Hepatic Artery Infusional Chemotherapy

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KEYWORDS

• Regional therapy • Hepatic metastases • Hepatic artery infusion pump

KEY POINTS

- Hepatic artery infusional chemotherapy is a well-studied, viable option for unresectable colorectal hepatic metastases and as adjuvant therapy after resection for colorectal hepatic metastases.
- When infused intraarterially, 5-fluoro 2-deoxyuridine (FUDR) has high levels of intratumoral concentration and a pharmacokinetic profile that makes it ideal for infusional hepatic therapy.
- Chemotherapeutic agents are best delivered via an implantable hepatic artery pump, which has been demonstrated to be both safe and technically feasible with acceptable morbidity.
- A methodical approach to both arterial isolation and evaluation of anatomy aids in optimizing successful hepatic artery pump insertion.

INTRODUCTION

Colorectal cancer remains the third leading cause of cancer related death in the United States.[1] Hepatic metastases develop in approximately 50% of 150,000 patients who are diagnosed, the majority of whom are not amenable to curative surgical resection. Over the course of the last several decades, advances in treatment regimens for patients with hepatic metastases from colorectal cancer have resulted in a significant improvement in overall survival (OS). Improvements in systemic chemotherapy options along with greater standardization in patient selection for, and the safety profile of, hepatic resection have primarily driven this trend.[2] Still, many patients will present with liver-only or liver-predominant metastatic disease that leads to their demise. It is in these patients where a liver-directed approach to therapy potentially offers a wider

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range of treatment options leading to improved disease control and quality of life. Arterial-based treatments such as radioembolization and transarterial chemoembolization are discussed elsewhere. The premise of hepatic artery infusion pump (HAIP) therapy, similar to these other regional therapies, is based on the understanding that hepatic metastases derive their nutritive blood supply from the hepatic artery, in comparison with hepatocytes, whose main blood supply is from the portal circulation.[3] Therefore, local infusion of cytotoxic agents can maximize the direct tumor effects while simultaneously minimizing deleterious systemic effects. However, the biliary tree also relies on arterial blood flow, thus putting it at risk for ischemic injury or direct chemotoxicity.

The use of an implanted catheter for the direct delivery of chemotherapy to the liver in the setting of advanced hepatic neoplastic processes was first studied by Sullivan and colleagues[4] in the late 1950s. The results in 21 patients, 9 of whom had colorectal primary tumors, were published in the *New England Journal of Medicine* in 1964. An objective response to therapy was noted in 10 of the 21 patients who received therapy. Since that time, identification of effective and pharmacologically suitable chemotherapeutic agents for hepatic artery infusion (HAI) therapy, along with the development of a sustainable and safe means of intraarterial delivery of these agents using an implanted pump has allowed for continued study and a better understanding of clinical efficacy and application. HAIP therapy has been studied most broadly in the setting of both resectable and unresectable hepatic colorectal metastases; however, ongoing research is looking at the role of this therapy for primary hepatic tumors, including cholangiocarcinoma and hepatocellular carcinoma.

5-Fluoro 2-deoxyuridine (FUDR) is the deoxyribonucleoside derivative of 5-fluorouracil (5-FU), a pyrimidine antimetabolite, and functions via the inhibition of thymidylate synthetase. Ensminger and colleagues[5] demonstrated that high extraction during the first pass by the liver (94%–99%) followed by rapid clearance occurred with systemic FUDR infusion. Additionally, when hepatic infusion is achieved via an intraarterial route, FUDR has been shown to have tumoral levels that are 15 times greater than if infusion were achieved through the portal vein,[6,7] and 400 times greater than that of systemic administration.[8] FUDR is easily concentrated and has favorable solubility properties, adding to ease of use with an implantable pump. These features collectively make it an optimal drug for HAI therapy. Although other agents have been studied, both individually and in multidrug combinations, FUDR remains the most widely used.

An implantable pump that allowed for the safe and effective continuous hepatic delivery of chemotherapeutic agents was evaluated and reported on by Buchwald and colleagues[9] in 1980. Multiple different manufacturers now offer pump devices that may be used in the setting of HAI therapy. In a recent review of more than 3000 patients who underwent insertion of either a (1) surgically placed catheter, (2) radiographically placed catheter, or (3) fully implanted pump, the lowest rate of complications and highest median number of chemotherapy cycles was associated with use of the fully implanted pump.[10] These devices are typically inserted during an open abdominal operation.[11,12] Minimally invasive techniques such as percutaneous transaxillary insertion of HAI pumps have been studied. However, although the reported duration of hospitalization was decreased with this method, there was a significantly higher rate of catheter-related complications that led to delay or cessation of treatment in the percutaneous group versus the laparotomy group (43% vs 7%; $P = .005$).[13] Laparoscopic placement has been studied by several authors, with comparable results to laparotomy, including management of anomalous arterial vasculature and success of pump placement.[14–16] As noted by Urbach and colleagues,[16] the effective use of this

