hepatic artery, originating from the superior mesenteric artery, was clipped. In these patients, trans-hepatic collateralization from left to right with bilateral hepatic perfusion was confirmed with an arteriography postoperatively. Acute morbidity from this laparoscopic procedure was low; all patients recovered from surgery and were discharged from the hospital within 4 days. One patient was admitted to the hospital 9 days following the intervention because of acute abdominal pain. Intra-abdominal bleeding from a necrotic hepatic artery was found at laparotomy. Unfortunately, the patient died of hemorrhagic shock. A preceding partial gastrectomy might have increased this patient's risk for such a severe complication.

*Administered treatment.* A median of 9 treatments was administered per patient (range 4-14). Treatment by HAI was stopped because of progression of disease (PD) in 2 patients only. Three patients stopped the HAI because of hepatic artery port dysfunction, 1 because of hypersensitivity to oxaliplatin (treatment was continued in this patient with the use of a desensibilization scheme), 1 patient because of grade 3 abdominal pain related to the HAI of oxaliplatin and 3 patients because of progressive elevation of liver enzymes and bilirubin, accompanied by fatigue.

Additional intravenous cycles of oxaliplatin and 5-FU/L-FA were administered in 3 patients (4, 4 and 11 cycles,

respectively) in whom the continuation of treatment by HAI had become impossible because of loss of hepatic artery port function (2 patients) or hepato-biliary toxicity related to HAI (1 patient).

*Adverse events.* Treatment-related adverse events that necessitated cycle extensions, dose reductions and/or a cessation of treatment were observed in 8 out of 9 patients (listed in Table II). In 1 patient, no cycle extensions or dose reductions were necessary and treatment was stopped because of PD after 7 cycles.

All adverse events that were considered to be possibly, probably or definitely related to the study treatment are summarized in Table III.

*Antitumor activity (CEA and radiological tumor response).* All patients had elevated CEA levels at the time of treatment (median 280 KU/l, range 50-2860). A normalization (< laboratory upper normal limits) that persisted for more than 4 weeks was documented in 3 patients. In an additional 5 patients, the CEA decreased more than 50%, while in 1 patient the CEA dropped to a lesser extent. The CEA nadir was reached after a median of 6 treatments (range 4-11 in individual patients).

In those patients who developed a gradual increase in liver enzymes during the study treatment, a remarkable

Table III. Laboratory and treatment-related clinical adverse events.

Table IIIA. All laboratory adverse events.

Adverse event	Grade (CTCv3.0) - Number of patients (%)				
	0	1	2	3	4
Leucopenia	6 (67)	0	2 (22)	1 (11)	0
Neutropenia	4 (44)	1 (11)	1 (11)	3 (33)	0
Lymphopenia	0	3 (33)	4 (44)	2 (22)	0
Thrombocytopenia	2 (22)	6 (67)	1 (11)	0	0
Amylase	4 (44)	3 (33)	1 (11)	0	0
Lipase	1 (11)	2 (22)	1 (11)	4 (44)	0
Serum glutamic oxalaoacetic transaminase (AST)	1 (11)	5 (56)	2 (22)	1 (11)	0
Serum glutamic pyruvic transaminase (ALT)	4 (44)	4 (44)	1 (11)	0	0
Alkaline phosphatase	0	2 (22)	5 (56)	2 (22)	0
$\gamma$ -Glutamyl transpeptidase ( $\gamma$ -GT)	0	0	1 (11)	7 (78)	1 (11)
Bilirubin	7 (78)	0	2 (22)	0	0
Albumin	0	0	3 (33)	0	0

Table IIIB. Treatment-related clinical adverse events of grades 2 and 3.

Adverse event	CTCv3.0 Grade- Number of patients (%)	
	2	3
Abdominal pain related to HAI of oxaliplatin	3 (33)	5 (56)
Asthenia	5 (56)	1 (11)
Fever	3 (33)	1 (11)
Nausea/Vomiting	3 (33)	1 (11)
Insulin-dependent diabetes mellitus <sup>1</sup>	0	1 (11)
Anorexia	0	1 (11)
Hypersensitivity to oxaliplatin	0	1 (11)
Polyneuropathy	2 (22)	0
Skin	1 (11)	0
Infectious cholangitis	1 (11)	0
Ascites (transudation) <sup>2</sup>	1 (11)	0

<sup>1</sup>Elevated glucose levels had been recorded in this patient before participation in this study; <sup>2</sup>this patient had a pre-existing history of a pelvic seroma following abdomino-perineal resection and radiation therapy for rectal cancer.

decrease of the CEA values was documented, indicating differential evolution of tumor response and chemotherapy-induced hepato-biliary injury (Figure 1).

A confirmed partial tumor response (PR) was observed in 5 patients, stable disease (SD) in 1 and PD in 3. The latter obtained a PR in the liver metastases, but small lung metastases were found at first evaluation during study treatment. Given the asymptomatic character of these lung

metastases and the regression of liver metastases, the study treatment was continued in these 3 patients.

