REVIEW

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Hepatic Oncology

Hepatic arterial infusional chemotherapy in the management of colorectal cancer liver metastases

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Practice points

- Hepatic arterial infusional (HAI) should be administered in combination with systemic chemotherapy within the context of a dedicated multidisciplinary program.
- Combination therapy is possible, especially due to the high hepatic extraction rates of floxuridine (FUDR), and is warranted to ensure intrahepatic and extrahepatic control of disease. This treatment mandates an experienced team from multiple disciplines to administer this treatment safely and effectively.
- Extrahepatic disease is a relative contraindication to HAI therapy.
- The efficacy of HAI in the presence of extrahepatic disease remains unclear. HAI in this setting should be used in highly selected cases.
- HAI-FUDR should not be combined with bevacizumab
- Three recent prospective trials have demonstrated that concomitant use of systemic bevacizumab is associated with significantly worse biliary toxicity when combined with HAI-FUDR.
- Data strongly support the role of HAI-FUDR in combination with systemic chemotherapy both in the first-line and chemorefractory setting.
- Combination therapy with HAI-FUDR and systemic chemotherapy is associated with high response rates both in the first-line and in chemorefractory setting and has resulted in high rates of conversion to complete resection.
- After resection, adjuvant HAI-FUDR combined with systemic therapy should be considered in selected patients.
- In the adjuvant setting, after complete resection of colorectal liver metastases, HAI-FUDR combined with 5-FU improves progression free and hepatic progression free compared with systemic 5-FU therapy alone in three of four randomized studies.

Colorectal liver metastases (CRLM) receive their blood supply predominantly through the hepatic artery. Intra-arterial drug delivery can optimize the dose and time exposure of chemotherapy to tumor cells while limiting systemic toxicity. Chemotherapy is most commonly administered through a catheter surgically placed in the gastroduodenal artery and connected to a subcutaneous pump. Due to its pharmacokinetics features, floxuridine is the most commonly used drug in the USA with hepatic arterial infusional (HAI) chemotherapy. To date, many clinical trials have shown the positive impact of HAI in the management

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of CRLM. Hence, in unresectable patients, HAI is associated with high response rates and commonly enables subsequent resection in both chemonaive and previously treated patients. Outcomes in patients converted to complete resection are similar to patients who present with initially resectable disease. In the adjuvant setting, HAI with floxuridine improves survival as well as hepatic and overall disease-free survival after complete resection of CRLM, as compared with 5-FU alone, in three of four randomized studies. To date, no trials have compared HAI combined with modern chemotherapy alone to modern chemotherapy alone in the adjuvant setting.

KEYWORDS

- adjuvant setting
- colorectal liver metastases
- floxuridine • hepatic artery • irresectability
- locoregional therapy
- oxaliplatin • pump

Approximately 140,000 new cases of colorectal cancer (CRC) are diagnosed each year in USA and at the time of primary CRC diagnosis, nearly 25% of patients have synchronous colorectal liver metastases (CRLM) [1]. The liver is the most common site for distant metastases from CRC, representing the first organ involved in the theoretical stepwise pattern of metastatic progression described by Weiss *et al.* [2]. Ultimately, approximately 50–60% of patients will develop CRLM [3]. Hepatic resection is the treatment of choice in the management of modern series, however, overall recurrence rates of up to 75% are reported [4,5]. Currently many technical advances have allowed resection of extensive bilobar CRLM with acceptable morbidity and similar survival [6]. Unfortunately, it is estimated that 75–90% are considered unresectable at presentation [7]. First-line systemic chemotherapy with or without targeted agents for all patients with metastatic CRC extends median overall survival to approximately 2 years and is usually associated with tumor response rates ranging from 50 to 75%. These responses have resulted in conversion to resection (with or without concurrent ablation) in a modest percentage of patients with an associated long-term survival. Second-line systemic chemotherapy efficacy remains extremely limited in terms of response rate (~10%) and median survival (up to 12 months) [8–14]. Given the lack of effective therapeutic alternatives after first-line treatment failure and the importance of liver disease control, HAI chemotherapy can have a major impact on hepatic disease control, survival and conversion to resection. It has also been shown that there is a significant correlation between HAI and major pathologic tumor response [15,16]. After CRLM resection, adjuvant HAI with floxuridine (FUDR) achieves liver disease control resulting in improved hepatic and overall disease-free survival (DFS) after complete resection of CRLM, as shown in randomized studies. The aim of this review is to provide a comprehensive analysis of HAI therapy from catheter

placement to long-term outcomes. This manuscript will review the high response rates and rates of conversion to resection of HAI therapy for the treatment of CRLM in the first-line and chemorefractory settings as well as its impact on survival and hepatic disease control in the adjuvant setting. Although HAI remains confined to a few specialized hospitals and has not been readily adopted in most centers, consensus statements favoring the use of HAI in CRLM management have been recently published reflecting the increasing popularity of this therapy [17].

Rationale for HAI

CRLM derive their blood supply principally from the hepatic artery, whereas the liver parenchyma has a dual blood supply from both the portal vein and hepatic artery [18]. Thus, intra-arterial chemotherapy is selectively delivered to tumor cells with relative sparing of liver parenchyma reducing hepatocyte toxicity [19]. In addition to providing higher intratumoral chemotherapy concentration, exposure of tumor cells to chemotherapy is prolonged when compared with systemic chemotherapy [20]. Therefore, when drugs with appropriate pharmacokinetic profiles and tumor chemosensitivity are used, HAI is a unique and effective treatment allowing selective chemotherapy delivery to intrahepatic tumor cells while sparing liver parenchyma.