operative strategy necessitates that the surgeon have both advanced laparoscopic skill as well as a thorough understanding of the open pump insertion technique. No randomized comparisons of the open versus laparoscopic technique have yet been published or are planned. Finally, 1 center has reported on robotic insertion of HAI pump using criterion similar to those noted for laparoscopic approach, documenting its feasibility and safety.[17] Suffice it to say, as has been reported in many advanced surgical procedures, that minimally invasive HAIP placement may have a role, but should be undertaken by the most experienced teams in the proper setting.

TECHNIQUE

Preoperative Evaluation

Patients are evaluated in the context of their underlying diagnosis. Thorough evaluation for the presence of extrahepatic disease should be undertaken, although the presence of limited extrahepatic disease is not necessarily an absolute contraindication to liver-directed therapy. We consider the clear presence of metastases to portal nodes preoperatively a relative contraindication to pump placement given the high likelihood of extrahepatic recurrence. Other considerations include:

- Less than 70% replacement of the hepatic parenchyma with tumor burden;
- Preserved hepatic function, including total bilirubin less than 1.5 mg/dL;
- No evidence of portal hypertension or portal vein thrombosis; and
- Good performance status (Eastern Cooperative Oncology Group 0 or 1) and able to tolerate laparotomy.

Patients with chronic hepatitis and/or cirrhosis may be eligible, as long as they are Child-Pugh class A.

Once a patient is deemed to be an appropriate candidate, the technical aspect of HAIP placement is addressed, specifically the hepatic arterial anatomy. This can most often be accomplished by preoperative computed tomography angiogram. The pump catheter is to be inserted into the gastroduodenal artery (GDA); therefore, note should be taken of the caliber of the vessel and its particular anatomic course. The GDA will need to be of adequate caliber to accommodate the 2.3-mm diameter catheter. The presence of aberrant or replaced arterial anatomy, although not an absolute contraindication to HAIP insertion, may greatly increase the technical difficulty of pump placement and/or lead to problems with perfusion in the future. Aberrant or accessory hepatic arterial vasculature may be intraoperatively ligated or embolized postoperatively. Michels[18] described variant hepatic arterial anatomy, estimated to be present in approximately 50% of patients, and categorized 10 different anomalies. Yezhelyev and colleagues have reported on the use of a saphenous vein graft for several different anatomic variants[19]; however, the GDA remains the preferred insertion point unless it is anatomically absent or hepatic arteries are replaced completely. In rare such circumstances, HAIP placement may not be feasible, reserving more complicated/novel placement approaches for the most experienced surgeons and centers.

Pump Preparation

Several pumps have been approved by the Food and Drug Administration for delivery of chemotherapy to the liver. At our institution, we have experience with the Codman 3000 Series constant flow implantable pump (Codman, Johnson & Johnson, Raynham, MA), although this is not an endorsement of 1 pump over another. The general schema of the pump configuration is demonstrated in **Fig. 1**.[20] The device is an

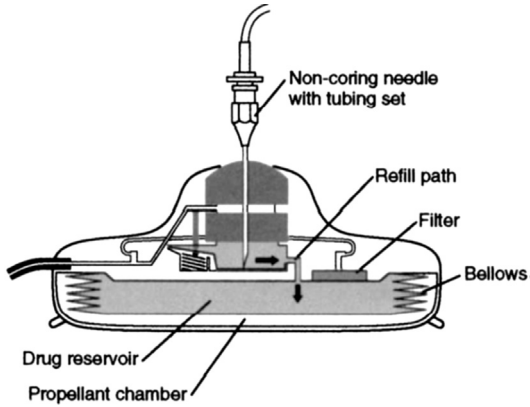

Fig. 1. Schema of pump configuration. (*Adapted from* Skitzki JJ, Chang AE. Hepatic artery chemotherapy for colorectal liver metastases: technical considerations and review of clinical trials. Surg Oncol 2002;11(3):125; with permission.)

implantable drug delivery device with an attached silicone rubber catheter that infuses at a preset flow rate, ideally suitable for an ambulatory patient. The internal components of the pump are divided into an inner and outer chamber by an accordion-like bellows. The inner chamber contains the drug to be infused, and the outer chamber contains a fluorocarbon propellant permanently sealed inside. The patient's body temperature warms the propellant, which then is able to exert a constant pressure on the bellows to allow the drug to flow out of the inner chamber, through a filter and flow restrictor, and then into the catheter. Some pump systems use an additional programmable, battery-operated mechanism to deliver drug through the catheter. In the operating room, before insertion, the pump is prepared on the back table. This generally entails filling it with heparin saline (30,000 units in 30 mL of saline) and warming it to body temperature, thus verifying flow through the catheter.

