An Update on Hepatic Arterial Infusion Chemotherapy for Colorectal Cancer

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ABSTRACT
Hepatic metastases are a frequent complication of colorectal cancer (CRC), affecting over half of all CRC patients. Resection of isolated metastases can result in long-term survival, but the majority of patients relapse, and most have unresectable disease. Hepatic arterial infusion (HAI) chemotherapy delivers high concentrations of cytotoxic agents directly to liver metastases with minimal systemic toxicities. Advances in surgical techniques, development of fully implantable pumps, and modification of drug regimens have decreased complications and improved patient tolerability. Randomized trials comparing HAI with systemic chemotherapy have demonstrated superior response rates and times to hepatic progression for unresectable disease, and have shown better times to progression and overall survival rates in the adjuvant setting following hepatic resection. HAI chemotherapy has unique toxicities, including chemical hepatitis and biliary sclerosis, which can be mitigated by the addition of dexamethasone to therapy. In an attempt to prevent extrahepatic progression, combinations of HAI with systemic chemotherapy, including newer agents such as irinotecan and oxaliplatin, are currently being investigated, with promising early results.

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INTRODUCTION
In 2003, an estimated 147,000 new cases of colorectal cancer (CRC) will be diagnosed in the U.S., with over 57,000 deaths [1]. Due to hematogenous spread of the tumor via the portal circulation, the liver is the most common site for metastasis, with involvement in up to 60% of patients. In a third of patients, it is the only site of metastatic disease. Prognosis is dismal for untreated patients, with median survival times of 6

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to 12 months and virtually no survivors at 5 years [2-4]. For selected patients with isolated liver metastases (usually four or fewer), surgical resection is the standard of care, as this is the only modality that consistently provides long-term disease-free survival in a substantial number of patients. Recent series have described 5-year survival rates of 25%-37% and 10-year rates of 20%-22% [5-7]. Unfortunately, 65%-80% of patients ultimately relapse, with half of the relapses occurring in the liver [5-10]. Also, less than 20% of patients are candidates for resection.

For patients with unresectable and/or extrahepatic disease, systemic chemotherapy with fluoropyrimidines has been the basis of care for over 40 years. Treatment with 5-fluorouracil (5-FU), with or without leucovorin (LV), produces a roughly 20% response rate and a 20% 2-year survival rate [11]. Adjusting the method of administration of 5-FU (i.e., continuous infusion versus bolus) can modestly improve response rates, without a significant impact on survival [12]. The addition of irinotecan and oxaliplatin to 5-FU-based regimens has resulted in superior response rates (40%-50%) as well as longer median survival times (15-17 months). The 2-year survival rate, however, remains poor (25%-30%), and long-term survivors are rare [13-15].

Because of the poor outcomes associated with metastatic CRC, alternative treatment strategies have been explored. One such strategy is hepatic arterial infusion (HAI) of chemotherapy for patients with liver-only metastases. This is not a new concept, with initial reports of HAI dating back to the early 1960s [16, 17]. In 1964, Sullivan et al. treated 16 patients with gastrointestinal tumors metastatic to the liver with continuous HAI and reported 10 objective responses with clinical benefit. Those authors concluded that “hepatic-artery infusion has a practical place in the management of liver cancer in selected cases” [17]. Multiple trials over the ensuing decades have confirmed this assessment of HAI as an effective treatment for liver metastases from CRC. This review focuses on the rationale for HAI, describes its technical aspects, and analyzes the data regarding its use, focusing on randomized, controlled trials. It describes the unique toxicities associated with this treatment, strategies for their management and prevention, and the potential impact of HAI on treatment costs. Finally, more recent investigations combining HAI with newer chemotherapeutic and biologic agents are reviewed.

**Rationale for HAI**

The concept of regional chemotherapy for hepatic metastases via HAI is based on several principles. First, tumor cells from gastrointestinal malignancies, especially CRC, spread hematogenously via the portal circulation, making the liver the first site of metastases in the majority of patients [18]. Given a possible stepwise spread of cancer from primary site to liver to other organs, direct treatment of hepatic metastases may prevent dissemination of tumor to other sites. Second, once hepatic metastases grow above 2-3 mm in size, they derive their blood supply from the hepatic artery, while normal hepatocytes are perfused mostly from the portal circulation [19]. Thus, infusion of chemotherapy via the hepatic artery could achieve toxic levels in tumor cells with relative sparing of normal hepatic parenchyma. Third, extraction of drug from the hepatic arterial circulation via the first-pass effect can result in high local concentrations and minimal systemic toxicity. The ideal agent should have a high dose-response curve, high extraction rate, and rapid total body clearance once infusion is discontinued. Of the various agents studied, 5-fluoro-2′-deoxyuridine (floururidine, FUDR) most approximates this ideal, with a demonstrated 95% hepatic extraction when given via HAI, resulting in a 16-fold higher concentration in hepatic tumors, compared with venous administration. HAI of 5-FU, mitomycin, cisplatin, and doxorubicin all showed significantly less extraction and therefore less advantage over systemic administration [20, 21]. Thus, FUDR has been the chemotherapeutic agent most utilized in studies of HAI in the U.S. (5-FU has frequently been used in Europe and Japan, in part due to a limited availability of FUDR). Finally, chemotherapy is given via a slow continuous infusion with the hope that the prolonged exposure of tumor cells to drug will result in a higher proportion of cytotoxicity. This concept has been borne out in CRC trials showing an advantage for fluoropyrimidines administered via infusional rather than bolus methods [12, 13].

