Hepatic arterial infusion plus systemic irinotecan in patients with unresectable hepatic metastases from colorectal cancer previously treated with systemic oxaliplatin: a retrospective analysis

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Background: Response rates to systemic chemotherapy are low after tumor progression on oxaliplatin regimens. Hepatic arterial infusion (HAI) therapy in patients with tumor progression is a viable alternative.

Patients and methods: Thirty-nine heavily pre-treated patients (all receiving prior oxaliplatin) with unresectable colorectal hepatic metastases were treated with systemic CPT-11 and concurrent HAI floxuridine (FUDR) and dexamethasone (DEX).

Results: Partial responses were seen in 44% of patients. Median time to hepatic progression was 8.6 months, and median time to overall progression was 6.5 months. Median survival from time of initiation of HAI was 20.1 months [95% confidence interval (CI) 16.9–21.4] and from the initiation of treatment of metastatic disease, 32.01 months (95% CI 29.1–34.6). After a median follow-up of 19.1 months, seven patients (18%) proceeded to potentially curative surgery. Grade 3/4 toxic effects included neutropenia (13%), diarrhea (15%), intra-abdominal hemorrhage (2%), and bleeding duodenal ulcer (2%). Elevated liver function tests were seen, including bilirubin concentration >3 mg/dl (7%), alkaline phosphatase 2X baseline (20%), and aspartate aminotransferase >3X baseline (26%).

Conclusions: HAI FUDR/DEX plus systemic CPT-11 achieves a response rate of 44% and a median overall survival of 20 months in heavily pre-treated patients with colorectal hepatic metastases all receiving previous oxaliplatin; 18% of patients proceeded to surgical resection or ablation.

Key words: colorectal cancer, hepatic arterial infusion, irinotecan, metastatic, oxaliplatin

introduction

The most common site of distal metastasis from colorectal cancer is the liver. Approximately 15% of patients will have liver metastases at the time of diagnosis and another 60% of people treated for colorectal cancer will develop liver metastases during or after treatment of their disease [1]. A minority of patients with liver metastases will have disease that is suitable for complete resection at the time of diagnosis, rendering these patients macroscopically clear of disease with an associated 30% survival at 5 years [2]. For the majority of patients, chemotherapy is needed.

Systemic chemotherapy for metastatic colorectal cancer has improved considerably in recent years. The combination of infusional fluorouracil (5-FU) and leucovorin (LV) with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) has achieved median survivals of 21.5 and 20.6 months, respectively, when administered as first-line therapy [3]. The addition of novel targeted agents, such as bevacizumab (an anti-vascular endothelial growth factor monoclonal antibody) and cetuximab (antibody against epidermal growth factor receptor) further enhances the efficacy of cytotoxic chemotherapeutic agents [4, 5]. Despite this progress in new systemic treatments, the long-term survival of these patients is still poor, with <5% surviving >3 years. Alternative treatment strategies such as hepatic arterial infusion (HAI) chemotherapy are therefore being explored.

The rationale for the use of HAI is based on the fact that tumor residing within the hepatic parenchyma is fed primarily by the hepatic artery, whereas normal liver tissue is supplied by the portal vein [6]. Therefore, direct infusion of chemotherapy into the hepatic artery may expose the tumor to higher drug concentrations. This method of administration also allows for minimal systemic toxicity by bypassing the effect of first-pass metabolism. Ten randomized studies have compared HAI with systemic chemotherapy and nine showed an increase in response rate in favor of HAI [7]. In the early studies, the improvements in overall survival (OS) were not significant, possibly attributable to the cross-over option permitted in some studies and the small sample sizes in others. Nevertheless, a meta-analysis, as well as a recently published
randomized Cancer and Leukaemia Group B (CALGB) trial did demonstrate an increase in median OS in favor of HAI [8]. In the CALGB trial, the HAI therapy produced a significant increase in median survival, 24.4 versus 20 months with systemic therapy alone (P = 0.0039).