Operative Technique

An incision is chosen based on the target anatomy, with consideration given to patient's body habitus and history of prior abdominal procedures. In our experience, a right subcostal incision is typically chosen. Once access to the abdomen has been attained, a retractor system is used to provide adequate exposure of the porta hepatis, duodenum, and lesser curvature of the stomach up to the right crus of the diaphragm. Peritoneal surfaces are examined along with the retroperitoneum to assess for extrahepatic metastatic disease that may preclude pump placement. If a colorectal primary is in place and planning to be resected at the same setting, we typically address this before pump placement. Although we recognize that it is ideal to undertake the cleanest portion of an operation first, undue retraction on the pump and catheter once in place potentially impacts its positioning and function. With proper attention to sterile technique, including removal of previously used instruments before pump placement, contamination is kept to a minimum with secondary infection of the pump being a rarity.

Exposure of the common hepatic artery and adjacent structures is attained in the area of the hepatoduodenal ligament. Any suspicious appearing lymph nodes in the region of the porta hepatis should be sent for further evaluation. Portal lymphatic disease is considered to be a relative contraindication to pump placement because these

patients generally have a lower response rate to HAIP.[21] Sampling of nonsuspicious nodes is also undertaken. These data from final hematoxylin and eosin staining are helpful for future planning of systemic therapy, but we do not consider occult portal metastatic disease a contraindication to regional therapy. Isolation and identification of the arterial structures is generally undertaken in a stepwise fashion.

1. The common hepatic artery is isolated circumferentially and any small branches ligated from approximately 2 cm proximal to the origin of the GDA, and distally as far as possible, at a minimum to the branch point of the left and right hepatic arteries.
2. The GDA should then be identified and circumferentially isolated, taking great care to divide any branches that are proximal to the pump insertion site, including the right gastric artery.
3. Any accessory or replaced hepatic arteries are identified and ligated.
4. Any vessels supplying the superior border of the distal stomach and proximal duodenum that arise from the celiac axis should be divided.

The division of these small branch vessels is critical to the success of the procedure to prevent any extrahepatic flow to the gastrointestinal tract, which could result in gastritis, pancreatitis, duodenitis, and ulceration.[22] We typically use an energy device to divide all small vessels and lymphatic tissue up the gastrohepatic ligament all the way to the right crus of the diaphragm, as well behind the portal vein and overlying the inferior vena cava after exposure by a very limited Kocher maneuver. Isolation and ligation of the GDA as distal as possible is generally completed early in the procedure to allow time for any vasospasm that may have occurred during the dissection to abate. Approximately 3 to 4 cm of GDA length is ideal to allow for safe seating of the pump catheter. A cholecystectomy should be completed for all patients who undergo pump insertion to avoid complications related to postoperative chemical/acalculous cholecystitis.[12,23]

Attention is then turned to creating the pump pocket. Our ideal location is in the left lower quadrant of the abdominal wall. This site is marked before incision at the very beginning of the operation as distortion of the abdominal wall related to retraction used for the operation is common. A thick abdominal wall owing to an abundance of subcutaneous fat poses a difficult problem for future pump access. In such cases, our preference is to choose a site on the left lower chest wall just inferior to the inframammary fold to allow easier access. If this is not possible, it is best to limit the size of the pocket to correlate closely with the size of the pump to minimize dead space. Sometimes it is necessary to remove some of the subcutaneous fat that will overly the pump access point to allow for easier palpation and needle insertion. The concern here is that too much dead space can result in fluid accumulation. This allows the pump to float, which eventually leads to erosion of the securing sutures out of the fascia, thus allowing the pump to flip over in the pocket. The dissection is carried down to the anterior fascia with strict attention to hemostasis, because complications related to hematoma could impede the timely delivery of therapy or impair proper pump function in the future. All perforators to the abdominal wall fascia should be obliterated. The pump, which is has been prepared before these steps, should then be placed in the pocket. A tonsil clamp is used to insert the catheter through the anterior abdominal wall by penetrating the peritoneum and advancing through the abdominal wall to the pump pocket. We try to minimize the size of this puncture to avoid bleeding and prevent abdominal fluid, if present, from following the catheter into the pump pocket after surgery. We tend to leave some redundant catheter within the pocket, coiled beneath the base of the pump. We typically orient the catheter/pump junction closest

to the liver within the pump pocket (eg, at 12 o'clock when in the lower quadrants and almost at 9 o'clock when over the left lower chest wall).