Drug delivery: technical aspects

• Types of delivery device

Initially, HAI was delivered through external portable infusion pumps and was associated with a significant incidence of complications that occur with prolonged infusions including catheter dislodgement, catheter sepsis and variability in flow rates [21]. These problems were significantly improved upon with the development of the totally implantable pump, first developed for delivery of chemotherapy to liver tumors in the late 1970s [22]. Currently, HAI can be administered through either an implanted port or pump. Both are surgically placed in a subcutaneous

pocket classically made on the abdominal wall for pumps or in the right inguinal fossa or on the lower thoracic wall for ports, and are connected to a catheter directly delivering drug to the hepatic arterial inflow. Catheter placement can be achieved either percutaneously into the hepatic artery or surgically into the gastroduodenal artery (see the ‘Surgical catheter placement’ section).

The mechanism of the implantable pump involves two chambers separated by a bellows. One chamber is permanently sealed and is a charging fluid chamber. The chamber on the other side of the bellows is the drug chamber, with a volume capacity of 20–50 ml (depending upon the manufacturer), which is accessible via a resealable septum for drug loading and has an outlet leading to the catheter. The charging fluid chamber contains a fluorocarbon liquid that is heated by the patient’s body temperature and is converted to a gas phase that exerts a constant pressure on the drug chamber and forces the drug chamber to empty into the catheter at a constant flow rate. When the drug chamber is depleted, percutaneous (PCT) refilling of the drug chamber compresses the gaseous phase contained in the charging chamber. Additionally, a side port on the pump allows bypassing the bellows allowing direct injections.

While both pumps and ports are currently used for HAI, pumps for HAI have many advantages when compared with ports. An important distinction is that ports only allow bolus injection whereas both continuous infusion and direct injection are possible through a pump. Thus, chemotherapy is delivered in a prolonged fashion at a relatively constant flow, increasing drug concentration and time of exposure in tumors on an outpatient basis. For this reason we, at MSKCC, almost exclusively use surgical placed HAI pumps.

• Preprocedural considerations

The presence of extrahepatic disease (EHD) is a relative contraindication to HAI therapy and therefore preprocedural radiologic investigations and intraoperative assessment should be performed to assess for EHD [23]. Patients undergoing surgical placement must also be fit for a laparotomy and careful assessment of comorbidities and performance status should be carried out. Further, an assessment of liver function and hepatic tumor burden is necessary to rule out relative contraindications such as total

bilirubin >1.5 mg/dl, extensive liver tumor burden (tumor volume >70%), ascites and portal vein thrombosis.

Assessment of anatomical considerations is also required to ensure optimal drug delivery to the liver and to avoid incomplete or extrahepatic perfusion (EHP). Hepatic arterial anatomy should be thoroughly studied prior to the catheter placement. Preoperatively, angiography of the hepatic artery is essential. Historically, invasive PCT arteriograms were obtained for this purpose but currently CT angiography is the standard approach. Celiac trunk narrowing from arcuate ligament syndrome or atherosclerosis should also be assessed. Although hepatic arterial anatomic variations are well described, all aberrant anatomy should be defined to enable complete liver perfusion. Autopsy series and extensive reviews have demonstrated that ‘normal’ hepatic arterial anatomy (**Figure 1**) is present in only 65% of cases [24,25]. Nevertheless, aberrant anatomy rarely precludes HAI catheter placement (see the ‘Surgical catheter placement’ section).

Figure 1. Variant hepatic arterial anatomy on preoperative CT-angiogram. (A) Standard hepatic arterial anatomy. Proper hepatic artery (thick arrow) and the gastroduodenal artery (thin arrow) arise from the celiac trunk (dotted arrow). (B) Example of aberrant hepatic arterial anatomy. Proper hepatic artery (thick arrow) arises from the superior mesenteric artery (thin arrow) and not from the celiac artery (dotted arrow).

• Surgical catheter placement

Laparotomy can be performed through a small subcostal, 'hockey-stick' or mid-line incision. Upon entering the abdomen, a careful exploration for EHD should be performed and any suspicious lesions sampled for frozen section analysis. Staging laparoscopy can be performed; however yields of laparoscopy with modern imaging are low [26]. Once gross EHD is ruled out, cholecystectomy is performed to avoid the development of chemical cholecystitis (perfusion through the cystic artery). The ligamentum teres must also be divided to avoid perfusion of the abdominal wall. In patients with normal hepatic anatomy, the lesser sac above the body of the pancreas and first portion of the duodenum is palpated to localize the common hepatic artery (CHA). Dissection is initiated along the CHA 1 cm proximal to the take off of the gastroduodenal artery (GDA) and continues along the proper hepatic artery (PHA) toward the bifurcation for a distance of at least 2 cm from the GDA origin. The distal CHA, GDA and proximal PHA are mobilized circumferentially, and the right gastric artery is ligated. All collateral branches

arising from the dissected CHA, GDA and PHA are identified and ligated to prevent EHP. The most common branches resulting in EHP originate from the right hepatic artery perfusing the duodenum or pancreas [27]. Dissection along the right hepatic artery and along the superior border of the proximal duodenum/head of the pancreas is therefore critical. Only when the abdominal wall subcutaneous pocket is complete and the GDA ready for cannulation should the pump be brought to the surgical field. Most commonly, the pump pocket is created in the left lower quadrant of the abdominal wall avoiding ribs and the iliac crest at the level of the fascia. The pump is filled with heparinized saline, the catheter flushed and warmed to body temperature. The catheter is passed into the abdominal cavity through the fascia directly posterior to the center of the pump. The pump, with the catheter positioned behind it, is then placed into the subcutaneous pocket to maintain temperature. Previously placed sutures are used to anchor the pump to the fascia. Next, the distal GDA is ligated and the proximal artery controlled with vascular clamps or vessel loops at the origin of the GDA. A distal transverse arteriotomy is then made in the distal GDA with a #11 blade. The catheter is then trimmed at a bevel adjacent to the tying beads and the catheter is advanced into the lumen of the GDA and secured with nonabsorbable ties such that the tip lies at the junction of the CHA/GDA. When advancing the catheter, one must avoid dissection of the wall of the vessel (Figure 2).

