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Hepatic arterial infusion chemotherapy: a review with technical notes

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Abstract

Combined hepatic artery infusion (HAI) and systemic chemotherapy have demonstrated its clinical efficacy in prolonging overall survival in unresectable intrahepatic cholangiocarcinoma and as a conversion to treatment strategy in a small proportion of patients. The utilization of HAI chemotherapy is restricted by the scarcity of surgeons and oncologists who are well-experienced in its use. This represents a significant drawback of this treatment method. In recent years, a solid push to expand its use, mainly in the United States and recently also in Europe, has been made possible by the HAI Consortium Research Network. Results of ongoing Clinical Trials are eagerly awaited to give the basis for further expansion of this technique and oncological treatment outside of historically established centers. In this technical note review, we aim to give a brief historical description of the origins and evolution of intra-arterial chemotherapy for unresectable intrahepatic cholangiocarcinoma. We will, therefore, discuss the surgical technique by providing some tips and tricks without neglecting the difficulties that may be encountered.

Keywords: Hepatic artery infusion, pump chemotherapy, intrahepatic cholangiocarcinoma, unresectable cholangiocarcinoma, conversion therapy

INTRODUCTION

First described in 1840 by Durand-Fardel, cholangiocarcinoma (CCA) encompasses a diverse group of

cancers derived from the epithelial cells lining the biliary tree, exhibiting characteristics of cholangiocyte differentiation[1]. The tumor develops from the canals of Hering to the main bile duct[2]. The different types of cholangiocarcinoma (CCA) are classified based on their location within the liver - intrahepatic (iCCA), perihilar (pCCA), and distal CCA (dCCA). CCA represents a significant portion of gastrointestinal and liver malignancies, accounting for approximately 3% of all gastrointestinal tumors and comprising around 15% of primary liver cancers, making it the second most common primary liver cancer[3-5]. By 2040, liver cancers, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, are projected to be the third leading cause of cancer deaths, after lung and pancreatic cancer, exceeding colorectal cancer[6].

While there have been recent improvements in surgical treatments for cholangiocarcinoma, the outlook for patients remains poor, with less than 5% surviving beyond five years. The average survival time for intrahepatic cholangiocarcinoma (iCCA) ranges from 18 to 30 months, but this drops to only 6 months if the tumor cannot be surgically removed. Surgery is currently the sole curative option for early-stage disease. Unfortunately, most patients are diagnosed at later stages when the cancer is metastatic, unresectable, or locally advanced, and only a quarter of them qualify for surgical resection[5,7]. For those unresectable, hepatic arterial infusion (HAI) of high-dose chemotherapy may provide some benefits[8].

Since the 80s, Nancy Kemeny has devoted her career to the treatment of patients with unresectable metastatic colorectal cancer and intrahepatic cholangiocarcinoma. She has established a critical role for regional Hepatic Artery Infusion (HAI) chemotherapy in both adjuvant and advanced settings. This therapy was initially not widely accepted outside of Memorial Sloan Kettering Cancer Center (MSKCC) in New York. However, its efficacy has since been demonstrated and is now widely used throughout America, Asia, and Europe.

HAI PUMP CHEMOTHERAPY FOR UNRESECTABLE CHOLANGIOCARCINOMA

The latest version of the NCCN clinical practice guideline for hepatobiliary cancers (v. 3.2023) specifies the criteria for selecting patients eligible for arterially directed therapies, which include TARE, TACE, DEBTACE, and HAI. Initially developed for the treatment of metastatic colorectal cancer, nowadays, the role of HAI chemotherapy has been found effective for patients suffering from advanced unresectable intrahepatic CCA that is confined to the liver[8-15] [Table 1].

In 2009, a study by Jarnagin et al. showed promising results for unresectable liver cancer treatment using HAI with floxuridine and dexamethasone, achieving a 47.1% response rate and a median survival of 29.5 months[9].

A 2011 trial by Kemeny *et al.* investigated the addition of systemic bevacizumab to HAI chemotherapy, resulting in a median overall survival of 31.1 months[10].