Insertion of the catheter into the GDA may then commence. The presence of "bumpers" at the end of the catheter allows the catheter to be secured within the lumen of the GDA to prevent proximal or distal migration. The catheter is trimmed with scissors to allow its tip to sit just beyond the origin of the GDA such that at least 1 securing bumper is within the vessel lumen. We typically trim the catheter with a very slight bevel so that the catheter tip is unable to seal flush against the opposing common hepatic artery wall should it migrate proximally. When sizing the catheter, it is important to consider retraction on the liver and stretch on the vessel, both of which will be relieved at the conclusion of the operation. If not already done previously, the distal GDA is ligated with a silk suture at this point. Temporary occlusion of the common and proper hepatic arteries with a bulldog vascular clamp allows for essentially bloodless catheter insertion. A #11 blade scalpel is used to create an arteriotomy on the anterior surface of the distal most aspect of the previously ligated GDA taking great care not to injure the back wall of the vessel. The catheter is then inserted to just distal to the ostium within the GDA (**Fig. 2**). Three-point ligation using #3–0 silk suture is undertaken: one on each side of the securing bumper inside the lumen of the GDA, and one circumferentially around the catheter and GDA at the point of insertion to maintain orientation of the catheter parallel to the vessel (see **Fig. 2**). These should be tied tightly enough to secure the catheter within the lumen of the vessel, but not so tight as to occlude the lumen of the catheter. Patency is verified by flushing the catheter with heparinized saline via the access port or using the bolus needle, depending on which system is being used. Note that spasm in the GDA or hepatic arteries often occurs during portal dissection or catheter insertion. This is self-limiting and rarely a problem for catheter placement, but can be aided by the use of papaverine.

Next, hepatic perfusion and the presence of any extrahepatic flow are assessed by fluorescein dye injection via the catheter while holding an ultraviolet lamp over the right upper quadrant. Baseline fluorescence of the field before the injection of fluorescein, particularly in the fat around the head of the pancreas and lesser curvature of the stomach, should be assessed first. The bowel is retracted away carefully before this step of the procedure so that there is a physical separation between the liver and the rest of the gastrointestinal tract. This step is to minimize any contamination from divided lymphatics, which may obscure visualization of extrahepatic flow. Any free fluid around the field should be suctioned away. Fluorescein (2 mL) is then injected slowly into the catheter. Some spasm is common at this point, so slow injection is important. A flush of 2 mL of heparinized saline should follow the injection of the

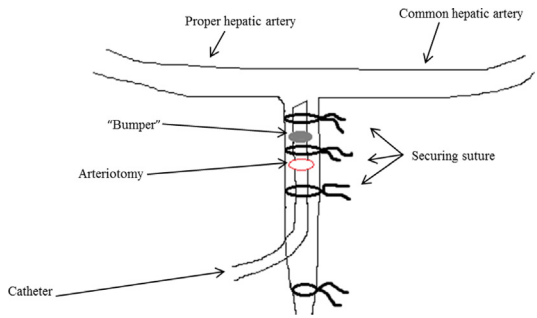

Fig. 2. Catheter insertion to the ostium within the gastroduodenal artery.

fluorescein to clear the catheter. The ultraviolet lamp is again used to assess the operative field after fluorescein injection. Of note, this step is primarily to assess for any extrahepatic flow so that small branch vessels or lymphatics may be ligated. Hepatic perfusion may not seem to be homogenous at this point owing to spasm, but will improve in the days and weeks after the operation. If any points of extrahepatic flow are indeed verified, those areas should be skeletonized and the branches ligated. Finally, the pump is secured to the anterior abdominal wall fascia using 4 points of fixation with permanent suture and the pump pocket is closed in layers including Scarpa's fascia (if possible), dermis, then skin.