In the second-line setting, HAI-based therapy has produced reasonable response rates in small single-institution studies. Using fluorouracil (FUDR)/LV/dexamethasone (DEX) in previously treated patients there was a 52% response rate, with a median survival of 13.5 months [9]. HAI FUDR/DEX plus mitomycin C (administered through the pump sideport) produced a 70% response rate in previously treated patients, with a median survival of 19 months [10]. Combining HAI with systemic CPT-11 produced a 74% response rate in patients who had received prior irinotecan or 5-FU with none receiving prior oxaliplatin [11, 12]. The median survival was 20 months.

The present retrospective study evaluates the efficacy of prior oxaliplatin [11, 12]. The median survival was 20 months. Combining HAI with systemic CPT-11 produced a 70% response rate in previously treated patients, with a median survival of 13.5 months [9]. HAI FUDR/DEX plus mitomycin C (administered through the pump sideport) produced a 74% response rate in patients who had received prior irinotecan or 5-FU with none receiving prior oxaliplatin [11, 12]. The median survival was 20 months.

### patients and methods

Patients for this retrospective analysis had histologically confirmed colorectal adenocarcinoma with unresectable hepatic metastases. All patients had received prior oxaliplatin, rendering them ineligible for an existing second-line HAI trial at Memorial Sloan Kettering Cancer Center designed for oxaliplatin-naive patients with unresectable hepatic metastases from colorectal cancer utilizing HAI FUDR/DEX plus systemic oxaliplatin and CPT-11. Baseline laboratory studies (including complete blood count (CBC), total bilirubin concentration, alkaline phosphatase (ALP), serum glutamic oxalacetic transaminase (aspartate aminotransferase, AST), carcinoembryonic antigen (CEA), and lactate dehydrogenase (LDH)) were obtained within 1 week of chemotherapy initiation. Computed tomography (CT) scans of the chest, abdomen, and pelvis were obtained before commencing chemotherapy. Patients with extrahaepatic disease on these scans were excluded from this study. During treatment, all patients had CBC and liver function tests every 2 weeks and CT scans every 2 months.

HAI pump insertion is done under general anesthesia, either as an open procedure or laparoscopically. The HAI pump is placed subcutaneously and sutured to the fascia of the abdominal wall; the catheter is then placed into the peritoneum and implanted into a branch of the hepatic artery, usually the gastroduodenal artery. During active treatment, the chemotherapy is injected using a noncoring needle through the skin of the abdomen and into the pump. The pump continuously delivers drug at a set flow rate by way of a fluorocarbon gas propellant which makes the pump function sensitive to heat and pressure.

Response was defined by the World Health Organization classification as follows: complete response required the disappearance of all disease on CT and normalization of CEA levels. A partial response (PR) denoted a reduction of ≥50% of the sum of the products of the greatest perpendicular diameters of tumor nodules. A reduction between 25% and 50% was considered a minor response (MR), a response of ≤25% was considered stable disease (SD) and an increase of ≥25% or more was considered progression of disease (POD). Confirmatory CT scans of best response were not always carried out within 4 weeks but were performed within 8 weeks. Confirmatory CEA levels, however, were carried out within 4 weeks.

### criteria for unresectable disease

Patients were considered ‘unresectable’ if disease involved all hepatic segments or if resection would leave behind an inadequate liver remnant (adequate liver reserve was at least two segments free of disease with good gross margins and intact portal vein inflow, hepatic vein outflow and one bile duct). Tumors that involved all three main hepatic veins or both inflow pedicles were also considered unresectable. Bilobar disease or number of metastases did not exclude a patient from consideration for resection, if sufficient liver remained to allow normal hepatic function. All cases were reviewed for resectability at a multi-disciplinary conference involving surgeons, radiologists, and medical oncologists.

