Original Article

Selective intra-arterial mitomycin-C infusions for treatment-refractory colorectal liver metastases

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Background: Mitomycin-C is an older drug which has a synergistic mechanism of action with irinotecan. This study evaluated the outcomes of selective intra-arterial mitomycin-C infusions in combination with bi-weekly systemic irinotecan for treatment of liver-dominant metastatic colorectal cancer (CRC) which progressed after hepatic arterial infusion (HAI) pump chemotherapy with floxuridine and at least two lines of systemic chemotherapy.

Methods: An IRB-approved retrospective review of patients receiving at least two sessions of selective monthly mitomycin-C infusions in interventional radiology (IR) was performed. Anatomic and metabolic imaging was initially obtained at 4 weeks after the second infusion, and every 2–3 months thereafter. Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and European Organization for Research and Treatment of Cancer (EORTC) criteria. Patient, disease and procedural parameters were recorded. Progression-free survival (PFS), liver progression-free survival (LPFS) and overall survival (OS) were assessed with Kaplan Meier methodology.

Results: From January 2019 to April 2023, 46 patients underwent a total of 190 selective infusions (range 2–10; median 4). Twenty-three/46 (50%) patients had *KRAS* mutations and 35/46 (76.1%) had extrahepatic disease at the time of the first infusion. On initial follow-up, liver disease control was observed in 38/46 using RECIST 1.1 (82.6%; partial response 13%, stable disease 69.6%) and 26/31 using EORTC criteria (83.9%; complete response 6.5%, partial response 48.4%, stable disease 29%). Median PFS, LPFS and OS were 4.1 [95% confidence interval (CI): 3.2–4.9], 5.5 (95% CI: 2.5–8.4) and 9.6 (95% CI: 8.2–11.1) months respectively. The infusions were discontinued in 26 (56.5%) patients due to disease progression. Eighteen patients (39.1%) discontinued the infusion protocol due to toxicities/complications, including hepatic/biliary toxicity (26.1%), hepatic arterial thrombosis (15.2%) and/or pulmonary toxicity (8.7%).

Conclusions: In this heavily pretreated population, addition of intra-arterial mitomycin-C was associated with initial liver disease control rates exceeding 80%. Toxicities were observed, particularly in patients with prolonged disease control who received ≥4 infusions.

Keywords: Colorectal liver metastases (CLM); hepatic arterial infusion chemotherapy; arterially-directed therapies; salvage treatments

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Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death for men and women combined, responsible for over 50,000 deaths annually in the United States (1). Colorectal liver metastases (CLM) develop in over one-third of patients with CRC; most patients are not eligible for liver resection either due to the disease extent or the presence of comorbidities (2-4). CLM are a significant cause of morbidity and mortality in this patient population, as progressing liver metastases can cause liver dysfunction and failure through parenchymal replacement, vascular inflow compromise and/or biliary obstruction (3).

Treatment of liver-dominant metastatic CRC with systemic chemotherapy involves a combination of fluoropyrimidines with oxaliplatin and/or irinotecan (5,6). Advancements in targeted molecular agents and immunotherapy over the past two decades have improved survival of patients with metastatic CRC, however most patients do not survive past three years (4). Hepatic arterial infusion (HAI) chemotherapy, administered through intra-arterial pumps or ports placed surgically or percutaneously, has been associated with longer liver progression-free survival (LPFS) and overall survival (OS) and increased response rates compared to chemotherapy alone, allowing conversion to resectable disease in more patients (7-13). Despite these improved outcomes, some patients develop CLM refractory to systemic and HAI chemotherapy, necessitating the administration of other salvage treatments.

Mitomycin-C is an older chemotherapeutic agent which has been used intra-arterially in the salvage setting for CLM (14-17). This agent can be administered through the sideports of the discontinued Codman HAI pumps (Johnson & Johnson, New Brunswick, NJ, USA; production halted in April 2018) (18) or newer Intera 3000 pumps (Intera Oncology, Newton, MA, USA). The Medtronic Synchromed pumps (Minneapolis, MN, USA), implanted at the authors' institution after discontinuation of the Codman pumps and prior to the availability of the Intera 3000 pumps, are not compatible for intra-arterial administration of mitomycin-C due to the small sideport size. For patients with progressing CLM and Medtronic pumps, selective catheterization of the hepatic artery was performed in interventional radiology (IR) for mitomycin-C administration. These infusions were performed with concurrent systemic irinotecan, a drug which synergizes with mitomycin-C through topoisomerase-1 activity modulation (19,20).

The purpose of this study was to evaluate the outcomes of selective monthly intra-arterial mitomycin-C infusions in IR, combined with bi-weekly systemic irinotecan for treatment of CLM progressing after HAI pump chemotherapy with floxuridine (FUDR) and at least two lines of systemic chemotherapy. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-725/rc).

Highlight box

Key findings

- For heavily pretreated patients with progressing liver metastases after hepatic arterial and systemic chemotherapy, salvage selective intra-arterial mitomycin-C infusions achieved initial disease control in >80% of patients.
- Median liver progression-free survival (LPFS) was 5.5 months and median overall survival (OS) was 9.6 months.

What is known and what is new?

