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REVIEW ARTICLE

Hepatic arterial infusion pump chemotherapy for colorectal liver metastases: an old technology in a new era

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ABSTRACT

Aggressive treatment of colorectal cancer (CRC) liver metastases can yield long-term survival and cure. Unfortunately, most patients present with technically unresectable metastases; conventional therapy in such patients consists of systemic therapy. Despite advances in the effectiveness of systemic therapy in the first-line setting, the tumour response rate and median survival remain low in the second-line setting. The preferential blood supply from the hepatic artery to CRC liver metastases allows for excellent regional delivery of chemotherapy. Here, we review efficacy and safety data for hepatic artery infusion (HAI) pump chemotherapy in patients with metastatic CRC from the 5-fluorouracil era and from the era of modern chemotherapy.

In selected patients with liver-only or liver-dominant disease who have progressed on first-line chemotherapy, HAI combined with systemic agents is a viable therapeutic option when performed at experienced centres. Furthermore, significantly improved survival has been demonstrated with adjuvant HAI therapy after liver resection in the phase III setting. The complication rates and local toxicities associated with HAI pump therapy are infrequent at experienced centres and can be managed with careful follow-up and early intervention. The major obstacles to the wide adoption of HAI therapy include technical expertise for pump insertion and maintenance, and for floxuridine dose modification. The creation of formal preceptor-focused education and training in HAI therapy for interdisciplinary medical professionals might encourage the creation and expansion of this liver-directed approach.

KEY WORDS

Colorectal metastasis, liver metastasis, review, hepatic artery infusion pump chemotherapy, intra-arterial chemotherapy

1. INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death in Canada[1]. Despite the implementation of CRC screening programs, the public health burden of CRC remains significant. The liver is the most common site of CRC metastasis, with 15% of patients presenting with liver metastases at the time of diagnosis and up to 60% of patients developing liver metastases during the course of their disease[2]. Surgical resection of liver metastases can lead to long-term disease-free survival, but unfortunately, only a small proportion of patients have disease amenable to resection.

Recognition of differences in the blood supply to metastases compared with that to normal liver parenchyma has allowed for the development of hepatic arterial delivery of systemic chemotherapeutic agents. The most commonly used agent is floxuridine (FUDR), a pyrimidine antimetabolite that is converted to 5-fluorouracil in the liver. Floxuridine has a very high rate of hepatic extraction and a short half-life, making it optimal for hepatic infusion[3].

Studies of hepatic arterial infusion (HAI) pump therapy demonstrated significant tumour response rates, with encouraging survival data, at a time when systemic therapy was associated with tumour response rates of less than 20%, and median overall survival was limited to less than 18 months. However, since the end of the 1990s, significant progress has been made with a number of chemotherapeutic and biologic agents approved for the treatment of metastatic CRC, and median overall survival is now reaching up to 24 months[4] in patients with liver-limited metastasis. Currently, the use of HAI is limited to a few specialized centres in the United States, with no availability in Canada.

Here, we review efficacy and safety data from HAI pump therapy studies in patients with metastatic CRC from the 5-fluorouracil (5FU) era and from the era of modern chemotherapy. A formal systematic review was not conducted; instead, PubMed was searched

for the terms "hepatic artery infusion pump," "HAI," and "colorectal cancer." Relevant studies were reviewed by both authors.

2. DISCUSSION

2.1 Efficacy of HAI for Unresectable CRC Liver Metastases

Three meta-analyses have consolidated data from studies of HAI chemotherapy (Table I). The first two meta-analyses, which included six of seven randomized studies, detected a survival advantage (27% relative risk reduction) in favour of HAI[5] and a response rate that was clearly superior to the rate with systemic therapy alone (41% vs. 14%)[6]. However, the extrahepatic recurrence rate was higher by a factor of 5 in the HAI pump group than in patients who received systemic therapy. A subsequent meta-analysis that included all ten published randomized trials up to 2007 demonstrated that, despite a higher tumour response rate (42.9% vs. 18.4%) in favour of HAI therapy, no difference was observed in the overall risk of death (hazard ratio: 0.90; $p = 0.24$). The authors concluded that the current evidence did not support the use of fluoropyrimidine-based HAI alone for treatment of patients with unresectable CRC liver metastasis[7]. Although 1277 patients were included in the meta-analyses, seven of the ten studies accounted for most of the patients, and two of the ten studies used 5FU, which has a much lower hepatic extraction rate than FUDR, as the chemotherapeutic agent delivered through the HAI pump[8,9]. The 5FU regimen was compared with systemic chemotherapy using FUDR (seven studies), sometimes plus leucovorin, or using leucovorin alone (four studies). Furthermore, four of the studies permitted eventual crossover to the HAI pump arm for patients receiving systemic therapy, which might explain why response rates differed but overall survival did not. Finally, the study findings are of limited significance given that the practice of HAI therapy in most centres had already evolved to combinations with systemic chemotherapy by the time the meta-analysis was published.

