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Treating Primary Liver Cancer with Hepatic Arterial Infusion of Floxuridine and Dexamethasone: Does the Addition of Systemic Bevacizumab Improve Results?

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Key Words
Floxuridine · Hepatic arterial infusion · Hepatocellular carcinoma · Intrahepatic cholangiocarcinoma

Abstract
Objectives: This study investigated the efficacy and safety of adding systemic (IV) bevacizumab (Bev) to hepatic arterial infusion (HAI) with floxuridine (FUDR)/dexamethasone (Dex) in unresectable primary liver cancer. ***Methods:*** Patients with unresectable intrahepatic cholangiocarcinoma (ICC) or hepatocellular carcinoma (HCC) were treated with HAI FUDR/Dex plus IV Bev. Results were compared to a recent study of HAI without Bev in a similar patient population. ***Results:*** Twenty-two patients (18 ICC, 4 HCC) were treated with HAI FUDR/Dex plus Bev; 7 (31.8%) had partial response and 15 (68.2%) had stable disease. Median survival was 31.1 months (CI 14.14–33.59), progression-free survival (PFS) 8.45 months (CI 5.53–11.05), and hepatic PFS 11.3 months (CI 7.93–15.69). In the previous trial with HAI alone (no Bev), the response was 50%; median survival, PFS, and hepatic PFS were 29.5, 7.3, and 10.1 months. In the present trial, bilirubin elevation (>2 mg/dl) was seen in 24% of patients and biliary stents were placed in 13.6%, versus 5.8 and 0%, respectively, in the HAI trial without Bev. Due to increased biliary toxicity, the trial was prematurely terminated. ***Conclusion:*** Adding Bev to HAI FUDR/Dex appeared to increase biliary toxicity without clear improvement in outcome (median PFS 8.45 vs. 7.3 months, and median survival 31.1 vs. 29.5 months, for HAI + Bev vs. HAI alone groups, respectively).

Introduction

Primary liver cancer is an increasingly important public health problem, accounting for nearly 18,910 annual deaths in the United States [1, 2]. The most common primary hepatic malignancies are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). HCC is among the most common cancers worldwide, accounting for nearly 1 million deaths annually [3, 4], and its incidence and mortality in the United States has increased substantially over the past several years [5]. ICC is a less common disease, but has also increased in both incidence and associated mortality. A recent analysis by the SEER (Surveillance, Epidemiology and End Results) database showed a 9% annual percentage increase in incidence of ICC and a 10-fold increase in ICC-related mortality since 1973 [6]. Complete resection remains the most

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effective therapy for both tumors, but is often not possible [2, 3, 7].

Median survival of patients with unresectable primary liver cancer (HCC or ICC) is usually less than 12 months [7]. Many systemic agents have been evaluated for both diseases with mixed results. Recently, two studies have documented modest but statistically significant improvements in survival for HCC and ICC [8, 9]. However, despite the results of these studies, the benefit of systemic therapy for primary liver cancer remains limited.

Hepatic arterial infusion (HAI) chemotherapy, delivered via a surgically implanted pump, has been evaluated in several studies [10–13]. Although used predominantly in patients with hepatic-only colorectal metastases, HAI chemotherapy has shown efficacy in patients with primary liver cancer [11, 14, 15], allowing some patients to undergo resection [14].

A recent phase II study at Memorial Sloan-Kettering Cancer Center (MSKCC) evaluated HAI of floxuridine (FUDR) plus dexamethasone (Dex) with no concomitant systemic therapy in patients with unresectable primary liver cancer [16]. In the updated results of this trial, there was a 50% partial response rate (53.8% for ICC and 25% for HCC) with a median survival of 29.5 months for the entire cohort.

Targeted therapies have produced encouraging results and are now commonly used to treat various gastrointestinal malignancies. Many of these agents inhibit angiogenic pathways, resulting in morphologic changes in the tumor vasculature. Such 'normalization' of tumor vascular beds [17], which appears to be the primary physiologic effect of bevacizumab (Bev), may improve delivery of cytotoxic agents. We hypothesized that the addition of Bev would augment regional delivery of FUDR in primary liver cancer, thereby increasing response and progression-free survival (PFS) compared to results obtained with FUDR alone.