**Technical Aspects of HAI**

**Methods of Infusion**

Early studies of HAI used hepatic arterial catheters placed surgically or percutaneously and attached to an external infusion pump. Treatment required prolonged inpatient stays and was complicated by frequent catheter-associated thrombosis, bleeding, infection, and migration of the catheter [21]. Another approach was the attachment of the catheter to a subcutaneous port, which could then be accessed intermittently or continuously for treatment. These ports still had a high failure rate, particularly with regard to hepatic arterial thrombosis [22, 23]. The development of a totally implantable infusion pump in the late 1970s eliminated many of the previous difficulties associated with HAI therapy. Slightly larger than a pacemaker, this pump is placed in a subcutaneous pocket created at the time of the surgical placement of the hepatic arterial catheter (Fig. 1). It can hold 30-50 ml of fluid and deliver the chemotherapeutic agent at a slow fixed rate. Typically, the reservoir is filled with a 2-week supply of chemotherapy, fol-
lowed by a 2-week infusion of heparinized saline. This con-
tinuous infusion decreases the rate of thrombosis, and filling
the pump every 2 weeks allows for more convenient ambula-
tory treatment. Most pumps also contain a side port for direct
infusion into the catheter, allowing the clinician to bypass the
reservoir, if desired. In one study, the implantable pump pro-
vided 115 days of chemotherapy administration, compared
with 31 and 25 days, respectively, for surgically and percuta-
nously placed catheters attached to an external infusion
device [24]. A recent single-institution retrospective compar-
ison of pumps versus ports found a lower therapy-relevant
complication rate (30% versus 47%) and a higher complica-
tion-free survival time (12.2 versus 7.3 months) in favor of
pumps [25].

Patient Selection and Evaluation

Candidates for regional therapy with HAI should have
metastatic disease localized to the liver and be medically
suitable for the surgical procedure. Extensive hepatic metas-
tases (>70% replacement with tumor), moderate or severe
hepatic insufficiency, and poor performance status are re-
late contraindications, as perioperative morbidity and mor-
tality in those situations are high. Patients with portal vein
thrombosis are at risk for significant hepatic ischemia and
should not be considered. The preoperative evaluation
should include a chest x-ray and computerized tomography
(CT) scans of the chest, abdomen, and pelvis to rule out
extrahepatic disease, as well as a recent colonoscopy for
patients with metachronous disease (Table 1). All patients
should undergo hepatic arteriography using CT angiography
to define the hepatic arterial anatomy. Patients with anatom-
ical variants that would preclude perfusion of the entire liver
should be excluded, though small vessels can often be tied
off to allow for proper perfusion. In the majority of cases
complete and specific hepatic perfusion is obtainable.

Pump Placement

At laparotomy, portal lymph nodes should be biopsied
to rule out extrahepatic disease. The catheter should be
inserted in the gastroduodenal artery, and ligation of distal
vessels supplying the stomach, duodenum, and pancreas
should be carried out to avoid misperfusion of these organs.
A cholecystectomy should be performed to avoid chemi-
cally induced cholecystitis from subsequent chemotherapy
[26]. Liver perfusion should be tested intraoperatively via
injection of fluorescein through the side port. Postopera-
tively, a technetium $^{99m}$Tc macroaggregated albumin perfu-
sion scan should be performed to confirm that perfusion is
limited to the liver (Fig. 2) and to rule out any arteriovenous
shunting. Extrahepatic perfusion should be confirmed with
an arteriogram, and the culprit vessel should be embolized,
if possible [27].
Early pump-related complications are uncommon (5%-10%) and usually technically related, including hepatic artery thrombosis, pump pocket hematomas, wound infections, underperfusion of liver, and/or extrahepatic perfusion. The 30-day mortality rate was low in two large recent series (0%-0.7%) [26, 28]. Late complications or device malfunctions, such as catheter thrombosis or displacement, pump pocket infections, hepatic artery thrombosis, pump failure, and gastric or duodenal ulceration, have been reported in up to 30% of patients [25, 26], though the incidence of technical complications varies considerably with surgeon experience. In one study, the complication rate of pump placement was 37% for inexperienced surgeons and 6.6% for experienced surgeons [29].

