

Hepatic Arterial Infusion Chemotherapy for Hepatic Colorectal Cancer Metastases

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Approximately two thirds of patients diagnosed with colorectal cancer will develop metastases. Fortunately, the majority of these will be confined to the liver. Over the past 20 years, data have accumulated that long-term survival can be achieved in colorectal cancer patients with hepatic metastasis by resection of isolated metastases.¹⁻³ Furthermore, a paradigm shift in the surgical management of patients with colorectal hepatic metastases has occurred in the last several years, leading to an increased pool of patients considered to be appropriate candidates for operative resection.⁴ Despite this expanded patient pool, however, the patient population likely to be cured by surgical resection remains limited. One of the most difficult challenges to overcome in the treatment of patients with hepatic colorectal cancer metastases has been the high rate of local recurrence. Clinical studies have demonstrated a benefit for anatomic segmental hepatic resections over “wedge” resections to decrease the frequency of recurrence at the resection margin.⁵ Despite this surgical advance, however, recurrence elsewhere within the liver remains a common cause of treatment failure. Hepatic artery infusion (HAI) chemotherapy delivered through an implanted subcutaneous constant-flow pump is a therapeutic strategy presently being investigated for such recurrences. HAI chemotherapy is also being studied for use at the time of initial liver resection, as well as for adjuvant therapy in patients with unresectable liver metastases.^{6,7} Although the concept of adjuvant HAI chemotherapy is not a recent technological advancement, modern data from prospective clinical studies support the efficacy of this approach in the management of patients with isolated hepatic metastases from colorectal cancer.

This article reviews the role that HAI chemotherapy may play in the treatment of these patients. The history and current state of HAI chemotherapy are discussed, as are the principles of pump placement and drug del-

ivery and the results of recent clinical trials evaluating the technique.

THE PROBLEM

Colorectal cancer metastases develop in up to two thirds of the 140,000 patients newly diagnosed with colorectal cancer each year in the United States.^{8,9} Approximately 60% of these patients develop metastatic disease confined to the liver. Unfortunately, in only 20% to 30% of these patients are the liver metastases completely resectable (**Figure 1**).

Because only a relatively limited number of patients are candidates for potentially curative surgical resection, the majority of patients with hepatic colorectal metastases (70%–80%) are treated with systemic adjuvant chemotherapy. Although systemic chemotherapy regimens are a mainstay of treatment, fewer than one third of patients with metastatic disease demonstrate a sustained response to chemotherapy alone, and historically, the 5-year survival rate for these patients is less than 3%,¹⁰ with a median survival of 6 to 12 months. After liver resection, the 5-year survival rate is 25% to 40%, with a median survival of 23 to 25 months.^{2,4}

HISTORY OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY

In 1959, the concept of arterial catheter chemotherapy (not specific to the liver) was introduced, thus enabling the delivery of antimetabolite chemotherapy into the arterial blood supply of a tumor.¹¹ This arterial chemotherapy technique required an external infusion pump to run the system. Insertion of a hepatic arterial catheter for delivery of liver-directed chemotherapy at

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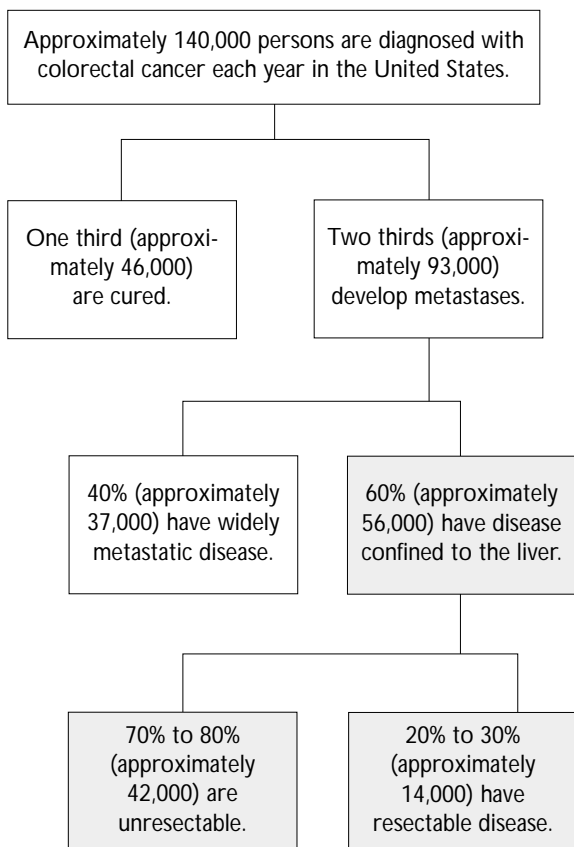


