Abstract. Aim: The aim of the present study was to evaluate single center experience with hepatic arterial infusion (HAI) of irinotecan, 5-fluorouracil and leucovorin in patients with liver metastases from colorectal carcinoma (CRC). Patients and Methods: A retrospective analysis of 68 patients treated between 1998 and 2007 was performed. Results: Among 60 patients who had no simultaneous liver-directed procedure (LDP), the best results obtained were complete response in two patients (3%), partial response in 18 patients (30%), and stable disease in 23 patients (38%), for an overall disease control rate of 72%. Median progression-free survival was 11 months, and median survival was 24 months. Overall survival was significantly better in patients with simultaneous LDP or secondary resection. Steatosis was present in all secondary resection specimens. Conclusion: Our data demonstrate the efficacy of HAI of irinotecan combined with 5-fluorouracil and leucovorin for liver metastases from CRC, specifically in patients also treated with LDP.

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The development of distant metastases remains the most significant problem in the management of colorectal carcinoma, with the liver representing the most common site of metastatic spread (1). Liver metastases in patients with colorectal carcinoma are frequently isolated, i.e. there is no extrahepatic metastatic spread (1). Therefore, liver-directed therapeutic strategies, including resection or therapeutic methods targeting tumor vasculature, are frequently considered appropriate for patients with isolated liver metastases of colorectal carcinoma (2). Hepatic resection, the only curative treatment in this setting, can be performed in only a minority of patients. Moreover, hepatic metastases ultimately recur in the majority of patients after resection (3). Patients with unresectable or recurrent liver metastases are currently treated with chemotherapy, or with the combination of chemotherapy and targeted agents, but virtually all patients will ultimately experience disease progression and die of metastatic disease. Therefore, the optimal therapeutic management still remains to be defined in patients with liver metastases from colorectal carcinoma.

Colorectal carcinoma is resistant to most cytotoxic agents. For active drugs, the maximum tolerated dose is usually administered, but dose escalation is limited by systemic side-effects. Various approaches that have been explored with the aim of enhancing the limited inherent selectivity of cytotoxic drugs include exploiting anatomical selectivity, e.g. administering the drug as a hepatic arterial infusion (HAI) (4). In patients with liver metastases, HAI has the advantage of higher drug concentrations in the tumor microenvironment with reduced systemic toxicity. Although it has been shown in randomized clinical studies that these theoretical advantages may translate into a superior response rate and quality of life (5, 6), it has been more difficult to demonstrate an improvement of survival. A survival advantage of HAI compared to systemic chemotherapy was demonstrated only recently using a regimen in the control arm that could no longer be regarded as the standard of care (7). Therefore, the use of HAI for colorectal cancer metastatic to the liver remains controversial. Although combination of fluoropyrimidines with oxaliplatin or irinotecan currently represents the standard chemotherapy regimens in patients with metastatic colorectal cancer, only limited data are available on the efficacy of HAI regimens with irinotecan. We present here a retrospective analysis of our single-center experience with HAI of irinotecan.
Patients and Methods

A retrospective analysis was performed of patients with histologically verified colorectal carcinoma treated at the Charles University Medical School and Teaching Hospital between January 1998 and December 2007 with HAI of irinotecan. A total of 68 patients, 42 males and 26 females, aged (mean ± standard deviation) 61 ± 9 (range = 36–79) years with colorectal carcinoma liver metastases were treated with at least one cycle of HAI of irinotecan. Five patients received part of the therapy using a common protocol in the Regional Hospital of Jindřichův Hradec, Czech Republic. Patient charts were searched for relevant information. Survival was calculated from the start of the first HAI course to death, or the last follow-up in 2011. No patients were lost to follow-up. Pilot experience with the first 15 patients of the present series has been published (8).