**Randomized Trials**

Early phase II trials of HAI of 5-FU or FUDR for CRC liver metastases showed promising results, with response rates of 29%-88% and longer survival compared with historical controls [30-33]. These led to a series of randomized phase III trials comparing HAI with systemic chemotherapy. Overall, results of nine trials have been published, with preliminary results of a tenth recently presented in abstract form (Table 2). Five trials compared HAI of FUDR with either i.v. FUDR [34-36], i.v. 5-FU [37], or i.v. 5-FU/LV (Mayo regimen) [38]. Two European trials [39, 40] compared HAI of FUDR with a control arm of i.v. 5-FU or best supportive care, based on the treating physician’s choice. All seven trials showed higher response rates for HAI compared with i.v. chemotherapy (42%-62% versus 9%-21%). While there were trends toward longer times to progression (TTP) and overall survival (OS) times for the HAI arms, these were statistically significant only in the two European trials. HAI was associated with a significant overall survival benefit in both of those trials (median, 15 versus 11 months [39] and 13.5 versus 7.5 months [40]). Given the proven benefit of systemic chemotherapy over best supportive care for metastatic CRC, these two trials would not be considered to have appropriate control arms today.

Two meta-analyses of these seven original trials were conducted, based on the premise that the individual trials were underpowered to detect a survival benefit. Over 600 patients were included. The Meta-Analysis Group in Cancer [41] confirmed the higher response rate seen with HAI (41% versus 14%). Overall, a 27% relative survival advantage was seen in the HAI arms ($p = 0.0009$) compared with the controls. When the European trials that included best supportive care were excluded, the survival advantage was 19%, but was no longer statistically significant ($p = 0.14$). Harmantas et al. [42] found a 12.5% 1-year ($p = 0.002$) and a 7.5% 2-year ($p = 0.026$) absolute survival difference in favor of HAI over systemic chemotherapy, which persisted even when the European studies were excluded. There are several potential reasons why the superior response rates with HAI in the individual trials did not translate into greater survival benefit. First, technical problems with pump placement and unexpectedly high rates of extrahepatic disease discovered at laparotomy led to a substantial number of patients who had never received regional therapy assigned to HAI arms (range 0%-34%, Table 2). This may have led to an underestimation of benefit when using an intention-to-treat analysis. Second, lack of experience in certain centers and the lack of a strict, predetermined dose-reduction schema in several trials may have led to greater toxicities and fewer cycles of therapy, which may have offset any survival benefit. Finally, three trials (conducted by the Memorial Sloan-Kettering Cancer Center [MSKCC], the Northern California Oncology Group [NCOG], and the City of Hope) allowed crossover to HAI therapy of patients who progressed on i.v. chemotherapy, which may have further diluted any survival benefit based on intention to treat.

Since those meta-analyses, two other randomized trials of HAI have been published. The German Cooperative Group randomized 168 patients with unresectable liver
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metastases from CRC to HAI of FUDR, HAI of 5-FU/LV, or i.v. 5-FU/LV [43]. Response rates were higher in the two HAI arms, with no significant differences in time to progression (the primary end point) or overall survival among the arms. Only 70% of patients in the HAI arms actually received the assigned treatment, and 51% of patients crossed over to other arms, making interpretation of these data difficult. There was a significantly lower rate of extrahepatic progression (13% versus 41%) and a higher rate of systemic toxicity (grade 3/4 68% versus 30%) for HAI 5-FU compared with HAI FUDR, consistent with the known lower hepatic extraction of 5-FU compared with FUDR. The Medical Research Council (MRC) and the European Organization for the Research and Treatment of Cancer (EORTC) groups compared HAI 5-FU/LV with i.v. 5-FU/LV, given as per the de Gramont regimen [44]. Crossover from the i.v. to the HAI arm was not allowed. Of 290 patients randomized, 221 (76%) received treatment as assigned, including only 66% assigned to HAI. Response rates were assessed in 183 patients at a single time point (12 weeks) and were nearly identical (22% for HAI, 19% for i.v. 5-FU/LV). No differences between the arms were noted for toxicity or progression-free or OS (Table 2).

Of note, both of the above trials utilized subcutaneous ports rather than implantable pumps and had significant catheter-related problems (36% of HAI patients in the MRC/EORTC trial [44]). Also, the MRC/EORTC trial utilized 5-FU instead of FUDR.

