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ORIGINAL ARTICLE

Feasibility of Hepatic Artery Infusion Chemotherapy for Colorectal Liver Metastasis in an Indian Setting

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Abstract

Hepatic artery infusion chemotherapy (HAIC) is a popular treatment modality for the treatment of colorectal liver metastasis (CRLM). The aim of this study was to determine the feasibility of HAIC for high-risk resected CRLM delivered using repeated femoral puncture and delivering 5-fluorouracil infusional chemotherapy along with systemic adjuvant chemotherapy. The present study is a retrospective review of a prospectively maintained database. All patients who underwent HAIC for colorectal liver metastases between July 2022 and July 2023 were included. A total of 12 patients were included in the study of which 11 completed four sessions as planned. The median age was 47 (29–73) years with nine male (81%) and two female (18%) patients. Rectum ($n = 7$, 63%) was the most common primary location. All patients received systemic chemotherapy with 5-fluorouracil-based regimens prior to HAIC (median 12 cycles). The median number of metastasis was 2 (1–8). Eight patients had metastasis in unilobar distribution (73%). On completion of HAIC treatment, nine patients (64%) were completely disease free with a median follow-up of 8 months. None of the patients experienced any immediate adverse events during or after completion of the procedure. Conventional HAIC comes with various challenges such as unavailability of the agent floxuridine and the specialized HAIC pump. Percutaneous HAIC has a lower chance of infection. The delivery of HAIC using repeated femoral punctures and 5FU chemotherapy was successful in over 90% of the patients making it a feasible option in the treatment of CRLM.

Keywords Colorectal liver metastasis · Infusional chemotherapy · HAIC · Safety

Introduction

Colorectal malignancies have been linked with the second highest incidence of cancer-related deaths across the world, attributed mainly to liver metastasis [1]. More than half of the patients with colorectal cancer develop liver metastases; however, only 15–20% of these are resectable initially. With the advent of effective systemic therapy and newer liver directed therapies, there is increased scope for resection of colorectal liver metastasis resulting in better rates of remission and survival. Despite this, recurrences are seen in 30–50% of cases of colorectal cancer [2–4].

Perioperative chemotherapy for resectable colorectal liver metastasis has failed to improve overall survival in randomized trials [5–7]. The commonest site of failure after resection of colorectal liver metastasis (CRLM) remains the liver. Thus, additional liver directed therapy is a plausible step towards achieving better outcomes. Hepatic artery infusion chemotherapy (HAIC) is one such modality that is gaining increasing popularity for unresectable and high-risk resectable CRLM and also for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC) [8–10]. Most studies have used a surgically placed catheter with a chemotherapy port that can be used to repeatedly puncture and deliver chemotherapy; however, these devices are not available in India. Moreover, the chemotherapeutic agent of choice has been FUDR (floxuridine) based on its extremely favorable pharmacokinetic profile suitable for liver perfusion. Unfortunately, FUDR is also unavailable in India.

To overcome these challenges, few centers have used catheters placed using femoral puncture for every chemotherapy instillation and have explored other drugs as well. Given the challenges of resources, the present study aimed to determine the feasibility of HAIC for high-risk resected

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CRLM delivered using repeated femoral puncture and delivering 5-fluorouracil (5-FU) infusional chemotherapy along with systemic adjuvant chemotherapy.

Materials and Methods

The study was carried out as a retrospective audit of the HAIC database of Tata Memorial Hospital. The treatment plan was formulated as per a detailed assessment carried out by a multidisciplinary team.

Patients fulfilling the following criteria were recruited: Those having resected or ablated colorectal liver metastasis (either synchronous/metachronous) were treated with curative intent:

1) Single lesion more than or equal to 5 cm,
2) Multiple lesions more than or equal to three in number, and
3) Normal liver function and renal function tests are assessed as follows: adequate hematological function (absolute neutrophil count $> 1.5 \times 10^9$/l, platelets $> 100 \times 10^9$/l, hemoglobin > 9 g/dl), adequate liver function (serum bilirubin <l, h× ULN; alkaline phosphatase and transaminases $< 5 \times$ ULN), and serum creatinine $< 1.5 \times$ ULN)

Patients with liver limited progression after first line therapy were also offered HAIC after a MDT board discussion.

Use of prior systemic therapy was permitted. Patients with extra hepatic disease (except three or less lung nodules less than 10 mm) or those with a history of prior hepatic artery infusion or radioembolisation were excluded.

Data collection was done in accordance with the Declaration of Helsinki [11].