Methods

Patient Selection and Pretreatment Evaluation

All patients had confirmed and measurable unresectable ICC or HCC. Unresectability was confirmed by hepatobiliary surgeons at a weekly multidisciplinary conference. Exclusionary factors included the following: extrahepatic metastases, prior hepatic radiation, Karnofsky performance status <60, primary sclerosing cholangitis, portal hypertension, serum albumin <2.5 g/dl, serum bilirubin >1.8 mg/dl, international normalized ratio >1.5, portal inflow occlusion on CT, white blood cell <3,500 cells/mm^3, concurrent malignancy (except for localized basal or squamous cell skin cancers), or active infection. Current or recent use of a thrombolytic agent and proteinuria (urine dipstick for proteinuria >2+ unless 24-hour protein was <1 g) was also exclusionary. Progression on prior chemotherapy was allowed. All patients were ≥18 years of age and provided informed consent. The protocol and informed consent were approved by the MSKCC Institutional Review Board.

Pretreatment evaluation included a complete history and physical examination, routine laboratory studies, and tumor markers (carcinoembryonic antigen, α-fetoprotein, and CA19-9). Disease extent was assessed with cross-sectional imaging (CT scan of chest, CT or MRI of abdomen/pelvis); suspicious extrahepatic findings were evaluated with targeted imaging – 2-(fluorine-18) fluoro-2-deoxy-D-glucose PET or bone scan – and/or biopsy. Patients with presumed ICC also underwent esophagogastroduodenoscopy, colonoscopy, and mammography (females). Hepatitis serology was checked prior to treatment. In order to determine adequate hepatic arterial anatomy and blood supply, all patients underwent preoperative hepatic CT angiograms with visualization of the celiac and superior mesenteric arteries.

Pump Placement

Guidelines for pump placement have been previously reported [18]. An intra-operative injection of methylene-blue dye was used to evaluate flow immediately after placement. Postoperatively, a perfusion study utilizing technetium-99m macroaggregated albumin via the pump sideport confirmed adequate liver perfusion and the absence of extrahepatic flow.

Chemotherapy Administration and Toxicity

HAI chemotherapy was initiated 2 weeks after pump placement, on a 4-week cycle. All patients received an infusion of HAI FUDR (0.16 mg/kg × 30/pump flow rate) and Dex 25 mg, with heparin sulfate (30,000 units) and saline to a volume of 30 ml on day 1 for a 14-day infusion. After each 2-week infusion, the residual volume was removed and heparinized saline (30 ml) was instilled (table 1). Systemic Bev (5 mg/kg) was given every other week starting 6 weeks after surgery. Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria v 3.0 [19]. The FUDR dose-adjustment schedule has been previously described (table 2).

Post-Treatment Evaluation

After starting treatment, patients were seen bi-weekly; history, physical examination and routine laboratory studies were obtained. Pretreatment MRI scans of the liver were carried out with conventional and dynamic sequences, and were repeated every 2 months to assess response. The RECIST criteria were used to categorize responses [20], based on tumor size measurements on conventional MRI sequences and confirmed by the study radiologist. CT scans of the chest were obtained at baseline and at 3-month intervals subsequently; additional tests were obtained as needed, depending on symptoms (i.e. bone or PET scans).