The regimen used in most patients comprised HAI of irinotecan (100 mg/m²) for 1–2 hours followed by leucovorin (50–350 mg) bolus or short infusion and 5-fluorouracil (750–1250 mg/m²) for 2–5 hours administered at weekly intervals. Modifications of this regimen were administered to some patients as outlined below. Premedication included intravenous injection of a setrone antiemetic (usually granisetron) and short infusion of dexamethasone (16 mg).

The staging of liver involvement (9) was based on operative reports and imaging studies. The response was evaluated by imaging studies of liver lesions using the standard World Health Organization criteria (10). HAI was administered through surgically implanted catheters with a subcutaneous port system, percutaneously implanted catheters with port system, or through a catheter introduced via femoral artery by the Seldinger technique as described elsewhere (11). Serum carcinoembryonic antigen (CEA) was determined by radioimmunoassay using a commercial kit (Immunotech, Marseille, France) as described elsewhere (12). Serum CEA was measured before the starting dose of irinotecan and every 2–3 weeks during treatment. Serum carcinoembryonic antigen (CEA) was measured before the starting dose of irinotecan and every 2–3 weeks during treatment. Serum carcinoembryonic antigen (CEA) was measured before the starting dose of irinotecan and every 2–3 weeks during treatment.

Progression-free survival and overall survival were evaluated with the Kaplan–Meier method, and the differences between patient subgroups were studied by log-rank test. The decision on statistical significance was based on $p = 0.05$ level. The analyses were performed using NCSS software (Number Cruncher Statistical Systems, Kaysville, UT, USA).

Results

Among 68 patients treated with HAI of irinotecan, 36 patients were treated in the first line of the treatment for metastatic disease, while 32 patients were treated in the second or higher line (29 patients in the second line and one patient each in the third, fourth and fifth lines). The median time from the diagnosis of liver metastases to the start of HAI was 3 (range = 1–60) months. The median time from the diagnosis of liver metastases to the start of HAI in patients treated in the first line and second or higher lines were 2 (range = 1–5) and 10 (range = 2–50) months, respectively. The catheters for HAI were placed surgically during an open procedure or percutaneously by an interventional radiologist in 60 patients and seven patients, respectively. In one patient, the single-use catheter was placed repeatedly using the Seldinger technique. In 67 patients with a port system, the median time from port system implantation was 0.5 (range = 0–22) months. In 29 patients, a single course of HAI of 5-fluorouracil/leucovorin was administered before the start of HAI with irinotecan after angiography performed to ascertain the vascular anatomy before the surgical placement of the catheter. The HAI of irinotecan was considered first-line therapy in these patients. Sixty-six patients were treated with the weekly regimen described above, while two patients received two modified regimens: HAI of irinotecan at 160 mg/m² for 2 hours on day 1, followed by leucovorin as 50 mg bolus and 5-fluorouracil at 675 mg/m² for 24 hours on days 1 and 2 every four weeks; and biweekly HAI of irinotecan at 90 mg/m² for 1 hour followed by leucovorin at 200 mg/m² for 2 hours and 5-fluorouracil at 350 mg/m² for 1 hour combined with systemic 5-fluorouracil at 1200 mg/m² for 46 hours, and weekly administration of cetuximab (400 mg/m² loading dose, then 250 mg/m² weekly). In three patients, the catheter for regional chemotherapy was placed into a portal vein tributary instead of the hepatic artery, and the therapy was administered as portal vein infusion. Among the patients treated with the weekly regimen, the initial dose of irinotecan was 100 mg/m² in 57 patients treated with the standard regimen, while the therapy was started at a dose of 60 mg/m² in nine patients that were elderly and/or had significant comorbidity. The doses of irinotecan and 5-fluorouracil were rounded up or down to allow for administration of the whole vial of the drug, and the actual starting dose of irinotecan administered was $99 ± 8$ mg/m² (range = 86–125 mg/m²) in patients scheduled to start at 100 mg/m², and $56 ± 8$ mg/m² (range = 41–65 mg/m²) in patients treated with the reduced dose. The actual starting dose of 5-fluorouracil administered was $758 ± 129$ mg/m² (range = 513–1301 mg/m²) and $665 ± 185$ mg/m² (range = 383–938 mg/m²), respectively. The reduction of the initial dose of irinotecan was necessary in 25 patients, including three patients who started the therapy at the reduced dose. The administration of HAI had to be delayed for toxicity, and was interrupted in four patients because of catheter malfunction before the re-implantation of the catheter. The median interval between the doses (excluding two patients who had an alternative regimen and four patients who had catheter re-implantation) was 1.4 (range = 1–2.8) weeks.