HAIC Procedure

A computed tomography (CT) scan was done prior to the procedure for a complete assessment of the vasculature. A 4 Fr SIM 1 catheter was used and the celiac trunk was cannulated. The proper hepatic artery was cannulated by a microcatheter. After securing these in place, chemoinfusion of 5-FU was given as a 5-h infusion at a dose based on the body surface area (1000 mg/m2 administered weekly). If HAIC was planned preoperatively, the right gastric artery and gastroduodenal artery were ligated intraoperatively for selective delivery of the drug and to prevent complications. The patient was kept under observation overnight after the infusion and discharged the following day. Any local or systemic complications were recorded. The procedure was performed every 7 days. Four such sessions were carried out for each patient.

Outcomes

The primary aim was to determine the feasibility of the procedure determined by the rate of successful catheterization, the number of cycles delivered by repeated punctures, and tolerability based on adverse events.

Success was defined as the delivery of the planned four cycles of HAIC along with systemic chemotherapy. A 70% success rate would be considered sufficiently acceptable.

Follow-up

After successful completion of the procedure, patients were advised to come for regular follow-ups once in every 3 months for 2 years, followed by once in every 6 months for the next 3 years and annually thereafter as per our protocol. Tumor markers and liver function test were assessed at each follow-up.

Results

Twelve patients were included in the study of which 11 patients completed four sessions as advised (91.67%; 95% confidence intervals, 61.5%–99.8%) (Table 1). One patient withdrew consent due to personal reasons. One patient received HAIC for unresectable disease and liver limited progression post systemic therapy. Of these, 9 (81.81%) were male and 2 (18.82%) were female. The median age was 47 years with a maximum of 73 years and minimum of 29 years.

Majority of patients had primary malignancy in the rectum (7 (63.63%)). Ten (90.90%) patients underwent surgical resection for the primary malignancy. A majority of these were of stage pT3N1 (4/11) or pT3N2 (4/11).

All the patients had been given systemic chemotherapy with 5-fluorouracil-based regimens prior to HAIC with median number of cycles being 12. The median number of metastasis was 2 ranging from 1 to 8. Eight patients had metastasis in unilobar distribution (72.72%). Of the 11 patients, 8 (72.72%) received 5-fluorouracil-based chemotherapy after completion of HAIC.

Ten patients underwent prior treatment for the liver metastasis in the form of surgical resection (72.72%) or radiofrequency ablation (45.45%).

For the eight patients with metachronous liver metastasis (72.72%), the median disease free interval (DFI) was 9.86 months. Two patients were diagnosed with limited extra hepatic lung metastasis along with liver metastasis.

On completion of HAIC treatment, nine patients were completely disease free with a median follow-up of 8 months. One patient who had unresectable disease at the

Table 1 Baseline characteristics and distribution of the sample population

	Median (range)	
Age (in years)	47 (29–73)	
Number of metastasis	2 (1–8)	
	Number (*n*)	Percentage (%)
Gender		
Male	9	81.8
Female	2	18.2
Total	11	100.0
Primary tumor		
Tx	0	0
T0	0	0
Tis	0	0
T1	0	0
T2	2	18.2
T3	8	72.7
T4	1	9.1
Regional lymph nodes		
Nx	0	0
N0	2	18.2
N1	4	36.4
N2	5	45.4
Metastasis		
Synchronous	3	27.3
Metachronous	8	72.7
Distribution of metastasis		
Unilobar	8	72.7
Bilobar	3	27.3
Location of primary lesion		
Colon	5	45.4
Rectum	6	54.6

time of initial presentation continued to progress despite successful completion of the treatment and one developed recurrence of liver lesions after 4 months and hence was planned for further chemotherapy.

None of the patients experienced any immediate adverse events during or after completion of the procedure. No major complications were observed at the time of follow-up.

Discussion

Perioperative chemotherapy in different forms has been explored in conjunction with surgery to reduce the chances of recurrence in colorectal cancers. Of these, hepatic artery infusion chemotherapy (HAIC) has been found to be effective in case of both resectable and unresectable liver metastasis [12, 13].

As liver metastasis derive their blood flow from the hepatic artery (as opposed to the portal venous system), HAIC has been used as a means of selective administration of drugs to the tumor cells while sparing normal hepatocytes. The success of HAIC depends on the agent used and the method of drug delivery. Drugs that have a high first-pass metabolism and short plasma half-life with steep dose-response curves are ideal. Insertion of a durable catheter for long-term drug delivery or use of an HAI pump is recommended [14].