End Points and Statistics

The study's primary aim was to evaluate the impact of adding systemic Bev on PFS; however, response rate, survival, toxicity, and conversion to resectability were also assessed. Laboratory evaluation – CBC, platelets, BUN, creatinine, bilirubin, SGOT (serum glutamic oxaloacetic transaminase), alkaline phosphatase, LDH – was performed every 2 weeks; patients were evalu-

Table 1. Protocol schema: cycle repeated every 4 weeks

Day 1	Day 15
Systemic chemotherapy IV Bev[1] (5 mg/kg IV over 10 min)	Systemic chemotherapy IV Bev
HAI with FUDR (0.16 mg/kg × pump vol/flow rate) + 25 mg Dex (continuous 14-day infusion)	Pump emptied and refilled with heparinized saline

[1] With the exception of cycle 1/day 1, on which the patient receives only HAI with FUDR/Dex. Systemic treatment with Bev commences on day 15 of cycle 1, and thereafter every 2 weeks.

Table 2. FUDR dose modification table

	Reference value	% of FUDR dose
SGOT (at pump emptying or day of planned retreatment, whichever is higher)	0 to <2 × reference value	100
	2 to <3 × reference value	80
	3 to <4 × reference value	50
	>4 × reference value	hold
Alkaline phosphatase (at pump emptying or day of planned retreatment, whichever is higher)	0 to 1.2 × reference value	100
	1.2 to <1.5 × reference value	50
	>1.5 × reference value	hold
Total bilirubin (at pump emptying or day of planned retreatment, whichever is higher)	0 to 1.2 × reference value	100
	1.2 to <1.5 × reference value	50
	>1.5 × reference value	hold

Reference value is the value obtained on the day the patient received last FUDR dose. If SGOT >4 × reference value, alkaline phosphatase >1.5 × reference value, or total bilirubin >1.5 × reference value, then treatment will be held and will not be reinstituted until values come down to more normal levels. SGOT = Serum glutamic oxaloacetic transaminase.

ated for toxicity every 2 weeks as well. Tumor markers were drawn if elevated before treatment, or at the discretion of the attending physician.

PFS was measured from the date of treatment initiation until first documented progression, death, or last follow-up. In the initial study using FUDR alone, with no systemic treatment, the median time to progression was approximately 7 months; we hypothesized that the addition of Bev would result in a 50% improvement over these initial results. We calculated that 48 events would be needed in this single-arm historical-control setting to provide 90% power to distinguish between median time to progression of 7 and 10.5 months, controlling the type I error at 10%, as it is usually done for phase II studies. We planned to enroll 55 patients, allowing for 15% censoring at the time of analysis. Our plan was to obtain a Kaplan-Meier estimate of the median time to progression along with a confidence interval, and determine statistical significance based on whether the historical control (median of 7 months) was contained in the confidence interval.

Overall, PFS and hepatic PFS probabilities were estimated by the Kaplan-Meier method. Statistical comparisons between the initial study and the current study were not considered due to lack of randomization, but data from the initial study is presented along with results from the current study to facilitate synthesis.

Results

Twenty-two patients were treated with HAI FUDR and Dex plus systemic Bev. The study was terminated early due to increased biliary toxicity. Patient characteristics are shown in table 3. The median tumor size was 9 cm (1.1–16.4) with 10% of patients' tumors >10 cm. Median serum albumin was 3.2 g/dl (2.7–3.9); 6 patients had baseline albumin <3 g/dl. Four patients had undergone previous chemotherapy, including gemcitabine/cisplatin, irinotecan/Xeloda, and Tarceva. Four patients had postoperative complications (1 fever, 1 fluid collection and infection at pump site, 1 acute pancreatitis, and 1 wound infection). All baseline characteristics were compared to the previous study without Bev (table 3).

The toxicities of HAI FUDR/dex plus Bev therapy are listed in table 4 and included thrombosis, duodenal tear, confusion, hyponatremia, syncope, and myocardial infarction. Liver toxicities included doubling of alkaline

Table 3. Patient characteristics comparing HAI FUDR/Dex with systemic Bev versus HAI FUDR/Dex alone

