Intra Arterial Hepatic Chemotherapy For unresectable Colorectal Metastases: (Review)

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Abstract

Background
Hepatic arterial infusion (HAI) chemotherapy is based on the idea that liver metastases are perfused almost exclusively by the hepatic artery. This approach has been extensively investigated in 1970s and 1980s. Currently, there is a worldwide growing interest in intra-arterial therapeutic approaches for hepatic metastases. The principal aim of this review was to define current role of HAI in the management of metastatic colorectal cancer

Methods
Data for this review were identified by searches of MEDLINE using the search terms “hepatic arterial infusion”, “colorectal cancer” and “chemotherapy”. Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English between 1966 and 2005 were included.

Results and Conclusion
There are 10 published randomised clinical trials comparing fluoropyrimidine-based HAI with systemic route. Two meta-analyses of the earlier 7 trials confirmed a statistically significant response rate and improved disease-free survival with HAI. However, the cost and complication rates were of primary concern. The last decade witnessed the introduction of new chemotherapeutic regimens including biologically targeted agents for the management of metastatic colorectal cancer patients and advancement in radiological and surgical techniques. These led to reconsideration of HAI-based therapeutic modalities with many running trials addressing its value in this new era. The results of these trials may help to clarify the role of HAI in the near future.

Key words
Hepatic, arterial, chemotherapy, colorectal, metastases

Introduction
Colorectal cancer (CRC) is the fourth commonest form of cancer world wide (1). Sixty percent of patients with colorectal carcinoma develop liver metastases during the course of their disease and the median survival for untreated patients is 6 to 12 months. The outlook has been considered poor for patients with this diagnosis and treatment options have been limited. Over the last few years, however, significant progress has been made. New effective chemotherapeutic agents have been introduced, and improved liver resection techniques have increased the number of patients who are considered suitable candidates for surgery. In addition, advances in ablative procedures and the delivery of regional chemotherapy have further expanded the options available for the treatment of hepatic metastases (2).

For many years, the only treatment for colorectal cancer was a combination of fluorouracil (FU) and leucovorin (LV), which produced response rates of approximately 20%, 2-year survival rates of 20% and median survival of approximately 12 months (3). With the introduction of Irinotecan (CPT-11) in 1996 and Oxaliplatin (Oxal) in 2002, the response rates have increased from 30% to 45%, with median survival times of 15 to 19.5 months, but 2-year survival rates remains low at 25% to 35% (4,5). Median survival of 17.4 months has been reported when Oxal was combined with
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CPT-11 and 19.5 months when combined with FU/LV, and 15 months with CPT-11/FU/LV (6). In previously treated patients, however, response rates with CPT-11 or Oxal drop to less than 30%, with median survival times of only 9 to 12 months (7-10). Three key trials were conducted in metastatic CRC and published in 2000 (4,5,11). Based on these trials, the irinotecan–5-FU/LV (IFL) regimen became the standard of care for metastatic colorectal cancer patients in the U.S. The role of IFL, however, was challenged in the N9741 intergroup trial, which were published in 2004 (6). The results of that trial compared IFL with FOLFOX4 (infusional 5-FU/LV with oxaliplatin) and with IROX (irinotecan plus oxaliplatin). Compared with IFL patients, patients on FOLFOX4 had a significantly longer time to progression (TTP) (median, 8.7 months vs. 6.9 months; p = .001), overall survival time (19.5 months vs. 15 months; p = .0001), and greater response rate (45% vs. 31%; p = .002). Survival with IROX was intermediate (17.4 months; p = .04 vs. IFL). That trial led to wide spread adoption of FOLFOX regimen as first line treatment for patients with metastatic colorectal cancer in US. In the same year, Tournigand et al (12) presented the results of a crossover trial that evaluated sequential folinic acid, 5-FU, and Oxaliplatin (FOLFOX6) followed by infusional 5-FU/LV with irinotecan (FOLFIRI) or the reverse sequence. At progression, irinotecan was replaced by oxaliplatin (arm A), or oxaliplatin by irinotecan (arm B). Median survival was 21.5 months in 109 patients allocated to FOLFIRI then FOLFOX6 versus 20.6 months in 111 patients allocated to FOLFOX6 then FOLFIRI (P = .99). In first-line therapy, FOLFIRI achieved 56% response rate (RR) and 8.5 months median PFS, versus FOLFOX6 which achieved 54% RR and 8.0 months median PFS (P = .26). Second-line FOLFIRI achieved 4% RR and 2.5 months median PFS, versus FOLFOX6 which achieved 15% RR and 4.2 months PFS. Based on these studies, current standard first-line regimens for metastatic CRC are FOLFOX (infusional 5-FU/LV with oxaliplatin) or FOLFIRI (infusional 5-FU/LV with irinotecan). Given the relative similarity in outcomes between the FOLFOX and FOLFIRI regimens, the initial choice is largely governed by patient and physician preference and differential toxicities between the two. In general, neurotoxicity, neutropenia, and thrombocytopenia are more frequent with FOLFOX, while febrile neutropenia, nausea/vomiting, mucositis, alopecia, and fatigue are more frequent with FOLFIRI (13).

