Isolated Liver Perfusion with Mitomycin C in the Treatment of Colorectal Cancer Metastases Confined to the Liver

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We evaluated the technical feasibility of isolated liver perfusion (ILP) in the treatment of patients with colorectal cancer metastases confined to the liver, and investigated whether ILP allows exposure of the tumor to high concentrations of mitomycin C (MMC). Furthermore, survival time and tumor response were studied. Nine patients were treated with 30 mg/m2 MMC recirculated for one hour in the isolated circuit. The MMC concentration in the perfusate and plasma was measured using a high-performance liquid chromatography assay. All complications directly related to the surgical procedure were treated effectively (no mortality). The peak concentration of MMC in the perfusate was 5 to 11 times higher than that measured in the plasma of patients treated with 20 to 60 mg/m2 MMC i.v., and the concentration remained significantly higher during the whole perfusion period. In contrast, the peak concentration of MMC in plasma was approximately two thirds of the lowest peak plasma level measured after i.v. administration of 10 mg/m2 MMC. No systemic toxicity was observed in any of our patients. However, four patients developed veno-occlusive disease of the liver which was mild in three but lethal in one. One of the eight evaluable patients had an objective complete response (25 months), one an objective partial response and five others a clear reduction in tumor size (25-50%). The median survival time was 17 months. This study demonstrates that ILP is technically feasible in patients, and in comparison with systemic therapy allows exposure of hepatic metastases to much higher concentrations of MMC, while systemic toxicity is absent. Remarkably, this single exposure to a high concentration of MMC resulted in a complete response and a median survival time comparable to that in recently published hepatic artery infusion studies with fluorouridine and leucovorin. However, due to the hepatotoxicity we are continuing our studies with melphalan to further exploit the possible therapeutic benefit of ILP.

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Key words: Isolated liver perfusion—Mitomycin C—Veno-occlusive disease—Regional chemotherapy—Colorectal cancer

Introduction

In experimental tumor models the principle of a steep dose-response curve has been well established.10 The total dose and dose schedule have proved to be fundamental to successful eradication of a malignant cell population. However, only a few clinical studies have evaluated these principles, and their clinical applicability has been questioned because of toxic side effects.2 During the last few years it has been demonstrated that for a number of tumors which are relatively sensitive to chemotherapy, e.g. breast cancer, ovarian cancer and lymphomas, “more is better” and “dose-response is alive and well”.1,2 The majority of these studies were retrospective analyses of drug dosages less than or equal to standard regimens. The effect of very high dosages in the treatment of clinically unresponsive tumors, e.g. lung cancer, colon cancer and pancreatic cancer, is largely
Table I. Characteristics of Treated Patients, and Complications, Survival Tumor Time and Cause of Death after ILP with 30 mg/m² Mitomycin C

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/Sex</th>
<th>Tumor stage (Dukes)</th>
<th>Months of liver metastases</th>
<th>PHR (%)</th>
<th>Survival months</th>
<th>Cause of death</th>
<th>Complications</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>C</td>
<td>9</td>
<td>25</td>
<td>22</td>
<td>H.M.</td>
<td>VOD/ascites</td>
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<td>30</td>
<td>28</td>
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</tr>
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<td>VOD/ascites</td>
</tr>
<tr>
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<td>30</td>
<td>5</td>
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</tr>
<tr>
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<td>53</td>
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<td>4</td>
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<td>ARDS</td>
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<td>12*</td>
<td>50</td>
<td>12</td>
<td>H.M.</td>
<td>VOD/ascites; DIC, renal insufficiency, portal hypertension and death</td>
</tr>
<tr>
<td>8</td>
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<td>9</td>
<td>51/M</td>
<td>D</td>
<td>0</td>
<td>30</td>
<td>27</td>
<td>H.M.</td>
<td>VOD</td>
</tr>
</tbody>
</table>

PHR, percentage hepatic replacement = mean of the percentage of tumor replacement in all CT-scan slices of the liver; *, treated with 5-fluorouracil (FUra) before ILP (25 months); †, treated with FUra and leucovorin before ILP; H.M., hepatic metastases; L.M., lung metastases; VOD, veno-occlusive disease of the liver; ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation.

unknown.