Figure 1. An algorithm demonstrating the natural history of colorectal cancer. The shaded boxes represent patients who are candidates for hepatic arterial infusion chemotherapy.

the time of laparotomy was first reported in 1964.¹² During the 1970s, researchers collaborated with a metal bellows manufacturer to develop an implantable drug infusion pump for use in clinical trials. This *Infusaid* implantable pump (no longer manufactured) was used until the early 1990s. The then cutting edge technology involved a 2-chamber device: one chamber contained the drug to be infused, and the other chamber contained the propellant freon. In 1982, the US Food and Drug Administration approved the simultaneous intra-arterial delivery of 5-fluorouridine and heparin for the treatment of liver metastases. HAI pumps now in use represent the second generation of constant flow devices; recent technical advances include improved flow rate constancy, welded titanium housings (instead of manually sealed plastic housings) and reduced device size. Presently, the most commonly infused chemotherapy agent in the treatment of colorectal cancer hepatic metastases is fluorodeoxyuri-

dine (FUDR). Other agents and drug combinations are under investigation.

Chemotherapy for the treatment of hepatic metastases has evolved from a systemic-only regimen to include a liver-directed regimen, based on the delivery of chemotherapeutic agent via the hepatic artery. HAI pump regimens using an implantable, automatic drug delivery system have made this feasible. FUDR is a pyrimidine antagonist related to 5-fluorouracil (5-FU) that has shown activity against hepatic colorectal metastases.¹³ FUDR-based regimens administered through HAI have improved median survival and, more importantly, maintained quality of life in selected patients¹⁴; other HAI drug regimens with and without FUDR have also shown promise.^{13,15,16} Chemotherapy delivered via HAI has demonstrated superior clinical response rates and limited toxicity compared with systemic treatments.¹⁴

PRINCIPLES OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY

Rationale of HAI Chemotherapy

The rationale of HAI chemotherapy is based on 3 key concepts. First, hepatic metastases greater than 3 mm in size derive their blood supply from the hepatic artery and not the portal vein.¹⁷ Second, a 4-fold increase in concentration of chemotherapeutic agent can be achieved in the liver when drug is delivered through the hepatic artery instead of being systemically infused.¹⁸ Third, certain chemotherapy agents (such as FUDR) are almost completely extracted during the first pass through the liver, allowing for large doses to be given via the hepatic artery with minimal systemic effects.¹³

Patient Selection

HAI pumps are available only at selected medical centers participating in clinical trials involving the devices. HAI chemotherapy is utilized to provide regional treatment for patients considered to be at high-risk for local recurrence, progression, or persistence of metastatic disease in the liver. Patients considered to be at high-risk include those presenting with synchronous colon and hepatic disease, those with hepatic metastases within 24 months of treatment of the primary tumor, and those undergoing hepatic resection with minimal (less than 1 cm) free margins or demonstrated persistent disease. Some investigators are also using HAI chemotherapy for unresectable disease. Various drug regimens and combinations are under investigation. The efficacy of HAI chemotherapy for metastatic colorectal cancer confined to the liver is currently the subject of several national multicenter randomized trials. Inclusion criteria

common to several ongoing clinical trials are listed in **Table 1**.

Patients meeting the criteria for enrollment into a clinical trial also must have favorable vascular anatomy for HAI pump placement and be medically capable of withstanding laparotomy. HAI chemotherapy requires that a catheter be introduced retrograde through the gastroduodenal artery and advanced toward the hepatic artery so that pump flow is directed toward the liver only. Favorable anatomy for pump placement must be verified prior to laparotomy. Traditionally, preoperative demonstration of the arterial anatomy has been accomplished by invasive celiac (visceral) angiography. Currently, the images obtainable by magnetic resonance angiography provide anatomic information that is at least equivalent to that of invasive angiography, although their use must be further defined and validated before they are used routinely in place of standard angiography.

Pump Placement

Although both laparoscopic and percutaneous techniques have been described, the preference at our institution is placement via laparotomy. The technique is designed to minimize the occurrence of complications such as chemical cholecystitis, peptic ulceration, and hepatic artery thrombosis. Patients should be prepared to undergo laparotomy via either vertical midline or right subcostal incision. Cholecystectomy is routinely performed to avoid chemical cholecystitis. The gastroduodenal artery is circumferentially dissected and arterial branches are cleared off for approximately 1 cm toward the duodenum and head of the pancreas, the proximal common hepatic artery, and the bifurcation of the proper hepatic artery. This meticulous dissection is necessary to ensure liver-only perfusion.

The gastroduodenal artery is isolated at the point where it enters the duodenum, an arteriotomy is made, and the catheter is advanced and secured in place. Flow out of the catheter will necessarily travel towards the liver only. The pump pocket is usually created on the left side of the abdominal wall. The pump is placed well below the left costal margin to prevent patient discomfort from the pump abutting against the ribs.