For patients whose metastases are confined to the liver, complete surgical resection is associated with 30% disease free survival at 5 years and 20% at 10 years (14,15). Therefore, the optimal approach, when feasible, is surgical resection, but only 10% to 20% of patients with liver metastases from colorectal carcinoma will benefit from this option currently (16). If resection is not possible because of the number or location of tumors, other local therapeutic modalities, such as radiofrequency ablation (17) or cryotherapy (18) are being used. Another liver-directed treatment is the administration of hepatic arterial infusion (HAI) therapy (19). Initial trials with HAI therapy used a regional approach without added systemic therapy. These trials demonstrated increased response rates and progression-free survival, but many of these trials did not show an increase in overall survival (20-23). The combination of new systemic chemotherapy treatments with HAI can effectively treat extrahepatic and intrahepatic disease and may lead to improved results (24, 80).

The rationale for hepatic arterial chemotherapy is based on both anatomic and pharmacological factors. Liver metastases are perfused almost exclusively by the hepatic artery (once lesions grow above 2-3mm in diameter) (25), whereas the normal liver derives most of its blood supply from the portal vein (26). HAI chemotherapy delivers high concentrations of cytotoxic agents directly to liver metastases with less systemic toxicity (22-24). The ideal agent for HAI must fulfil certain criteria [Table-1]: it must be extracted in significant concentration by the liver; it should have a short half-life to avoid accumulation in the systemic circulation and have a high total-body clearance. If a drug is not rapidly cleared, recirculation diminishes the advantage of hepatic arterial delivery (27). Several cytotoxic agents have been used and a few new drugs are being evaluated for
A. Effective in tumour type being treated.
   1. Possess near linear dose-response curve for effectiveness.
   2. Systemic administration creates exposure at low end of dose-response curve.

B. Have pharmacokinetics properties to generate higher exposure with HAI.
   1. High total body clearance (\(\text{Cl}_{TB}\)).
   2. High hepatic extraction (\(\text{E}_H\)).
   3. Dose rate used not saturating of either \(\text{Cl}_{TB}\) or \(\text{E}_H\).

C. Appropriate physical properties.
   1. Stable at 37° for a long time.
   2. Compatible with titanium, stainless steel, silicone rubber and polyurethane.
   3. Very soluble relative to dose rate, ie, infusible in small volumes.

D. Miscellaneous.
   1. Approved by FDA for HAI.
   2. Nonsclerotic to arteries and subcutaneous tissues.

Table 1: Ideal drug properties for use in hepatic artery infusion chemotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (min)</th>
<th>Estimated Increased Exposure by HAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil (FU)</td>
<td>10</td>
<td>5- to 10-fold</td>
</tr>
<tr>
<td>5-Fluoro-2-deoxyuridine (FUDR)</td>
<td>&lt;10</td>
<td>100- to 400-fold</td>
</tr>
<tr>
<td>Bischlorethylnitrosourea (BCNU)</td>
<td>&lt;5</td>
<td>6- to 7-fold</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>&lt;10</td>
<td>6- to 8-fold</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20-30</td>
<td>4- to 7-fold</td>
</tr>
<tr>
<td>Adriamycin (doxorubicin hydrochloride)</td>
<td>60</td>
<td>2-fold</td>
</tr>
</tbody>
</table>

HAI = hepatic arterial infusion.

Table 2: Drugs utilised in Hepatic Arterial Infusion. (29)

their effectiveness in HAI. However, the gold standard agent until now is Floxuridine (FUDR). Ensminger et al (29) demonstrated that 94% to 99% of FUDR is extracted by the liver during the first pass, compared to 19% to 55% of 5-FU. The pharmacological properties of various chemotherapeutic agents for hepatic arterial infusion are summarized in [Table-2].

The purpose of this review is to evaluate the current role of HAI chemotherapy in the management of colorectal liver metastases. New trials using novel agents are ongoing, and understanding and optimising the delivery of intraarterial therapeutic agents may open a new horizon in the management of liver tumours.