	HAI + Bev (n = 22)	HAI alone (n = 34)
Clinical variables[1]		
Age ≥65 years	8 (36.3)	15 (44.1)
Female gender	12 (54.5)	22 (65)
KPS ≥80	15 (68.1)	18 (52.9)
ICC	18 (81.8)	26 (76.4)
HCC	4 (18.1)	8 (23.5)
Chronic hepatitis (serology)	0	4 (11.7)
Cirrhosis/fibrosis (histology)	6 (27.2)	5 (14.7)
Previous treatment		
Systemic chemotherapy	3 (13.6)	3 (8.8)
Resection	0	2 (5.8)
Ablation	1 (4.5)	5 (14.7)
Asymptomatic disease	3 (13.6)	4 (11.7)
Portal vein thrombosis	2 (9.0)	5 (14.7)
Solitary	7 (31.8)	12 (35.2)
Multifocal	15 (68.1)	22 (64.7)
Tumor diameter >5 cm	17 (77)	29 (85)
Baseline laboratory studies[2]		
Bilirubin, mg/dl	0.8 (0.5–1.7)	0.7 (0.3–2.4)
Alkaline phosphatase, units/l	154 (50–729)	143 (76–1,147)
SGOT, units/l	35 (15–100)	37 (20–229)
Albumin, g/dl	3.2 (2.7–3.9)	3.3 (1.8–4.6)
α-Fetoprotein, ng/ml	5.1 (2.2–2,463)	5.7 (1.1–8,000)
INR	1.05 (0.86–1.32)	0.97 (0.01–3.56)
Platelets, thousands/μl	370 (110–741)	340 (180–823)

KPS = Karnofsky performance status; INR = international normalized ratio.
[1] Data presented as n (%). [2] Data presented as medians (ranges).

Table 4. Toxicity comparing HAI FUDR/Dex with systemic Bev versus HAI FUDR/Dex alone

Variables (grade 3–4)	HAI + Bev (n = 22)	HAI alone (n = 34)	p value
Neutropenia	0	0	
Thrombocytopenia	0	0	
Duodenal tear	1 (4.5)	0	
Confusion	2 (9.0)	0	
Hyponatremia	1 (4.5)	0	
Syncope	1 (4.5)	0	
Hyperglycemia	1 (4.5)	0	
Myocardial infarct	1 (4.5)	0	
Diarrhea	0	0	
Thrombosis	2 (9.0)	0	
Bilirubin >3 mg/dl	3 (13.6)	0	0.056
Alkaline phosphatase	1 (4.5)	0	0.39
SGOT	5 (22.7)	0	0.007
Bilirubin ≥2 mg/dl	5 (22.7)	2 (5.8)	0.09
Biliary stent	3 (13.6)	0	0.15
Doubling of alkaline phosphatase[1]	6 (27)	0	0.002

Data presented as n (%). [1] Does not refer to NCI criteria.

Table 5. Responses comparing HAI FUDR/Dex with systemic Bev versus HAI FUDR/Dex alone

	HAI + Bev (n = 22)		HAI alone (n = 34)	
	ICC (n = 18)	HCC (n = 4)	ICC (n = 26)	HCC (n = 8)
PR	7 (38.8)	0	15 (57.6)	2 (25)
SD	11 (61.1)	4 (100)	10 (38.4)	3 (37.5)
PD	0	0	1 (3.8)	3 (37.5)

Data presented as n (%). PR = Partial response; SD = stable disease; PD = progression of disease.

phosphatase in 6 (27%) patients, a 5-fold increase in SGOT in 5 (22.7%) patients, and bilirubin >2 mg/dl in 5 (22.7%) patients – in the study using HAI without Bev, these values were 0, 0 and 5.8%, respectively (table 4). Three (13.6%) patients required stents for biliary strictures, versus none in first trial without Bev. After consultation with our institutional review board, with information from concurrent studies using Bev with HAI in our colon cancer trials also showing increased biliary toxicity [21], the study was closed to accrual.

During the first 3 months of therapy, patients were able to receive 74% (33–100) of the expected dose of FUDR, and 98% of the Bev dose. Calculating expected doses over 6 months, the numbers decrease to 45% (17–75) for FUDR and 73% (9–100) for Bev. In the older study without Bev, patients received 85% (50–100) of the expected FUDR dose at 3 months, and 62% (27–100) at 6 months.