The Cancer and Leukemia Group B (CALGB) recently completed trial 9481 (Fig. 3), which compared systemic 5-FU/LV via the Mayo clinic regimen (considered a standard of care at the time of the trial design) with HAI of FUDR, LV, and dexamethasone, a regimen that had produced high response rates (78%) and low toxicity (3% biliary sclerosis) in a phase II study [45]. No crossover was permitted. Unfortunately, only 135 patients, out of an accrual goal of 340, were randomized, in part because of delays caused by a temporary halt in production of FUDR and implantable pumps by their respective manufacturers. The majority of patients had

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**Table 2. Randomized trials of HAI for unresectable liver metastases**

<table>
<thead>
<tr>
<th>Study group (year)</th>
<th>Arms</th>
<th>n (%) receiving assigned treatment</th>
<th>Crossover to HAI</th>
<th>Responses (CR + PR)</th>
<th>Median TTP (months)</th>
<th>Median TTHP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC (1987) [34]</td>
<td>FUDR</td>
<td>48 (94)</td>
<td>Yes</td>
<td>50%*</td>
<td>9</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>i.v. FUDR</td>
<td>51 (98)</td>
<td></td>
<td>20%</td>
<td>5</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>NCI (1987) [35]</td>
<td>FUDR</td>
<td>32 (66)</td>
<td>No</td>
<td>62%*</td>
<td>—</td>
<td>—</td>
<td>17†</td>
</tr>
<tr>
<td></td>
<td>i.v. FUDR</td>
<td>32 (92)</td>
<td></td>
<td>17%</td>
<td>—</td>
<td>6.5</td>
<td>15.8</td>
</tr>
<tr>
<td>NCOG (1989) [36]</td>
<td>FUDR</td>
<td>67 (75)</td>
<td>Yes</td>
<td>42%*</td>
<td>—</td>
<td>13†</td>
<td>16.5</td>
</tr>
<tr>
<td></td>
<td>i.v. FUDR</td>
<td>76 (86)</td>
<td></td>
<td>10%</td>
<td>—</td>
<td>5.3</td>
<td>11.6</td>
</tr>
<tr>
<td>City of Hope (1990) [37]</td>
<td>FUDR</td>
<td>31 (100)</td>
<td>Yes</td>
<td>55%*</td>
<td>8.8</td>
<td>—</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU</td>
<td>10 (100)</td>
<td></td>
<td>20%</td>
<td>7.5</td>
<td>—</td>
<td>11.6</td>
</tr>
<tr>
<td>NCCTG (1990) [38]</td>
<td>FUDR</td>
<td>39 (85)</td>
<td>No</td>
<td>48%</td>
<td>6.0</td>
<td>15.7</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU/LV</td>
<td>35 (103)</td>
<td></td>
<td>12%</td>
<td>5.0</td>
<td>6.0</td>
<td>10.5</td>
</tr>
<tr>
<td>French (1992) [39]</td>
<td>FUDR</td>
<td>81 (87)</td>
<td>No</td>
<td>44%*</td>
<td>—</td>
<td>14.5</td>
<td>15†</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU or BSC</td>
<td>82 (50)</td>
<td></td>
<td>9%</td>
<td>—</td>
<td>5.5</td>
<td>11</td>
</tr>
<tr>
<td>English (1994) [40]</td>
<td>FUDR</td>
<td>51 (96)</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>13.5†</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU or BSC</td>
<td>49 (10)</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7.5</td>
</tr>
<tr>
<td>German (2000) [43]</td>
<td>FUDR</td>
<td>54 (69)</td>
<td>Yes</td>
<td>43%*</td>
<td>5.9</td>
<td>—</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>HAI 5-FU/LV</td>
<td>57 (70)</td>
<td></td>
<td>45%*</td>
<td>9.2</td>
<td>—</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU/LV</td>
<td>57 (91)</td>
<td></td>
<td>20%</td>
<td>6.6</td>
<td>—</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU/LV</td>
<td>145 (87)</td>
<td></td>
<td>19%</td>
<td>6.7</td>
<td>—</td>
<td>14.8</td>
</tr>
<tr>
<td>CALGB (2003) [45]</td>
<td>FUDR</td>
<td>68 (87)</td>
<td>No</td>
<td>48%*</td>
<td>5.3</td>
<td>9.8</td>
<td>22.7†</td>
</tr>
<tr>
<td></td>
<td>i.v. 5-FU/LV</td>
<td>67 (87)</td>
<td></td>
<td>25%</td>
<td>6.8</td>
<td>7.3</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Note: response rate calculations are based on patients who actually received the assigned treatment. TTP, TTHP, and survival calculations based on intention to treat.

*Statistically significant difference ($p < 0.05$) compared with control group.

†Not reported, but calculated based on Kaplan-Meier survival curves published in original citations.

‡Responses in this trial were calculated at a single time point (12 weeks) in 77 HAI and 108 control patients.

Abbreviations: NCI = National Cancer Institute; NCCTG = North Central Cancer Treatment Group; BSC = best supportive care; CR = complete response; PR = partial response; — = not reported; TTHP = time to hepatic progression.
>30% liver involvement (70%), synchronous metastases (78%), and were chemotherapy naïve (97%). The response rate (48% versus 25%, \( p = 0.009 \)) was higher in the HAI group, though TTP was not significantly different (5.3 versus 6.8 months, \( p = 0.8 \)), with time to hepatic progression (TTHP) better in the HAI arm (9.8 versus 7.3 months, \( p = 0.017 \)) and time to extrahepatic progression better in the systemic arm (7.8 versus 23.3 months, \( p = 0.0007 \)). The median OS time was significantly better in the HAI arm (22.7 versus 19.8 months, \( p = 0.027 \)) [46]. Resource utilization, quality of life, and molecular markers of prognosis, such as thymidylate synthase (TS) and p21 gene expression, were examined prospectively in this study, and a final analysis of these factors in assessing the overall benefit of HAI therapy will be important.