Twenty-one patients had stage 1 liver metastases according the Bengtsson classification, 46 patients had stage 2, and one patient had stage 3 liver metastases. Eight patients were treated with HAI immediately after other liver-directed procedures (resection in four, ethanol injection in three and radiofrequency ablation in one). Seven additional patients had an earlier history of liver-directed procedures and were treated with HAI for recurrent or persistent disease. The median duration of HAI was 34 (range = 1–137) weeks, and the median number of doses administered was 23 (range = 1–105). In patients not having simultaneously liver-directed procedure, the best response assessed by imaging was complete response in two patients (3%), partial response in
18 patients (30%), and stable disease in 23 patients (38%), for an overall response rate of 33% and disease control rate of 72%. Progressive disease was observed in eight patients (13%), and in nine patients the response was not evaluable. Seven patients underwent secondary resection after HAI with irinotecan (Table I). In most of the resection specimens, partial necrosis of tumor tissue with neoplastic cell viability between 50% and 100% and replacement by scar was observed. Pathological complete response with no evidence of malignant cells was observed in two cases. In the liver parenchyma, steatosis (predominantly macrovesicular) was observed in all cases. In addition, in some cases, regressive changes of hepatocytes (apoptosis and/or monocellular necrosis) with mild inflammatory response and incipient fibrosis, corresponding to steatohepatitis, were seen.

The median progression-free survival of the whole cohort was 11 months, and the median survival was 24 months. Three-, 4-, 5- and 7-year survival rates were 32%, 22%, 18% and 15%, respectively. In patients who had no initial liver-directed procedure, the median progression-free and overall survival times were 11 and 23 months, respectively. Overall survival was significantly longer in patients who underwent other liver-directed procedure immediately before the start of HAI (median survival 81 vs. 23 months, \( p=0.002 \)), and, in the cohort of patients who did not undergo primary liver-directed procedure in those who had secondary resection (median 60 vs. 22 months, \( p=0.002 \)) (Figure 1). The median progression-free survival and overall survival in patients treated in the first and second or higher line of therapy were 13 and 11 months, and 27 and 24 months, respectively.

Pre-treatment carcinoembryonic antigen (CEA) concentrations were available for 58 patients. Among 44 patients with baseline CEA concentrations above 5 μg/l, subsequent measurements were not available for three patients (including two with clinical progression), and a more than 50% decrease of CEA concentration was observed in 30 cases. CEA concentrations were stable in eight patients. A sustained rise of CEA concentration was observed in five patients, including two with initial CEA concentrations below 5 μg/l. A CEA surge, characterized by rising concentrations after the start of therapy followed by a decrease of serum concentrations, was observed in nine patients who subsequently had a more than 50% decrease of CEA levels or in whom the CEA level was stable.