Figure 2. Technical point. Catheter tip in the gastroduodenal artery placed at the junction with the common hepatic artery.

Afterward, hepatic perfusion must be assessed. Methylene blue or fluorescein (utilizing a Woods lamp) is injected via the pump side port and the liver assessed for uniform dye distribution. Evaluation for evidence of EHP is carried out. In the event of abnormal liver perfusion and/or EHP, surgical reexploration should be carried out to identify and ligate any potential branches causing the perfusion abnormality. Retesting after further correction is mandatory. Following satisfactory completion of the perfusion test the catheter is flushed with heparinized saline and the wounds are closed.

In the case of aberrant vascular anatomy, the most successful strategy is to place the catheter in the GDA and ligate all accessory/replaced vessels. Placement of the catheter in vessels other than the GDA is associated with an increased risk of catheter-related complications and pump failure [28]. Ligation of accessory and/or replaced

hepatic artery branches is safe as long as there is normal portal flow and biliary drainage. Cross-perfusion is nearly universal and usually identified within minutes with perfusion retesting in the operating room. Early postoperative liver perfusion studies show complete bilobar perfusion in nearly all patients. In those that do not develop early cross-perfusion retesting will eventually show this to occur in nearly all patients [29]. In rare cases, vessels other than the GDA must be used in order to perfuse the liver. For example, in the case of irreversible celiac artery stenosis with reversal of flow through the GDA, the CHA can be ligated and cannulated while liver arterial inflow is supplied through the GDA from the superior mesenteric artery (SMA). If the GDA is not usable for some reason, we prefer using the left or right hepatic artery as conduits. Additionally, advanced techniques using vascular grafts have been described to deal with specific technical issues [30].

Minimally invasive surgical placement of HAI catheters has been described. A review of 27 patients undergoing laparoscopic HAI catheter placement demonstrated an average operative time of 45–55 min and reported an overall catheter-related complication rate of 11% [31]. Nevertheless, the benefit of these minimally invasive techniques require further investigation and we feel that, in general, the safest method is through an open incision if a surgical approach is chosen [32].

• Percutaneous catheter placement

Nonsurgical catheter placement is favored at some institutions when concurrent surgery is not required. PCT catheter placement was first performed through the axillary artery because of the relative ease of passage through the aorto-celiac angle compared with the femoral approach. Improvements in endovascular devices have overcome this technical issue and the femoral

artery approached is currently favored. This technique consists of utilizing a catheter with a side hole at 10 cm from its distal tip. The catheter is manipulated through the celiac axis into the hepatic artery and as far as possible into the GDA such that the side perforation is exactly at the GDA–CHA junction. Chemotherapy is delivered directly into the PHA through this side hole. Typically, embolization of the GDA, right gastric artery and any other collateral/accessory branches of the PHA with coils is performed to prevent EHP. Cystic artery embolization is controversial and is not performed routinely [33,34]. In the event of a missing or previously ligated GDA, the distal catheter tip can be placed in either the right or left branch of the PHA such that the side perforation is in the PHA. After the device is connected, the catheter is heparinized and placed into a subcutaneous pocket in the anterior chest wall (axillary artery approach) or in the right inguinal area (femoral artery approach).

• Post-procedural management

After pump or port placement, a baseline technetium-99m (^{99m}Tc)-sulfur colloid pump flow scan should be performed to confirm bilobar hepatic perfusion and rule out EHP. In our practice, FUDR delivery is started 2 weeks after pump placement in the case of unresectable disease and 4 weeks after liver resection. In the case of PCT catheter placement, some centers repeat the angiography before catheter use, after two or three cycles to ensure proper location or in the case of unexplained abdominal pain [34].

• Drugs

While many drugs have been explored through HAI delivery, only FUDR and oxaliplatin (oxali) are routinely used in current CRLM management (Table 1) [20]. FUDR is used in USA but has not been easily available for HAI administration

Table 1. Pharmacokinetics of chemotherapeutics delivered via the hepatic artery.

Drug	% Hepatic extraction	Plasma half-life (min)	Fold increase exposure with hepatic arterial infusion	Retained systemic exposure relative to iv. administration (%)
5-fluorouracil	22–45	10	5–10	60–70
Oxaliplatin	47	900–1140	4:3	–
Floxuridine	69–92	<10	100–400	<5
Mitomycin C	22	≤10	6–8	80–90
Cisplatin	–	20–30	4–7	100
Doxorubicin	45–50	60	2	40–50

iv.: Intravenous.

Adapted from [20].

in most countries outside of USA. HAI with oxaliplatin (HAI-ox) has recently been used in France for unresectable CRLM but is delivered through a subcutaneous port for bolus injections. When comparing pharmacokinetic profiles, FUDR appears to be the ideal drug for HAI therapy. Indeed, high first-pass extraction and a short plasma half-life for FUDR result in a 100–400-fold greater drug exposure within the liver (compared with systemic exposure) and a 15-fold higher drug concentration within tumor cells (as compared with normal hepatocytes) [20]. This high first-pass clearance, of over 90%, limits systemic exposure to clinically irrelevant amounts of drug, eliminating systemic toxicity and allowing concomitant administration of full doses of systemic chemotherapy.