To study the effect of locally high cytostatic drug concentrations in the treatment of colorectal cancer metastases confined to the liver, isolated liver perfusion (ILP) techniques have been developed.5-8 The advantage of this approach is that systemic toxicity is not a factor that limits the use of very high drug dosages. In an experimental rat colon cancer model and in clinical studies, 5-fluorouracil, still considered the standard drug for the treatment of advanced colorectal cancer, proved to be ineffective after short-term high-dose treatment.9,10 With mitomycin C the response rate following systemic treatment of colorectal cancer in man is little less than with 5-fluorouracil, and mitomycin C has been used with some success as a salvage treatment for patients with hepatic metastases from colorectal cancer.11,12 In rats ILP with mitomycin C resulted in complete remissions and significantly prolonged survival, while that with 5-fluorouracil did not.10,13 Furthermore, in a clinical study addition of mitomycin C to 5-fluorouracil in the perfusate resulted in an increase of tumor responses from 16% to 67% in ILP-treated patients.14 Moreover, the data indicated that ILP with high-dose 5-fluorouracil and mitomycin C could provide a three- to five-year disease-free survival period in patients with metastases confined to the liver. We studied ILP with mitomycin C in nine patients with non-resectable colorectal cancer metastases confined to the liver in a phase I/II trial.

Patients and Methods

Patients

This phase I/II study was approved by the Medical Ethics Committee of the University Hospital, Leiden. From May 1990 to May 1991, nine patients with four or more hepatic metastases of colon cancer scattered throughout the liver, and therefore considered non-resectable, were selected. The characteristics of the patients are given in Table I. With informed consent, all the patients underwent ILP at the University Hospital, Leiden. The primary colon tumor had been resected. Eight patients had tumor growth confined to the liver, as demonstrated by coloscopy, a CT scan of the abdomen, and a preoperative chest x-ray. One also showed two lung metastases on a chest x-ray just prior to surgery, but in consultation with the patient, the procedure was carried out as planned. Four patients had metastases at the time of resection of the primary colon cancer (synchronous). In the other patients metastases were diagnosed 9, 9, 11, 12 and 53 months after resection of the primary tumor. Non-resectability of the liver metastases was confirmed by preoperative as well as per-operative imaging (ultrasound) and per-operative inspection and palpation. Eight patients were treated with 30 mg/m² mitomycin C by ILP within 2 months after detection of liver metastases. One patient with metachronous metastases (detected 12 months after resection of the primary) was first treated with 5-fluorouracil until progression of the
MITOMYCIN C IN ISOLATED LIVER PERFUSION

metastases after 25 months. About two months later she was treated with ILP. Patient 9 with synchronous metastases was treated with 5-fluorouracil and leucovorin for three months, and after progression with ILP.

Isolated Liver Perfusion in Patients (Fig. 1)

Isolation: The liver is mobilized from the diaphragm and identifiable diaphragm veins are ligated. To control the suprahepatic caval vein, the pericardium is opened by incising the diaphragm just anterior to the caval vein and the caval vein is dissected free of adhering tissue and secured with tape. Lumbar veins are identified and transected. The common bile duct, the portal vein, the common hepatic artery and the gastroduodenal artery are dissected from the hepatoduodenal ligament. The common bile duct, common hepatic artery and the gastric branches are clamped during perfusion.

 Cannulation: After heparinization the intrahepatic caval vein is cannulated with a specially designed double-lumen catheter (Braun Melsungen: long tube: length 240 mm; central lumen = I.D. 10 mm; O.D. 12 mm; short tube on top of lower half of the long tube: length 115 mm; I.D. 4 mm; O.D. 5.5 mm). The central lumen allows undisturbed blood flow from the intrahepatic caval vein to the heart, and has side ports for a temporary portacaval shunt, and for the renal veins. The outer lumen collects the hepatic venous outflow. The portal vein and the gastroduodenal artery (and if present an aberrant hepatic artery) are cannulated to establish the arterial and venous inflow limbs of the isolated circuit.

