Original Article

Randomized Controlled Trial of Irinotecan Drug-Eluting Beads With Simultaneous FOLFOX and Bevacizumab for Patients With Unresectable Colorectal Liver-Limited Metastasis

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BACKGROUND: Reports have demonstrated the superior activity of combining both irinotecan and oxaliplatin (FOLFOXIRI) therapy. An option for gaining similar benefits with less toxicity would be the administration of irinotecan through a hepatic artery approach. The aim of this study was to assess the response and adverse event rates for irinotecan drug-eluting beads (DEBIRI) with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) and bevacizumab as a first-line treatment for unresectable colorectal liver metastasis. **METHODS:** Patients with colorectal liver metastases were randomly assigned to modified FOLFOX (mFOLFOX) and bevacizumab or mFOLFOX6, bevacizumab, and DEBIRI (FOLFOX-DEBIRI). The primary endpoint was the response rate. The secondary endpoints were adverse events, the rate of conversion to resection, and progression-free survival. **RESULTS:** The intention-to-treat population comprised 70 patients: 10 patients in the pilot and then 30 patients randomly assigned to the FOLFOX-DEBIRI arm and 30 patients randomly assigned to the FOLFOX/bevacizumab arm. The 2 groups were similar with respect to the extent of liver involvement (30% vs 30%), but a greater percentage of patients in the FOLFOX-DEBIRI arm had an Eastern Cooperative Oncology Group performance status of 1 or 2 (57% vs 31%) and extrahepatic disease (56% vs 32%, $P = .02$). The median numbers of chemotherapy cycles were similar (10 vs 9), and there were similar rates of grade 3/4 adverse events (54% for the FOLFOX-DEBIRI group vs 46% for the FOLFOX/bevacizumab group). The overall response rate was significantly greater in the FOLFOX-DEBIRI arm versus the FOLFOX/bevacizumab arm at 2 (78% vs 54%, $P = .02$), 4 (95% vs 70%, $P = .03$), and 6 months (76% vs 60%, $P = .05$). There was significantly more downsizing to resection in the FOLFOX-DEBIRI arm versus the FOLFOX/bevacizumab arm (35% vs 16%, $P = .05$), and there was improved median progression-free survival (15.3 vs 7.6 months). **CONCLUSIONS:** The simultaneous administration of mFOLFOX6 (with or without bevacizumab) and DEBIRI through the hepatic artery (FOLFOX-DEBIRI) is safe and does not cause treatment delays or increase the systemic toxicity of chemotherapy. This strategy leads to improved overall response rates, improved hepatic progression-free survival, and more durable overall progression-free survival in patients downsized to resection. ***Cancer* 2015;000:000-000.** © *2015 American Cancer Society*.

KEYWORDS: hepatic artery therapy, irinotecan, liver-directed therapy, liver-dominant metastatic colorectal cancer, metastatic colon cancer.

INTRODUCTION

Surgical resection provides the potential for a long-term disease-free interval; it still remains the ultimate goal for patients who present with initially unresectable liver metastases.[1] Therefore, a major goal of current therapeutic strategies is to optimize the response and downsize metastatic disease to resectability.[2,3]

The current optimal first-line therapy for patients with unresectable colorectal liver metastases is typically multiagent chemotherapy based on either folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) or folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX). Recent single-institution studies have demonstrated enhanced response rates

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with the use of a FOLFIRINOX-based regimen with high rates of downsizing to resection and acceptable R0 resection rates.[4] The challenge with the use of either FOLFIRINOX- or FOLFOX-based chemotherapy has been the ability to tolerate more than approximately 4 to 6 cycles. In particular, older patients have limited tolerance for more aggressive systemic chemotherapy with the former and a high risk of chemotherapy-associated endothelialitis with the latter.[5,6]

Recent advances in hepatic-directed therapy in the setting of liver metastasis for metastatic colorectal cancer have been published.[7,8] The use of irinotecan drug-eluting beads (DEBIRI) has been published recently, and researchers have demonstrated initial safety,[9] tolerance,[7,10] and minimal to negligible systemic exposure of irinotecan when irinotecan is delivered into the hepatic artery through a lobar approach in combination with systemic intravenous FOLFOX and bevacizumab.[8]

Thus, we hypothesize that patients who are treated concurrently with systemic FOLFOX (with or without bevacizumab) and DEBIRI will have a similar chemotherapeutic toxicity profile, enhanced overall response rates at 2, 4, and 6 months, responses of longer duration and greater durability, and possibly greater rates of downsizing to resection.