The existence of variant arterial anatomies underscores the importance of preoperative assessment of vascular anatomy. For example, up to 15% of patients have an accessory left hepatic artery arising from the left gastric artery. In order to maintain drug delivery to the liver only, this vessel must be identified and ligated. Failure to appropriately identify and ligate aberrant arteries and arterial branches results in malperfusion (ie, the delivery of chemotherapy to an unintended organ) and has

Table 1. Common Inclusion Criteria for Clinical Trials of Hepatic Arterial Infusion Chemotherapy

History of histologically confirmed colorectal adenocarcinoma metastatic to the liver with no clinical or radiographic evidence of extrahepatic disease
Liver metastases comprising < 70% of the liver parenchyma
Leukocyte count > 3.5×10^3 cells/mm ³
Platelet count > 150×10^3 cells/mm ³
Serum albumin > 2.0 g/dL
Total serum bilirubin < 2.0 mg/dL
No active concurrent malignancies
No active infection, ascites, or hepatic encephalopathy
Prothrombin time within 1.5 seconds of normal

Data from Kemeny et al.¹⁹

been the major cause of HAI-related gastritis, peptic ulceration, duodenitis, and pancreatitis²⁰

Liver-only perfusion is confirmed intraoperatively by a fluorescein test and reconfirmed three days postoperatively by a nuclear medicine scan. This confirmation of liver-only pump perfusion is necessary prior to the initiation of HAI chemotherapy.

COMPLICATIONS

Many practitioners may be aware of the relatively high complication rate from the early experience with HAI pump placement.²¹⁻²³ Since that time, however, significant improvements in surgical technique and the second-generation devices have reduced the associated operative complication rate (pump pocket infection, hepatic artery thrombosis, catheter dislodgment) to less than 10%.¹⁹ Chemical cholecystitis has been obviated by removal of the gallbladder at the time of pump placement. Malperfusion leading to peptic ulceration or perforation has been reduced by identification and ligation of aberrant or accessory arteries.²⁴ Sclerosing cholangitis and cirrhosis from hepatic artery chemotherapy have been reduced by FUDR dose reduction and the use of less hepatotoxic drug combinations.^{7,25,26} Hepatic artery fistulas have been reported as rare complications.²⁷ Nausea, vomiting, and World Health Organization (WHO) grade 3 and 4 diarrhea have been reported as common complications of floxuridine-based or 5-FU-based HAI chemotherapy.^{28,29}

HOW DOES THE PUMP WORK?

The HAI pumps currently in use are entirely self-contained in the subcutaneous pocket. No battery or

external power source is required. The pump houses two chambers. In one chamber, a 2-phase (gas/liquid) charging fluid is permanently sealed between the bellows and the outside wall and pump cylinder. The other chamber is a drug reservoir that can be filled using a self-sealing septum (similar to those used in subcutaneous venous access ports). Filling of the drug reservoir compresses the charging fluid and returns it to a liquid state through an increase in pressure. As the charging fluid is warmed by the patient's body temperature, it becomes a vapor and exerts a continuous pressure on the drug reservoir. This forces the drug from the reservoir through a filter and a flow-restricting tubing assembly. The drug then enters the silicone catheter that has been surgically placed into the gastroduodenal artery. A constant flow rate of a therapeutic agent can be delivered in this fashion. Based on the amount of charging fluid that is contained within the pump, the delivery rate per day can be accurately programmed, and the range of delivery flow rates can be adjusted according to the patient's need.

Flow-adjusted pumps may be required for patients residing in high altitude cities, requiring a slower pump. In general, factors such as systemic blood pressure or normal body temperature with occasional temperature spikes do not alter the flow rate of these devices.

Patients undergo HAI chemotherapy in an outpatient setting. They are required to return to the clinic every 2 weeks to refill the pump. Most HAI chemotherapy regimens consist of 2-week cycles of chemotherapy separated by rest periods of 2 to 4 weeks. When not delivering chemotherapy, the pump is charged with heparinized saline. Criteria for removal of the pump include catheter or pump infection, malfunction, or malposition. Once complete response and cure has been achieved, the pump may be removed, requiring laparoscopy or laparotomy.