The side-effects of therapy included diarrhea (any grade) in 37 patients and neutropenia (any grade) in 26 patients. Serious toxicity, defined as toxicity of grade 4 or requiring hospitalization, or second malignancy was observed in 28 patients, including diarrhea in 13 cases (accompanied in one case by febrile neutropenia and in two cases by sepsis), deep vein thrombosis in four cases, coronary events (myocardial infarction or unstable angina) in two cases, pneumonia in two cases, symptomatic deterioration in two cases, infusion reactions (anaphylactic reaction to irinotecan and infusion reaction after cetuximab) in two cases, vomiting in one case and two cases with second primary tumors. The two second primary tumors, including non-Hodgkin lymphoma and prostate cancer, were considered unrelated to therapy. Two patients died because of tumor progression accompanied by symptomatic...
deterioration, two patients died of pneumonia that was not accompanied by neutropenia, but there were no deaths directly attributed to the toxicity of the therapy. Subsequent therapy was administered to 48 patients. In addition to the patient treated with cetuximab in combination with HAI of irinotecan, 17 patients were subsequently treated with targeted agents (cetuximab in 10 patients, bevacizumab in five patients and both agents in two patients).

Table I. Patients undergoing secondary liver resection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Time between HAI start and resection (weeks)</th>
<th>Bengtsson Line Regimen</th>
<th>OR</th>
<th>Changes in the tumor (pathological response)</th>
<th>Histological changes in liver parenchyma</th>
<th>Patient status</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>64</td>
<td>40</td>
<td>1 1</td>
<td>W</td>
<td>PR 100% Viable tumor cells surrounded by scarring and calcifications</td>
<td>Centrolobular macrovesicular steatosis (20%), chronic inflammatory periportal infiltrate, hepatocyte monocellular necrosis, mild periportal fibrosis</td>
<td>D</td>
<td>20</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>60</td>
<td>64</td>
<td>1 1</td>
<td>W</td>
<td>PR Extensive scarring, 50% viable tumor cells</td>
<td>Macrovesicular steatosis (70%), mild periportal fibrosis, monocellular necrosis of hepatocytes</td>
<td>D</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>64</td>
<td>41</td>
<td>2 1</td>
<td>W</td>
<td>PR pCR Predominantly macrovesicular steatosis (60%), chronic inflammatory periportal infiltrate, mononuclear necrosis of hepatocytes, mild periportal fibrosis</td>
<td>AWD</td>
<td>61</td>
<td>103+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>52</td>
<td>21</td>
<td>2 3</td>
<td>W</td>
<td>SD Scarring, 70% viable tumor cells</td>
<td>Predominantly macrovesicular steatosis (70%), mild chronic inflammatory periportal infiltrate with mild interface necrosis, monocellular necrosis of hepatocytes, mild periportal fibrosis</td>
<td>D</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>51</td>
<td>22</td>
<td>1 1</td>
<td>W</td>
<td>PR Scarring, 60% viable tumor cells</td>
<td>Mild steatosis (10%), inflammatory periportal infiltrate, mild periportal fibrosis, necrosis of individual hepatocytes</td>
<td>D</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>61</td>
<td>67</td>
<td>1 1</td>
<td>W</td>
<td>PR pCR Predominantly macrovesicular steatosis (60%), mild portal inflammatory infiltrate, interface necrosis, monocellular necrosis of hepatocytes, no fibrosis</td>
<td>ANED</td>
<td>96+</td>
<td>96+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>61</td>
<td>41</td>
<td>2 5</td>
<td>C</td>
<td>SD Scarring, 70% viable tumor cells</td>
<td>Macrovesicular steatosis (40%), mild chronic periportal inflammatory infiltrate with interface necrosis, monocellular necrosis of hepatocytes, mild periportal fibrosis</td>
<td>D</td>
<td>27</td>
<td>60</td>
</tr>
</tbody>
</table>

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ANED, Alive, no evidence of disease; AWD, alive with disease; C, cetuximab (400 mg/m² loading dose, then 250 mg/m² weekly) plus biweekly HAI of irinotecan 90 mg/m² for 1 hour followed by leucovorin 200 mg/m² for 2 hours and 5-fluorouracil 350 mg/m² for 1 hour and systemic 5-fluorouracil 1200 mg/m² for 46 hours; D, died; F, female; M, male; OR, objective response; OS, overall survival; PFS, progression-free survival; pCR, pathological complete response; PR, partial response; SD, stable disease; W, weekly (standard dose).
Discussion