**Implantation Technique**

Regional hepatic arterial therapy can
be delivered using either surgically or percutaneously placed intraarterial catheters connected to a subcutaneous port or an implanted pump. Implantable pumps are installed in a subcutaneous pocket created in the lower abdomen while the ports are fixed in front of the right lower ribs.

The classical route of hepatic arterial catheter (HAC) insertion is by laparotomy. Laparoscopy should be performed before laparotomy to exclude the presence of extrahepatic metastatic disease. The coeliac and periportal lymph nodes should be carefully inspected and biopsies sent for frozen-section if suspicious. The common hepatic artery is then dissected up to the bifurcation and both right and left branches exposed. The gastroduodenal artery must be isolated, and at least 1 cm of length is required for cannulation, this also prevent chemotherapy induced gastroduodenal mucosal toxicity. This necessitates the division of the right gastric artery, and of small arteries along the first part of the duodenum. The gallbladder is always removed to avoid chemical cholecystitis. The gastroduodenal artery is then ligated distally and the HAC introduced proximally by a longitudinal arteriotomy. It is important that the tip of the HAC lies exactly at the junction of the gastroduodenal artery and common hepatic artery. If it protrudes within the common hepatic artery the risk of thrombosis is high. Furthermore, the reverse is true, if the ligation is too low on the gastroduodenal artery, there is a risk of stagnation of the chemotherapy in the artery that may also produce thrombosis or favour catheter displacement. The HAC is secured with non-absorbable sutures placed behind the fixing rings of the catheter. Infusing 5 ml of fluorscein into the HAC then assesses perfusion of the liver. The perfused liver parenchyma turns green, and a Woods lamp is not necessary to check this.

The original design of the pump was a 2-chambered unit made of titanium. One chamber contained the drug and could be accessed from outside. The other, called the charging fluid chamber, was filled with Freon and totally sealed off. Fluids are infused into the drug chamber by means of a percutaneously placed needle. The filling of the chamber pushes the diaphragm of the charging chamber. The compressed Freon would then exert its energy by pushing up on the diaphragm of the device and in turn slowly push out fluid through the catheter of the pump. The first pumps used were made by the Infusaid Corporation (Norwood, Mass) and had a 50-mL reservoir (Fig. 1). The pump should be kept in a warmer throughout the first part of the operation and not brought to the field until the subcutaneous pocket is completed. If the pump is not warm (i.e., at least body temperature), there will be no pressure in the catheter and consequently there may be retrograde flow from the artery into the pump catheter. This may cause clotting of the catheter. When the pocket is ready for implantation the pump should be primed with a heparin solution that should be kept in the warmer too before it is placed into the pump. A hole is made in the fascia of the pocket so that the catheter can be pulled through it. The body of the pump should then be placed in the pocket, but not sewn in. It is important not to let the pump cool down too much below body temperature during the process of insertion. Next, the catheter is inserted into the gastroduodenal artery. In recent years different manufacturers have redesigned the pump with variations in the

Fig. 1: Cross section of the Infusaid (Infusaid Corporation, Norwood, Mass) pump

With kind permission of D. M Kemeny Laparoscopic placement of intra-arterial hepatic catheters has been reported in three clinical trials involving small number of patients. These trials reported acceptable operative times, intraoperative blood loss and no intraoperative complications or deaths secondary to catheter placement. Methylene blue was used instead of fluorescine to confirm complete hepatic
<table>
<thead>
<tr>
<th>Study Group (Year)</th>
<th>HAI No of Patients</th>
<th>Systemic No of Patients</th>
<th>Response to HAI FUDR %</th>
<th>CR**</th>
<th>PR***</th>
<th>Median TTHP* (Months)</th>
<th>Median Survival (Months)</th>
<th>Crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen-Mersh TG et al UK (1994)</td>
<td>FUDR 51</td>
<td>FU / SC</td>
<td>6%</td>
<td>37%</td>
<td>14.5</td>
<td>5.5</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Rougier P et al France (1992)</td>
<td>FUDR 81</td>
<td>FU / SC</td>
<td>50%</td>
<td>20%</td>
<td>_</td>
<td>_</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Kemeny N et al MSKCC (1987)</td>
<td>FUDR 48</td>
<td>FUDR 51</td>
<td>42%</td>
<td>10%</td>
<td>13</td>
<td>6.5</td>
<td>16.5</td>
<td>15.8</td>
</tr>
<tr>
<td>Chang AE et al NCI (1987)</td>
<td>FUDR 21</td>
<td>FUDR 29</td>
<td>55%</td>
<td>20%</td>
<td>_</td>
<td>_</td>
<td>13.8</td>
<td>11.6</td>
</tr>
<tr>
<td>Hohn DC et al NCOG (1989)</td>
<td>FUDR 50</td>
<td>FUDR 65</td>
<td>48%</td>
<td>12%</td>
<td>15.7</td>
<td>6.0</td>
<td>12.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Wagman LD et al City of Hope (1990)</td>
<td>FUDR 31</td>
<td>FU 10</td>
<td>5.4%</td>
<td>37.8%</td>
<td>12.7</td>
<td>17.6</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Martin JK et al NCCTG (1990)</td>
<td>FUDR 33</td>
<td>FU/LV 36</td>
<td>48%</td>
<td>25%</td>
<td>9.8</td>
<td>7.3</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Lorenz M et al German (2000)</td>
<td>FUDR 37</td>
<td>FU/LV 52</td>
<td>48%</td>
<td>19%</td>
<td>14.7</td>
<td>14.8</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>Kemeny N et al CALGB (2003)</td>
<td>FUDR 59</td>
<td>FU/LV 58</td>
<td>22%</td>
<td>19%</td>
<td>14.7</td>
<td>14.8</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