Overall median survival from the time of initiation of HAI with Bev was 31.1 months (CI 14–33.59) (fig. 1). In the first study without Bev, overall survival was 29.5 months (CI 21.28–32.70). Median hepatic PFS in the HAI and Bev study was 11.28 months (CI 7.93–15.69) (fig. 2), versus 10.08 (CI 7.14–12.86) in the first study without Bev.

Median PFS in this study was 8.45 months (CI 5.53–11.05) (fig. 3), which is less than the target median of 10.5 months. The confidence interval contains the historical control of 7.5 months, and points to a lack of improvement. However, since this study was stopped prematurely for reasons of tolerability, we do not have sufficient

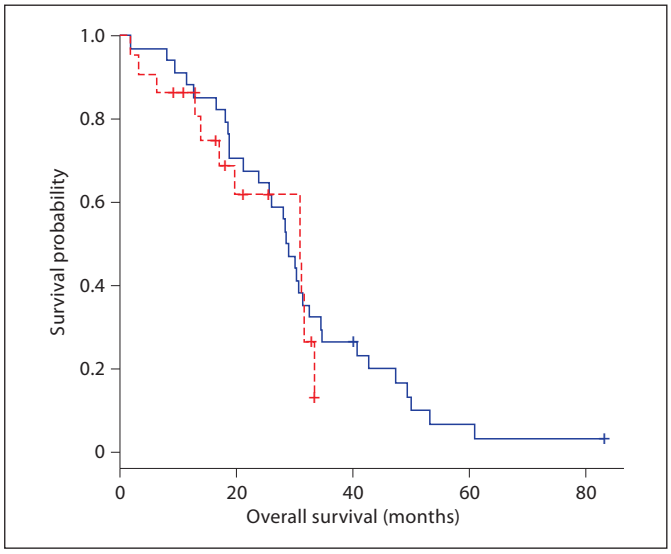

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Fig. 1. Overall survival comparing HAI FUDR/Dex with systemic Bev (broken line) versus HAI FUDR/Dex alone (solid line). Median survival time with Bev = 31.1 months (CI 14.14–33.59). Median survival time without Bev = 28.93 months (CI 21.28–32.75).

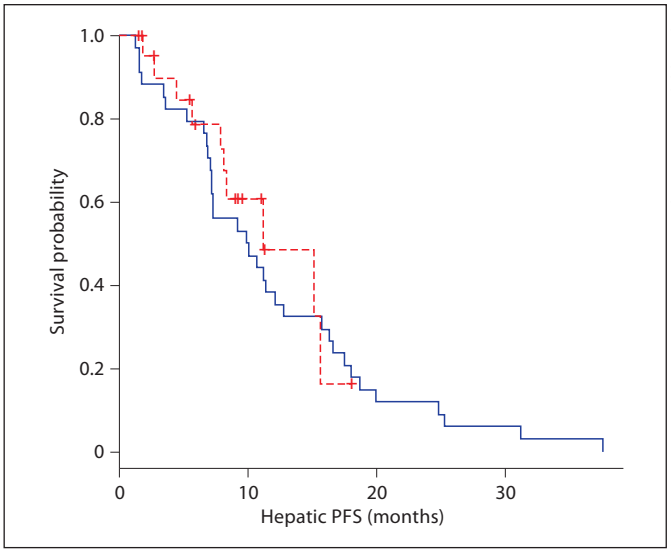

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Fig. 2. Hepatic PFS comparing HAI FUDR/Dex with systemic Bev (broken line) versus HAI FUDR/Dex alone (solid line). Median hepatic PFS with Bev = 11.28 months (CI 7.93–15.69). Median hepatic PFS without Bev = 10.08 (CI 7.14–12.86).

power to rule out the possibility that the improvement could have been significant had the study accrued the planned number of patients.