The present cohort ranks among the largest series of patients with colorectal cancer liver metastases treated with HAI of combination of cytotoxic agents and indicates the efficacy of HAI with irinotecan combined with 5-fluorouracil and leucovorin in patients with colorectal cancer metastatic to the liver. However, the toxicity of HAI using this combination was still relatively high. Despite the limited number of patients treated with this combined modality approach, overall survival was significantly better in those treated with a primary liver-directed procedure or secondary liver resection. Because of the inclusion of patients undergoing other liver-directed procedures, survival and progression-free survival rather than objective response rate were the primary end-points investigated in the present analysis. The objective response is frequently used in clinical studies to assess the efficacy of treatment as a surrogate for survival. In the present study, the standards of imaging varied over time and the objective response may be difficult to assess in individual patients, therefore the data on objective response may not be as reliable as in prospective studies. Given the long duration of follow-up, the survival data in the present cohort are mature and represent the best estimate of treatment efficacy. Moreover, the patients were mostly treated at the time when options for subsequent lines of therapy were limited, as evidenced by the low number of patients treated with targeted agents. The median progression-free survival of 11 months and overall survival of 24 months compare favorably with survival reported for patients treated with HAI, as well as with the results of combined systemic chemotherapy (13-17). Similar efficacies were observed for the therapy administered in the first or second or higher lines of treatment.

Chemotherapy represents the principal therapeutic modality in patients with metastatic colorectal carcinoma. In the early 1990s, systemic chemotherapy was demonstrated to significantly improve survival over best supportive care in patients with metastatic colorectal cancer (18). Later, irinotecan and oxaliplatin, were introduced, and further incremental survival gains have been demonstrated for the combination of fluoropyrimidines with these agents (13, 17), with median survival ranging between 16 and 22 months. More recently, further improvement of survival has been proven for targeted agents administered simultaneously with or sequentially to chemotherapy (19, 20).

Although different cytotoxic agents have been administered as HAI to patients with colorectal carcinoma liver metastases, the majority of these clinical trials have investigated fluoropyrimidines, 5-fluorouracil, usually combined with leucovorin, or 5-fluoro-2’-deoxyuridine (floxuridine). Flouxuridine has been regarded as a standard agent for HAI and has been used in many trials of HAI (14-16), but a randomized trial demonstrated that the results obtained with 5-fluorouracil are at least as good as with floxuridine (21). Reports have also been published on HAI of irinotecan (22-24). The liver tissue is known to possess high activity of carboxylesterase, the enzyme that converts irinotecan to SN-38, the active metabolite of irinotecan (25). This enzymatic activity is responsible for the higher conversion rate of irinotecan to SN-38 with HAI compared to systemic administration. The maximum tolerated dose of irinotecan administered for five days every three weeks in a phase I trial was 25 mg/m² (24). The conversion rate to SN-38 was higher for HAI compared with intravenous infusion in the same individual. The systemic concentrations of irinotecan were lower with HAI, but systemic concentrations of SN-38 were similar using HAI and intravenous infusion (24). Using a different schedule, the recommended dose from another phase I trial of irinotecan administered as HAI monotherapy was 200 mg/m² every three weeks (22). The objective response rate in the phase I cohort was 14%, but in the phase II cohort, in pretreated patients, the response rate was 33%. HAI of irinotecan, 5-fluorouracil and leucovorin was combined in a phase II trial with oral administration of UFT (combination of tegafur and uracil at a 1:4 molar ratio) and leucovorin in 31 patients, resulting in partial response in 20 (65%) patients, and median survival of 36 months (23). Irinotecan can also be administered regionally as sulfonate hydrogel microsphere, drug-eluting beads (DEBIRI). In a study of 55 heavily pretreated patients with metastatic colorectal carcinoma treated with DEBIRI, an objective response was observed in 36 (65%) patients, the median progression-free survival was 11 months and the median survival was 19 months (26). In another phase I/II study, systemic administration of irinotecan was combined with HAI of 5-fluorouracil and oral UFT (27). The recommended dose of irinotecan from the phase I part of the trial was 140 mg/m². In the phase II part of the study, 19 out of 22 patients (86%) had partial responses and 14 patients subsequently underwent liver resection (27). Systemic administration of irinotecan was studied in combination with HAI of floxuridine in 39 extensively pretreated patients, resulting in a 44% response rate, with a median survival of 20 months (28). HAI with the combination of oxaliplatin, irinotecan and 5-fluorouracil administered in a chronomodulated regimen was studied in 29 heavily pretreated patients with metastatic colorectal carcinoma (29). Partial response was observed in 10 patients (35%) and liver resection was performed in four patients. The median progression-free survival and overall survival were 5 months and 18 months, respectively (29). Chen et al. reported on HAI of oxaliplatin, irinotecan and doxifluridine in combination with systemic administration of doxifluridine and leucovorin in 32 patients (30). An objective response was noted in 61% of patients treated in the first line and in 29% of pretreated patients. The anecdotal experience in the present cohort with the patient treated with the combination of cetuximab and HAI in the fifth line of therapy who underwent...
subsequent liver resection and survived 60 months is encouraging, but, similarly to the pilot study of eight patients with five partial responses reported by Neyns et al. (31), needs to be confirmed in a larger prospective trial.