- Limited options are available for patients with chemorefractory colorectal liver metastases.
- The oncologic outcomes (LPFS and OS) reported in this study are within the reported range after salvage yttrium-90 radioembolization.

What is the implication, and what should change now?

- Mitomycin-C infusions can be considered for select patients with colorectal liver metastases in the salvage setting, noting that patients with prolonged responses after repeated infusions are more likely to develop toxicities.

Methods

This single-institution retrospective study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center (protocol No. 16-402; date of approval: May 3, 2016). Individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients

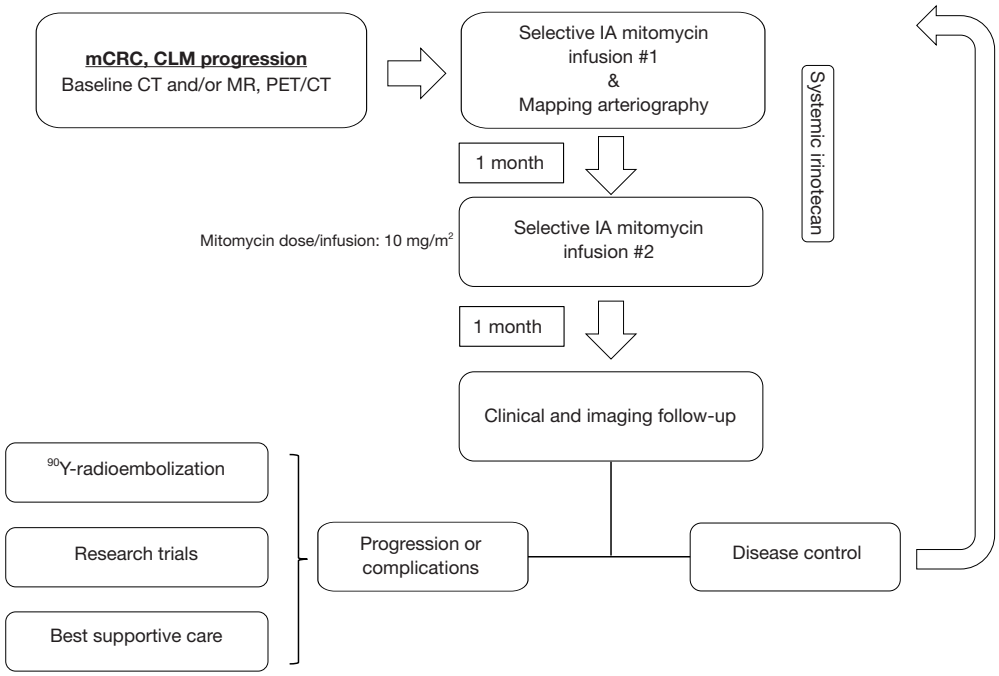

Figure 1 Selective intra-arterial mitomycin-C infusion protocol. mCRC, metastatic colorectal cancer; CLM, colorectal liver metastases; CT, computed tomography; MR, magnetic resonance; PET, positron emission tomography; IA, intra-arterial.

with liver-dominant metastatic CRC who underwent selective monthly intra-arterial infusions of mitomycin-C under fluoroscopic guidance in IR were examined. Patients included in the study met the following criteria: (I) histologically confirmed primary adenocarcinoma of the colon or rectum; (II) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (III) liver metastases not amenable to surgical resection or percutaneous ablation; (IV) prior HAI pump placement and exposure to FUDR; (V) progressing CLM despite systemic and hepatic arterial chemotherapy; (VI) inability to receive mitomycin-C through the HAI pump due to presence of a Medtronic pump or due to a contraindication to usage of a Codman pump; (VII) performance of at least two selective mitomycin-C infusion sessions and (VIII) availability of follow-up imaging for evaluation of treatment response.

Patients were evaluated in IR clinic following referral by the gastrointestinal oncology service. Laboratory values (complete blood count, comprehensive metabolic panel, prothrombin time) and tumor markers [carcinoembryonic antigen (CEA)] were recorded. Recent baseline imaging (within 30 days from the anticipated date of the first procedure) was reviewed and included at least one anatomic modality [computed tomography (CT) and/or magnetic resonance imaging (MRI)] and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT.

Infusion protocol

The infusion protocol is presented in *Figure 1*. Patients would receive two infusion sessions of selective intra-arterial mitomycin-C one month apart, while concurrently receiving systemic bi-weekly intravenous irinotecan. During the first mitomycin-C infusion procedure, mapping arteriography was also performed with technetium-99m labeled macroaggregated albumin (^{99m}Tc-MAA), in preparation for possible Yttrium-90 (^{90}Y) transarterial radioembolization (TARE), in the event of continued CLM progression on follow-up. The radiotracer (^{99m}Tc-MAA) was delivered after the infusion of mitomycin-C. Patients would be subsequently transferred to the nuclear medicine department, where they would undergo single-photon emission computed tomography (SPECT)/CT for radiotracer localization and calculation of the lung shunt fraction. One month after the second mitomycin-C infusion, patients were evaluated in clinic with new

imaging and labs; if disease control was achieved, patients would repeat the cycle of two infusion sessions. If disease progression or complication was documented, the infusion protocol was discontinued and patients were evaluated for salvage ^{90}Y TARE, research trials or best supportive care.