* TTHP: time to hepatic progression
** CR: complete response
*** PR: partial response
SC: Supportive care

Table 3: Randomized trials of HAI chemotherapy in unresectable colorectal hepatic metastases:
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perfusion via the catheter with no extrahepatic leak. Regional hepatic chemotherapy may be used as part of a totally laparoscopic multimode approach to the treatment of liver metastases, which includes techniques such as ablation (radiofrequency ablation or cryotherapy) or limited wedge resection. A completely laparoscopic approach to regional therapy may prolong the survival of these patients and offer them a better quality of life than they would have had with a laparotomy (35).

Early studies with percutaneously placed hepatic artery catheters needed repeated catheterisation for each cycle of chemotherapy. Clotting of the catheters and the hepatic artery, duodenal ulcers, and bleeding from around the catheters led to the abandonment of this technique (35-36). Currently, interventional radiological placement of indwelling intraarterial catheters has improved results with good rates of catheter and hepatic artery patency and low risk of infection (37). Percutaneous techniques usually introduce the catheter via the axillary or femoral artery. The axillary, subclavian or brachial artery route is preferred as it avoids sharp angulation of the catheter at the origin of the common hepatic artery from the celiac trunk. However, it carries higher rate of complications with 3% incidence of aneurysms and 0.5%-1% risk of stroke. Strokes may occur when the body of the catheter lies in front of the origin of the left vertebral artery or when thrombus dislodges from around the catheter on attempted removal (38). According to a review of the initial studies using percutaneous indwelling intra-vascular catheters for HAI, catheter dislocation and hepatic arterial obstruction occur at rate ranging from 5.6%-43.8% and 0%-22.2% (39-44). To overcome these drawbacks, a modified version of the procedure is used, in which the catheter tip is fixed to a vessel with the use of embolizing coils and/or liquid glue, and the anticancer agents are infused through a side hole of the catheter (45-47). This technique showed lower rates of 2.2%-4.4% for catheter dislocation and 5.4%-6.8% for hepatic arterial obstruction (48).

Toxicity

The most common complications of HAI are hepatic toxicity and ulceration of the stomach and duodenum (49). Consequences of inadvertent delivery of chemotherapeutic agents to non-target vessels have resulted in gallbladder ischaemia/necrosis (via the cystic artery), duodenal ulceration (gasroduodenal artery), gastric mucosal inflammation and necrosis (right gastric artery), diarrhoea and small bowel necrosis (supraduodenal and/or retroduodenal artery) and skin irritation (with faliform artery embolization) (50). Only 57%-61% of the population has what is considered to be the classic hepatic arterial perfusion pattern, emphasising the need to recognise not only the normal anatomy but also the variations. Much of the toxicity of intraarterial infusion can be prevented by selective cannulation of the hepatic artery and blockage of non-targeted branches (51).

Inaba et al (52) demonstrated that the incidence of acute gastric mucosal lesions confirmed endoscopically was only 3% (five of 192) in patients with adequate right gastric artery (RGA) embolization, whereas it was 36% in patients without RGA embolization and this difference was significant (P<0.01).