2.2 HAI Pump Plus Systemic Chemotherapy

All of the studies included in the meta-analysis by Mocellin *et al.* used HAI alone, without concurrent administration of systemic chemotherapy, because all of the studies were conducted before approval of irinotecan and oxaliplatin. Given that extrahepatic recurrences were commonly observed and that systemic toxicity from FUDR is rare, HAI pump therapy evolved to include systemic chemotherapy. A number of single-arm phase I and II studies and retrospective analyses have since investigated the use of HAI pump therapy in combination with systemic chemotherapy.

One of the first-reported studies examined the combination of FUDR plus dexamethasone by HAI, with systemic delivery of irinotecan in a phase I design[10]. In 46 pretreated patients (45% had previously received irinotecan systemically), the maximal tolerated dose of irinotecan was 100 mg/m^2 given weekly for 3 weeks with 1 week off. The irinotecan was combined with FUDR 0.16 mg/kg daily. No effect of FUDR HAI pump therapy on the metabolism of irinotecan was observed. Of 38 patients with unresectable disease who did not undergo cryosurgery, the response rate was 74%. The median time to progression was 8.1 months, and the median overall survival reached 20 months.

Another phase I study from Memorial Sloan–Kettering published in 2005 reported the addition

TABLE I Published meta-analyses of hepatic arterial infusion (HAI)

Reference	*Studies* (n)	*Subjects* (n)	*Outcomes for HAI vs. systemic therapy*	
			Response rate (%)	*Overall survival (months)*
Meta-Analysis Group in Cancer, 1996[5]	7	654	41 vs. 14 $p<10^{-10}$	16 vs. 12.2 HR: 0.73 p=0.0009
Harmantas *et al.,* 1996[6]	6	579	Not available	Not reported 1-Year survival difference: 10%; p=0.041 2-Year survival difference: 6%; p=0.124
Mocellin *et al.,* 2007[7]	10	1277	42.9 vs. 18.4 $p<0.0001$	15.9 vs. 12.4 HR: 0.90 p=0.24

HR = hazard ratio.

of two different oxaliplatin-based systemic chemotherapy regimens to FUDR-based HAI therapy[11] in 36 patients, most of whom had already received systemic therapy with irinotecan. The 21 patients in one group were treated with a combination of oxaliplatin (85–130 mg/m^2) and irinotecan (150–200 mg/m^2), which were separately dose-escalated. The remaining patients received systemic chemotherapy consisting of a fixed dose of oxaliplatin (100 mg/m^2) with an escalating dose of infusional 5FU. The tumour response rate was 90% and 87% respectively, and the median overall survival was 36 and 22 months. The most common grades 3 and 4 toxicities were diarrhea, neutropenia, and neurotoxicity. Interestingly, 7 patients in the oxaliplatin–irinotecan group were able to undergo liver resection after HAI pump therapy, and 2 patients were found to have a pathologic complete response in liver.

A subsequent study of 49 patients with CRC liver metastasis (53% previously treated) who received FUDR HAI pump therapy with systemic irinotecan and oxaliplatin, achieved a response rate of 92%, with 47% of patients subsequently undergoing liver resection[12]. Median overall survival for the previously treated and untreated patients was 35 and 50.8 months respectively.

Several phase II studies have set out to determine the efficacy and safety of HAI pump therapy combined with systemic chemotherapy. In 2003, a French group published a phase II study using an anthracycline, pirarubicin, delivered through a femorally placed hepatic artery catheter, plus systemic irinotecan, 5FU, and leucovorin given every 2 weeks[13]. Although the tumour response rate was 48%, 75% of patients experienced grades 3 and 4 neutropenia. The extrahepatic progression rate was not reported.