Infusion procedure

The infusions were performed by four interventional radiologists (V.S.S., M.T.S., J.C.C., C.T.S.) under moderate sedation or monitored anesthesia care. Informed patient consent was obtained prior to each infusion. Using common femoral or left radial arterial access, the hepatic arterial system was cannulated with 5 French angiographic catheters and microcatheters under fluoroscopic guidance. Digital subtraction arteriography (DSA) was performed with every infusion session to confirm patency of the hepatic arterial system. As mentioned above, mapping arteriography was performed with the first infusion in integrated angiography-computed tomography suites (InterACT Discovery RT, GE Healthcare, Chicago, IL, USA) for acquisition of cone-beam CT and/or selective CT angiographic images. Superselection of lobar or segmental hepatic arteries with microcatheters was performed at the discretion of the performing interventional radiologist. The mitomycin-C was delivered as selectively as possible, such that all the CLM were covered while sparing the normal liver parenchyma. Additionally, the mitomycin-C dose was divided and delivered selectively if there was CT-angiographic evidence of preferential flow to a portion of the liver.

The dose of mitomycin-C was 10 mg/m^2 for the initial two infusions in all patients. Based on the follow-up imaging and laboratory values, the dose could be adjusted between 8–10 mg/m^2 for subsequent infusions. Once in appropriate position, the catheter was connected to an infusion system to ensure controlled delivery. For patients treated before August 2021, the total mitomycin-C dose was mixed in 500 mL normal saline and infused over 30 minutes using a large volume infusion pump (Alaris Pump, BD, Franklin Lakes, NJ, USA). Due to frequent issues with this system, likely related to the increased pressures in the arterial system and resistance within the microcatheters, infusions after August 2021 were performed using a syringe pump (Perfusor Space, B. Braun Medical Inc., Bethlehem, PA, USA). The concentration of mitomycin-C administered through the syringe pumps was 0.5 mg/mL. This solution was infused at a rate of 1–1.5 mL/min. Once the infusion was completed, repeat hepatic arterial DSA was performed, the catheter(s) were removed and access site hemostasis was obtained. Following recovery in the post-anesthesia care unit, patients were discharged from IR on the same day.

Data collection

Patient demographics (age, sex), disease characteristics [primary tumor location, *KRAS* status, CLM timing (synchronous *vs.* metachronous), presence of extrahepatic disease at the time of first infusion, disease intervals], prior treatments [liver surgery, systemic and hepatic artery infusion pump (HAIP) chemotherapy], procedural parameters (number of infusions per patients, infusion location, mitomycin-C dose), laboratory values and CEA levels were recorded. Electronic medical records were reviewed to determine the primary etiology for discontinuation of the infusion protocol and if ^{90}Y TARE was performed after.

Baseline, intra-procedural and follow-up imaging was reviewed by two attending interventional radiologists (V.S.S., M.T.S.). Anatomic and metabolic treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and European Organization for Research and Treatment of Cancer (EORTC) criteria, respectively.

Progression-free survival (PFS) was defined as the time from the initial infusion to the documentation of disease progression at any site, based on RECIST 1.1 and/or EORTC criteria (whichever occurred first). LPFS was defined as the time from the initial infusion to the documentation of disease progression within the treated liver volume. OS was defined as the time from the initial infusion to patient death or last follow-up.

Toxicities for the duration of the infusion protocol and up to 60 days after the final infusion were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis

The paired samples *t*-test was used to assess differences in CEA levels. Fisher's exact test was used to compare nominal data. Survival times were estimated using Kaplan-Meier methodology. Variables were evaluated as predictors of survival outcomes using the log-rank test. P values <0.05 were considered statistically significant. Data analysis was

Table 1 Patient and disease characteristics

Characteristic	Value
Age (years)	51.5 [34–81]
Sex	
Female	21 [46]
Male	25 [54]
Primary tumor location	
Left-sided	19 [41]
Right-sided	11 [24]
Rectum	16 [35]
KRAS mutation	23 [50]
Synchronous CLM	41 [89]
Time from diagnosis of CLM to first mitomycin-C infusion (months)	22.5±16.5
Time from placement of HAIP to first mitomycin-C infusion (months)	12.3±12.4
Extrahepatic disease (at first mitomycin-C infusion)	35 [76]
Lung	30 [65]
≥2 extrahepatic sites	12 [26]
ECOG performance status at first infusion	
0	2 [4]
1	44 [96]

Data are presented as median [range], n [%] or median ± SD. CLM, colorectal liver metastasis; HAIP, hepatic arterial infusion pump; ECOG, Eastern Cooperative Oncology Group.

performed with statistical software (SPSS version 26, IBM Corp., Armonk, NY, USA).