A distinct advantage of HAI is less toxicity compared to systemic therapy that is reflected in improved quality of life (6). The toxicities of systemic treatment, e.g. gastrointestinal toxicity induced by cytotoxic drugs (32), or the skin toxicity associated with the anti-epidermal growth factor receptor (EGFR) therapy (33) have a major impact on the quality of life. Although regional administration as HAI would be expected to result in less systemic toxicity, the toxicity of HAI of irinotecan combined with 5-fluorouracil and leucovorin in the present series was considerable. A direct comparison with systemic chemotherapy is not possible in a retrospective cohort study, but toxicity characteristic of irinotecan-based combination chemotherapy, mainly diarrhea, was observed in a significant proportion of patients. Theoretically, it may be argued that hepatotoxicity of cytotoxic agents administered by HAI might present a potentially serious problem, but, in clinical practice, liver toxicity of agents administered in HAI regimens seems to be, with few exceptions, limited. Liver toxicities associated with the administration of agents commonly used in colorectal carcinoma include non-alcoholic fatty liver disease after 5-fluorouracil, sinusoid obstruction syndrome after oxaliplatin, and steatohepatitis after irinotecan (34). These toxicities could result in postoperative complications (34), but there are no data indicating that liver toxicity is more prominent after HAI. In the present series, histological examination of the liver parenchyma was possible in seven patients who had secondary liver resections. Thus, the present cohort could be the largest reported series of patients examined after HAI of irinotecan. As already reported for the systemic administration of irinotecan (34), all seven patients had histological evidence of steatosis, progressing to steatohepatitis in some cases.

Little or no information is currently available regarding biomarkers that might predict the efficacy of HAI (4). Future studies should also address the effect of HAI on the immune response against the tumor. It has been documented that the systemic immune activation that is present in patients with metastatic colorectal cancer (12) is associated with depressed immune response in patients with advanced cancer, including those with liver metastases (35, 36). Prospective studies should elucidate whether HAI that results in tumor suppression with less systemic toxicity could actually enhance the host immune response.

In conclusion, the present data demonstrate the efficacy of HAI of irinotecan, 5-fluourouracil and leucovorin in the treatment of liver metastases from colorectal carcinoma. As expected, the best results were observed in patients treated simultaneously with other liver-directed procedures, and in patients in whom secondary liver resection was subsequently possible.

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References