A phase I/II study published in 2011 by the Japan Interventional Radiology in Oncology Study Group explored HAI using gemcitabine, with a response rate of 7.7% and a median overall survival of 389 days[11].

In 2014, a retrospective study by Ghiringhelli *et al.* examined HAI of GEM followed by systemic oxaliplatin as second-line treatment in patients with unresectable iCCA, reporting a median PFS of 9.2 months and a median OS of 9.1 months[12].

Table 1. Summary of studies. HAI +/- SYS chemotherapy treatments for unresectable iCCA.

Study	Number and Type of Patients	Treatment Regimen	PFS	OS
Jarnagin *et al.*, 2009[9]	34 PLC •26 iCCA •8 HCC	4-week cycle HAI: FUDR (0.16 mg/kg × 20/pump flow rate) and DEXA 25 mg on day 1 for 14 days of each cycle	7.4 months	29.5 months
Kemeny *et al.*, 2011[10]	22 PLC •18 iCCA •4 HCC	4-week cycle HAI: FUDR (0.16 mg/kg × 30/pump flow rate) and DEXA 25 mg on day 1 for 14 days of each cycle SYS: bevacizumab 5 mg/kg every other week.	8.45 months (CI 5.53-11.05)	31.1 months (CI 14.14-33.59)
Inaba *et al.*, 2011[11]	13 iCCA	4-week cycle HAI: GEM 1000 mg/m^2 30-min infusion on days 1, 8, and 15 for 5 cycles	-	389 days (CI 158-620)
Ghiringhelli *et al.*, 2013[12]	12 iCCA	Second-line treatment 2-week cycle HAI: GEM (1000 mg/m^2 given over 30 min) followed by OX (100 mg/m^2 given over 2 h)	9.2 months (CI 2.1-29.4)	20.3 months (CI 13.2-49.7)
Massani *et al.*, 2015[13]	11 iCCA	2-week cycle HAI: Day 1: 100 mg/mq of OX Day 2: 5 FU 7 mg/kg at 2 mL/h in CI for 48 h	-	17.6 months
Konstantinidis *et al.*, 2016[14]	104 iCCA •78 HAI/SYS •26 SYS	4-week cycle HAI: FUDR (0.16 mg/kg × 20/pump flow rate) and DEXA 25 mg on day 1 for 14 days of each cycle SYS: mostly GEM-based	HAI/SYS 12 months SYS 7 months	HAI/SYS 30.8 months SYS 18.4 months
Higaki *et al.*, 2018[15]	12 iCCA	42-day cycle HAI: CIS 65 mg/m^2 2 mL/min on Day 1 SYS: S-1 60 mg/m^2 per day 1-28	-	10.1 months (CI 3.6-23.2)
Cercek A, *et al.*, 2020[8]	38 iCCA	4-week cycle HAI: FUDR (0.12 mg/kg × 30/pump flow rate) and DEXA 30 mg/pump on day 1 for 14 days of each cycle SYS: GEM (800 mg/m^2) with OX (85 mg/m^2) on Day 1 or 15, every 2 weeks	11.8 months (1-sided 90% CI, 11.1)	25.0 months (95%CI: 20.6-not reached)

PFS: progression-free survival; OS: overall survival; BTC: biliary tract cancer; PLC: primary liver carcinoma; iCCA: intrahepatic cholangiocarcinoma; HCC: hepatocarcinoma; CI: confidence interval; HAI: hepatic arterial infusion; SYS: systemic; FUDR: floxuridine; GEM: gemcitabine; CIS: cisplatin; OX: oxaliplatin; DEXA: dexamethasone; 5-FU: 5-fluorouracil.

Massani *et al.* published a retrospective analysis of HAI treatment alone (fluorouracil and oxaliplatin) in unresectable iCCA patients, revealing a median OS of 17.6 months[13].

An analysis by Konstantidinis *et al.* of patients with locally advanced intrahepatic CCA demonstrated improved OS in those receiving combined HAI and systemic chemotherapy compared to systemic chemotherapy alone (30.8 *vs.* 18.4 months)[14].