Results

From January 2019 to April 2023, 46 patients underwent a total of 190 selective infusions (range 2–10; median 4). Twenty-three of 46 (50%) patients had *KRAS* mutations and 35/46 (76.1%) had extrahepatic disease at the time of the first infusion. The first mitomycin-C infusion was performed after a median of 22.5 months after the diagnosis of CLM and 12.3 months after HAIP placement. Patient and disease characteristics are listed in *Table 1*. Treatments prior to the first mitomycin-C infusion are listed in *Table 2*. Mitomycin-C infusion procedure details are listed in *Table 3*. Most patients (38/46; 83%) had Medtronic

Table 2 Treatments prior to mitomycin-C infusions

Treatment	Value
Lines of systemic chemotherapy per patient	
Two	20 [43]
Three	21 [46]
Four	5 [11]
FOLFOXIRI	11 [24]
Median number of cycles	8 (range, 4–12)
FOLFOX or CAPEOX	39 [85]
Median number of cycles	8 (range, 2–15)
FOLFIRI	46 [100]
Median number of cycles	13 (range, 2–40)
Bevacizumab	26 [57]
Cetuximab	10 [22]
Panitumumab	8 [17]
Trifluridine/tipiracil	2 [4]
Trastuzumab	2 [4]
Ramucirumab	1 [2]
Pembrolizumab	1 [2]
Durvalumab	1 [2]
HAI floxuridine	46 [100]
Median cumulative dose (mg)	730 (range, 310–1,850)
Liver resection	20 [43]

Data are presented as n [%] unless otherwise specified. HAI, hepatic arterial infusion.

Table 3 Mitomycin-C infusion procedure details

Variable	Value
Median number of mitomycin-C infusions per patient	4 (range, 2–10)
Infusion location(s) during first procedure	
PHA	18 [39]
Lobar x1 (LHA or RHA)	13 [28]
Lobar x2 (LHA & RHA)	10 [22]
One or more segmental branches	5 [11]
Median mitomycin-C dose/session (mg)	20 (range, 14–24)

Data are presented as n [%] unless otherwise specified. PHA, proper hepatic artery; LHA, left hepatic artery; RHA, right hepatic artery.

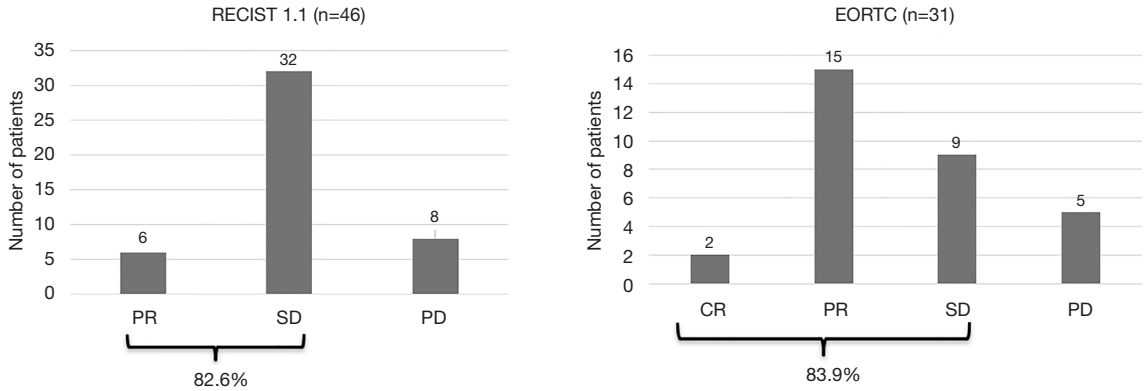

Figure 2 Initial evaluation of response in the treated liver volume after two mitomycin-C infusions using anatomic (RECIST 1.1; A) and metabolic (EORTC; B) criteria. Liver disease control was initially achieved in over 80% of patients. RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease; CR, complete response; EORTC, European Organization for Research and Treatment of Cancer.

pumps in place. Eight (17%) patients had Codman pumps that could not be used for mitomycin-C administration due to catheter fracture/obstruction (n=4), abnormal pump scintigraphy (n=2), extravasation during attempt to administer mitomycin-C through the pump (n=1) or removal (n=1).

Initial response

On initial imaging after two mitomycin-C infusions, liver disease control was observed in 38/46 using RECIST 1.1 (82.6%; partial response 13%, stable disease 69.6%) and 26/31 using EORTC criteria (83.9%; complete response 6.5%, partial response 48.4%, stable disease 29%) (*Figure 2*). CEA levels were significantly lower at the first follow-up [median: 36.2, mean: 369, standard deviation (SD): 1,017] compared to baseline (median 46.1, mean: 445, SD: 887) (P<0.001).

PFS, LPFS and OS

Median follow-up was 25.4 months. From the first infusion, median PFS was 4.1 months [95% confidence interval (CI): 3.2–4.9], median LPFS was 5.5 months (95% CI: 2.5–8.4) and median OS was 9.6 months (95% CI: 8.2–11.1) (*Figure 3*). Timing of liver progression and death relative to the duration of the mitomycin-C infusions is depicted in *Figure 4*. From the diagnosis of CLM, median OS was 36.6 months (95% CI: 26.3–46.9). Baseline variables were evaluated as predictors of survival outcomes (*Table 4*); presence of extrahepatic disease at the time of first mitomycin-C infusion was a statistically significant predictor of shorter PFS (P=0.02) and OS (P<0.001), whereas *KRAS* mutant disease was associated with shorter OS from CLM diagnosis (P=0.02).