**Additional liver-directed treatment.** One patient was treated with stereotactic radiotherapy for a residual liver metastasis which was found to be unresectable at laparotomy (invasion of the diaphragm). A biopsy, taken at the time of marker implantation (for guidance of the stereotactic radiotherapy), revealed no tumor cells.

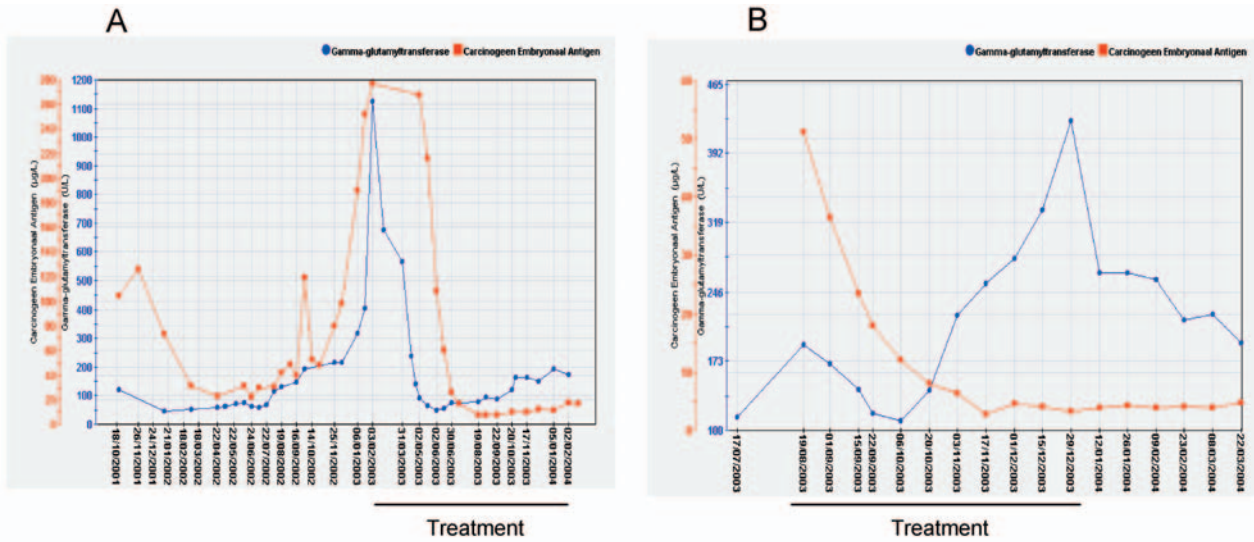
Two patients were offered radiofrequency ablation (RFA) of the residual liver metastasis. One of these patients underwent an additional surgical metastasectomy of a residual metastasis that could not be treated safely with RFA. On histopathological examination, no residual tumor was found (see Figure 2).

**Survival.** According to Kaplan-Meier survival estimates, the median time to progression of our study patients was 7.2 months (95% CI 1.3-13.0) and the median time to progression in the liver 9.4 months (95% CI 5.9-12.9). The median overall survival from diagnosis was 26.7 months (95% CI 23.7-29.8) and the median overall survival from the initiation of study treatment 18.3 months (95% CI 16.3-20.3).

Remarkably, 2 patients, who developed PD in the lungs while responding in the liver, experienced an indolent progression of these lung metastases afterwards. This was in sharp contrast to the more rapid and aggressive evolution of their liver metastases before the initiation of HAI. Both these patients remained asymptomatic and were able to lead a normal life for up to 12 and 14 months, respectively, after stopping HAI and in the absence of any other anticancer therapy. In 1 of these patients, there was no recurrence of disease within the liver at the last follow-up (20 months following the initiation of study treatment and in the absence of other therapy).

## Discussion

HAI of the fluoropyrimidines (5-FU and FUDR) increases the response rate in liver metastases of metastatic CRC as compared to *i.v.* therapy. The HAI use of 5-FU has decreased during the last decade for a number of reasons. Two European phase III trials (1 in the adjuvant and 1 in the metastatic setting) failed to demonstrate a survival advantage for the HAI of 5-FU and HAI was associated with additional morbidity related to the hepatic arterial port (17). Furthermore, oxaliplatin and irinotecan were introduced during the nineties, demonstrating superior anti-tumor activity and survival advantage when combined with infusional 5-FU (7, 8). The HAI of oxaliplatin and irinotecan has only recently been studied (18, 19, 21-23). Based on the interesting results obtained with the HAI of oxaliplatin, we decided to



port by laparoscopy in our institutional experience, which currently includes more than 25 patients. Other groups have also reported the safety and feasibility of this laparoscopic procedure (28, 29). We, therefore, consider laparoscopic placement as more appropriate than laparotomy because of the lower morbidity. As compared to repeated or permanent percutaneous catheterization, the laparoscopic procedure offers the advantage of being able to perform a cholecystectomy in order to avoid the risk of chemical cholecystitis.

Hepatic artery port dysfunction, before or within the first 2 months of treatment, has been a frequent event in previous studies. We did not experience early port dysfunction in our patients, although port failure did occur before PD in 3 of our patients. Taking into account that the maximal radiological regression and CEA nadir were obtained at the time of dysfunction of the port in these patients, we do not believe that dysfunction of the hepatic port had an important impact on the outcome of our study patients.