A 2018 Japanese pilot study compared HAI of cisplatin plus oral S-1 to conventional therapies in patients with unresectable iCCA, showing a median OS of 10.1 months in the combined treatment group[15].

In 2020, a phase II trial by Cercek *et al.* investigated HAI FUDR chemotherapy combined with systemic gemcitabine and oxaliplatin in unresectable ICC patients, reporting a median PFS of 11.8 months, a median OS of 25.0 months, and a 1-year OS rate of 89.5%[8].

The NCCN panel recommends locoregional therapy for unresectable or metastatic cholangiocarcinoma without extrahepatic disease, but HAI chemotherapy is only recommended for clinical trials or tertiary referral centers[16].

HISTORY AND RATIONALE

Novel methods for regional chemotherapy with nitrogen mustard were described independently by Calvin T. Klopp and Howard R. Bierman in the late 1950s[17,18]. After the publication of these findings, the use of chemotherapy via arterial administration was explored for several types of cancer, including liver cancer. In 1964, Sullivan *et al.* first described the method of chemotherapy by continuous hepatic arterial infusion and reported "significant tumor regression"[19]. Other investigators have demonstrated the clinical benefit of HAI with tumor response rates up to 73%. Unfortunately, the high morbidity rate related to pump port and catheter placement and the not negligible mortality rate have at first prevented the widespread use of infusion chemotherapy[20-23]. During the 1970s, the usage of the technique was given a boost due to the advancement of technology which led to the development of an implantable subcutaneous pump that made it feasible to safely administer arterial infusions to outpatients[24,25]. In 1980, this device was successfully experimented with by infusing fluorodeoxyuridine (FUDR) into the hepatic artery[26].

Sigurdson *et al.* established the scientific basis for arterial infusion in 1987. They demonstrated that drugs delivery to the tumor is significantly greater with hepatic artery infusion than with portal vein infusion. The mean level of tumor FUDR after HAI was 12.4 ± 12.2 nmol/g, which was much higher than the mean level of tumor FUDR after portal vein infusion, which was 0.8 ± 0.7 nmol/g, $P < 0.01$[27]. Drug selection needed a rational basis, including agents with short half-lives and evidence of antitumoral activity. The liver has a unique dual blood supply system that enables the targeted delivery of chemotherapy drugs to tumor cells via the arterial blood supply while preserving the healthy liver tissue by utilizing the portal blood flow. FUDR was demonstrated to have a half-life of less than 10 min and an estimated increased hepatic exposure by HAI (based on hepatic extraction, total body drug clearance, and hepatic arterial blood flow) of 100- to 400-fold[28]. Due to hepatic extraction and first-pass metabolism, systemic exposure and toxic effects are decreased by up to 99%, while also achieving higher and more targeted drug concentrations in the tumor compared to systemic administration[8,28]. Considering these assumptions and the positive outcomes of initial smaller studies in the 1970s and 1980s, delivering chemotherapy directly to the liver through a surgically implanted pump under the skin gained widespread adoption[29-31].

Over the last thirty years, the implementation of potential randomized controlled trials has provided more substantial proof of enhanced response rates and survival rates over systemic therapy in specific patients. Following the publication of the first randomized trial on HAI in MSKCC in 1987[32], more than 100 publications from the center have showcased the effectiveness of regional chemotherapy on liver neoplasms[33-35].

SURGICAL TECHNIQUE AND CHALLENGES

Hepatic arterial anatomy variations

The evaluation of hepatic vascular anatomy before surgery is vital and should involve an arterial phase CT. A normal hepatic arterial anatomy is characterized by the common hepatic artery originating from the celiac axis and the gastroduodenal artery (GDA) arising from the common hepatic artery before the bifurcation of the right and left hepatic arteries. However, 30% to 50% of patients exhibit anatomical variations in the hepatic arterial supply, which can be in the form of accessory or replaced hepatic arteries[36,37]. The most common are aberrant origin of the GDA from either the right and left hepatic artery or as a trifurcation (6% to 11% of patients), accessory left hepatic artery (2% to 10%), accessory right hepatic artery (4% to 16%), replaced left hepatic artery with no native left (4% to 16%), and replaced right hepatic artery with no native right (6% to 16%).