In contrast, modern second-line chemotherapy studies using biologic therapy have demonstrated only modest tumour response rates and survival gains. For example, the addition of aflibercept, a recombinant fusion protein that functions as a decoy receptor that binds to vascular endothelial growth factors A and B and placental growth factor, was associated with an increase in median survival to 13.50 months in those who received aflibercept with FOLFIRI (leucovorin, 5FU, irinotecan) from 12.06 months in those who received placebo with their chemotherapy[14]. The tumour response rate was also higher in the aflibercept arm (19.8% vs. 11.1%). The continuation of bevacizumab from the first-line to the second-line setting was also observed to improve survival to 11.2 months from the 9.8 months seen in patients who received chemotherapy alone[15]. When retrospectively calculated, the median overall survival from the start of first-line therapy was 23.9 months for the bevacizumab group and 22.5 months for the chemotherapy-alone group. However, the tumour response rates were 5% and 3% for the bevacizumab and chemotherapy arms respectively.

2.3 Adjuvant HAI Pump Therapy

Although surgical resection remains the standard of care for patients with technically resectable CRC liver metastases, the liver remains the only site of recurrence in approximately half the patients who experience a relapse[16]. A pilot study exploring the utility of FUDR HAI therapy combined with systemic 5FU and leucovorin established doses appropriate for use in the adjuvant setting after liver resection[17]. Since that time, several other trials have examined the role of HAI in the adjuvant setting (after liver resection).

A U.S. multicentre study randomized 156 post–liver resection patients either to FUDR HAI plus systemic 5FU with or without leucovorin for 6 cycles or to 6 weeks of systemic therapy alone. The primary endpoint—overall survival at 2 years—was superior in the group that received only systemic therapy (86% vs. 72%, $p = 0.03$). Importantly, significantly more patients in the HAI pump group remained free of recurrences in the liver at 2 years (90% versus 60% in those who did not have a pump, $p < 0.001$). However, the magnitude of the improvement in overall progression-free survival was less than the benefit in improving hepatic progression, thus emphasizing the importance of optimizing the systemic therapy that is combined with FUDR pump therapy.

In contrast, a larger Intergroup trial that randomized patients with resected liver metastasis to either FUDR HAI therapy combined with systemic 5FU (continuous infusion) or to no postoperative therapy was forced to close prematurely because of poor accrual over a 9-year period[18]. Despite 109 patients being randomized, only 75 patients were evaluable, and just 30 of the 53 patients randomized to the HAI pump arm were assessable. The 4-year recurrence-free rate was 25% in the observation arm compared with 46% in the chemotherapy arm ($p = 0.04$); the 4-year liver-free recurrence rate was 43% and 67% respectively ($p = 0.04$). The study was not initially powered to detect a difference in overall survival, and a nonsignificant difference of 14.3 months ($p = 0.6$) in favour of the chemotherapy arm was observed.

Subsequent studies have examined the addition of newer systemic chemotherapy agents to FUDR HAI pump therapy in the adjuvant setting. Although no further phase III studies have been conducted in that setting, the studies that have proceeded have generally increased in sample size. The chemotherapeutic agents that have been explored in a combined approach in the adjuvant setting include irinotecan[19] and oxaliplatin with infusional 5FU[20]. More recently, a phase II study of adjuvant HAI and oxaliplatin-based systemic therapy with or without bevacizumab was associated with no improvement in relapse-free survival, but an increase in biliary toxicity[21].

2.4 Complications Associated with the Use of HAI

Despite strong evidence suggesting that HAI chemotherapy is effective at controlling CRC liver metastases, enthusiasm and widespread adoption have been limited in part because of the significant complication rate associated with this therapy. Adverse events can be technical (related to the catheter, port, or pump) or toxicities related to chemotherapy (Table II).

The largest single-institution experience with technical complications was reported by Allen and colleagues from Memorial Sloan–Kettering Cancer Center[22]. During a 15-year period, 544 patients underwent HAI pump placement for the treatment of unresectable CRC liver metastases. Technical complications with the pump occurred in 120 patients overall (22%). The most common complications were arterial thrombosis (6%), catheter occlusion or dislodgement (6%), extrahepatic perfusion (3%), and pump pocket infection or hematoma (3%). Pump malfunction was rare, occurring in only 6 patients (1%). Notably, most complications were salvaged, so that the overall pump failure rate was 9% at 1 year and 16% at 2 years. As with many other surgical procedures, experience with pump implantation appears to be important: the complication rate was found to be 31% among surgeons who had performed fewer than 25 procedures and 19% among surgeons with 25 or more implantations. Pump complications were also higher in patients with variant arterial anatomy (28% vs. 19%) and substantially higher when the catheter was inserted into a vessel other than the gastroduodenal artery (42% vs. 21%). A quarter of the patients underwent concomitant resection of colon or rectum; the dual surgery did not alter the complication rate.