The bile ducts derive their blood supply almost exclusively from the hepatic artery and may be perfused with relatively high doses of chemotherapy. In an autopsy series of patients who had received HAI, damage to the biliary tree associated with small vessel necrosis was universal (53). Hepatic toxicity is manifested clinically by raised serum aspartate transaminase (AST), alkaline phosphatase and bilirubin. In lesser grades of toxic injuries, these abnormalities resolve on cessation of treatment. However in advanced cases it does not. In these patients who develop permanent toxicity, endoscopic retrograde cholangiopancreatography (ERCP) may show lesions resembling sclerosing cholangitis. If biliary sepsis is present drainage by ERCP or PTC stent placement may be helpful (54). A recent study of 60 patients receiving HAI reported that thin-section helical
CT was useful in determining the diagnosis, monitoring changes and guiding treatment (55).

Several approaches were used in order to decrease hepatic and biliary toxicity of HAI. Combining of dexamethasone with cytotoxic agents of hepatic arterial infusion may decrease biliary toxicity. In a randomized study, 50 patients with liver metastases from colorectal cancer were randomly selected to receive FUDR, 0.3 mg/kg/d, for 14 of 28 days, with or without a total dose of 20 mg of hepatic arterial dexamethasone for 14 of 28 days. There was a trend toward decreased levels of serum bilirubin in the group receiving dexamethasone plus FUDR versus the group receiving FUDR alone (9% and 30%, respectively, P = 0.07). There was a trend towards increased survival with the addition of dexamethasone (median, 23 months and 15 months, respectively; P = 0.06) (56). Modification of the gold standard FUDR regimen has been tried in phase I and II trials in order to increase response and decrease hepatic toxicity (24).

In attempt to get maximum response with least toxicity depending on mismatched pharmacokinetics of FUDR and 5-FU, Stagg et al (57) used alternating HAI of continuous FUDR at 0.1 mg/kg of body weight per day on days 1 through 8 followed by an HAI bolus of 5-FU at 15 mg/kg given on days 15, 22, and 29, with the cycle repeated every 35 days. This study included 64 patients, of whom 30 (47%) had received prior chemotherapy. A major response (complete response plus partial response) was observed in 32 (50%) of 64 patients with a median survival from pump implantation of 22.4 months. In contrast to the experience with the single-agent HAI FUDR regimen, no patient had treatment terminated because of drug toxicity. Based on the success of previous trials, an additional study was performed using HAI FUDR, leucovorin, and dexamethasone. The response rate to this combination regimen in previously untreated colorectal cancer patients was 78%, and the median survival was 24.8 months. A strict dose-reduction schema reduced the incidence of biliary sclerosis to 3%, although dose adjustments or temporary cessation of therapy was often necessary in nearly every patient (58).

**Randomised trials:**

There are now ten randomized phase III trials comparing the relative benefits of HAI fluoropyrimidine-based chemotherapy (FUDR) with systemic chemotherapy or best supportive care in the management of unresectable liver metastases from colorectal cancer [Table 3] Two trials compared HAI using FUDR with a control arm intravenous 5-FU or best supportive care depending on the choice of patients and physicians (59, 60). Another three trials compared the results of using FUDR via HAI versus using it systemically (20, 21, 22). Three trials compared HAI of FUDR with intravenous 5-FU/Leucovarin (LV) (23, 62, 75). A single trial assessed FUDR infusion in the hepatic artery versus intravenous 5-FU alone (63) while the last study published by Kerr et al (64) compared HAI of FU/LV versus intravenous combination of the same medications and this is the only randomised study that did not use FUDR.

Two meta-analyses of the first seven trials between 1986-1994 were carried out in 1996 to provide an objective and quantitative appraisal of the benefits of HAI in terms of tumour response rate and overall patient survival (66,67). In all trials, complete response (CR) was defined as the disappearance of all detectable tumor, and partial response (PR) was defined as a 50% reduction in the sum of the products of the largest perpendicular diameter of all measurable disease, without new lesions. The minimum required response duration was 4 weeks in most of the trials. In the meta-analysis, patients with minimal response, stable disease, or tumor progression were considered as “no response”. A total of 315 patients who received HAI of FUDR were compared with a control group of 322 patients. These overall numbers may statistically overcome the individual trials underpowered to detect survival benefit. Trials involving fewer than 200 patients often contain significant imbalances in patient characteristics that can lead to misleading conclusions (65).