Crossover liver perfusion has first been described by Redman[38] and Koehler[39]. Koehler demonstrated cross-perfusion on a small consecutive series of patients treated with hepatic artery ligation for otherwise uncontrolled bleeding. After the ligation, collateral vessels that supply arterial flow to the liver start developing as early as four hours. These collaterals come from different sources such as the replaced or accessory hepatic artery, interlobar liver collaterals, phrenic artery, gastroduodenal artery through arterial branches in the pancreas duodenum and omentum, collateral branches of the GDA as they pass into the porta hepatis, and recanalization of the ligated hepatic artery. Over the next six months, these collateral vessels continue to grow in size and number[39]. Rayner *et al.*[40] in 1986 and Cohen *et al.*[41] in 1987 provided additional evidence illustrating that hepatic lobar arteries do not function as end arteries. Their research also revealed the rapid restoration of blood flow to the contralateral hepatic lobe through collateral vessels following the occlusion of a variant vessel. During the placement of a hepatic arterial pump, technical difficulties may arise in the presence of anomalies. In the case of unusual anatomy, it is recommended to insert the catheter into the GDA and tie off any accessory or replaced vessels while depending on cross-perfusion[31]. Collateral blood flow to the hypoperfused lobe of the liver typically develops within two to four weeks in almost all patients when there is incomplete liver perfusion following ligation of a replaced or accessory artery[36,42].

Pump placement technique

The surgical procedure typically starts by dissecting the porta hepatis and performing a cholecystectomy. This action helps to clear the operative area and identify the common bile duct. In addition, it reduces the likelihood of chemotherapy-related cholecystitis, which can affect 20%-30% of patients otherwise. The dissection of the hepatic artery commences medially to the common bile duct and then continues to the artery's proximal end. Afterwards, it proceeds onto the common hepatic artery for a distance of roughly 1 cm and onto the gastroduodenal artery for approximately 2 cm. Finally, the gastroduodenal artery segment and the hepatic artery's proximal and distal sections are dissected free of surrounding tissue with the ligation of all the small arterial branches encountered. A GDA occlusion test is routinely performed before proceeding with surgical maneuvers to verify the persistence of flow of the proper hepatic artery. Artery occlusion can be temporarily accomplished with the use of a bulldog clamp. The suprapyloric arterial branches and the right gastric artery are cut and tied off. This process of gastroduodenal devascularization is necessary in order to minimize the chances of incorrect blood supply to the stomach and duodenum, which can cause gastritis, duodenitis, and gastroduodenal ulceration when undergoing HAI chemotherapy[36,43].

The GDA is tied off 2 cm from where it branches off, and a small cut is made before the ligature. It is important to be careful not to create a tear in the inner lining if the lumen is gently widened. A "flute-shaped" catheter is inserted and positioned at the junction where the hepatic and gastroduodenal arteries meet to prevent any turbulence that could harm the catheter or the cannulated artery's long-term viability[36].

The catheter is secured in place with ties above and below the insertion point, ensuring a firm hold without obstructing the catheter's flow. However, complications like catheter tip movement into the hepatic artery, GDA, or complete dislodgement can occur. These may lead to vessel or catheter blockage, aneurysm, GDA rupture, or bleeding. To verify liver-only pump perfusion, a dye solution (methylene blue or fluorescein) is injected into the pump and its distribution is observed. The Codman 3,000 pump (Intera Oncology, Boston, USA), which was used in hepatic artery infusion (HAI) procedures, was discontinued in 2018. As a result, there was no FDA-approved HAI device available until the Synchromed II infusion pump was approved (Medtronic, Minneapolis, Minnesota, USA). The pump has a 20cc capacity and a flow rate of 1.0 ml/die; it is MRI compatible (1,5 to 3,0 Tesla magnetic field) and is designed to last 6.5 years. Subcutaneous placement of the positioning lodge is carried out in the lower left abdomen, as per the technique

recommended by the Memorial Sloan Kettering Cancer Center (MSKCC)[37] [Figure 1]. Contraindications are the presence of a stoma, an inflammatory/infectious process, or a distance from the skin greater than 2,5 cm.