Oxaliplatin (diaminocyclohexane platine) is known to be effective in CRC, particularly when combined with fluorouracil (FU) and leucovorin (LV). HAI-Ox has been evaluated in preclinical models, demonstrating slightly increased tissue concentrations in the tumor versus healthy parenchyma in a ratio of 4:3 and reduced plasma concentration compared with intravenous oxaliplatin delivery [19]. However, in comparison with FUDR, oxaliplatin has a much lower first-pass extraction rate (47%) and a longer plasma half-life (15–19 h), resulting in systemic exposure [35]. Therefore, oxaliplatin-related systemic toxicity remains significant. Fortunately, major grade 3/4 toxicity is relatively uncommon with neutropenia at 30% and neuropathy at 4% in one trial [36].

• Complications

A complete understanding of the complications related to pump placement and HAI chemotherapy is critical to its successful use. Complications possibly due to the placement or presence of a catheter were initially reported to vary between 30 and 79%. Currently, however these rates are 20% and mostly minor and salvageable [37–39]. After HAI-catheter placement, complications are critical to avoid as they can delay the initiation of chemotherapy or even prevent HAI treatment altogether.

Catheter-related complications

Allen *et al.* reported the most comprehensive study of technical pump-related complications on 544 patients with unresectable CRLM receiving HAI FUDR after surgical pump placement through a laparotomy [28]. Overall,

the catheter-related complication rate was 22%. Complications related to the arterial system (thrombosis, incomplete perfusion, extra hepatic perfusion and hemorrhage) were most common (51% of complications). The overall pump salvage rate for all complications was 45%. Stratification of complications into those occurring late (>30 days) versus early (<30 days) revealed late complications to be more common and less likely to be salvaged compared with early complications (salvage rate: 30 vs 70% respectively; $p < 0.001$). Independent risk factors for pump-related complications in this study were non-GDA cannulation and surgeon learning curve.

Catheter-related complications appear to vary with respect to the placement approach. A retrospective study of 111 patients compared trans-femoral PCT HAI catheter plus port placement ($n = 56$) to LPT ($n = 55$) [34]. The LPT group presented with significantly more hepatic artery thrombosis ($n = 7$ vs $n = 1$; $p = 0.004$), and catheter occlusion ($n = 4$ vs $n = 1$; $p = 0.006$), whereas significantly more EHP ($n = 20$ vs $n = 5$; $p = 0.04$), and catheter tip migration ($n = 8$ vs $n = 0$; $p = 0.005$) occurred in the PCT group. However, no difference in complication rates or HAI therapy disruption was found.

Of particular note, these results were reported many years ago and outcomes in expert centers have been significantly improved in recent years.

Arterial thrombosis

Acute intraoperative thrombosis and/or intimal dissection of the GDA or CHA have been reported during pump insertion but remain scarce. Overall rates of arterial thrombosis range from 2 to 22% depending on the series. Systematic review of over 17 studies of implantable pumps revealed a thrombosis rate of 6.6% [40]. Thrombosis can occur early (<30 days) and is usually related to catheter malposition and flow disturbance. Late (>30 days) arterial thromboses are more common following pump insertion and are probably due to chronic exposure to cytotoxic drugs causing local arterial inflammation and subsequent thromboses. To prevent both situations catheter tip placement in the GDA stump is likely important (Figure 2). The catheter tip should be placed exactly at the junction of the CHA/GDA. If the catheter tip protrudes past this junction it could disrupt HA flow and cause thrombosis. Conversely, if the tip is into far into the GDA stump this may promote

pooling of chemotherapy and local arteritis leading to pseudoaneurysm and/or thrombosis. Of note, use of thrombolytics and/or anticoagulants, results in salvage rates of approximately 30%.

Extrahepatic/incomplete perfusion

As discussed above, misperfusion should be discovered at the time of catheter placement or in the early postoperative course. Incomplete hepatic perfusion (IHP) occurs in 2% of cases. It can result from failure to ligate an unrecognized accessory/replaced hepatic artery or from failure of collaterals to develop following ligation of an accessory/replaced hepatic artery. Patients with IHP are asymptomatic and the diagnosis is dependent on the postoperative pump flow study. In general, most patients with IHP in the setting of a ligated accessory/replaced hepatic artery will eventually develop intrahepatic arterial shunts. Indeed, repeat imaging scans in 2–4 weeks have been associated with near 100% resolution of IHP [30]. Alternatively, IHP secondary to a patent accessory artery must be managed with angiographic embolization or in rare cases, operative ligation.

EHP occurs in 2–9% of cases. It is typically related to vessels arising along the hepatic artery (most commonly the proper and right hepatic artery) and its branches leading to perfusion of the stomach, duodenum and less commonly the pancreas. These complications may be detected early with a postoperative perfusion study (Figure 3), or later, with symptomatic chemotherapy infusion. EHP is most commonly diagnosed postoperatively on a flow study. Later after pump treatment initiation, EHP may also occur and is commonly associated with signs and symptoms such as epigastric pain or diarrhea with infusion. In this setting, EHP should be suspected until proven otherwise. In this setting infusion is discontinued, drug emptied from the pump and investigations including pump flow studies and endoscopy are completed. In general, management consists of a diagnostic angiogram and selective embolization of the involved vessel that solves the problem in the majority of cases. Figure 3 shows an example of abnormal technetium-99m (^{99m}Tc)-sulfur colloid scan in which EHP is evident in the area of the head of the pancreas. After selective embolization a repeat flow scan reveals complete resolution of EHP. Sofocleous *et al.* evaluated the use of embolization for pump salvage in 475 patients

with implantable pumps. Of these 475 patients, 45 (9.5%) had liver perfusion scans suggestive of EHP and 32 (7%) were found to have concomitant angiographic abnormalities. Embolization was not possible in 25% of these patients because of HA thrombosis or catheter tip migration. In the remaining 24 patients, embolization was performed and was technically successful in 21 (87.5%) cases, achieving a pump salvage rate of 79% [41].