Extracorporeal Circuit and Perfusion: After establishing vascular isolation, perfusion is started. The hepatic venous outflow (perfusate = intrahepatically trapped blood and one liter Haemaccel® (Hoechst, Hoovelaken, The Netherlands)) is collected and returned to an oxygenator, a reservoir and a heat exchanger (37±1°C). Two roller pumps infuse the perfusate into the liver via the portal vein (flow ± 320 ml/min) and via the hepatic artery (flow ±400 ml/min). Leakage from and to the extracorporeal circuit is monitored by adding radio-labeled (Tc) red blood cells to the perfusate and placing detectors in the extracorporeal circuit as well as in the systemic circulation. Mitomycin C is added after leakage has been excluded. After one hour of perfusion with the cytostatics, a washout is performed using 1.5 l of Haemaccel, the shunt is removed and normal circulation is re-established.

Sampling for Measurement of Mitomycin C Concentration

Heparinized 5-ml samples of systemic blood were taken at 0, 30, 60, 65, 70, 75, 90, 105 and 120 min, and of perfusate at 0, 5, 10, 15, 30, 45 and 60 min. T = 0 represents the time before injection of MMC into the perfusate. All samples were placed immediately on ice until centrifugation at 2000 rpm for 15 min. The plasma and perfusate supernatants were removed and stored at -30°C until analysis. Prior to analysis, the supernatants were thawed and centrifuged at 6000 rpm. The new supernatants were diluted with water and injected (10 µl) directly into the HPLC.

Drug Analysis

Standards and samples were analyzed using HPLC. The HPLC system consisted of a high-pressure pump (Familic 330s; Jasco, Tokyo) combined with an LC-UV variable-wavelength detector (Spectroflow 773; Kratos, Ramsey, NJ). Samples were injected using a Promis autosampler (LKB, Bromma, Sweden), and integration was done by a model C-R3A integrator (Shimadzu, Kyoto). The column was a stainless steel tube (100 mm long and 3 mm in inside diameter) packed with Nucleosil C8 µm particles (Macherey-Nagel, Düren, Germany). The flow rate was 0.5 ml/min, and the UV detector was set at 360 nm.

Response Criteria

Objective tumor response was defined as
complete: disappearance of all lesions on CT scan; partial: reduction of more than 50% of the product of the perpendicular diameters of measurable lesions without the occurrence of new lesions; and stable: less than 50% reduction of tumor size without progression of any lesion. During the first year, follow-up CT scans were performed every three months.

Results

No patient died as a direct result of the operative procedure. The duration of the operation ranged from 3 to 7 h (mean 4.5 h), and blood loss was 1.6 to 7.5 l (mean 4.8 l) including 1-1.5 l lost in the perfusion circuit. The leakage from the isolated circuit into the systemic circulation ranged from 14% to 67% (mean 18%). With increasing experience, the duration of the operation blood loss and leakage were decreased. The time of admission ranged from 11 to 40 days (median 14 days), including 1 to 38 days in the intensive care unit (median 3 days).

Postoperative Chemistry

Postoperatively, all patients showed a minor to marked increase in the level of lactate dehydrogenase (LDH), serum aspartate aminotransferase (ASAT) and serum alanine aminotransferase (ALAT) (Table II). All elevated levels returned to normal within the first seven to 10 postoperative days. ASAT levels following the perfusion are shown in Fig. 2. Bilirubin (BIL) was elevated in patients 2, 5, and 6 only. The level of alkaline phosphatase (APH) remained slightly elevated during the follow-up period in all patients except patient 2. Patient 8, who died on day 38, also had peak levels of LDH, ASAT and ALAT in the first week comparable with the other patients. However, the bilirubin level increased steadily from day 12 until death (day 38), reaching 684 \( \mu \text{mol/l} \) (599 \( \mu \text{mol/l} \) conjugated).

Renal function and hematologic parameters were not affected in any of the patients except for patient 8, who developed multiple deorgan failure.

Complications

The complications were divided into those attributable to the surgical procedure (n 6), and those to mitomycin C (n 8) (Table I). The former included bacteremia in patient 9, probably from a wound infection after the previous abdominoperineal resection of the rectum, temporary encephalopathy (patient 9), bleeding from the retroperitoneum (patient 5), necessitating laparotomy twice, pneumonia (patient 5) which was successfully treated with antibiotics, and adult respiratory distress syndrome (patient 7), for which mechanically assisted ventilation was necessary for two days. The main complication encountered after ILP with mitomycin C was directly related to the drug’s liver toxicity. In three patients the clinical symptoms of veno-occlusive disease were observed, and in one patient a biopsy of the liver showed the histology of veno-occlusive disease although no clinical symptoms were present. The case summaries of these patients follow.