Most studies evaluating HAIC involve the use of floxuridine (FUDR) which is unavailable in India. Its intra-arterial use has also been linked with biliary sclerosis which is a major limiting factor in its use for HAIC [15]. In contrast, 5-FU has a similar efficacy and good biological rationale and is the backbone of systemic therapy in colorectal cancer. Although it has a moderate first-pass metabolism, it is safer in terms of potential biliary toxicity.

Two primary modalities have been explored for administration of HAIC. Hepatic artery infusion pumps are not available in India and require an additional surgical procedure for patients with unresectable disease or those undergoing ablation. In contrast, percutaneous administration of HAIC has a lower chance of infection although it requires an expert team of interventional radiologists for repeated cannulation.

Over the last few years, there have been massive advancements in the management of colorectal liver metastasis to improve the overall survival. Multimodality therapy including surgical resection, chemotherapy, and monoclonal antibody therapy are especially useful. HAIC has been widely studied in this regard and its efficacy proven; yet, its use remains limited [16–18].

Conversely, a meta-analysis by Mocellin et al. had dismissed the role of HAIC and its utility in treating liver metastasis [19]. However, this study had several limitations that were not accounted for such as the variation in technique and limited number of participants in individual studies that were predominantly single-center. Another deterrent is the fact that traditional HAIC techniques used an implantable port-catheter system that required specialized equipment and had to be performed under general anesthesia or as a minimally invasive procedure with radiological guidance. In contrast, recent studies have shifted to a method of repeated hepatic artery catheterization to reduce vascular complications and infections [20].

In the present study, we opted to use a microcatheter to cannulate the hepatic artery at every visit. The delivery of HAIC using repeated femoral punctures and 5FU chemotherapy was successful in over 90% of the patients; this provides a viable alternative to the use of surgically placed microcatheters and pumps. Moreover, the toxicity profile of 5FU HAIC in combination with systemic FOLFOX was found to be well tolerated [21].

The role of HAIC as an adjuvant therapy for the treatment of colorectal liver metastasis has now been well established by many studies. A systematic review by Buisman et al. showed that the pooled HR for overall survival of patients who underwent adjuvant HAIC after resection of colorectal liver metastases was better than patients without adjuvant HAIC (HR for OS of 0.77, 95% CI:0.64–0.93) [1]. A significant limitation in the analysis of various randomized clinical trials is the wide variation in therapeutic agents, techniques, and concomitant or preceding treatments in the form of surgery or systemic chemotherapy. Two ongoing trials are currently underway to analyze the effect of adjuvant HAIC [11, 22].

One of the benefits of HAIC is reduced systemic toxicity as the procedure allows for a higher intrahepatic concentration of the drug. This led to a concern of potential hepatotoxicity [23]. In our study, there were no immediate adverse effects and all the patients were able to complete four cycles. Long et al. found that HAIC was associated more commonly with nausea and vomiting, hypoalbuminemia, pain, anemia, and liver toxicity compared to other treatments used for unresectable liver metastasis [24]. There has also been concern regarding potential hepatic toxicity following HAIC. However, this was not found to be a major concern. Longer follow-up is required to assess systemic toxicity after HAIC.

The advantages of this study were the good selection of fit patients who could be given systemic chemotherapy and tolerated the sessions of HAIC well. The availability of an expert team of interventional radiologists ensured adequate periprocedural care of infusional 5-FU.

The major limitations of the present study include a small sample size owing to its retrospective nature and shorter period of follow-up. However, these were adequate to assess the technical feasibility of the procedure with a success rate of 91.67%. Regular scanning to evaluate the efficacy of HAIC and its potential to treat and prevent metastasis are required. Long-term follow-up and prospective comparative studies will be beneficial. The PACHA and PUMP trial results are eagerly awaited to understand the oncological efficacy of adjuvant HAIC in CRLM of varied risks [11, 22].

Conclusion

HAIC is an effective and feasible technique that can be utilized in the treatment of CRLM with a minimally invasive technique. This can be used in combination with multikinase inhibitors, immunotherapy, and other liver directed therapies as its mechanism of cytotoxicity is different. Further studies are necessary to determine the exact role and timing of HAIC as a part of multimodality treatment of CRLM.

Author Contribution Study conception and design was done by MG, SP, ALD, and APS. Material preparation, data collection, and analysis were performed by SP, MK, and SGB. The first draft of the manuscript was written by SGB, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Data Availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval This is an observational study, hence no ethical approval is required.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication The authors affirm that human research participants provided informed consent for publication.

Competing Interests The authors declare no competing interests.

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