Postoperative Care and Imaging

Routine postlaparotomy and/or liver resection care follows the insertion of the HAIP. Before filling the pump with chemotherapeutic agent(s), nuclear imaging using Tc^{99}-labeled macroaggregated albumin through the pump should be completed to evaluate hepatic perfusion and again assess for any evidence of extrahepatic perfusion. We typically complete this study immediately before discharge for patient convenience. If evidence of extrahepatic flow is illustrated, this may be potentially owing to extravasation from the cut edge of the liver if the patient has undergone a resection or from divided lymphatic vessels that have not yet sealed. As such, we repeat the study at first follow-up with a planned refill of heparinized saline. If there is still evidence of extrahepatic flow at this point, then angiography with embolization of any aberrant vessels is undertaken. There must be confirmation of the absence of extrahepatic flow before the initiation of chemotherapy. The most common reported source of anomalous flow is a relatively proximal branch arising from the proper hepatic artery or the right or left hepatic artery.[24] In such cases, extrahepatic flow can be managed successfully using angioembolization in the majority of patients, with surgical intervention rarely being necessary.

MANAGEMENT OF CHEMOTHERAPY

The infusion of FUDR is managed by a multidisciplinary team that consists of a pharmacist, a nurse practitioner, a medical oncologist, and the surgeon. Our institution's practice is to begin the infusion at a rate of 0.1 mg/kg per day (initial dose of 0.12 mg/kg per day is commonly reported). Body weight is calculated using ideal body weight. Aspartate aminotransferase, alkaline phosphatase, and total bilirubin are measured both before and at each 2-week interval while therapy is ongoing. Dose reductions are made based on these values as needed (**Table 1**). Patients are followed with repeat imaging as clinically indicated, typically every 3 months. The use of concomitant systemic therapy is generally safe, the data for which are described elsewhere in this paper.

FUDR is initiated on a cycle of 2 weeks on therapy followed by 2 weeks off of therapy. During off weeks, heparinized saline is placed in the pump reservoir. Given the size of the pump reservoir and the risk of catheter thrombosis if the pump is allowed to completely empty, patients must be compliant with their postoperative visit schedule. The willingness and ability of the patient to be fully compliant should be taken into consideration at the initial evaluation for HAIP therapy. When a patient elects to travel, we prefer that the pump not contain chemotherapy and be as full as possible before departure. Such precautions stem from concerns that the pump flow rate may be impacted by changes in elevation and were issues with the pump to occur during travel, or if the patient had an unanticipated delay in their return, it is undesirable for the patient to be away from the resources necessary to manage these issues with chemotherapy infusing. As such, the pump should be filled with

Table 1
Management of side effects for patients receiving hepatic artery infusion pump therapy

Test		Parameter[a]		FUDR Dose
Aspartate aminotransferase	Reference	≤50 U/L	>50 U/L	—
	Current value	0 to <3 × ref	0 to <2 × ref	100%
		3 to <4 × ref	2 to <3 × ref	20% dose reduction
		4 to <5 × ref	3 to <4 × ref	50% dose reduction
		≥5 × ref	≥4 × ref	Hold
	If held, restart when:	<4 × ref	<3 × ref	50% last dose
Alkaline phosphatase	Reference	≤90 U/L	>90 U/L	—
	Current	0 to <1.5 × ref	0 to <1.2 × ref	100%
		1.5 to <2 × ref	1.2–1.5 × ref	20% dose reduction
		≥2 × ref	≥1.5 × ref	Hold
	If held, restart when:	<1.5 × ref	<1.2 × ref	25% last dose
Total bilirubin	Reference	≤1.2 mg/dL	>1.2 mg/dL	—
	Current	0 to <1.5 × ref	0 to <1.2 × ref	100%
		1.5 to <2 × ref	1.2 to <1.5 × ref	50% dose reduction
		≥2 × ref	≥1.5 × ref	Hold
	If held, restart when:	<1.5 × ref	<1.2 × ref	25% last dose

[a] Reference (ref) is the value at time of last dose of 5-fluoro 2-deoxyuridine (FUDR) and current represents the value at time of pump filling for planned treatment.

Adapted from Power DG, Kemeny NE. The role of floxuridine in metastatic liver disease. Mol Cancer Ther 2009;8(5):1021.

heparinized saline or glycerin when trips longer than the calculated capacity of the pump are planned.

Complications associated with HAIP therapy are largely technical problems with the pump itself (discussed elsewhere in this paper) and the biliary toxicity of FUDR, which is closely monitored during therapy. Elevations in liver enzymes are described collectively as chemical hepatitis, and occur approximately 42% of the time.[20] Additional toxicities include biliary sclerosis, gastritis, peptic ulcer, and diarrhea. Dose reductions may be necessary to mitigate biliary toxicity, and an algorithm for management of side effects is intrinsic to caring for patients receiving HAIP therapy.[23,25,26] Our institution's algorithm has been adopted from other experienced institutions and is outlined in Table 1. The addition of dexamethasone during FUDR infusion reduces biliary toxicity and, when evidence of toxicity develops, may be added to the heparinized saline after chemotherapy removal.[27] Mild biliary toxicity is often self-limited and managed by dose reduction and/or temporary cessation of therapy. If hyperbilirubinemia develops and is persistent despite these maneuvers, cholangiography should be undertaken to assess for biliary stricture. Disease progression may also be a cause for apparent biliary toxicity, and so should be considered. Balloon dilation with or without stent placement may be indicated if discrete biliary strictures are identified.