### chemotherapy administration

Patients received systemic chemotherapy and HAI concurrently. Therapy was administered on a 4-week cycle; patients received regional therapy via the HAI pump (Codman pump; Johnson & Johnson, Norton, Massachusetts). FUDR at 0.16 mg/kg x 30/(pump flow rate) was administered with DEX at 1 mg/m²/day x 30/(flow rate) and 30 000 IU heparin with saline to fill the 30-cc chamber. The drug was infused continuously over 14 days, alternating with 14 days of heparin saline. Systemic irinotecan was administered on a 4-week schedule, 3 weeks on 1 week off at 100 mg/m², as per our phase I study. For patients with borderline performance status this was a difficult regimen. The majority of patients were treated on an every-other-week schedule (23 of 39 patients). Some patients were elderly with medical comorbidities and were started on an every-other-week schedule, and nine patients had toxicity on the three- or four-off schedule and were changed to the every-other-week schedule after cycle 1. Patients received treatment until (i) there was a reduction in the extent of disease that rendered the patient a candidate for resection; (ii) there was hepatic or extrahepatic POD, or (iii) excessive toxicity was experienced.

### toxicity assessment and dose modification

All toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). FUDR dose modifications were dependent on liver function tests (Table 1). Because patients exhibited varying degrees of hepatic enzyme elevations caused by disease, hepatic toxicity from treatment was defined as a significant increase over individual baseline values: two-fold or greater for ALP, three-fold or greater for AST, and bilirubin concentration ≥3 mg/dl. In the case of elevated transaminases and/or bilirubin concentration, FUDR administration was held and lowered after laboratory values improved as indicated and the dose was never again increased. Epigastric pain prompted workup with an upper gastrointestinal endoscopy. If an ulcer or gastrroduodenitis was documented, HAI therapy was held for 1 month to allow healing. Severe

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>17/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>58</td>
<td>30–82</td>
</tr>
<tr>
<td>BL percent liver involvement</td>
<td></td>
<td>40</td>
<td>25–80</td>
</tr>
<tr>
<td>No. with BL extrahepatic disease</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>No. of previous regimens</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td></td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three or more</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>BL CEA (ng/dl)</td>
<td></td>
<td>80</td>
<td>2.4–6884</td>
</tr>
<tr>
<td>BL ALP (µ/l)</td>
<td></td>
<td>155</td>
<td>65–642</td>
</tr>
<tr>
<td>BL LDH (µ/l)</td>
<td></td>
<td>246</td>
<td>145–948</td>
</tr>
</tbody>
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BL, baseline; CEA, carcinoembryonic antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.
Results

Thirty-nine patients (17 males and 22 females) with unresectable colorectal cancer metastatic to the liver were treated with concurrent HAI and systemic CPT-11. This was a heavily pre-treated population, with all patients having received oxaliplatin prior chemotherapy, and 11 patients (28%) previously treated with CPT-11 as well. The breakdown of the number of previous chemotherapy regimens was one (16 patients), two (17 patients), and three or more (six patients). Patient characteristics are outlined in Table 1. The median age of patients was 58 (range 30–82). Baseline CT scans showed a median liver involvement of 40% (range 15–80). Nine patients (23%) had extrahepatic disease at the time of treatment initiation, which was not clearly seen at baseline scan, and only seen on the second scans when extrahepatic progression was noted. Median baseline CEA was 80 ng/dl (range 2.4–6844.4) with 92% of patients having an abnormal baseline CEA. Median baseline LDH was 246 mg/dl (range 145–948) with 24 patients (67%) having an abnormal baseline LDH. Median baseline ALP was 155 u/l (35–642) with 32 patients (82%) having abnormal baseline ALP.

Response and survival

A PR was seen in 17 patients (44%; exact 95% CI 28% to 60%); MRs were seen in five patients (13%), and SD in nine (23%). The median duration of response among all patients was 4 months (average = 6 months, range 0–25 months) and there was no relationship between schedule of CPT-11 and response. Seventeen of the 22 responding patients (PR + MR) had a persistent reduction in CEA at least 4 weeks after best response.