A recent systematic review assessed complications in 3172 patients treated with intra-arterial hepatic chemotherapy at a variety of institutions[24]. The authors included 16 studies of surgically-placed catheters connected to ports, 14 studies of radiologically-placed catheters connected to ports, and 17 studies of fully-implantable pumps. The complication rate for these three varieties of HAI was 34%, 36%, and 16% respectively. Substantial heterogeneity between the studies was observed, but regardless of technique, the most common complication types were similar to those reported by the Sloan–Kettering group: namely, arterial thrombosis, catheter thrombosis or dislocation, and infection. Patients with implantable pumps received a median of 12 cycles of chemotherapy, compared with 8 cycles in patients treated with surgically-implanted ports and just 6 cycles in patients with radiologically-implanted ports.

Because of the high hepatic uptake of FUDR administered via the hepatic artery, systemic toxicity is minimal, being predominantly related to the systemic chemotherapy that is delivered concurrently with HAI. The most limiting hepatic toxicity related to HAI is biliary sclerosis, typically manifested by elevations in serum alkaline phosphatase or bilirubin (or both). Biliary sclerosis may be severe, leading to intra- and extrahepatic biliary strictures requiring stents, with the potential for chronic liver damage. The incidence of biliary sclerosis was reported to be as high as 23% in the initial experiences with HAI[25]. Since that time, a randomized controlled trial has demonstrated a marked decrease in the frequency of biliary sclerosis when dexamethasone is administered concurrently with FUDR via HAI[26].

TABLE II Hepatic arterial infusion pump complications

Complication type	*Frequency (%)*	*Pump salvaged (%)*
Arterial thrombosis[22]	6	30
Catheter occlusion or dislodgement[22]	6	21
Extrahepatic perfusion[22]	3	81
Pump-site infection or hematoma[22]	3	47
Biliary sclerosis[23]	5	NA

NA = not applicable.

In the largest modern series focused on biliary sclerosis, the overall incidence rate among 393 patients treated with HAI FUDR was 4.6%[23]. The incidence of biliary sclerosis was much higher (13.4%) in patients receiving HAI FUDR combined with mitomycin as part of a protocol. An important difference was noted between patients treated with HAI in the adjuvant setting (after liver resection) and those with unresectable liver metastases (5.5% vs. 2.0%). Biliary sclerosis was also associated with abnormal postoperative flow scans (18.8% vs. 1.8%), postoperative infectious complications (50.0% vs. 14.8%), and larger doses of FUDR. Notably, no patients in the series died directly of biliary sclerosis, and overall survival was not diminished in patients who developed biliary sclerosis. In summary, the incidence of biliary sclerosis in patients treated with FUDR HAI for unresectable CRC liver metastasis is low and can be effectively managed if detected early.

3. SUMMARY

The liver remains the single most common site of metastasis from CRC. Despite improvements in systemic chemotherapy and the addition of biologic therapies, tumour response rates remain low in the second-line setting, and median overall survival approaches 12 months. The preferential blood supply from the hepatic artery to CRC liver metastases allows for excellent delivery of chemotherapy, especially FUDR, through a HAI pump, achieving a high tumour response rate and little systemic toxicity. In selected patients with liver-only or liver-dominant disease who have progressed on first-line chemotherapy, HAI

combined with systemic agents is a viable therapeutic option when performed at experienced centres. Furthermore, significantly improved survival has been demonstrated with adjuvant HAI therapy after liver resection in the phase III setting. The complication rates and local toxicities associated with HAI pump therapy are infrequent at experienced centres and can be managed with careful follow-up and early intervention. The major obstacles to the wide adoption of HAI therapy include technical expertise for pump insertion and maintenance, and for FUDR dose modification. The creation of formal preceptor-focused education and training in HAI therapy for interdisciplinary medical professionals might encourage the creation and expansion of this liver-directed approach.

4. CONFLICT OF INTEREST DISCLOSURES

No financial conflict of interest exists.

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