**ADJUVANT THERAPY AFTER RESECTION OF HEPATIC METASTASES**

As stated previously, while patients who undergo resection of liver metastases from CRC can have prolonged survival, the majority will ultimately relapse, frequently in the liver. Therefore, the investigation of adjuvant therapies designed to decrease this risk of relapse is warranted. Adjuvant 5-FU-based systemic chemotherapy has not been shown to have a significant survival benefit [47-49]. Single-arm studies of HAI chemotherapy following hepatic resection have demonstrated the feasibility of this approach, with lower recurrence rates compared with historical controls treated with surgery alone [50, 51]. In a subset of the City of Hope trial [37], which included 91 patients in multiple different treatment groups, 11 CRC patients with solitary liver metastases were randomized to resection alone or resection plus HAI of FUDR. TTP was longer in the HAI arm, with no significant difference in survival. The small number of patients in that study precludes meaningful conclusions.

Three larger randomized trials of adjuvant HAI have been performed (Table 3). In the German Cooperative multicenter study [52], 226 patients were randomized to resection alone or resection plus 6 months of HAI of 5-FU/LV given as a 5-day continuous infusion every 28 days. The study was terminated early, as an interim analysis suggested a very low chance of demonstrating a survival benefit with adjuvant therapy. The impact of HAI therapy in that study is difficult to assess, as only 74% of patients assigned to HAI initiated this treatment and only 30% completed it. No differences in TTP, TTHP, or median OS were noted in an intention-to-treat analysis. When patients were analyzed “as treated,” TTHP (45 versus 23 months) and TTP or death (20 versus 12.6 months) were better in the HAI arm. Grade 3/4 toxicities, including stomatitis and nausea/vomiting, were noted in 63% of patients receiving adjuvant therapy, again reflecting significant systemic absorption of 5-FU when given via HAI.

The Intergroup study [53] randomized 109 patients to resection alone or resection followed by four cycles of HAI of FUDR and infusional systemic 5-FU, followed by eight more cycles of systemic 5-FU. Patients with more than three liver metastases or extrahepatic disease at laparotomy were taken off study; therefore, only 80 of 109 patients were actually included in the study. Based on intention to treat, there were no differences in median survival or 4-year overall survival between the groups. When patients were analyzed as treated \( (n = 75) \), 4-year disease-free survival (46% versus 25%, \( p = 0.04 \)) and 4-year hepatic disease-free survival (67% versus 43%, \( p = 0.03 \)) were better in the adjuvant therapy arm, though overall survival was not significantly different (62% versus 53%, \( p = 0.6 \)) (Table 3) [53]. Currently, 5-year survival is 60% versus 45% favoring adjuvant therapy (M.M. Kemeny, personal communication).

In the MSKCC study [54], 156 patients with resected hepatic metastases were randomized to 6 months of systemic 5-FU/LV or systemic 5-FU/LV plus HAI of FUDR/
The primary end points were 2-year overall survival and progression-free survival. Forty percent of patients had received prior adjuvant chemotherapy following resection of their primary CRC, and 15% had received prior chemotherapy as treatment for metastatic disease. Randomization was performed intraoperatively after complete resection of metastases, and patients were stratified based on the number of metastases and prior treatment history. Ninety-two percent of patients received treatment as assigned. The 2-year survival rate was 86% in the combined-therapy group versus 72% for systemic therapy alone (p = 0.03), with median survivals of 72.2 and 59.3 months, respectively. The 2-year hepatic progression-free survival (HPFS) rate was 90% for combined therapy and 60% for monotherapy (p < 0.001), with a trend toward a superior 2-year overall progression-free survival rate (57% versus 42%, p = 0.07) and median TTP of 37.4 and 17.2 months, respectively. Toxicities were moderate, with 39% of patients in the combined therapy group requiring hospitalization for diarrhea, neutropenia, mucositis, or small bowel obstruction, compared with 22% of the monotherapy group (p = 0.02). There were no significant differences between the groups in therapy-related deaths (one combined, two monotherapy) and in biliary sclerosis requiring stents (four combined, two monotherapy).

The latter two studies demonstrate lower hepatic and extrahepatic rates of recurrence for combined systemic 5-FU and HAI of FUDR therapy after surgical resection. The 2-year survival rate after liver resection (86%) was significantly better with the combined therapy in the MSKCC study and compared favorably with adjuvant systemic therapy alone (72%) and with historical 2-year survival rates for patients treated with resection alone (55%-70%) [5-10]. Further studies of adjuvant HAI of FUDR, combined with more active systemic chemotherapeutic agents (see below) are ongoing.