Confirmatory CT scan at 8 weeks demonstrated persistent response in all but one of these patients. The median time to hepatic progression was 8.6 months (95% CI 6.0–26.5), and the median time to overall progression was 6.5 months (95% CI 4.7–8.6). With a median follow-up of 19.1 months, median survival from time of initiation of CPT-11 + HAI was 20.1 months (95% CI 16.9–21.4), with 18 patients alive at most recent follow-up (Figure 1). Median survival from first treatment of metastatic disease was 32 months (95% CI 29.11–34.56). Seven patients (18%) proceeded to potentially curative surgery (one patient resected, one patient ablated, and five patients resected and ablated). Of these seven patients, five had a PR to treatment whereas two had mixed response. The central lesion in both of these patients became smaller which enabled resection. Five R0s and two R1s were carried out and these patients are still alive. Twenty-six patients (70%) showed a >50% reduction in CEA, and 30 patients (81%) showed >30% reduction in CEA. The median number of treatment cycles received was 4 (range 1–25).

The following variables were assessed as potential predictors in univariate Cox models of survival, PFS, and time to hepatic progression: age, gender, baseline CEA, baseline LDH, baseline ALP, baseline percent liver involvement, prior CPT (Y/N), and synchronous tumors (Y/N). Baseline percent liver involvement was a significant predictor of OS (P = 0.002), log of baseline CEA was a significant predictor of time to hepatic progression (P = 0.01), as well as of PFS (P = 0.009), while baseline percent liver involvement was marginally significantly associated with PFS (P = 0.06). A cut point of 60% for baseline liver involvement was found to best separate patients in terms of their survival (adjusted minimum chi-square P = 0.03), with patients having a >60% involvement at baseline demonstrating worse survival (Figure 2). For patients with >60% liver involvement, there were two of 17 (12%) who had a PR. Since baseline percent liver involvement (treated as continuous) was the only significant predictor (at 0.1 level) for OS and log of baseline CEA was the only significant predictor for time to hepatic progression, multivariable Cox models were not built for these end points. Baseline percent liver involvement and log of baseline CEA were both significant predictors for PFS (at 0.1 level);
Liver metastases, the 5-year survival is £60% or <60%. Unfortunately, when entered together in a multivariable Cox model, only log of baseline CEA remained significantly associated with PFS (hazard ratio of 1.5, 95% CI 1.0–2.3, p = 0.05), whereas baseline percent liver involvement was no longer a significant predictor (hazard ratio of 1.2, 95% CI 0.9–1.5, p = 0.3).

toxicity

Three patients (8%) developed a bilirubin concentration >3 mg/l. The bilirubin concentration normalized in one of these patients when FUDR was held, while in the other two patients there was POD and they were taken off treatment. No patient required biliary stenting while on treatment, but three patients required stenting while on other treatment at 8, 16, and 27 months following the start of HAI therapy. Eight patients (20%) had a greater than two-fold increase in ALP, while 10 patients (26%) had a three-fold or greater rise in AST. All responded with normalization of liver functions following FUDR dose reduction. Grade 3/4 neutropenia was seen in 15% and diarrhea in 13%. Twelve patients (31%) required hospitalization during their treatment. Of these, six (50%) were admitted for reasons related to chemotherapy toxicity (i.e. fatigue, shortness of breath, neutropenic fever). The six remaining patients were admitted for reasons which could not be determined to be related solely to chemotherapy (i.e. postoperative complications including fluid collections and bowel obstruction, one patient with urinary tract infection and one fell at home). One patient presented to the emergency department with a bleeding hepatic artery, leading to discontinuation of treatment, and one patient developed a bleeding duodenal ulcer while on treatment, necessitating discontinuation.

discussion

The liver is the only site of metastatic disease in one-third of patients with colorectal cancer, and with surgical resection of liver metastases, the 5-year survival is ~30%. Unfortunately, resection is possible only in patients who have a limited number of lesions in locations amenable to surgery. This excludes most patients with hepatic metastases. Even with newer systemic therapies, the 2-year survival rate is generally <40% and drops rapidly with £5% surviving at 5 years.

One of the questions arising from the success of newer systemic agents is the treatment of metastatic colorectal cancer when there is progression on first-line therapy. FOLFOX (with or without bevacizumab) is one of the most commonly used first-line therapies [14]. After FOLFOX, second-line systemic therapy has a low response rate. Tournigand compared FOLFOX with FOLFIRI in a phase III study. At progression, irinotecan was replaced by oxaliplatin in one arm and in the other oxaliplatin by irinotecan [3]. In second-line therapy, FOLFIRI after FOLFOX produced a 4% response and a median PFS of 2.5 months. Surgery to remove metastases could be performed in two patients. In this trial, irinotecan was also used as second-line therapy, but only 18 of our patients received one prior regimen, while 21 (54%) were treated with two or more.