General operative morbidity

Nonpump-related morbidity is low and similar to any other elective laparotomy (abscess, dehiscence, hematoma, early postoperative pain and ventral hernia). Likewise, pump or port pocket complications are relatively uncommon but can significantly impact the ability to deliver therapy. Infection of the pocket has been reported to occur in 2–3% of cases [42]. Simple cellulitis over the pump pocket may be conservatively managed; however, deeper soft tissue infections or collections require surgical drainage and long-term antibiotics. Some infections require either moving the pump to a different site or complete removal of the pump. Resistant sepsis or pump extrusion warrants reoperation, at which time the catheter should be tied off and the pump resited. Pump pocket hematomas may also occur (<1%) and usually require symptomatic treatment. Rarely a pump hematoma must be evacuated urgently. Chronic pocket seromas which are typically mild can be managed expectantly or evacuated through needle aspiration.

Chemotherapy-related complications

Patients receiving HAI require close monitoring with serial liver function tests (aspartate aminotransferase, ALT, alkaline phosphatase, total bilirubin) every 2 weeks, and formal clinical examination/toxicity assessment every 4 weeks. As shown in Table 1, each drug possesses different pharmacokinetic profiles and therefore toxicity is variable. Due to its high first-pass extraction and a short plasma half-life, HAI FUDR systemic toxicity is very low. Local toxicity is generally limited to hepatobiliary and upper gastrointestinal tracts. Gastritis, duodenitis and peptic ulcer disease have been reported. While EHP should be ruled out, it is also hypothesized that FUDR excreted into the bile is in itself ulcerogenic, leading to gastritis/duodenitis/ulceration in up to 50% of patients and warranting systematic proton pump inhibitor therapy. Any

Figure 3. Abnormal technetium-99m (^{99m}Tc)-sulfur colloid scan. Extrahepatic perfusion visible in the head of pancreas (green arrows), in a patient presenting with abdominal pain and diarrhea after first hepatic arterial infusional regimen (top panel). Resolution of extrahepatic perfusion after angiographic embolization (bottom panel).

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endoscopic lesion may require halting HAI delivery until mucosal healing is documented endoscopically [37].

Chemically induced hepatitis is also common with HAI-FUDR. Rates have been reported anywhere from 30 to 70% depending on the definition. Typically this complication is mild and manifests only as serum biochemical abnormalities. **Table 2** outlines an FUDR dose reduction schedule based on laboratory evaluation of aspartate aminotransferase, alkaline phosphatase and total bilirubin [43]. In the great majority of cases enzyme abnormalities resolve with careful adherence to dose reduction schedules.

The most dreaded chemotherapy-related complication is biliary sclerosis, which is observed in 1–26% of patients, mainly affecting the common hepatic duct and occurring more commonly in the adjuvant setting [44,45]. This point is explained by the fact that 40% of the arterial blood supply to the extrahepatic bile duct comes from the HA (60% comes from infraduodenal retroportal and retroduodenal arteries) and the majority of intrahepatic bile ducts derive their blood supply from the HA [46,47]. The reliance on blood supply from the hepatic artery subjects the bile ducts to high concentrations of FUDR. The addition of dexamethasone (Dex) to FUDR has been shown to significantly decrease

FUDR-related biliary toxicity. In a prospective trial of FUDR alone versus FUDR/Dex rates of biliary toxicity were 30 and 9%, respectively, $p = 0.07$. Following this study all HAI-FUDR is administered with Dex. More recently, it has been reported that the use of systemic bevacizumab (Bev) in conjunction with HAI-FUDR significantly increases the risk of biliary sclerosis and is now contraindicated [48]. Other risk factors such as postoperative infectious complications, abnormalities in the flow scan, and also especially, higher doses of FUDR per cycle (corrected for BSA and BMI) have been reported [45]. Notably, biliary sclerosis should be carefully evaluated when biochemical abnormalities fail to resolve with dose reduction/cessation and/or the presence of an isolated elevation in total bilirubin. Biliary imaging with cross-sectional imaging (CT scan or MRCP) should be carried out. Dominant strictures in the face of a persistently elevated serum bilirubin are typically treated with endoscopic or PCT (depending on the location of the stricture) dilatation and/or stenting. Ito *et al.* recently reported that no patient with biliary sclerosis requiring biliary stenting/dilation in their series died as a direct result of the biliary stricture [45].

Due to a low hepatic extraction rate, HAI-Ox toxicity is mainly systemic, resulting in hematologic toxicity (leukopenia, neutropenia and

thrombopenia), neurotoxicity and GI toxicity (abdominal pain, diarrhea). A recent retrospective study from the Institut Gustave Roussy in Paris, of 44 patients undergoing treatment with HAI-Ox plus systemic LV and FU in the adjuvant setting, showed that major toxicity related to oxaliplatin leading to discontinue HAI-OX was limited (18%) [49].

Clinical outcomes

• HAI for unresectable CRLM

HAI-FUDR alone

Mocellin *et al.* reviewed all randomized clinical trials (RCT) of HAI-FUDR alone for unresectable metastatic CRC isolated to the liver and assessed the effects of HAI-FUDR on tumor response rates and overall survival as compared with SCT [50]. Ten RCT reported from 1987 to 2010 were included in this meta-analysis, encompassing 1277 patients, of whom 673 (52.7%) were allocated to the HAI arm. While nine studies eligible for response analysis reported a significantly higher response rate in patients receiving HAI-FUDR when compared with fluoropyrimidine-based SCT (objective response 41–62 vs 9–27%, RR = 2.26; $p < 0.001$, respectively), clinical benefit such as impact on survival remained unclear in HAI group. However, this conclusion is highly questionable, given that seven of these 10 RCTs were

Table 2. Hepatic arterial infusion floxuridine dose reduction algorithm.