Infusion discontinuation

The primary etiologies for discontinuation of the mitomycin-C infusions are listed in *Figure 5*. The infusions were discontinued in most patients (26/46; 56.5%) due to disease progression. Of these patients, nine subsequently underwent ^{90}Y TARE based on the mapping arteriogram performed with the first infusion, all with glass microspheres (TheraSphere, Boston Scientific, Marlborough, MA, USA). Median OS after ^{90}Y TARE was 5.7 months (95% CI: 4.1–7.2). Eighteen patients (39.1%) discontinued the infusion protocol due to toxicities/complications, described in detail in the next section.

Toxicities and complications

Most patients (32/46; 70%) reported self-limiting fatigue and/or nausea (grade 1–2) lasting 1–3 days after at least one infusion. Hematologic and liver function test toxicities are listed in *Table 5*. Myelosuppression was common, with grade 2 or higher thrombocytopenia seen in 21 (46%) patients and leukopenia in 23 (50%) of patients. Romiplostim and pegfilgrastim were administered at least once to 19/46 (41%) and 27/46 (59%) patients during the infusion protocol,

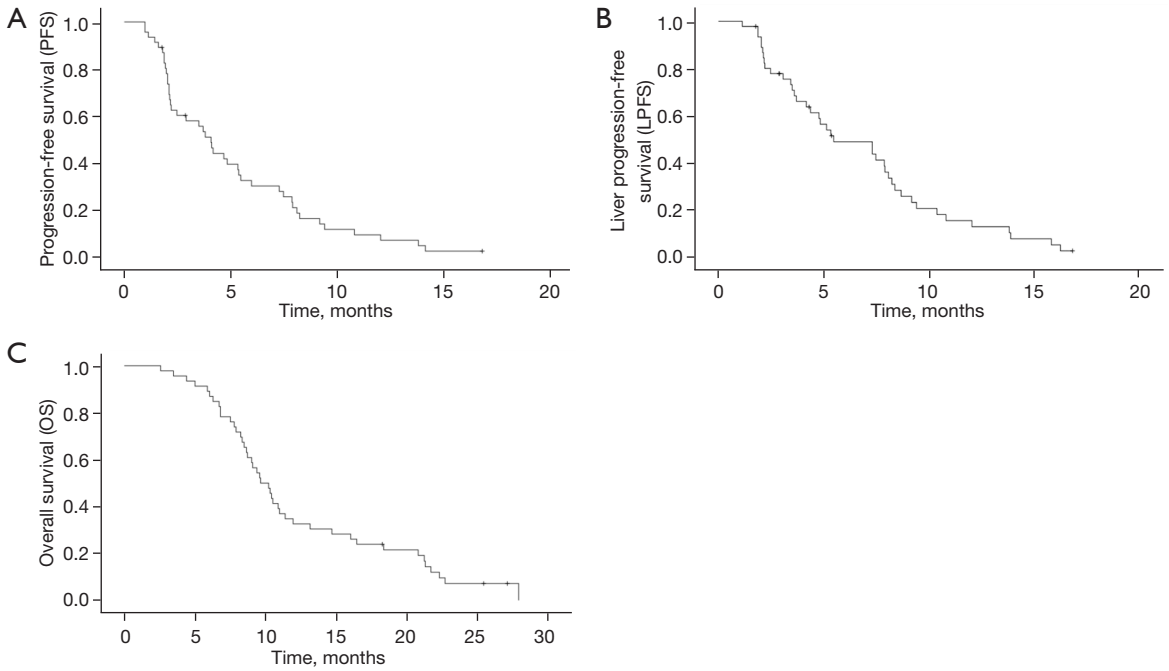

Figure 3 Kaplan-Meier curves for PFS (A), LPFS (B) and OS (C) from the first mitomycin-C infusion. PFS, progression-free survival; LPFS, liver progression-free survival; OS, overall survival.

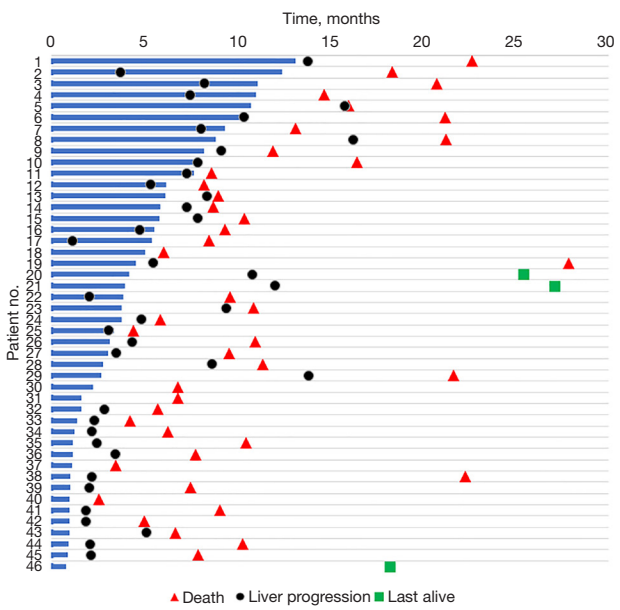

Figure 4 Swimmer plot showing for each patient the infusion duration (blue bar, from first to last mitomycin-C infusion) and the timing of liver progression and death.

respectively.