Once patients have completed therapy and/or anticipate an interval off of therapy, the pump may be filled with glycerin. Depending on the concentration of the glycerin used, these injections can last anywhere from 37 to 133 days, thus prolonging the interval necessary for the patient to present to the infusion location. When or if the pump is to be removed, the procedure is straightforward and can be done as an outpatient procedure. The pump pocket is opened, remaining securing sutures to the pump are

removed, the pump is elevated out of the pocket, and the catheter is ligated then divided, thus leaving the intraabdominal portion of catheter in situ with redundancy. We prefer to use multiple titanium clips for ligation. The patient may then be discharged home after appropriate recovery from anesthetic.

MANAGEMENT OF TECHNICAL COMPLICATIONS

Complications associated with the use of the implantable pump for HAI have been reported in the range of 12% to 41% of patients.[28] These include issues related directly to the pump, such as seroma or infection of the pocket, wound dehiscence, or a pump that flips in the pocket. Additionally, problems related to the catheter, including erosion, displacement, and thrombosis, have been reported but are rare. Finally, vascular complications such as arterial thrombosis, dissection, and extrahepatic perfusion or incomplete perfusion are additional concerns. In a retrospective review of 15 years of experience at Memorial Sloan-Kettering looking at 544 patients, pump-related complications were identified in 120 patients (22%). The hepatic arterial system was most commonly implicated in 51% of these complications. Catheter-related issues were less common (26%), as well as pocket (16%) and device issues (5%). The majority of complications occurred at greater than 30 days after the implantation of the pump.[28] Similar pump complication rates have been noted by other groups, with a decline over time being noted as greater experience is gained.[10,11,29]

Pump Pocket Complications

Pump pocket–related complications, although uncommon, may result in a delay in the initiation of or timely delivery of scheduled therapy. Seroma formation may typically be managed expectantly; however, needle aspiration may be undertaken should there be failure to resolve in the anticipated timeframe or if access is affected. Hematoma formation is very uncommon. If identified, however, the size of the collection should be quantified using radiographic imaging. Larger collections may require formal evacuation. Hematomas that occur early in the perioperative setting should be taken back to the operating room for evacuation of the clot and identification of the bleeding source. Infection of the pump pocket that is limited to cellulitis is treated with antibiotics, oral or intravenous, depending on the severity of the cellulitis and the patient's clinical condition. When an infected fluid collection within the pump pocket is suspected, attempts at pump salvage should be reserved for those without evidence of systemic infection. In such cases, we have removed the pump from the pocket in the operating room and wrapped it in a betadine-soaked sponge for 10 minutes without dividing the catheter. Concomitantly, the pump pocket is debrided, cultured, and packed with a betadine-soaked sponge. The pump is then reseated and secured in place. The patient is monitored closely in the hospital for signs of systemic infection and continuance of intravenous antibiotics for 24 to 48 hours. If no signs of systemic infection occur, the patient can be discharged on oral antibiotics for the balance of a 2-week course with close outpatient follow-up. Any signs of recurrent infection would result in pump removal. Wound dehiscence that results in a compromise of the integrity of the device would also mandate removal. If the pump were to flip in the pocket, elective operative intervention may be undertaken so as to return the pump to its appropriate position, fixing it in place at 4 points. The pump housing can be replaced as needed with a new pump without the need for laparotomy by dividing the catheter and placement of a new pump using a splicing kit from the manufacturer, assuming that the catheter is not thrombosed.

Vascular and Catheter Complications

Arterial or catheter thrombosis can occur at any time point during which the patient is undergoing treatment; however, it more commonly occurs greater than 30 days after pump insertion. With proper pump refilling, catheter thrombosis is uncommon. Pump flow rates are estimated at each refill by dividing the amount infused (volume of loaded infusate minus residual volume in pump) by the number of days since last refill. A decrease in the infusion rate suggests clot or fibrin formation at the tip of the catheter. This situation can be managed with installation of enough volume of fibrinolytic agent to fill the catheter (see package insert) via the access port or using the bolus needle. This is allowed to dwell and slowly drip through the catheter by being pushed by heparinized saline from the infusion chamber over the next infusion interval. Failure of the flow rate to improve after 1 or 2 attempts should be evaluated radiographically. Erosion of the GDA, displacement of the catheter itself, or the development of a pseudoaneurysm is managed with either direct surgical intervention or with the use of angioembolization, depending on the patient's clinical circumstances. It is important for the patient and any associated providers to be aware that patients with HAI pumps who present with new abdominal pain must be evaluated to exclude bleeding or pseudoaneurysm.