Lymphadenectomy

As a routine procedure, locoregional lymphadenectomy is performed on the hepatic artery, hepatoduodenal, portocaval, and peripancreatic stations (8, 12, and 13). It has a dual function to provide a clear operative field and good exposure and to determine nodal staging[30,40].

The effectiveness of routine lymphadenectomy for intrahepatic cholangiocarcinoma remains a topic of debate[44]. While there is no conclusive evidence regarding the necessary extent of lymphadenectomy for accurate staging and its prognostic value, it has been observed that it can provide significant benefits in unresectable patients. Specifically, it can help alleviate portal tumor burden and prolong survival[45]. To ensure adequate nodal staging, the American Joint Committee on Cancer's eighth edition requires at least six harvested lymph nodes[46], while the National Comprehensive Cancer Network recommends hilar lymphadenectomy[16]. Additionally, an expert panel sponsored by the American Hepato-Pancreato-Biliary Association recommends lymphadenectomy as a part of the standard surgical therapy for iCCA[47].

COMPLICATIONS

High-volume centers report low mortality rates (under 1%) for pump placement procedures, with overall patient morbidity ranging from 12% to 41%[37,42,48-51] [Table 2]. In 2005, the MSKCC study group conducted a large retrospective study on 544 patients who were treated between 1986 and 2001. The study's findings on the long-term durability of the pumps were encouraging, with low failure rates of 5%, 9%, and 16% at six months, one year, and two years post-implantation, respectively. These results indicate that the pumps tested are a durable and reliable treatment choice for patients[37].

Complications that may occur after pump therapy can be categorized as related to the pump/pocket, catheter, vascular, or biliary systems. These complications may arise early in the postoperative period or after the initiation of pump therapy. It is important to identify, assess, and treat such complications promptly to save the infusion pump, as up to 45% of these complications can be resolved with early and aggressive treatment[52]. Complications that occur within the first 30 days are more likely to be successfully treated compared to those that occur later, with salvage rates of 70% and 30%, respectively[37].

Pump pocket infections are uncommon, up to 2%, but care must be taken intra- and postoperatively to avoid any source of contamination. Early identification of infection symptoms is crucial in managing cellulitis associated with infusion pumps. Conservative antibiotic therapy may be effective in treating mild cellulitis, but true infections may necessitate the relocation of the infusion pump. This process involves the removal of the pump, catheter isolation, and rerouting to a new site, after which a new pump is connected to the catheter.

Additionally, pump migration should be suspected if clinical signs such as skin erosion or ulceration, blistering, or pump displacement are observed. In the case of skin erosion or ulceration, the pump should be considered contaminated and removed and re-sited. Moreover, the pump can rotate or flip, especially in obese patients, where it is helpful to consider the placement in the chest wall routinely. In this case, re-siting in the same pocket may be possible. In < 5% of cases, complications are related to pump malfunction.

Table 2. Hepatic Artery Pump-Related Complications

Pump Pocket-Related	
Seroma	10%
Hematoma	5%
Infection	5%
Pump migration	< 1%
Catheter-Related	
Occlusive	10%-26%
Migratory	5%-18%
Erosion	< 1%
Vascular	
Dissection	< 0.5%
Thrombosis	6%
Pseudoaneurysm	< 5%
Biliary	
Transaminases, Bilirubin, Alkaline Phosphatases elevation	26%
Biliary Sclerosis	2%-8%

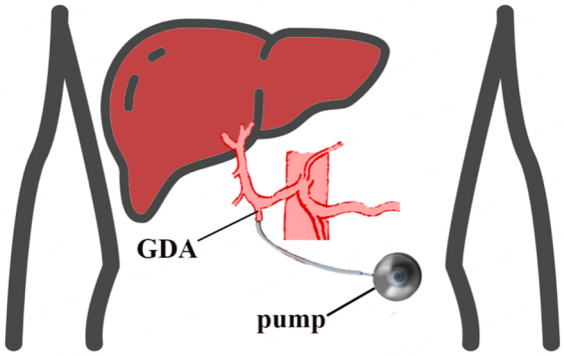

Figure 1. Placement location for hepatic arterial infusion chemotherapy pump. The catheter tip is placed at the origin of the gastroduodenal artery (GDA).