Patients who underwent four or more mitomycin-C infusions were more likely to develop grade 2 or higher hyperbilirubinemia (P=0.02). Hepatobiliary toxicities were responsible for discontinuation of the infusion protocol in 12/46 (26%) patients. Nine (20%) patients required biliary intervention during or after the infusion protocol [percutaneous metallic stent and/or biliary drain placement (n=5); percutaneous biloma drainage (n=2); endoscopic biliary stent placement (n=2)]. One of these patients developed multiple bilomas after four mitomycin-C infusions and required multiple percutaneous drainage procedures and drain exchanges due to recurrent cholangitis. This patient eventually received a liver transplant and remained without evidence of disease 25 months after the first infusion session.

Angiographic abnormalities in the hepatic arterial vasculature were seen in 9/46 (20%) patients, with 7 (15%) developing occlusion/thrombosis of the target artery for the infusion, leading to discontinuation of the infusion

Table 4 Univariate analysis of baseline variables for predictive significance of survival outcomes (PFS, LPFS, OS, and OS from CLM diagnosis)

Variable	P values			
	PFS	LPFS	OS	OS from CLM diagnosis
Age	0.54	0.71	0.31	0.78
Sex	0.80	0.26	0.68	0.39
Left *vs.* right-sided primary	0.45	0.70	0.82	0.70
Synchronous *vs.* metachronous CLM	0.30	0.97	0.35	0.53
KRAS status	0.77	0.98	0.45	0.02
Unilobar *vs.* bilobar CLM at 1st infusion	0.76	0.54	0.60	–
Extrahepatic disease at 1st infusion	0.02	0.07	<0.001	–

PFS, progression-free survival; LPFS, liver progression-free survival; OS, overall survival; CLM, colorectal liver metastases.

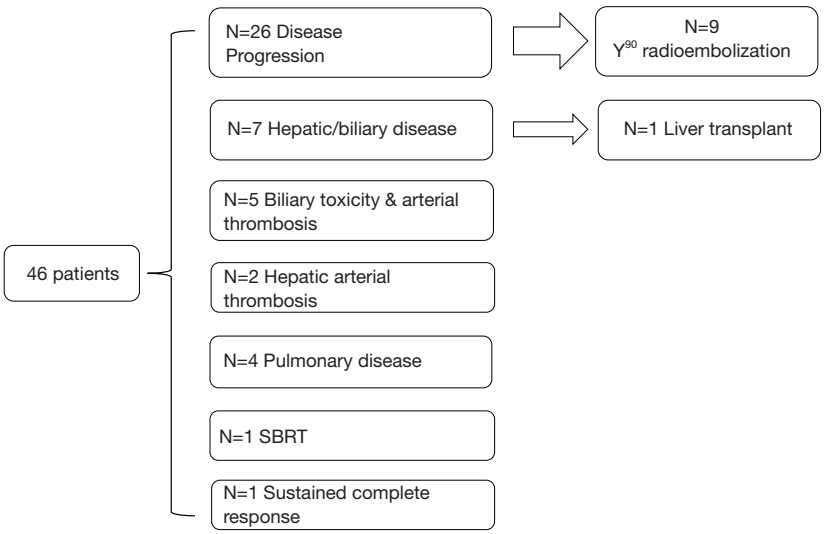

Figure 5 Primary etiologies for discontinuation of the infusion protocol. SBRT, stereotactic body radiation therapy.

Table 5 Hematologic and liver function test toxicities during the infusion protocol, graded according to the CTCAE version 5.0

Grade	Thrombocytopenia	Leukopenia	Hyperbilirubinemia	Hypoalbuminemia	Elevated ALT	Elevated AST	Elevated ALP
2	6 [13]	17 [37]	13 [28]	15 [33]	3 [7]	1 [2]	18 [39]
3	6 [13]	6 [13]	6 [13]	2 [4]	2 [4]	4 [9]	3 [7]
4	9 [20]	–	2 [4]	–	–	–	–

Data are presented as n [%]. CTCAE, Common Terminology Criteria for Adverse Events; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