CLINICAL OUTCOMES

Adjuvant Hepatic Artery Infusional Therapy for Resectable Colorectal Hepatic Metastases

The quest for a systemic adjuvant therapy that prolongs survival after resection of colorectal liver metastases (CRLM) has thus far been unsuccessful with only FOLFOX showing some marginal potential. HAI chemotherapy in the adjuvant setting after resection of CRLM, alone or in combination with systemic therapy, is appealing given the high likelihood of intrahepatic recurrence after hepatectomy. The majority of these recurrences will occur within 2 to 3 years after resection.[30,31] Therefore, the use of regional therapy with or without systemic therapy may address both micrometastases in the liver as well as aid in the prevention of extrahepatic spread.

To date, arguably the only data supporting adjuvant therapy after hepatectomy for CRLM stems from a randomized controlled trial of HAI plus systemic chemotherapy by Kemeny and colleagues.[32] In this trial, 156 patients who underwent hepatic resection were assigned to receive either HAI FUDR/dexamethasone (Dex) plus intravenous 5-FU/leucovorin or intravenous 5-FU/Leucovorin alone. Study endpoints included OS, hepatic recurrence-free survival, and disease-free survival (DFS) at 2 years. The median OS was 72.2 months in the dual therapy group compared with 59.3 months in the systemic therapy alone group. The 2-year OS was 86% in the HAI chemotherapy and 74% in the systemic group ($P = .03$), and hepatic recurrence free survival was notably 90% versus 60% ($P \leq .001$) between the HAI chemotherapy and systemic therapy group, respectively. DFS at 2 years was not significant (57% vs 42%; $P = .07$) for the HAI chemotherapy arm and the systemic therapy arm, respectively. The most common site of extrahepatic recurrence was the lung. Toxicity was greater in the combined group and resulted in therapy dose reductions. However, despite an increased number of hospitalizations in these patients, the overall number of deaths during treatment was not different.

Follow-up of this study in 2005, now with a median follow-up time of 10 years, demonstrated DFS in the combined therapy group of 31.3 versus 17.2 months ($P = .02$) in the monotherapy group.[33] The 10-year survival rates were 41.1% for the HAI chemotherapy group and 27.2% in the systemic therapy group.

As understanding of chemotherapy for colorectal cancer has continued to evolve, trials evaluating these more modern agents in conjunction with HAI therapy have been undertaken. Specifically, 2 phase I and II trials have evaluated HAI FUDR/Dex plus FOLFOX and HAI FUDR/Dex plus irinotecan.[34,35] These trials were able to successfully identify the maximum tolerated dose and safety profile for those therapeutic combinations. Continued evaluation with phase III trials remains to be accomplished.

A retrospective review of 125 patients treated between 2000 and 2005 who underwent hepatic resection followed by adjuvant HAI-FUDR/Dex in combination with systemic FOLFOX or FOLFIRI demonstrated on multivariate analysis that HAI-FUDR was independently associated with improved liver recurrence-free survival (hazard ratio, 0.34; $P \leq .01$), overall recurrence-free survival (hazard ratio, 0.65; $P = .01$), and disease-specific survival (hazard ratio, 0.39; $P = .01$).[36] Finally, a recent study by Goere and colleagues[37] looked at patients with 4 or more CRLM who received postoperative HAI combined with either systemic 5-FU or FOLFOX/FOLFIRI versus systemic therapy alone. In this patient population, with a median follow-up of 60 months, the 3-year DFS was significantly higher with HAI therapy compared with systemic therapy alone (33% vs 5%; $P<.0001$). However, the 3-year OS was only slightly higher in the HAI group and did not attain statistical significance.

Although there remains a paucity of large randomized phase III trials of HAI in the adjuvant setting for resected CRLM, the data to date point to a clear improvement in DFS as well as hepatic recurrence-free survival, with evidence suggesting an advantage in OS.