The Meta-Analysis report (66) highlighted the benefit of HAI compared to intravenous
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Chemotherapy (IVC). The objective tumour response rate was 41% for patients allocated to HAI (CR, 3%; PR, 38%) and 14% for patients allocated to IVC (CR, 2%; PR, 12%). In four trials (20-23), the odds ratios indicated a statistically significant advantage in response rate for HAI. The overall response odds ratio was 0.25 (95% CI=0.16-0.40), indicating a significant advantage for HAI (P<10-10). Treatment was the only significant prognostic factor for tumor response. In this meta-analysis the impact of HAI on survival was less clear. Individual trials were too small to signify survival benefit. In two trials (59, 60), HAI was confirmed to be superior to a no HAI control group in which some patients were left untreated until symptoms occurred (hazard ratio=0.67; P=0.002). A consistent trend toward better survival in the HAI group was seen when compared with IVC group, but the benefit appeared to be smaller and not statistically significant (hazard ratio=0.81; P=0.14). The authors were not able to acquire the raw data from the study by Hohn et al (22) that was excluded from the analysis. Given the significant sample size of this trial (n=143), the authors commented that had the individual patient data been available, the statistical power to detect a possible difference between regional and systemic therapy would have been higher. However, Harmantas et al (67) were able to incorporate the Hohn et al (22) study, but excluded Rougier et al (59) and Allen-Mersh et al (60) studies from the final analysis because the control groups did not uniformly receive systemic chemotherapy, thus allowing for bias of treatment effect. This analysis identified 12.9% increased survival at one year for patients who received HAI compared to those who had systemic chemotherapy. The 2-year survival difference was 7.5% (95% CI, 0.9% to 14.2%) with an associated P value = 0.026.

The benefit of HAI may be masked or underestimated in these meta-analyses, as there are limitations of the technique, particularly with quality of radiological staging and intervention at the time these studies were conducted. Furthermore, analyses based on treatment actually given rather than intention to treat would inherently be biased and were avoided. The English (59) and French (60) studies that were excluded because some patients in the control group did not receive systemic chemotherapy may further minimise the value of HAI as both trials showed significant survival difference. Another factor that masked the result of HAI was the crossover of patients to HAI at the time of failure of IVC in three trials (20,22,63). The number of patients that converted to HAI was 31 of 51 in the MSKCC trial (20), 28 of 76 in the NCOG trial (22), and all six patients in the City of Hope study (63). It is possible that these crossovers may have led to an underestimation of survival advantage with HAI.

Four years after the publication of these two meta-analyses the German Cooperative Group on Liver Metastases (62) published the results of a randomized, multicentre, prospective study that enrolled a total of 168 patients at 25 centres. Based on the results of 5 European studies (68-72) of HAI 5-FU plus leucovorin (LV; folinic acid) that demonstrated response rates similar to or better than those obtained with HAI FUDR, this study was designed to compare the efficacy and tolerability of HAI FUDR (the gold standard) with two newer treatment modalities: 5-FU plus LV administered via HAI and 5-FU plus LV administered via intravenous (IV) infusion. Although this study looks recent compared to the previous Meta analysis studies, the patients were enrolled between April 1991 and June 1995 and the results were reported five years later. Eligible patients were randomized into three groups to receive either HAI or IV 5-FU/LV or HAI FUDR. After crossover or withdrawal of treatment; 40 patients received HAI 5-FU/LV, 37 HAI FUDR and 71 IV 5-FU/LV. The median times to progression were 9.2 months for the HAI 5-FU/LV group, 6.6 months for the IV 5-FU/LV group and 5.9 months for the HAI FUDR group. Subgroup analysis revealed a nearly two-fold increase in the time to progression among patients with an intrahepatic tumor burden of less than 25% who were treated with HAI 5-FU/LV. No clinically significant differences between treatment groups in time to progression were observed among patients with an intrahepatic tumor burden of > 25% which is the commonest scenario in unresectable tumours. Median survival times among patients...
treated with HAI 5-FU/LV, IV 5-FU/LV, and HAI FUDR were 18.7 months, 17.6 months, and 12.7 months, respectively. Once more, subgroup analysis revealed a survival benefit among patients with an intrahepatic tumor burden of less than 25% who were treated with HAI 5-FU/LV. No clinically significant differences between treatment groups in survival were observed among patients with an intrahepatic burden of >25%. Of special interest in this study is the significant difference in the rate of extrahepatic disease progression in patients treated with intrahepatic 5-FU/LV (13%) compared to those who received intrahepatic FUDR (41%). The assumption is that because FUDR is 95% metabolised in the liver, no significant cytostatic systemic levels accumulate. The next trials have evaluated targeted plus systemic versus systemic treatment alone.