Liver blood test	Values	Values	FUDR dose
AST			
Reference range	≤ 50 U/l	> 50 U/l	
Current value	0 to $< 3 \times$ ref	0 to $< 2 \times$ ref	100%
	3 to $< 4 \times$ ref	2 to $< 3 \times$ ref	80%
	4 to $< 5 \times$ ref	3 to $< 4 \times$ ref	50%
	$\geq 5 \times$ ref	$\geq 4 \times$ ref	Hold
If held, restart when	$< 4 \times$ ref	$< 3 \times$ ref	50% of last dose
ALP			
Reference	≤ 90 U/l	> 90 U/l	
Current value	0 to $< 1.5 \times$ ref	0 to $< 1.2 \times$ ref	100%
	1.5 to $< 2 \times$ ref	1.2 to $< 1.5 \times$ ref	80%
	$\geq 2 \times$ ref	$\geq 1.5 \times$ ref	Hold
If held, restart when	$< 1.5 \times$ ref	$< 1.2 \times$ ref	25% of last dose
Total bilirubin			
Reference	≤ 1.2 mg/dl	> 1.2 mg/dl	
Current value	0 to $< 1.5 \times$ ref	0 to $< 1.2 \times$ ref	100%
	1.5 to $< 2 \times$ ref	1.2 to $< 1.5 \times$ ref	50%
	$\geq 2 \times$ ref	$\geq 1.5 \times$ ref	Hold
If held, restart when	$< 1.5 \times$ ref	$< 1.2 \times$ ref	25% of last dose

Adapted from [43].

significantly biased and heterogeneous with many methodologic flaws (sample size, percentage of patients receiving assigned treatment in each arm, crossover to HAI, and variability of delivered doses). Moreover, when considering only the two RCT defined as very high quality in this meta-analysis, HAI appears to be favored regarding overall survival (OS) with HR = 0.68 (95% CI: 0.52–0.89) and HR = 1.12 (95% CI: 0.99–1.26), respectively [51,52].

HAI plus systemic therapy

Since the initial studies of HAI-FUDR alone, modern first-line oxali- or irinotecan-based chemotherapy have yielded better long-term outcomes than prior systemic regimens (OS and progression-free survival, PFS) [53,54]. Nearly half of patients with liver only metastases will develop EHD, suggesting that EHD might be radiologically occult at the time of diagnosis and is not treated by HAI alone, especially with FUDR due to its high hepatic extraction rate [55]. Thus, combination HAI therapy with systemic therapy is warranted to treat both intra and EHD.

A Phase I trial comparing patients treated with HAI-FUDR/Dex along with systemic oxaliplatin and irinotecan or with systemic FU and LV in 36 patients showed that combination therapy was well tolerated and safe [56]. Median overall survival, as measured from the time of initiation of HAI, in both groups was 36 and 22 months, respectively. Partial response rates were 90 and 87%, respectively. Of note, seven patients (33%) ultimately underwent liver resection in the group receiving HAI-FUDR plus oxaliplatin and irinotecan; of whom two were shown to have a complete pathologic response. High rates of complete tumor response under HAI are well reported. In one study of 39 patients with 118 lesions experiencing radiologic complete response (CR) to chemotherapy for initially unresectable CRLM, 75 lesions (64%) were found to have a pathologic CR at resection or a radiologically assessed durable CR [15]. HAI-FUDR was significantly correlated with pathologic and durable radiologic CR in this study (OR = 6.2, $p = 0.02$).

Another Phase I trial reported on 49 patients undergoing HAI-FUDR plus systemic oxali and irinotecan. Response rates were very high and 47% of patients were converted to complete resection (with or without concurrent ablation). The median survival of the whole cohort as measured from the time of pump therapy initiation

was 39.8 months [57]. The conversion rate was 57% in the 23 chemotherapy-naïve patients with a 100% response rate. In the remaining 26 previously treated patients, the response rate was 85% and conversion to complete resection occurred in 38%. OS was significantly higher in the chemo-naïve patients (50.8 vs 35 months; $p = 0.02$). More recently, a Phase II trial was conducted at MSKCC to specifically evaluate conversion to resection as a primary outcome in 49 unresectable patients. Patients were treated with combination HAI-FUDR-Dex plus oxali/irinotecan or 5-FU/irinotecan and Bev depending on their prior chemotherapy exposure [58]. In this study, irresectability criteria was predefined and carefully reviewed by a multidisciplinary team. Overall conversion rate was 47% with a response rate of 76%. Again, response rate (82%) and resection rate (59%) were higher in the 17 chemo-naïve patients. Landmark analysis showed that patients resected within 12 months after initiation of pump therapy ($n = 10$) had a higher associated 3-year OS (80%) compared with patients not resected (26%). The addition of Bev was stopped during the protocol because of major biliary toxicity. This finding concurred with previous conclusions about the increase of biliary toxicity due to Bev [48,59]. Since no clinical benefit was found in patients receiving Bev ($n = 24$), Bev is no longer recommended in combination with HAI-FUDR.

A retrospective study of HAI-Ox plus systemic LV5FU2 conducted in 44 patients after failure of prior systemic chemotherapy, reported a median OS and PFS of 16 and 7 months, respectively [60]. Complete resection (with or without concurrent ablation) was achieved in seven cases (16%). More recently, a multicenter Phase II RCT has also been conducted in 36 chemo-naïve patients with unresectable or borderline resectable CRLM. This protocol combined HAI-Ox with LV5FU2 and added cetuximab to the subset of patients with wild type KRAS/BRAF tumors and demonstrated an acceptable major toxicity. Tumor response rate and conversion rate were 85 and 66%, respectively, and associated with a median PFS of 29 months [61]. Even though some patients included were deemed borderline unresectable, this trial still underlines the significant impact of HAI on the rate of conversion to complete resection. Additionally, in the subset of 31 wild type KRAS/BRAF patients (91%) receiving cetuximab, response rate and secondary resection rate

reached 92 and 74%, respectively. Similarly, HAI-Ox has been reported as significantly associated complete pathologic response [16].