Of the twenty-two patients we enrolled, 18 patients had ICC and 7 patients (38.8%) had a partial response with median duration of 11 months (6–20; table 5). Eleven patients had stable disease with median response duration of 6 months (1–11); 8 of the 11 patients with stable disease had a decrease in tumor size from 15–29%. Of the four patients with ICC, all had stable disease. A comparison of these responses and those from the first study without Bev are found in figure 4. Twelve patients had an elevated CA19-9 at treatment initiation and 4 (33%) had a 50% reduction after treatment. Three patients responded sufficiently to undergo resection, and 1 patient had 85% tumor necrosis histologically. Of the 4 patients with HCC, all had stable disease with median response duration of 9 months (1–16). Three of the 4 HCC patients had an elevated α-fetoprotein at initiation of treatment and 1 had a 50% reduction in α-fetoprotein.

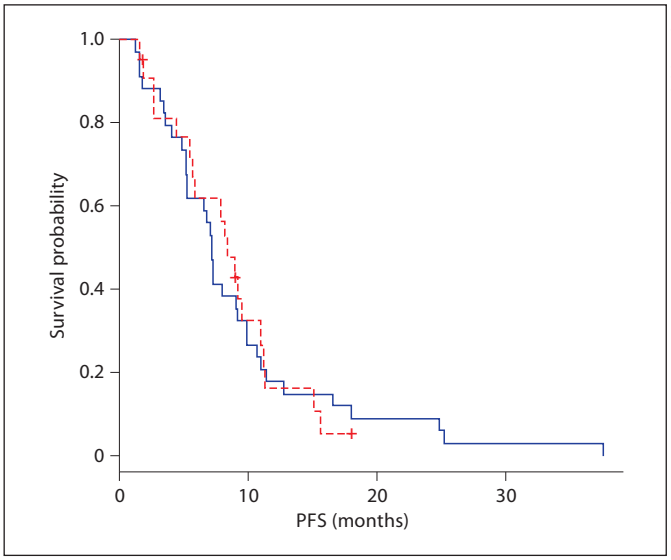

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Fig. 3. PFS comparing HAI FUDR/Dex with systemic Bev (broken line) versus HAI FUDR/Dex alone (solid line). Median PFS with Bev = 8.45 months (CI 5.53–11.05). Median PFS without Bev = 7.27 months (CI 5.30–9.28).

Discussion

The incidences of HCC and ICC have increased over the past several years. Since the most patients have unresectable disease, there is a need for more effective therapy. A review of systemic chemotherapy trials reported an average median survival of 9.3 months for cholangiocarcinoma [22]. Many agents have been evaluated for both diseases with marginal results. Two recent studies have