The results of the German study were consolidated by a trial of the Medical Research Council (MRC) and the European Organization for the Research and Treatment of Cancer (EORTC). Supported by the results of HAI of 5-FU/LV study and because Floxuridine was not licensed for use in the UK and the implantable pumps required for its delivery were expensive, and the study design had been finalised before the emergence of Irinotecan and Oxaliplatin, a fluorouracil-based schedule was proposed. The primary endpoint was overall survival. Secondary endpoints were progression-free survival, toxicity, and quality of life. Response was assessed to decide whether or not to continue treatment. On the basis of results from previous MRC/EORTC trial, the authors predicted that median survival of patients with hepatic metastases satisfying the eligibility criteria was 10 months, and fewer than 10% would survive 18 months from randomisation. To detect a 50% increase in median survival from 10 to 15 months, equivalent to a hazard ratio of 0.67, or an increase in survival at 18 months from 10% to 22%, they calculated that 312 patients were required.

Between December 1994 and August 2000, 290 patients from 14 UK, one Irish, and one German centre were randomly assigned to enter treatment via HAI or IV fluorouracil. The trial was stopped shortly before the target sample size of 312 was achieved because of a fall-off in recruitment. 50 patients (37%) allocated to HAI did not start treatment, and another (29%) had to stop before receiving six cycles of treatment because of catheter failure. The HAI group received a median of two cycles (0-6), compared with 8.5 (6-12) for the intravenous group. (51%) HAI patients who did not start or did not receive six cycles switched to intravenous treatment. Median overall survival was 14.7 months for the HAI group and 14.8 months for the intravenous group with no significant difference. Furthermore, there was no significant difference in progression-free survival. In the HAI group, median progression-free survival was 7.7 months and disease had not progressed in 28% patients at 1 year, and 4% at 2 years. In the intravenous treatment group, median progression-free survival was 6.7 months and 20% patients were progression free at 1 year, and 6% at 2 years. The results of this study should be considered carefully as FUDR (Gold standard treatment) was not used and it only assessed different modes of delivery of chemotherapy. Ports rather than subcutaneous pumps were used which resulted in the high failure rate of maintaining catheters for infusion.

Wickremeskera et al reported problems in 33% of patients, which prevented continued use of ports. Gennari et al noted a much higher device failure rate with ports (90%) than with pumps (32%). Consequently, the HAI group received inadequate treatment with a median of two cycles compared to 8.5 cycles in the IV group. As the study showed no clinical significance between the two groups with this marked difference in cycles of treatment received, it could be interpreted as showing a greater effect from HAI.

The Cancer and Leukaemia Group B (CALGB) reported an abstract showing statistically significant difference in response rates and overall survival between IV 5-FU/LV and HAI of FUDR, LV, and dexamethasone. The regimen had produced high response rates (78%) and low toxicity (3% biliary sclerosis) in a phase
II study. Out of target of 340, 135 patients were randomised, in part because of commercial non-availability of FUDR and implantable pumps. The response rate was higher (48% versus 25%, P=0.009), and time to hepatic progression was longer (9.8 versus 7.3 months, P=0.017) in the HAI arm. The HAI group had a significantly longer median survival time (24 versus 20 months, P=0.0034). However, extra hepatic progression was more rapid (8 versus 24 months) in HAI group. The scope of this study included quality of life, cost-effectiveness and measurement of thymidylate synthase (TS) and p21 (cyclin dependent kinase inhibitor) in tumor by PCR as predictors of prognosis. When the analyses of these factors become available by the end of the study, a new concept may be created regarding HAI therapy. However, an unanswered question will be there, regarding the high rate of extra hepatic progression in HAI group that did not receive systemic chemotherapy. It will however provide a base line for comparison with other phase I and phase II studies incorporating novel agents in HAI.

New Trials

The initial trials of HAI used a regional approach without added systemic therapy. These trials revealed increased response rates and progression-free survival. However, the majority failed to demonstrate survival benefits. Based on high response rates of Fluoropyrimidine, Irinotecan or Oxaliplatin combination therapy for colorectal cancer, these agents have been used in HAI trials, attempting to effectively treat both extrahepatic and intrahepatic disease.

A French multicentre trial used 100 mg/m² of Oxaliplatin infused intra-arterially combined with systemic 5-FU/LV with an overall response rate of 64%. This study enrolled 28 patients of whom 4 (15%) underwent resection of their metastases after treatment response. One and 2-year overall survival rates were 82% and 63%, respectively, and 1- and 2-year progression-free survival rates were 67% and 55%. Another study enrolled 12 patients with colorectal liver metastases, all pre-treated with evidence of progressive disease. These included 3 after partial remission induced by oxaliplatin, folinic acid and 5-FU, 3 after partial remission induced by irinotecan, folinic acid and 5-FU and 6 patients after failing a 5-FU and folinic acid regimen. They all received HAI with Oxaliplatin. Dose-limiting toxicity was observed at 175 mg/m²/cycle. Following phase I, all patients received 150 mg/m² for six cycles. They reported 4 cases of partial remission (33%) lasting 24, 15, 12 and 10+ weeks, respectively, 2 with disease stabilisation (17%) lasting more than 12 weeks and 6 with progression (50%). The median survival was 13 months (range 6-19). An Australian study reported similar results and showed that previous chemotherapy administration did not alter response rates or survival time in this group of patients.