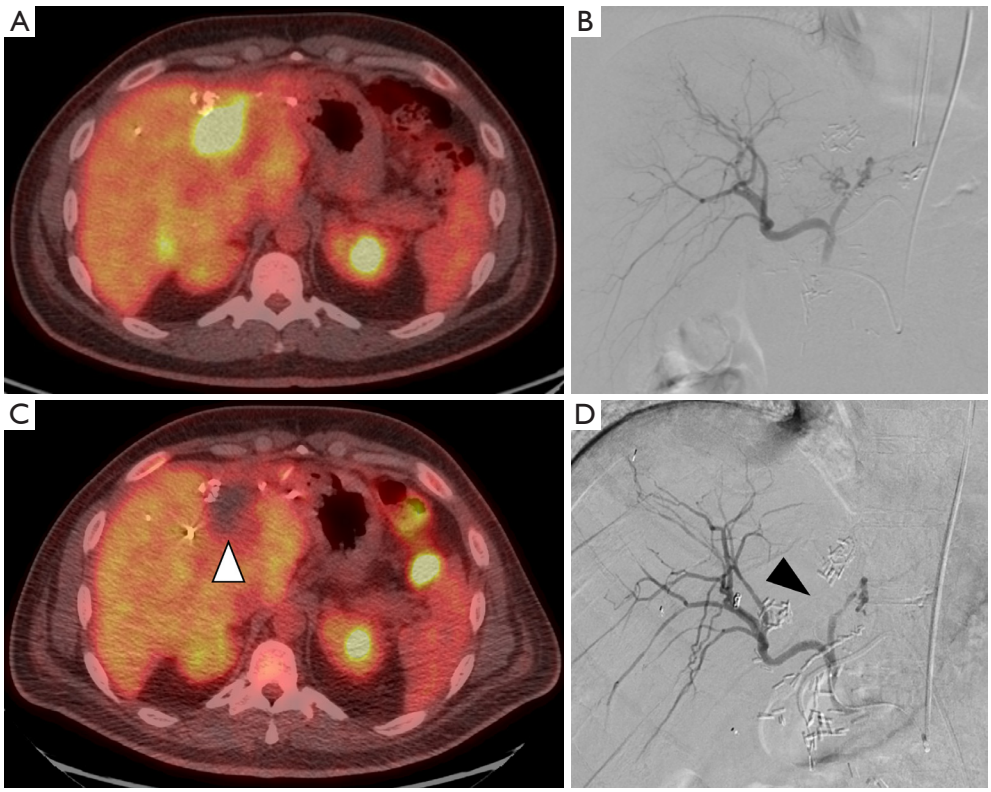

Figure 6 49-year-old man with metastatic ascending colon cancer, status post right colectomy, cholecystectomy, hepatic arterial infusion pump placement and hepatic resection, with progressing bilobar liver metastases after two lines of chemotherapy and intrahepatic floxuridine. (A) Baseline PET/CT shows one of the FDG-avid hepatic tumors in segment 4. (B) Proper hepatic arteriogram before the 1st mitomycin-C infusion demonstrates the hepatic arterial anatomy. Due to the extent of disease, infusions were performed from the proper hepatic artery. (C) Follow-up PET/CT after 8 infusion sessions (10 months after the 1st infusion) shows photopenic defect in segment 4 (white arrowhead), compatible with complete metabolic response. (D) Proper hepatic arteriogram after the 8th infusion shows diffusely abnormal appearance of the intrahepatic arterial branches, with multifocal stenoses, vessel contour irregularities, pruning of the distal branches and interval occlusion of the segment 4 branch (black arrowhead). Due to the angiographic findings and rising bilirubin levels, the infusions were discontinued. PET/CT, positron emission tomography/computed tomography; FDG, fluorodeoxyglucose.

protocol. Eight of nine (89%) patients with angiographic abnormalities in the hepatic arterial vasculature had LPFS exceeding 6 months, compared to 11/37 (30%) of those who did not (P=0.002) (*Figure 6*). Both patients with initial complete metabolic response had angiographic evidence of arterial branch occlusion. Two patients developed asymptomatic left radial artery dissections after the third and sixth infusions respectively, related to the arterial access; these patients continued the infusions from a common femoral arterial access.

Severe pneumonitis (CTCAE grade 3 or higher) was observed in 4 (9%) patients, leading to discontinuation of the infusion protocol. These patients developed symptomatic bilateral ground glass opacities without other clear etiology after 2, 2, 5 and 10 mitomycin-C infusion sessions respectively.

Discussion

In contrast to normal liver parenchyma, CLM are primarily perfused by branches of the hepatic artery (21). This has been the basis for the development of regional intra-arterial treatments (HAI chemotherapy, chemoembolization and ^{90}Y TARE), in an effort to limit damage to the surrounding liver and systemic toxicities. Specifically, HAI chemotherapy has been shown to achieve longer LPFS and OS, as well as increased response rates compared to chemotherapy alone, allowing conversion to resectable disease in more

patients (7-13). Management of CLM progressing after both systemic and regional chemotherapy is extremely challenging and warrants administration of salvage treatments. Chemoembolization and ^{90}Y TARE are typically offered to select patients after progression on systemic and/or HAI chemotherapy (5,22-29).

Mitomycin-C, an alkylating agent that inhibits DNA synthesis and replication, has been studied in numerous cancers including CRC (14). Systemic administration of this drug is associated with marginal activity in CRC and with significant toxicities, therefore is not recommended for treatment of chemorefractory disease, either as a single-agent or in combination with other chemotherapeutics (5,14). However, intra-arterial administration of mitomycin-C for CLM can mitigate systemic toxicities and has demonstrated some salvage benefit in patients after disease progression or intolerance to HAI FUDR (15). Improvement in objective response and disease control rates was also reported in patients treated with HAI mitomycin-C after failing arterial oxaliplatin, with an acceptable toxicity profile (17). Addition of intra-arterial mitomycin-C to HAI FUDR (30) or 5-fluorouracil (16) has been shown to achieve relatively high response rates, however was associated with biliary and vascular toxicities.

Based on the evidence above, HAI mitomycin-C has been used at the authors' institution for treatment of chemorefractory CLM, delivered through the sideport of the discontinued Codman pumps. Since the Medtronic pumps could not be used for mitomycin-C injection, the infusions were performed in IR with selective catheterization of the hepatic artery. This method of mitomycin-C delivery had the disadvantage of requiring monthly performance of an invasive procedure. On the other hand, this offered the ability to perform selective infusions within the liver and focus on the tumor-containing liver volumes. Moreover, hepatic arteriography before and after each infusion in IR permitted evaluation for interval change in the angiographic appearance of the hepatic vasculature, an assessment that cannot be performed when mitomycin-C is administered through the pump in clinic.