These findings demonstrated significant efficacy well beyond what is seen with systemic therapy alone or other regional approaches for patients with unresectable metastatic CRC. Tumor response rates with modern systemic therapy alone are lower than those observed with HAI, in both chemo-naïve patients (50–75% vs 90% or greater) and in the chemorefractory setting (10–15% vs 50–75%) [8–14]. Other regional approaches including Yttrium-90 radioembolization, mainly used in the chemorefractory setting, have reported response rates up to 44% [62]. Additionally, a recent Phase III trial comparing chemoembolization using irinotecan-loaded drug-eluting beads alone to systemic FOLFIRI in unresectable patients, reported an increased response rate (68.6 vs 20%) and a significantly longer median overall survival (22 vs 15 months) in the chemoembolization group [63]. It is critical to note that to date, no randomized trial has compared modern systemic chemotherapy, radioembolization or drug eluting beads to HAI.

Overall, these HAI single arm trials suggest major efficacy in terms of response, conversion to resection and survival. The outcomes justify the idea of randomized trials of HAI and systemic therapy compared with systemic therapy alone. The use of HAI and systemic therapy in the first-line and refractory settings for patients with unresectable metastatic CRC are well justified by these results [17].

• Adjuvant HAI after CRLM resection

After resection, up to 75% of resected patients will recur within the liver and nearly one-third in the liver alone [4,5,55]. Given this recurrence pattern, there is a strong rationale for adjuvant therapy including HAI. However, the impact of adjuvant chemotherapy after CRLM resection remains unclear and questionable. Indeed, while current recommendations generally favor adjuvant chemotherapy, especially in the absence of preoperative chemotherapy and in patients at high risk of recurrence, several Phase III trials have failed to demonstrate an OS benefit for adjuvant systemic chemotherapy alone [64–67].

To date, the clinical impact of adjuvant HAI after CRLM resection compared with surgery alone was investigated in two randomized trials. Lorenz *et al.* compared adjuvant HAI 5-FU plus folinic acid ($n = 113$) to surgery alone

($n = 113$) [68]. An intention to treat analysis did not favor adjuvant HAI. However, when the study cohort was analyzed ‘as treated,’ increased median DFS (20 vs 12.6 months) and median hepatic DFS (44.8 vs 23.3 months) in the adjuvant treatment group was observed. This trend toward a significant clinical impact of adjuvant HAI has been corroborated in another RCT comparing HAI-FUDR combined with systemic chemotherapy to surgery alone [69]. This multicenter trial included 109 low risk patients (less than three liver lesions) and demonstrated a benefit in term of four-year DFS (46 vs 25%) and four-year hepatic DFS (67 vs 43%) but no significant difference in OS. The main issue in this study was that randomization occurred before surgery and 29 of the 109 patients enrolled in this study, were excluded after surgery (more than three liver metastases, unresectability, EHD).

Adjuvant HAI compared with systemic therapy has been investigated in many trials. In one study, 156 patients were randomly assigned to adjuvant HAI along with systemic 5-FU/leucovorin or systemic 5-FU/leucovorin alone [70]. The endpoint, 2-year survival, was significantly increased for the HAI group (86 vs 72%; $p = 0.03$). However, only 26% of patients in the treatment arm received more than half of the planned dose of FUDR due to toxicity-related dose reductions. In a later report of this same trial with a median follow-up of 10.3 years, the 10-year survival was 41.1 and 27.7% for the HAI and systemic-alone groups, respectively ($p = 0.10$) [71]. PFS was 31 versus 17 months ($p = 0.02$) and hepatic PFS was not reached versus 32.5 months ($p = 0.001$) for the HAI and systemic-alone groups, respectively. Another RCT compared 62 patients receiving adjuvant locoregional intra-arterial chemotherapy (HAI mitomycin plus 5-FU) plus systemic chemoimmunotherapy (mitomycin plus IL-2) to 60 patients treated with systemic chemoimmunotherapy (mitomycin plus IL-2) alone. In this study, 5-year DFS and 5-year hepatic DFS were significantly increased in patients receiving adjuvant HAI along with systemic chemotherapy 60 versus 35% ($p = 0.002$), and 5-year survival, 73 versus 60% ($p = 0.05$), for adjuvant HAI along with systemic chemotherapy versus systemic immunochemotherapy alone groups, respectively [72].

It is important to stress that these randomized trials compared adjuvant HAI to systemic 5-FU

and not modern systemic chemotherapy. Recent retrospective studies have reported adjuvant HAI results as compared with more modern systemic chemotherapy. House *et al.* compared 125 patients receiving HAI-FUDR/Dex plus systemic FU, LV and oxali or CPT-11 to 125 patients undergoing systemic FU, LV and oxali or irinotecan alone [73]. On multivariable analysis, adjuvant HAI therapy was associated with significantly higher actuarial 5-year DSS (75 vs 55%; $p = 0.001$), 5-year RFS (48 vs 25%; $p = 0.009$) and 5-year hepatic RFS (79 vs 55%; $p = 0.0005$). Another retrospective review of over 1000 patients who underwent liver resection for CRLM, demonstrated that adjuvant HAI was independently associated with prolonged survival on multivariate analysis (68 vs 50 months; $p < 0.001$) [74].