Case Reports

Patient 8

Postoperatively there were no complications until the fifth day. The patient rapidly developed ascites.
(up to 251 a day), and the levels of conjugated and unconjugated bilirubin rose. Occlusion of the portal vein was excluded. Veno-occlusive disease (VOD) of the liver was most probably the cause of the rapid ascites production. Subsequently the patient developed symptoms of multiple organ failure with respiratory failure (for which mechanically assisted ventilation was needed for 28 days) and renal failure (serum creatinine level between 200 and 300 μmol/l). Coagulation disorders were also present. Secondary to portal hypertension (due to VOD) the patient had intermittent bleeding of esophageal varices, of which he died on the 38th postoperative day.

**Postmortem Examination**

**Macroscopic Findings:** The liver was slightly enlarged (1800 g) and had multiple round necrotic lesions. The tumor volume had been reduced to less than 50% of that before the procedure. There were various signs of portal hypertension including splenomegaly (840 g), esophageal varices, and a hemorrhagic mucosa of the distal rectum.

**Microscopic Findings:** The liver metastases consisted of largely necrotic material, with only a few possibly viable tumor cells remaining at the rim of the lesions. The liver parenchyma showed prominent congestion with bridging fibrosis. The portal triads could easily be recognized with a slight increase in fibrosis. However, the efferent veins could hardly be recognized in the fibrotic structures. Around the efferent veins the liver parenchyma showed necrotic hepatocytes. Some lumina of the small veins were completely obliterated by loosely scattered reticulum fibers (Fig. 3). These findings were in agreement with long-standing VOD of the liver.

**Patient 2**

On the tenth day after ILP, patient 2 went home in good condition and without serious complaints. On day 23 she was readmitted complaining of sudden diffuse pain in the right upper quadrant of the abdomen. Palpation of this area was very painful for her. She had gained weight, and her abdomen had swollen during the previous week. Ascites was found, but cytology revealed no malignant cells. A duplex scan showed a patent portal vein. Results of all liver tests were normal. A CT scan showed regression of the liver metastases. The ascites was effectively treated with a peritoneo-venous shunt. Five months later she was readmitted with ascites and a non-functional peritoneo-venous shunt. The patient had progressive liver metastases and jaundice, and lung metastases. Hematemesis due to esophageal varices occurred 3.5 months later, and she died one week later, nine months after ILP.

**Patient 4**

Nine days after ILP, patient 4 left the hospital in good condition. On the 32nd post-operative day she developed pain in the right upper quadrant of the abdomen, which had become swollen together with a gain in weight. The liver was not palpable. A duplex scan showed that the portal vein was patent. Results of all liver tests were normal. A CT scan showed possible central necrosis of the hepatic metastases. Again the ascites was effectively treated with a peritoneo-venous shunt. Five months later she was readmitted with ascites and a non-functional peritoneo-venous shunt. The patient had progressive liver metastases and jaundice, and lung metastases. Hematemesis due to esophageal varices occurred 3.5 months later, and she died one week later, nine months after ILP.

**Patient 9**

On day 14 after ILP, patient 9 went home in good condition with normalized liver functions. On day 39 he was readmitted because of abdominal complaints, which were found to be due to a bulbar ulcer and gastritis, which were treated effectively with ranitidine. Furthermore the patient was confused, due to hepatic encephalopathy. This was effectively treated by reduction of protein intake for 6 months. Sixteen months after ILP, a suspect lesion was seen on follow-up CT scan of the liver. A biopsy showed the histology of VOD, but no metastases. Up to 24 months the patient had no physical complaints and there were no clinical signs of tumor growth except for a rise in the CEA level. Rather suddenly he developed ascites and obstruction icterus, and a CT scan showed tumor.
growth in the liver. Two months later (26 months after ILP), the patient died due to progressive tumor growth.

**Mitomycin C Concentrations in Biofluids**

In the first two patients, 1 and 2, MMC (30 mg/m²) was infused into the common hepatic artery during 30 min. In these patients, the highest MMC concentration in the perfusate was measured at t = 30 min: 5.95 µg/ml and 3.91 µg/ml (Fig. 4). In patients 3 to 9, MMC was given as a bolus in the oxygenator, resulting in the highest concentrations of MMC at t = 5 min: 9.25 µg/ml to 22.25 µg/ml (Fig. 4).