Hepatic Artery Infusional Therapy for Unresectable Colorectal Hepatic Metastases

Multiple randomized controlled trials evaluating HAI therapy in the setting of unresectable CRLM have been undertaken, three of which have been completed since 2000.[38–40]

The German Cooperative group studied 168 patients who were enrolled into 1 of 3 treatment arms: (1) 5-FU/leucovorin via HAI, (2) 5-FU/leucovorin systemic therapy, and (3) HAI FUDR. They observed a median time to progression of 9.2, 6.6 and, 5.9 months and median survival of 18.7, 17.6, and 12.7 months, respectively. Although differences in OS were not significant, the time to progression significantly favored HAI 5-FU/leucovorin over HAI FUDR ($P = .033$).[40] Subsequently, in 2003, Kerr and colleagues[39] published their results of 290 patients randomized to either HAI 5-FU/leucovorin versus systemic 5-FU/leucovorin. No difference was noted in median OS between groups (14.7 vs 14.8 months; $P = .79$), and no differences were noted in progression-free survival.[39] Most recently, the CALGB 9481 trial, which was published in 2006, randomized 135 patients to receive either HAI FUDR/leucovorin/Dex or systemic 5-FU/leucovorin. Unlike other studies preceding it, crossover between arms was not allowed. OS was significantly improved in the HAI therapy group as compared with the systemic treatment group, with a median of 24.4 versus 20 months ($P = .0034$). Additionally, response rates were notably different at 47% in the HAI group versus 24% in the systemic therapy group. Of note, this trial was the first to document a significant difference in OS with HAI chemotherapy for unresectable CRLM.

The ability to convert patients with unresectable disease to resectable has been found to be between 25% and 47% in recent studies using HAI in combination with systemic chemotherapy suggesting that, for a specific group of patients, even further benefit may be dervived,[41,42] because surgery remains the only potentially curative treatment for CRLM. In 1 group of patients with advanced CRLM, HAI was used as an adjunct along with systemic chemotherapy and 2-stage hepatic resection. The

median overall disease-specific survival was 52 months, with 88% of patients able to undergo both stages of hepatic resection.[43] These studies emphasize the role that HAI may play in bridging patients to surgical resection.

Combination therapy using HAI along with systemic chemotherapy has been evaluated in the setting of second-line therapy for those patients who have failed first-line chemotherapy. Using modern chemotherapy agents, several phase I trials have evaluated the inclusion of HAI. A phase I trial using HAI FUDR plus systemic irinotecan in 46 patients who had previously received systemic therapy showed no adverse increase in toxicity when the therapies were combined; median OS was 17.2 months.[44] A second phase I study looked at the use of HAI FUDR and either systemic oxaliplatin/irinotecan or systemic FOLFOX.[45] Response rates were noted to be 87% in the HAI plus oxaliplatin/irinotecan group and 90% in the HAI plus FOLFOX group. These promising results demonstrate significant potential benefit from HAI chemotherapy in conjunction with modern systemic chemotherapy in patients with unresectable CRLM who fail first-line therapy.

Primary Liver Tumors and Hepatic Artery Infusional Therapy

An evolving new target for HAI therapy is primary cancer of the liver, including intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma. Although there is only a small body of literature to date, initial results demonstrate that the therapy is feasible and safe. Jarnagin and colleagues[46] reported a phase II trial in 2009 using HAI FUDR/Dex in 34 patients with unresectable primary liver cancer, including both ICC and hepatocellular carcinoma. Partial response was seen in almost one-half of the patients treated (47%), and median survival was 29.5 months.[46] A recent update to these data looked at 44 patients with ICC treated with HAI FUDR/Dex or HAI FUDR/Dex plus bevacizumab, which again demonstrated a partial response in approximately one-half of the patients (48%) and a median OS of approximately 28 months.[47] It is important to note that the addition of bevacizumab significantly increased toxicity. Ongoing clinical trials will aim to better address what role HAI will have in unresectable ICC and hepatocellular carcinoma in the future.

SUMMARY

HAI therapy represents a well-studied and viable regional therapy for patients with hepatic metastases, as well as an evolving role for primary liver cancers. Implantable pump devices may be safely placed intraarterially with minimal morbidity in experienced hands. Like other regional therapies, HAI treatments can be used as an adjunct to systemic therapy, not a replacement. Future trials may address the sequencing of therapies, alternating between systemic and regional approaches, and the combination thereof. These treatments, however, are not without their complications. Thus, they require close monitoring and attention to detail. When used properly and followed appropriately, HAI therapy offers reasonable control of liver tumor burden with high levels of patient satisfaction. As such, they are ideally managed in concert between medical and surgical oncologists dedicated to a successful program.

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