CLINICAL TRIALS

Most studies comparing HAI chemotherapy following resection of liver metastases versus resection alone favor the addition of HAI for improved survival.^{6,30–32} Several studies have compared HAI with systemic chemotherapy for hepatic colorectal metastases. Data suggesting a greater tumor response with HAI are frequent,³³ but few studies have also shown a positive effect on survival.^{14,19,28,34} A meta-analysis published in 1996 evaluated 7 randomized trials comparing HAI versus intravenous (IV) 5-FU or floxuridine-based chemotherapy. This study showed a significantly higher tumor response rate for HAI (41% versus 14%), but the effect on survival did not achieve statistical signifi-

cance.³⁵ A meta-analysis by Harmantas and colleagues of 6 randomized prospective trials published before 1995 comparing HAI chemotherapy with IV chemotherapy (5-FU or FUDR) revealed a survival advantage of 10% at 1 year and 6% at 2 years for HAI chemotherapy.³⁶

In a report published in 1994, Allen-Mersh and colleagues investigated both quality of life and survival in a prospective, randomized study of 100 patients comparing conventional palliative treatment for metastatic colorectal cancer versus conventional treatment plus HAI chemotherapy with floxuridine.¹⁴ At that time, conventional therapy was defined as analgesic corticosteroids and systemic chemotherapy. The authors demonstrated that survival with normal quality of life could be prolonged by HAI chemotherapy. Quality of life was self-assessed through physical symptoms using the Rotterdam checklist, and anxiety and depression were measured by the Hospital Anxiety and Depression scale. Deterioration in quality of life did not occur until late in the disease process for both groups. In the HAI group, 95% of the survival time was spent with normal quality of life scores, suggesting that HAI was at least able to maintain normal quality of life survival, rather than merely sustaining life. In addition, the researchers found that hepatic tumor involvement and carcinoembryonic antigen level were reduced at 4 and 6 months respectively in the HAI group. Median survival was also improved from 226 days in controls to 405 days in the HAI group. It is important to note that their findings were potentially biased by the fact that only 22% of patients in the control group were either advised to have, or accepted, standard chemotherapy as part of their palliation. Nevertheless, this investigation was designed only to evaluate the effect of HAI chemotherapy on a palliative treatment regimen; there was no intent to cure the disease.

In a complementary study, Kemeny and colleagues investigated the survival advantage of HAI chemotherapy with floxuridine and dexamethasone on patients undergoing resection of colorectal cancer hepatic metastases.¹⁹ Their prospective, randomized trial of 156 patients who underwent hepatic tumor resection compared a postresection regimen of HAI chemotherapy and systemic chemotherapy (fluorouracil with or without leucovorin) to a postresection regimen of systemic chemotherapy alone. They found that the actuarial survival at 2 years was improved in the HAI group (86% versus 72%). Median survival was 72.2 months in the HAI group and 59.3 months in the control group. At 2 years, 90% of survivors in the HAI group were free of hepatic recurrence, compared with only 60% of

survivors in the control group. Overall progression-free survival was also improved in the HAI group at 2 years, at 57% versus 42%. This trial was well designed and appears to have demonstrated a positive survival benefit for the HAI treatments investigated. However, one must remember that this was a single institutional trial performed at a specialty center and that more studies will have to be performed before complete validation of this approach is obtained.

ONGOING TRIALS

At present, clinical trials examining the issues of tumor response and survival are ongoing. The Cancer and Leukemia Group B has an ongoing phase III study (CALGB-9481) of HAI FUDR and leucovorin versus systemic 5-FU and leucovorin for colorectal cancer hepatic metastases. The National Cancer Institute Cooperative Group Program is sponsoring three trials investigating the role of HAI chemotherapy in patients with hepatic metastases secondary to colorectal cancer: a phase III randomized study of hepatic artery infusion of floxuridine, leucovorin calcium (CF), and dexamethasone versus IV fluorouracil and IV CF (E-C9481); a phase II trial of hepatic arterial infusion with floxuridine and dexamethasone followed by systemic therapy with oxaliplatin in patients with surgically resected liver metastases from primary colorectal carcinoma (NSABP-CI-66); and a phase I trial of hepatic intra-arterial floxuridine and dexamethasone with IV oxaliplatin, fluorouracil, and CF with or without cryosurgery in patients with unresectable hepatic metastases from colorectal cancer (NCI-G00-1896). Additionally, the American College of Surgeons Oncology Group has several studies proposed and currently under development to assess the benefit of combination modality treatments, including radiofrequency ablation and hepatic artery infusion pumps.

SUMMARY

Data support a benefit for the resection of colorectal cancer liver metastases^{1-3,5}; however, the roles of systemic and HAI chemotherapy independently or as consolidation therapy remain to be clearly defined. In the absence of an effective systemic chemotherapy regimen to treat hepatic colorectal metastases, investigation of regional therapies is warranted. HAI pump placement is associated with low morbidity and mortality rates, and promising data suggest that HAI regimens improve survival and quality of life. The efficacy of HAI chemotherapy for metastatic colorectal cancer confined to the liver is currently the subject of several national multicenter randomized trials. **HP**

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