After two infusions, liver disease control was achieved in 82.6% and 83.9% of patients using anatomic and metabolic response criteria respectively. These rates are relatively high considering that the patient population was heavily pretreated with progressing CLM after multiple lines of systemic and HAI FUDR chemotherapy. At the same time point, response was more likely to be documented with metabolic assessment (55% *vs.* 13%), an observation known to apply to liver-directed locoregional treatments, highlighting the importance of baseline and follow-up PET/CT (25,31). Despite the initial encouraging liver disease control rates, median LPFS was only 5.5 months, with over half (56.5%) of patients discontinuing the infusion protocol due to disease progression after a median of 4 infusions. Of note, patients initiated the infusion protocol late in their disease course, after a median 22.5 months since the diagnosis of CLM. In this salvage setting, a median OS of 9.6 months from the first infusion was observed.

Toxicities were the primary etiology for discontinuation of the mitomycin-C infusions for 39% of patients. The hepatic extraction of intra-arterial mitomycin-C is about 23% (32), significantly lower than FUDR (94–99%) (33). As a result, systemic toxicities, such as thrombocytopenia and leukopenia, were expected. These hematologic toxicities were subclinical and managed with romiplostim and pegfilgrastim administration. The appearance of severe pneumonitis in four patients was also likely a consequence of the low hepatic extraction of mitomycin-C. Pulmonary toxicity of mitomycin-C has been reported in 2–12% of exposed patients and appears to be dose-dependent, occurring at cumulative dose levels of 20 mg/m^2 or above (which all four patients had received) (34,35).

Chemotherapy-induced biliary sclerosis (CIBS) can complicate HAI FUDR, resulting from ischemic changes to the peribiliary vascular plexus, which is primarily supplied by hepatic arteriolar branches (36,37). Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been shown to potentiate bile duct toxicity when administered concurrently with HAI FUDR (38). Both HAI FUDR and recent exposure to bevacizumab have been associated with significantly increased biliary complications after thermal ablation (39), indicating that exposure to these agents places patients at increased risk for biliary toxicity with subsequent liver-directed treatments. This was confirmed in the present study, as 46% of patients developed grade 2 or greater hyperbilirubinemia and 26% had to discontinue the infusion protocol due to hepatobiliary toxicities.

Mitomycin-C has been shown to cause vascular toxicity, with studies in rats showing a spectrum of pathologic changes ranging from focal endothelial cell damage to fibrosis of the vascular intima and adventitia (40). These changes were likely responsible for the development of biliary toxicities (at a terminal arteriole level) and angiographic abnormalities (at a macroscopic level). The incidence of hepatic arterial thrombosis in this study

(15%) was similar to that reported by Liu *et al.* in 2002 (16%) (16). Interestingly, patients who developed abnormal angiographic findings during the infusion protocol were more likely to have PFS exceeding 6 months, suggesting that the observed response may have been driven by vascular toxicity and ischemia, as opposed to the direct antitumor effect of mitomycin-C.

Comparison of these results to studies reporting outcomes of other salvage liver-directed treatments is difficult due to the presence of lead-time bias, absence of prior HAI chemotherapy in most series and the confounding effect of newer systemic treatments (e.g., trifluridine/tipiracil, regorafenib). In a phase I trial of ^{90}Y TARE for CLM progressing after systemic chemotherapy and HAI FUDR, median LPFS and OS were 5.2 and 14.9 months respectively. In other larger cohorts, reported median OS after salvage ^{90}Y TARE for CLM ranged between 6.1 and 12.7 months, with mostly mild toxicities (25,41-45). The median OS observed in this study falls within this range, therefore selective mitomycin-C infusions can also be considered in the salvage setting when there is limited access to ^{90}Y TARE. Performance of ^{90}Y TARE requires a mapping arteriogram, followed usually by one or two treatment sessions. This presents advantages compared to repeated monthly mitomycin-C infusions, as it limits the number of invasive procedures. Even though mitomycin-C can now be administered through the sideports of the newer Intera 3000 pumps without the need for invasive arteriography, the toxicities observed in this study should prompt careful consideration before proceeding with intra-arterial mitomycin-C administration.

There are numerous limitations in this study. A small number of patients were included, and the retrospective nature of the analysis was prone to selection bias. All patients had received HAI FUDR, a factor limiting widespread applicability. Finally, the location(s) of the mitomycin-C infusion within the hepatic arterial system was determined by the interventional radiologist performing the procedure, thus prone to operator variability.

Conclusions

Selective intra-arterial mitomycin-C infusions in heavily pretreated patients with progressing liver metastases were associated with initial liver disease control rates exceeding 80%, however median LPFS (5.5 months) and OS (9.6 months) were relatively brief. Toxicities were observed, particularly in patients with prolonged disease control who received ≥4 infusions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-725/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the

institutional review board of Memorial Sloan Kettering Cancer Center (protocol No. 16-402; date of approval: May 3, 2016) and individual consent for this retrospective analysis was waived.

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