**TOXICITIES AND THEIR MANAGEMENT**

Because of its high extraction rate by the liver, HAI of FUDR alone is rarely associated with systemic side effects such as myelosuppression, stomatitis, nausea, vomiting, or diarrhea. The most common toxicities are peptic ulceration, chemical hepatitis, and biliary sclerosis. Ulceration or inflammation of the stomach or duodenum usually results from inadvertent perfusion and drug delivery to these organs. Persistent abdominal pain, melena, or diarrhea in patients on HAI therapy mandates prompt holding of therapy and endoscopic evaluation. Methylene blue can be infused via the side port during upper endoscopy; if blue staining of the ulcer appears, an angiogram to identify the aberrant vessel and to possibly embolize it is warranted [27].

Chemical hepatitis refers to an elevation in liver enzymes or bilirubin and is the most common toxicity associated with HAI therapy, occurring in 42% of patients in the randomized trials [55]. Liver enzymes and bilirubin should be monitored every 2 weeks while on therapy, and strict guidelines regarding dose reductions and/or cessation should be followed.
When managed appropriately, most cases of hepatic toxicity resolve. In some cases, progressive biliary sclerosis develops, which radiographically resembles idiopathic sclerosing cholangitis [56]. This complication is usually associated with FUDR, not 5-FU, with an incidence of 3%-26% in randomized trials [55]. Patients with progressive jaundice require endoscopic retrograde cholangiopancreatography to distinguish this finding from malignant strictures and to provide palliative stenting if possible.

Cholecystitis is no longer a problem now that cholecystectomy is routinely performed at the time of pump placement. Several attempts to decrease the hepatotoxicity of HAI have been made. Pathologic studies of liver specimens in patients with biliary toxicity from FUDR demonstrate both an acute and chronic inflammatory infiltrate in portal triads [57]. Kemeny et al. added dexamethasone to HAI of FUDR alone [58] or with LV [45] in an attempt to decrease the rate of biliary sclerosis, compared with a 21% rate with FUDR/LV alone in a previous phase II trial, without compromising response rates. The 2-year survival rate was 57% in previously untreated patients [45]. Currently, we combine 20 mg dexamethasone with FUDR in all of our HAI trials. If patients continue to have elevated levels of bilirubin or alkaline phosphatase despite discontinuation of FUDR, we add dexamethasone to saline in the pump until levels normalize. Other attempts to reduce hepatic toxicity have included alternating HAI of FUDR with 5-FU [59], with some success in early studies.

### COST ANALYSES OF HAI

HAI chemotherapy is expensive, and economic analyses have been performed to assess its cost-effectiveness. The Meta-Analysis Group in Cancer analyzed the costs incurred in the seven randomized trials included in its 1996 meta-analysis [41, 60]. Costs were computed for the entire duration of follow-up and were based on actual costs (in 1995 U.S. dollars) at two trial centers, in Paris, France and Palo Alto, California. The average cost per patient for HAI therapy (which included the pump and its implantation, initial hospitalization, administration of chemotherapy, and all related complications) was $29,562 in Paris and $25,208 in Palo Alto. The additional cost

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**Table 4. MSKCC guidelines for FUDR dose modification**

<table>
<thead>
<tr>
<th>Aspartate Aminotransferase</th>
<th>FUDR dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50 U/l</td>
<td>&gt;50 U/l</td>
</tr>
<tr>
<td>Current value</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;3 × ref</td>
<td>0 to &lt;2 × ref</td>
</tr>
<tr>
<td>3 to &lt;4 × ref</td>
<td>2 to &lt;3 × ref</td>
</tr>
<tr>
<td>4 to &lt;5 × ref</td>
<td>3 to &lt;4 × ref</td>
</tr>
<tr>
<td>≥5 × ref</td>
<td>≥4 × ref</td>
</tr>
<tr>
<td>If held, restart when</td>
<td></td>
</tr>
<tr>
<td>&lt;4 × ref</td>
<td>&lt;3 × ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alkaline phosphatase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤90 U/l</td>
<td>&gt;90 U/l</td>
</tr>
<tr>
<td>Current value</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;1.5 × ref</td>
<td>0 to &lt;1.2 × ref</td>
</tr>
<tr>
<td>1.5 to &gt;2 × ref</td>
<td>1.2 to 1.5 × ref</td>
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<tr>
<td>≥2 × ref</td>
<td>≥1.5 × ref</td>
</tr>
<tr>
<td>If held, restart when</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 × ref</td>
<td>&lt;1.2 × ref</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total bilirubin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.2 mg/dl</td>
<td>&gt;1.2 mg/dl</td>
</tr>
<tr>
<td>Current value</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;1.5 × ref</td>
<td>0 to &lt;1.2 × ref</td>
</tr>
<tr>
<td>1.5 to &lt;2 × ref</td>
<td>1.2 to &lt;1.5 × ref</td>
</tr>
<tr>
<td>≥2 × ref</td>
<td>≥1.5 × ref</td>
</tr>
<tr>
<td>If held, restart when</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 × ref</td>
<td>&lt;1.2 × ref</td>
</tr>
</tbody>
</table>