In patients 1 to 7, the maximal concentration of MMC in plasma was found at t = 30 min, ranging from 67 to 825 ng/ml (Fig. 5). In the last two patients, 8 and 9, the peak concentration of MMC occurred at t = 65 min, just after isolation had been discontinued and systemic blood had mixed with the blood in the hepatic vasculature. The peak concentration in plasma was relatively low in these two patients, 101 ng/ml and 66 ng/ml. This was in agreement with the lowest concentrations of Tc-labeled red blood cells in the systemic circulation, indicating minimal leakage of perfusate into the systemic circulation in these patients. Furthermore, patients with the highest concentrations in the perfusate had the lowest concentrations in plasma, which again was most pronounced in patients 8 and 9.

**Response and Survival**

All patients had gross liver invasion by metastatic colorectal cancer; each had six or more metastases and the tumors were clearly non-resectable. Five patients had a clear decrease in tumor size on follow-up CT scans but not all the tumor deposits could be measured accurately enough to reliably differentiate between an objective partial response and stable disease. One patient showed an objective complete response on follow-up CT scans (patient 9) which lasted for 24 months. Patient 1 had an objective partial response for six months. Patient 6 had stable disease at 3 months. A concurrent decrease of more than 50% in the level of CEA was observed in all eight surviving patients (Fig. 6). After initial decreases in the CEA levels, they increased steadily in seven patients who lived for more than 6 months after treatment.

At postmortem examination of patient 8, all the liver metastases had been reduced to less than 50% of that before ILP and were largely necrotic.

Patients 1, 2, 3, 4, 6, 7 and 9 died due to progressive liver metastases (Table I). Patient 5 presented with lung metastases at admission for ILP, and although extrahepatic metastasis was an exclusion criterion, she agreed to undergo the procedure. She died 5 months later due to the lung metastases. Although she showed a clear reduction in tumor size, her liver metastases became progressive before the time of death.
Discussion

In this phase I/II study ILP with mitomycin C was evaluated with respect to feasibility, toxicity, drug concentrations in biofluids, and tumor response. The results demonstrated that ILP is technically feasible. Although ILP is a complex surgical procedure, all patients survived the operation, and the complications directly related to it were treated effectively. The hepatotoxic side effects of mitomycin C were the source of major complications. Four of our nine patients (patients 2, 4 and 8 symptomatic) had hepatic VOD, probably due to exposure of the central venous intima to very high concentrations of MMC, with fibrosis and ultimately occlusion of the veins. The clinical syndrome of hepatic VOD has been reported as a rare observation after high-dose MMC alone (60, 75, or 90 mg/m²). In contrast, VOD is a complication frequently seen in (autologous) bone marrow transplantation patients given high-dose chemotherapy (with drugs other than MMC) alone or in combination with radiation. Based on the wide occurrence of VOD in these bone marrow transplantation studies, the condition is characterized by the clinical triad of (1) jaundice, (2) hepatomegaly and/or right upper quadrant pain, and (3) ascites or unexplained weight gain occurring within 4–5 weeks after (autologous) bone marrow transplantation.

The different grades of VOD severity seen in our four patients have also been described by others: (1) asymptomatic VOD discovered incidentally at autopsy, (2) symptomatic, non-serious VOD with resolution of clinical and laboratory features, and (3) symptomatic, serious VOD with progressive, lethal liver failure. One of our patients (patient 9) had asymptomatic VOD that was discovered incidentally at biopsy of a suspect lesion detected by follow-up CT scan of the liver. Two of our patients (patients 2 and 4) developed the symptomatic but non-serious form and one the symptomatic serious form (patient 8) with coagulopathy, encephalopathy, fluid overload, congestive heart failure, pulmonary insufficiency, renal failure and portal hypertension with gastrointestinal bleeding.

At 30 mg/m² VOD was an unexpected finding, since the same dose was administered using a similar ILP procedure by Aigner et al. without serious hepatotoxic side effects.