A phase II study using HAI with Irinotecan at 200mg/m² enrolled 12 patients, of whom 6 progressed after initial response to systemic 5-FU/LV and Oxaliplatin therapy. Sustained partial response and stable disease of at least 8 weeks duration was noted in 4 (33%) and 3 (25%) patients, respectively. A recent study reported the response to HAI Irinotecan at a dose of 150 mg/m² given over one hour. After 2 weeks of rest chronomodulated 5FU, leucovorin and carboplatin were given. After 10 days’ rest another HAI was given. Each therapy included 2 HAI courses and 2 chronotherapy courses in between. Ten patients had previously been treated with 5FU and leucovorin while, 5 patients were chemonaive. The mean number of cycles given was 11.6 per patient (range 8-19). Partial response was achieved in 6 patients (40%) and was followed by laparoscopic radiofrequency ablation in 5 patients (33%). Disease stabilization was observed in 2 patients (13%) and disease progression in 7 patients (47%) mainly after previous chemotherapy failure.

To try to further improve the outcome for unrespectable hepatic metastases, Kemeny et al designed a study combining novel systemic chemotherapy agents with HAI of FUDR and dexamethasone. Thirty-six patients (89% previously treated) with unresectable liver metastases were treated with HAI and systemic Oxal plus Irinotecan (Group A= 21 patients) or
Oxal and 5-FU/LV (Group B=15 patients). The complete and partial response rate was 90% for group A and 87% for group B. Median survival time was 36 and 22 months for group A and B respectively. Seven patients (33%) of group A ultimately underwent liver resection. This high response rate should encourage further trials using this regimen in the neoadjuvant setting and possibly in patients with progression on first-line chemotherapy.

**Conclusion**

Colon cancer with advanced liver disease represents a significant public health problem because of its frequency and cost of its treatment. Until the early 1980s, metastatic colorectal cancer to the liver was often left untreated. Data from that era clearly demonstrate untreated disease to be rapidly fatal, with a median patient survival of only five to 10 months. In recent years, a number of phase III clinical trials have reported median survival times approaching 20 months with the administration of modern combination chemotherapy. However, this approach is still considered palliative because long-term survival or cure is extremely rare. This has led to substantial research exploring different modalities of local control of liver metastases. For patients with isolated metastases confined to the liver, resection offers the only hope for cure. In selected patients who undergo potentially curative resection, survival has ranged from 23-65% at 3 years, from 25-45% at 5 years, and is approximately 27% at 10 years. Unfortunately, only small proportion of patients with hepatic metastases from colorectal carcinoma will be eligible for and benefit from surgical resection.

Recent trials have demonstrated that up to 15% of initially categorised unresectable disease might be converted to resectable with the use of neoadjuvant systemic chemotherapy. HAI of chemotherapeutic agents will in theory maximize the cytotoxic effect of locally delivered drugs with minimal systemic effects, allowing more cases to be candidates for surgical resection or at least to gain local control of the disease. Proponents of HAI highlight the high response rates that have been confirmed in many phase III trials. Most trials failed to demonstrate survival benefits, which may be related to inadequacies of randomisation, crossover between systemic, and HAI groups, availability of FUDR and the use of other cytotoxic drugs and combination of HAI with standard versus new second line systemic chemotherapy.

The cost of placing a hepatic chemotherapy pump is not insubstantial. In one study by the Meta-Analysis Group in cancer, the cost of HAI, including pump placement and hospitalisation was calculated to be $29,562 at Henri Mondor Hospital in Paris and $25,208 at Stanford University Medical Center in Palo Alto, California. The main gain in life expectancy was 3.7 months (standard error = 1.3 months) for patients in the HAI group compared with patients in the control group. The cost-effectiveness ratios of hepatic arterial infusion compared with control treatment were $63,717 in Paris and $65,867 in Palo Alto per year of added survival.

There continues to be a debate on the pros and cons of HAI chemotherapy. The need for randomized trials that evaluate management plans for colorectal liver metastases including both new systemic therapy and local modalities of controlling disease has never been greater.

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