*Reference value is the value obtained on the day patient received the last FUDR dose.
†Current value is the value obtained at pump emptying or on the day of planned treatment (whichever is higher).
over control treatment (systemic chemotherapy in five trials, chemotherapy or best supportive care in two trials) was $19,636 in Paris and $19,280 in Palo Alto. Cost-effectiveness with respect to survival was $73,635 per life-year (LY) gained in Paris and $72,300/LY gained in Palo Alto, which was considered within the accepted range for therapies of life-threatening illnesses [60]. For comparison, cost-effectiveness estimates of hemodialysis range from $55,000-$80,000/LY gained [61], while estimates for lung transplantation range from $77,000-$176,000/LY gained [62, 63]. Another analysis was performed to compare the costs of HAI of FUDR, systemic 5-FU/LV, and best supportive care in two British randomized trials [64]. HAI was more cost-effective than systemic chemotherapy (£24,604 sterling versus £32,788) with regard to cost per LY gained, and equally effective with regard to cost per normal quality of life gained. The economic analysis done prospectively in the CALGB 9481 trial comparing HAI with systemic chemotherapy will be important in comparing the cost-effectiveness of these two treatments, as will analyses of the costs of combination chemotherapy regimens that use newer, more expensive agents.

**NOVEL APPROACHES TO USING HAI FOR CRC**

One observation drawn from the trials of HAI has been that, despite better control of liver metastases, the rate of (and time to) development of extrahepatic metastases has generally been inferior to that seen with systemic chemotherapy, which may explain the only marginal survival benefit associated with HAI. In addition, the superior rates of response and survival reported with irinotecan- and oxaliplatin-based regimens [13-15, 65] have created a new standard of care for first-line treatment of metastatic CRC and have, in retrospect, made the control arms used in previous HAI trials inadequate by today’s standards. Finally, novel surgical approaches, such as cryotherapy and radiofrequency ablation, have added more treatment options for patients with unresectable disease. With this in mind, combinations of HAI with these and other novel therapies are currently being investigated.

**HAI and Systemic Fluoropyrimidines**

A study of 44 patients with unresectable liver metastases compared HAI of FUDR with concurrent HAI and i.v. FUDR. A lower rate of extrahepatic spread was seen in the combination group (33% versus 61%), but response rates, toxicities, and survival were similar in the two arms [66]. Another single-arm study treated 40 patients with sequential HAI of FUDR and i.v. 5-FU/LV. The response rate was 62%, with a median TTP of 9 months and a 45% incidence of extrahepatic progression [67]. Of note, CRC metastases to the lung, the most common site of extrahepatic spread in patients treated with HAI therapy, have been shown to express higher levels of TS compared with hepatic metastases [68]. This is clinically significant, because high TS expression has been reported to predict resistance to 5-FU therapy [69], implying that combinations of HAI therapy with fluoropyrimidines may have limited efficacy in preventing extrahepatic disease.

**HAI and Irinotecan**

Irinotecan is a topoisomerase I inhibitor with proven efficacy in first- and second-line treatment of metastatic CRC. The activity of irinotecan is not inhibited by high TS activity [70]; thus, combining systemic irinotecan with HAI therapy may result in better control of extrahepatic disease. In a phase I study at the MSKCC, 38 patients with unresectable liver metastases received HAI of FUDR/dexamethasone and systemic irinotecan in escalating doses. All patients were previously treated, and 16 had prior second-line therapy with irinotecan. The regimen was well tolerated, with dose-limiting toxicities of diarrhea and myelosuppression. The response rate was 74%, median TTP was 8.1 months, and median survival was 17.2 months. Thirteen of 16 patients who had previously received irinotecan had partial responses (Fig. 4) [71]. The updated median survival is 20 months (N. Kemeny, unpublished data).

Another nonrandomized study used HAI of FUDR with systemic irinotecan as adjuvant therapy following cytoreduction of unresectable hepatic CRC metastases. The
cytoreduction was defined as using cryosurgery or radiofrequency ablation and/or partial resection to treat all identifiable sites of disease. Seventy-one patients received adjuvant therapy and were compared with an historical control group receiving cytoreduction alone. TTP (19 versus 10 months), median survival (30.6 versus 20 months), and the 2-year survival rate (75% versus 35%) were better in the group receiving adjuvant HAI plus irinotecan [72]. The use of an historical control group mandates caution in interpreting these results, as surgical experience and techniques likely have improved over time. At the MSKCC, a phase I/II study administered HAI of FUDR plus systemic irinotecan as adjuvant therapy following complete hepatic resection in 90 CRC patients. The maximum tolerated dose of irinotecan was 200 mg/m² every other week with 0.12 mg/kg FUDR for 14 days a month. With a median follow-up of 40 months, the 2-year survival rate was 87% [73]. Studies of direct intra-arterial infusion of irinotecan are under way as well [74] but, as significant hepatic extraction of irinotecan has not been demonstrated, it is unclear if this approach will offer any advantage over systemic administration.