In less than 1% of patients, postoperative bleeding may occur. Conservative therapy is sufficient for managing minor bleeding into the pump pocket. However, in the event of a significant pump pocket hematoma that expands, surgical revision and evacuation of the clot are necessary, even if a compressive dressing has been applied. An arterial dissection can be manifest intra-operatively during catheter placement because of difficulty passing into the lumen of the GDA. In the context of a dye perfusion study, the presence of dye in the arterial wall may be observed. When this occurs, it is usually advisable to refrain from performing surgical maneuvers that could compromise the integrity of the hepatic artery. Instead, leaving the catheter in place and assessing the situation through postoperative angiography is often a more prudent course of action[52].

Arterial pseudoaneurysm is a rare condition that affects less than 5% of patients. It can be asymptomatic and found incidentally during restaging or can cause sudden, severe symptoms such as acute abdominal pain, anemia, and shock. Effective management of this condition requires angiography and either stenting or embolization.

In the early postoperative course, a clot in the catheter can be treated with a gentle heparin flush or lytic therapies through the pump catheter. However, if there is a delayed thrombosis or occlusion due to the presence of an extensive fibrin sheath within the catheter lumen, it can lead to high pump failure rates and pose significant challenges. In case the thrombosis extends into the hepatic artery, one should avoid catheter-directed therapy as it may result in the formation of pseudoaneurysm and result in bleeding.

Catheter migration or dislodgement can occur in 5% to 18% of patients. The severity of the issue depends on the timing and location of the displacement. In rare cases, the catheter may erode into the abdominal viscera, particularly around the site of insertion, such as the duodenum, or even in a distant area. When necessary, surgical revision is required[52-53].

Toxicity caused by hepatic arterial infusion chemotherapy can lead to a range of adverse effects, including chemical hepatitis, gastritis, peptic ulcer, and biliary sclerosis (BS). The occurrence of BS is especially concerning due to the possible requirement for a biliary stent and the potential for long-term liver damage[54]. It was first described by Hohn et al. in 1986[40] and further confirmed by Kemeny *et al.* in 1985[55] and in a randomized trial in 1992[56] and in 2012 by Ito *et al.*[54] on 475 consecutive patients who received HAI chemotherapy. Patients who received floxuridine-based chemotherapy had a BS incidence between 0.9% and 26%[32,43,48,57-63]. Regular monitoring of biochemical parameters is essential when signs of BS are observed, as indicated by increased levels of serum alkaline phosphatase and/or total bilirubin. In the event of abnormal liver function tests, HAI can be interrupted or conducted at lower doses but with a watchful eye on the blood chemistry trend. Intra-arterial steroids, specifically dexamethasone 4 mg, are commonly used during hepatic artery infusion (HAI) chemotherapy to mitigate or prevent the occurrence of biliary sclerosis (BS).

CONCLUSIONS

The combination of hepatic artery infusion and systemic chemotherapy has demonstrated clinical efficacy in extending overall survival in unresectable intrahepatic cholangiocarcinoma, and has served as a conversion to treatment strategy in a minority of patients. A noteworthy limitation of HAI chemotherapy is the restricted availability of experienced surgeons and oncologists. Recent efforts have been made to broaden its application, particularly in the United States and, more recently, in Europe, facilitated by the HAI Consortium Research Network. Anticipated results from ongoing clinical trials are poised to provide the foundation for the expanded utilization of this technique and oncological treatment beyond traditionally established centers.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception, manuscript drafting and revision: Stecca T, Massani M
Performed manuscript drafting and revision: Greco A, Brollo P

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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