The occurrence of this complication in our patients raises the question of the ideal dose to administer and the local drug concentration achieved. Lazarus et al. suggested a relationship between the dose of mitomycin C (3 days at 20, 3 days at 25, and 3 days at 30 mg/m²) and development of VOD. In our study the peak mitomycin C concentrations measured in the perfusate after bolus injection were 5 to 11 times higher than the highest plasma concentration reported in patients receiving 20 mg/m² as a bolus i.v. or 30 mg/m² i.v. infusion during 15 min or 60 mg/m² i.v. infusion during 60 min (Fig. 4). Thus in our patients the liver tissue was exposed to higher concentrations of mitomycin C which may have caused the relatively high incidence of VOD observed.

Systemic toxicity was not seen following administration of 30 mg/m² mitomycin C by ILP due to the low systemic levels of the drug. Lazarus et al. suggested a relationship between the dose of mitomycin C and development of VOD. In our study the peak mitomycin C concentrations measured in the perfusate after bolus injection were 5 to 11 times higher than the highest plasma concentration reported in patients receiving 20 mg/m² as a bolus i.v. or 30 mg/m² i.v. infusion during 15 min or 60 mg/m² i.v. infusion during 60 min (Fig. 4). Thus in our patients the liver tissue was exposed to higher concentrations of mitomycin C which may have caused the relatively high incidence of VOD observed.

In two patients the liver isolation was complete, resulting in a very low level of mitomycin C in plasma during perfusion and a low peak plasma level just after the end of isolation (patients 8 and 9). In all other patients leakage during perfusion resulted in peak plasma levels at t = 30 min. Most probably, a vein dorsal to the caval vein just above the renal veins (this was discovered in patient 8 and subsequently ligated in patients 8 and 9), and also the lumbar veins dorsal to the liver, were responsible for this leakage.

Tumor response was evaluated by CT scan every three months and by CEA monitoring. These examinations showed the efficacy of this treatment modality. One patient had an objective complete response evident on CT scan which lasted for 24 months after treatment. Another had an objective partial response, and in five other patients clear
reductions in tumor size were observed. Furthermore, in patient 8 no vital hepatic metastases could be found at autopsy. In all patients, the initial CEA levels decreased more than 50% after ILP. However, within six months in six patients the CEA levels rose, indicating recurrent tumor growth.

Eight out of nine patients died due to tumor progression. Their median survival time was 17 months. This result is well within the range of the median survival time reported for intra-arterial chemotherapy studies (Table III), and was also true for the percentage of complete responses. However, our study was a phase I/II study and included only a small number of patients due to the unexpected hepatic toxicity of MMC. We feel that we have not yet exploited the potential benefit of our ILP technique, and the question of whether isolated liver perfusion in patients with colorectal cancer metastases confined to the liver is indeed beneficial has not yet been answered.

Therefore, drugs which are less toxic to the liver and allow higher concentrations to be used in the perfusate will be studied. In our experimental colorectal cancer model melphalan was more effective than mitomycin C and there were no hepatotoxic side effects. In the first 37 patients treated with melphalan in a phase I and phase II study with doses up to 3.0 mg/kg, no hepatotoxic side effects were detectable.

In conclusion, ILP is a complicated surgical treatment which is technically feasible in patients with a low complication rate directly related to the procedure. ILP with mitomycin C induced one objective complete response, one objective partial response and a clear decrease in tumor size in several other patients. The median survival time was 17 months. Unfortunately, VOD, a hepatotoxic side effect of mitomycin C, occurred mildly in three patients but was lethal in one and therefore was dose-limiting.

Finally, these data show that the tumor response in, and the median survival time of patients treated with a single exposure of liver metastases of colorectal cancer to a high concentration of mitomycin C by ILP approximates that of patients treated with continuous intraarterial 5-fluorodeoxyuridine. These data confirm that exposure to much higher concentrations of particular drugs can improve the efficacy of treatment of relatively drug-resistant tumors. Therefore, we plan to continue our phase II study with high-dose (200 mg total) melphalan using ILP, producing no hepatotoxic side effects and allowing exposure of the tumors to high, and probably more effective, drug concentrations.

<table>
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Table III. Complete Remission of Hepatic Metastases and Median Survival Time with Intra-arterial FUDR/5FU + LV/FUDR + LV + Dec

Acknowledgments

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