**HAI and Oxaliplatin**

Oxaliplatin is a new cytotoxic agent with a mechanism of action similar to that of other platinum derivatives, but with a different spectrum of activity and toxicity. Clinical response rates, when combined with 5-FU/LV (FOLFOX), have been greater than 50%, with a median survival of 16.2 months in untreated patients with metastatic CRC [15, 65]. Preliminary studies utilizing systemic oxaliplatin-based regimens combined with HAI of FUDR have demonstrated the feasibility and safety of this approach, with promising early results [75, 76]. In the MSKCC phase I studies, 27 previously treated patients (74% prior irinotecan) with unresectable hepatic metastases received HAI of FUDR/dexamethasone plus either systemic oxaliplatin/5-FU/LV or systemic oxaliplatin and irinotecan. Both regimens were well tolerated, and response rates were 87% and 92%, respectively [76]. Phase I studies of direct HAI of oxaliplatin have demonstrated the tolerability of this approach as well [77, 78]. Once the appropriate dosing and timing of administration have been determined, larger trials to test the efficacy and, ultimately, to compare combined HAI and systemic oxaliplatin- or irinotecan-based regimens with systemic therapy alone are warranted.

**HAI of Biologic Agents**

HAI has been examined as a means of regional delivery of gene therapy for liver metastases. Based on the fact that the p53 gene is frequently defective or deleted in CRC and other cancers, two approaches using recombinant adenoviruses are being investigated. The first uses a replication-incompetent virus encoding wild-type p53 to infect cancer cells and replace the deficient gene product. HAI of one such adenoviral vector (Adp53 or SCH58500) was well tolerated in a phase I study and achieved significant transgene expression at higher doses; this vector is currently being studied further, both alone and in combination with HAI of FUDR [79]. A second approach uses replication-selective viruses lacking the E1B 55-kDa gene as a means of targeted oncolysis. This gene product binds to p53 and inhibits it, allowing for viral replication and cytotoxicity. A virus lacking the E1B 55-kDa gene is unable to inhibit wild-type p53, and therefore, selectively replicates in p53-deficient cancer cells while sparing normal cells. One such virus, Onyx-15 (aka d1520) was administered via HAI to 11 patients with refractory metastatic gastrointestinal cancers to the liver, with no dose-limiting toxicity and documented replication in vivo [80]. Further studies of these approaches are warranted.

Other novel approaches have included HAI of biologic agents such as cytokines. A study of HAI of recombinant human tumor necrosis factor (TNF) showed significant toxicity with few objective responses (14%) [81]. More recent studies combining HAI of TNF [82] or interleukin-2 [83] with HAI chemotherapy have reported promising response rates, with further follow-up ongoing. Regional infusion of a replication-competent, genetically engineered herpes virus has demonstrated oncolytic activity in preclinical studies, and phase I studies of this approach are under way in humans [84, 85]. Trials of HAI chemotherapy in combination with antiangiogenesis agents or epidermal growth factor receptor inhibitors have not been reported.

**Conclusions**

A great deal of progress has been made in the regional treatment of CRC liver metastases since the introduction of HAI chemotherapy over 40 years ago. Improvement in surgical techniques and the development of implantable pumps have decreased technical complications and improved patient tolerability of treatment. Several randomized trials of HAI therapy in patients with unresectable liver metastases from CRC have demonstrated higher response rates and longer TTHP than those seen with systemic fluoropyrimidine-based chemotherapy. Analysis of survival benefits is limited by methodological flaws, technical problems, and high toxicity in early studies; however, a recent CALGB multicenter study demonstrated an overall survival benefit for HAI of FUDR and dexamethasone versus systemic 5-FU and LV. Whether this benefit will hold up in comparison with more active systemic regimens using irinotecan or oxaliplatin is unknown. However, the median survival of 22.7 months in the CALGB study is encouraging and is among the highest reported of any multicenter study in metastatic colon cancer.
The use of HAI of FUDR and systemic 5-FU/LV following resection of hepatic metastases clearly decreases local recurrence and can improve 2-year survival, and further study of HAI in this setting is warranted. Both hepatic and extrahepatic relapses remain a problem and, therefore, initial studies combining HAI with newer systemic agents, such as irinotecan and oxaliplatin, are under way. These should provide a framework to guide us as to which combination regimens are the most effective and well-tolerated. Ultimately, this should lead to randomized trials of HAI therapy plus systemic chemotherapy versus our most active systemic chemotherapy alone in order to determine the best approach to treating hepatic CRC metastases.

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