Our study regimen used doses for HAI of both oxaliplatin and 5-FU comparable to those used in the systemic FOLFOX6 regimen (6). We did not include a bolus of 5-FU in order to simplify the regimen and because we question the importance of adding such a bolus to an optimal-dosed infusion of 5-FU. The pattern of treatment-related toxicity that we observed indicates a specific hepatic toxicity related to HAI, but to systemic toxicity as well. Systemic toxicity from both chemotherapeutic agents was expected since pharmacokinetic studies with HAI of oxaliplatin and 5-FU had demonstrated almost equivalent systemic exposure with HAI as compared to *i.v.* administration of these drugs. Our small patient population, however, did not allow accurate comparison of the incidence of treatment-related toxicity with those reported in the literature for FOLFOX6.

The HAI of oxaliplatin has been reported to cause upper abdominal pain, as was also observed in our study (21, 22). This pain syndrome can manifest itself as acute and severe pain during the first administration, as occurred in 1 of our patients, which prohibited further HAI of oxaliplatin over 6 hours. This acute pain syndrome probably results from the excitation of visceral pain sensors within the biliary system and might be the equivalent of acute oxaliplatin-triggered peripheral neuropathy after *i.v.* administration. We did not observe any evidence of acute tissue damage by laboratory investigation of the hepato-biliary and pancreatic enzymes and bilirubin, or by CT-scan, at the time of acute pain.

Generally, in HAI, oxaliplatin-related pain manifested as a mild to intense pain in the upper abdomen that occurred during and after the HAI of oxaliplatin and sometimes persisted during the complete treatment cycle. This pain syndrome is probably also related to the documented hepato-biliary toxicity. The gradual increase in cholestatic

enzymes observed in most patients with increasing treatment cycles reflected this tissue damage (an increase in the  $\gamma$ -GT levels was most sensitive). In contrast to what is usually seen with *i.v.* chemotherapy, a decrease in CEA levels (reflecting tumor regression) was accompanied by a gradual rise in cholestatic enzymes (mainly  $\gamma$ -GT) in most patients. In 2 out of 9 patients, a grade 2 rise in bilirubin was also observed. The elevations of  $\gamma$ -GT and bilirubin were reversible upon withdrawal of HAI, except for 1 patient in whom grade 1-2 elevated bilirubin levels persisted. This patient had been treated by hepatic radiotherapy before treatment with HAI and had progressive hepatic metastases, which could have contributed to these persistent biochemical alterations.

Hepato-biliary toxicity related to chemotherapy has been reported with *i.v.* regimens (30). Although reversible, the observed hepato-biliary toxicity in our study should caution against the use of such a HAI regimen in patients who are candidates for resection of hepatic metastases. Decreased liver function resulting from this toxicity is likely to put patients at a higher risk of hepatic failure following hepatectomy.

We believe that the observed anti-tumor activity and survival with this regimen is encouraging. The 5 out of 9 objective responses we observed compare favorably with the reported 10-20% response rates with the FOLFOX regimens in patients who had previously failed irinotecan/5-FU-based regimens (7). This high rate of tumor response in our patient cohort was certainly biased by the selection of patients who still had liver-confined metastatic disease after failing first-line therapy. Extra-hepatic progression did occur in 3 out of 9 patients who responded in the liver, illustrating the superior activity of HAI on liver metastases. More profound screening of patients for extra-hepatic disease by spiral CT-scan of the chest and FDG-PET scanning is likely to identify patients with existing extra-hepatic disease before the initiation of HAI. However, since hepatic failure from progressive metastatic disease is the most important threat to patients with limited extra-hepatic disease, more active therapy against the liver metastases might still be warranted.

The achievement of a pathologically complete remission in the resection specimen and biopsy of residual metastatic lesions in 2 of our patients is illustrative of the antitumor activity of HAI of oxaliplatin and 5-FU. Our experience adds to the observations of frequent complete pathological regression of liver metastases in patients treated by HAI, as reported by Kemeny *et al.* (31).

In conclusion, the feasibility of administering both oxaliplatin and 5-FU by HAI in patients with hepatic metastases from CRC was demonstrated. Although treatment by HAI is more complex and is associated with an abdominal pain syndrome and cumulative, but reversible, hepato-biliary toxicity as compared to *i.v.*

treatment, further investigation is warranted. At present, and despite continued improvement, non-resectable CRC liver metastases remain a lethal disease with a grim prognosis. Exploiting the increased activity of HAI in a first-line setting might offer more patients the possibility of achieving long-term remission, pathological CR and to benefit from surgery or other ablative procedures at the time of best response. The management of potential hepato-biliary toxicity and the optimal sequencing of all available active drugs is an important challenge for future studies. We are currently investigating our regimen in a first-line setting in a multi-center phase II trial. Although regimens that incorporate HAI might not be of true benefit to more than 10-20% of CRC patients who have unresectable metastases to the liver only, the benefits in terms of prolonged survival or even cure could be rewarding.

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