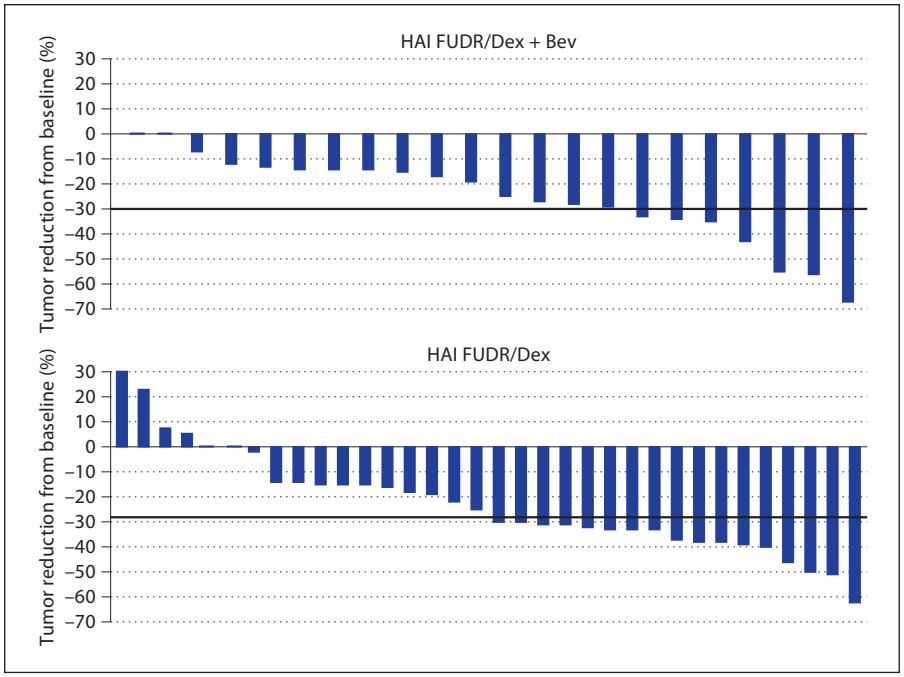

Fig. 4. Maximum reduction from baseline using RESIST (tumor size change ≥30% considered a response).

produced improved results. In ICC, a recent trial demonstrated gemcitabine plus cisplatin versus gemcitabine alone produced a median survival of 11.7 versus 8.1 months ($p = 0.001$), and median PFS of 8 and 5 months ($p < 0.001$), respectively [9]. In patients with HCC a randomized study of sorafenib versus control produced increases in median survival (10.7 vs. 7.9 months, respectively; $p < 0.001$) and median PFS (5.5 and 2.8 months, respectively; $p < 0.001$) [8].

Liver-directed chemotherapy administered through a surgically implanted pump has primarily been used in patients with hepatic colorectal metastases and has demonstrated efficacy in both the adjuvant (post-liver resection) and the metastatic population, as well as in patients who failed first- or second-line systemic regimens [22–26]. The efficacy of HAI in primary liver cancer is less well established, although studies have suggested benefit [10–13]. The initial report from MSKCC showed a response rate of 47.1% (50% updated), overall PFS of 7.3 months (CI 5.30–9.28), hepatic PFS of 10.1 months (CI 7.14–12.86), and overall survival of 29.5 months (CI 21.28–32.70). One patient was converted to resectability and was found to have a complete pathologic response [16].

The rationale for adding Bev to the HAI regimen in the current study was to effect changes in the tumor vasculature that may result in improved delivery of FUDR, leading to improved response and longer PFS. However, the trial was terminated early due to an increase in biliary toxicity with Bev combined with the HAI regimen. The increase in biliary toxicity was cause for concern since two other studies using Bev with HAI therapy in trials treating colorectal cancer at MSKCC showed significant increases in biliary toxicity [21]. In one randomized trial, the addition of Bev versus no Bev with HAI and systemic therapy as adjuvant therapy after hepatic resection of colorectal metastases significantly increased biliary-related complications. Biliary stent placement was required in 11% of patients who received Bev compared to 0% in the group without Bev, respectively ($p = 0.05$) [26].

Patients with HCC and ICC do have differing disease biologies; however, since we included both groups in the earlier study, they were included in this study to facilitate comparison. There is always the possibility of unknown differences in patient characteristics, but laboratory values and other factors suggest that these groups are comparable prior to initiating treatment.

Bev may have resulted in changes within the tumor vasculature that resulted in changes in the delivery of FUDR, but it may have also produced changes in the bile ducts that increased the incidence of biliary injury. Interference with normal tissue repair mechanisms may have exacerbated the insult caused by Bev. Many chemotherapeutic agents cause tissue injury that heals during interruptions in therapy. Inhibition of the tissue repair process

by Bev may be a source of enhanced toxicity as observed in other studies, such as perforated nasal septum [27] and tracheoesophageal fistula [28]. Since the present study was terminated after 22 patients due to increased biliary toxicity, the proposed number of patients to demonstrate an increase in PFS was not attained, thus limiting statistical comparisons. The results of the current study were similar to those observed in the first trial using HAI therapy alone for the treatment of primary liver cancers, median survivals of 31.8 and 29.5 months and median PFS of 8.45 and 7.3 months for HAI plus Bev and HAI alone, respectively.

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Disclosure Statement

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