Newer agents such as cetuximab were approved in the second-line setting based on the results of a European trial in patients with advanced colorectal cancer whom treatment with irinotecan had failed (plus oxaliplatin in a number of patients). Patients were randomly assigned to cetuximab and irinotecan or cetuximab alone. The response rates for the combined therapy versus cetuximab alone were 22.9% and 10.8%, median time to progression 4.1 and 1.5 months and median survival 8.6 and 6.9 months, respectively. In a subgroup analysis of the patients who had received oxaliplatin in addition to irinotecan before entering the study, the response rate was 22.2% in the combination group and 8.1% in the cetuximab group. In another study of patients who had all failed irinotecan and the majority (85%) had also failed oxaliplatin treatment, bevacizumab was added to each arm [15]. The response rates for the two-drug group versus the three-drug (bevacizumab, cetuximab and irinotecan) group were 23% and 35% and median TTP were 4.0 and 5.8 months, respectively. A phase II study of 86 patients on lapatinib, an orally active, reversible inhibitor of the tyrosine kinase activity of ErbB1 (EGFR) and ErbB2 (HER2/neu) demonstrated limited activity as second-line monotherapy in patients with recurrent metastatic colorectal cancer pre-treated with 5-FU in combination with irinotecan or oxaliplatin [16]. Only one PR was seen, and median TTP and OS were 8 and 42.9 weeks, respectively.

Studies have investigated HAI-based therapy used in combination with systemic chemotherapy in the second-line setting. A phase I study of HAI FUDR combined with systemic irinotecan in previously treated patients (45% had previously received irinotecan but none had received prior oxaliplatin) reported a response rate of 74%, a time to disease progression of 8.1 months, and a median survival of 20 months [11]. A phase I trial of oxaliplatin plus HAI FUDR/DEX or oxaliplatin plus irinotecan with concurrent HAI FUDR/DEX in 36 previously treated patients (74% had received prior irinotecan, none previous oxaliplatin) produced response rates of 86%, with a median survival of 36 months and a 1-year survival of 80% [12].

In the present study all patients had received prior oxaliplatin/5-FU/LV or oxaliplatin and capcitabine and 11 patients (28%) had previously received systemic irinotecan. Many had been treated with more than one systemic regimen and six patients had received three or more previous systemic regimens. The response rate was 44% with a median survival from time of initiation of treatment of 20 months. Median survival from initiation of treatment of
metastatic disease was 32 months. Seven patients (18%) to date have proceeded to surgical resection and/or ablation.

We identified a number of baseline characteristics that were significantly associated with outcome. In our univariate analysis baseline percent liver involvement was a significant predictor of OS, while log of baseline CEA was a significant predictor of time to hepatic progression and PFS. Log of baseline CEA was the only significant predictor for PFS in a multivariable Cox model. Given the small sample size of the study, however, caution is required when interpreting these results. These variables should be assessed in a prospective manner in a larger group of patients to confirm their predictive power.

A cut point of 60% for baseline liver involvement was found to best separate patients in terms of their survival, with patients having a >60% involvement at baseline demonstrating worse survival. As is the case for surgical resection of hepatic metastases, a degree of subjective interpretation is used when choosing candidates for HAI therapy. This baseline characteristic may guide patient selection, although it needs to be confirmed on a prospective study.

In conclusion, HAI plus systemic irinotecan is an acceptable approach in heavily pre-treated patients with hepatic metastases from colorectal cancer who had previously received oxaliplatin. The combination of other systemic agents, including newer targeted therapies, with HAI may further improve response rates and result in a greater number of patients proceeding to potentially curable surgical resection.

**conflict of interest**

Dr Kemeny has reported that she has received Honoraria from Pfizer.

**funding**

Pfizer and Codman.

**references**