More recently, two Phase I/II trials explored the safety of adjuvant HAI-FUDR combination treatment with modern chemotherapy such as irinotecan and oxaliplatin, respectively [75,76]. Both reported feasibility and safety and were associated with promising long-term outcomes. Combination HAI-FUDR with modern chemotherapy did not appear to increase HAI-FUDR toxicity. Two-year OS rate was 89% in patients receiving HAI-FUDR plus Dex and irinotecan. Combination with oxali-based systemic therapy achieved four-year OS and DFS of 89 and 50%, respectively [76]. Similarly, Alberts *et al.* reported results from an NSABP study of systemic capecitabine and oxaliplatin alternating with HAI FUDR after resection of liver metastasis. The 2-year survival rate was a promising 88% (95% CI: 82–98) with a median follow-up of 4.8 years [77]. Lastly, a Phase II trial assessing HAI-FUDR plus systemic modern therapy with or without Bev reported that the addition of Bev did not impact long-term outcomes [59]. Four-year OS was 85% (95% CI: 60–95%) in the no Bev arm and 81% (95% CI: 56–93%) in the Bev arm respectively ($p = 0.5$). Similarly, the four-year RFS were 46 and 37%, respectively ($p = 0.4$). As previously mentioned, biliary toxicity was significant in the Bev group.

Promising long-term outcomes have also been observed with adjuvant HAI-Ox. Goéré *et al.* recently reported a retrospective comparative study on 98 patients, who had undergone curative resection of at least four CRLM [49]. Among them, 44 (45%) had received postoperative HAI-Ox combined with systemic 5-FU and 54 (55%) had received 'modern' systemic

chemotherapy alone. Three-year DFS was significantly longer in the HAI group (33 vs 5%; $p < 0.0001$).

Overall, these findings highlight the impact of HAI on disease control after resection of CRLM resulting in prolonged DFS and dramatically improved hepatic DFS. Early trials demonstrated OS benefits compared with 5-FU therapy and surgery alone but prospective randomized trials comparing outcomes in the era of modern systemic chemotherapy have not been performed [78]. A RCT is necessary to compare combined HAI therapy to modern systemic chemotherapy.

• Prophylactic HAI

HAI therapy has also been explored as a therapy to prevent CRLM in high-risk CRC patients. To date, two randomized controlled studies have been conducted in patients with stage II or III colon cancer. In 2004, Sadahiro *et al.* reported results of preoperative HAI-5-FU before resection of the primary CRC [79]. Of 316 randomized patients, 158 were assigned to prophylactic HAI, but 119 received HAI-5-FU, through a pump percutaneously placed in the HA, from 1 week prior to surgery to 2 weeks after surgery. Perioperative mortality was nil and after a median follow-up of 59 months, there was a significant difference in 5-year OS and 5-year DFS in favor of HAI therapy (89 vs 76% and 86 vs 68% respectively, $p < 0.001$). However, in subset analysis with respect to the T stage, HAI-5-FU seemed to significantly impact OS and DFS only in stage III patients ($n = 56$). This study also demonstrated and improved hepatic DFS rate which was 94% in the HAI arm versus 79% in the control arm at 3 years, and 87 versus 73%, respectively, at 5 years ($p < 0.001$). Thus, in the HAI arm, the risk ratio for liver metastasis-free survival was 0.38 (95% CI: 0.22–0.66; $p = 0.0005$). Similar results were reported from another Eastern center, performing HAI-FUDR plus mesenteric arterial oxaliplatin seven days before primary resection, in 240 patients with clinical stages II and III [80]. This indication for HAI therapy has not been universally accepted and requires confirmatory studies.

Conclusion

HAI therapy to treat CRLM both in the unresectable and adjuvant setting has been extensively studied over many decades. Currently, HAI therapy is only given combined with

systemic chemotherapy and has to be tailored to the patients chemotherapy treatment history. While randomized trials comparing HAI combined therapy to modern systemic therapy alone are lacking, prospective single arm studies show that combined HAI therapy is associated with significant efficacy. For patients with unresectable CRLM, HAI is associated with very high response rates, even in the chemorefractory setting and results in high rates of conversion to resection. In the adjuvant setting HAI combined therapy is associated with dramatically decreased hepatic recurrence-free survival and promising OS outcomes. The great majority of HAI therapy is administered in experienced centers with excellent safety. HAI therapy is deserving of prospective comparisons to modern systemic therapy.

Future perspective

The optimal method of hepatic artery catheter placement has not been determined. Options range from PCT placement to minimally invasive surgical placement to open surgical placement. Each of these methods has their own pros and cons. Further research is required to more clearly define the optimal procedure that minimizes trauma to the patient while minimizing catheter-related complications.

FUDR and oxali are the two most commonly used drugs for HAI and are now commonly combined with varying systemic chemotherapy regimens. There is great potential to study novel

dosing and timing strategies. HAI with new drugs ranging from antibody therapy to targeted agents to immunotherapeutic agents all hold promise as regionally administered drugs and provide substantial material for future study. These potential strategies provide opportunities to optimize HAI-related toxicity and efficacy and are deserving of prospective study.

Probably the most important future perspective for HAI therapy is to study this approach in randomized trials comparing to more commonly utilized systemic approaches. It is clear that HAI therapy is limited to a small number of experienced centers and dissemination has not been successful. Therefore, ultimately, a multicenter trial would be ideal. HAI for unresectable disease as well as the adjuvant setting have strong and very promising outcome data that justify such trials and it is our hope that these kinds of trials will come to fruition.

Financial & competing interests disclosure

NE Kemeny has received Consulting and Speakers Fees from Amgen. A Doussot received research fellowship grants from the French Association of Hepatobiliary Surgery and Transplantation (ACHBT) and from Université de Bourgogne while completing this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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