MATERIALS AND METHODS

A Federal Drug Administration–exempted (Investigational Drug Exemption submission G080230-S001), University of Louisville institutional review board–approved, prospective, multi-institutional phase 2 clinical evaluation of DEBIRI (LC/DC Bead; Biocompatibles UK, Ltd) in combination with systemic mFOLFOX6 was performed from June 2009 to March 2014 (Fig. 1). Informed consent was obtained from all subjects before any treatment. The first 10 enrolled patients were mandated by the Food and Drug Administration to be treated only in the treatment arm (FOLFOX-DEBIRI) for safety and pharmacokinetic studies; it then allowed 60 patients to be randomly assigned to either the treatment arm (30 patients) or the control arm (FOLFOX; 30 patients).

The inclusion criteria required patients to be older than 18 years, have histologically proven colorectal cancer to the liver, be chemotherapy-naive for their metastatic disease, have liver-dominant disease (defined as $\geq$80% of the tumor body burden being confined to the liver) but less than 60% liver replacement by the tumor, and have an Eastern Cooperative Oncology Group performance status score ≤ 2.

Exclusion criteria included being eligible for curative treatment (ie, resection or radiofrequency ablation) and not fitting the inclusion criteria defined previously. Surgical resectability was the ability to leave adequate inflow and outflow for hepatic hypertrophy and recovery as defined by prior consensus guidelines.[11]

The treatment scheme involved standard chemotherapy administration on days 0 and 14 and the delivery of DEBIRI on days 7 and 21 (Table 1). Modified FOLFOX6 dosing was used, with the oxaliplatin dose set at 85 mg/m^2.[8] The use of bevacizumab was left to the discretion of the treating medical oncologist and was based on potential contraindications (eg, intact primary tumor with a history of bleeding, recent surgery, and cardiovascular issues).

The DEBIRI treatment technique has been described in detail in our prior studies.[11,12] In short, it was performed through a femoral or axillary artery puncture, and after appropriate anatomic identification of the right and left hepatic arteries, 1 vial of beads was eluted with the desired amount of irinotecan chemotherapy. The treatment was performed with a lobar approach on the basis of the extent and distribution of the disease, with most treatments being performed in the outpatient setting. A technical DEBIRI success was defined as the ability to deliver at least 75% of the planned dose (ie, beads loaded with 75 mg of irinotecan). The number of treatments was determined by the physician after reevaluation with imaging after the 4 cycles of FOLFOX and 2 DEBIRI treatments on the basis of the degree of response, tolerance of combination therapy, and quality of life.

The device used to deliver irinotecan in this DEBIRI study was an n-Fil sulfonate–modified, spherical hydrogel device. Unloaded LC Bead has Food and Drug Administration 510(k) clearance as a class II embolic device, and it is Conformité Européenne mark–approved as a drug delivery embolization system loadable with irinotecan for the treatment of liver metastases of colorectal cancer. Irinotecan was loaded into DEBIRI at 50 mg/mL for a total dose of 100 mg per vial.

All adverse events were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events (version 3.0).[12]

Follow-up assessments included a triphasic computed tomography scan of the liver within at least 1 to 2 months of treatment completion to evaluate the enhancement pattern of the target lesion and tumor response rates, which were measured according to the modified Response Evaluation Criteria in Solid Tumors (RECIST).[13] A target lesion (either hepatic or nonhepatic) was defined as any lesion ≥ 1 cm in size. Hepatic target lesions were defined as the largest lesions (up to 5) within the liver that were $\geq$1 cm in size. Nontarget liver lesions were any lesions ≥ 1 cm in size other than the 5 lesions that were

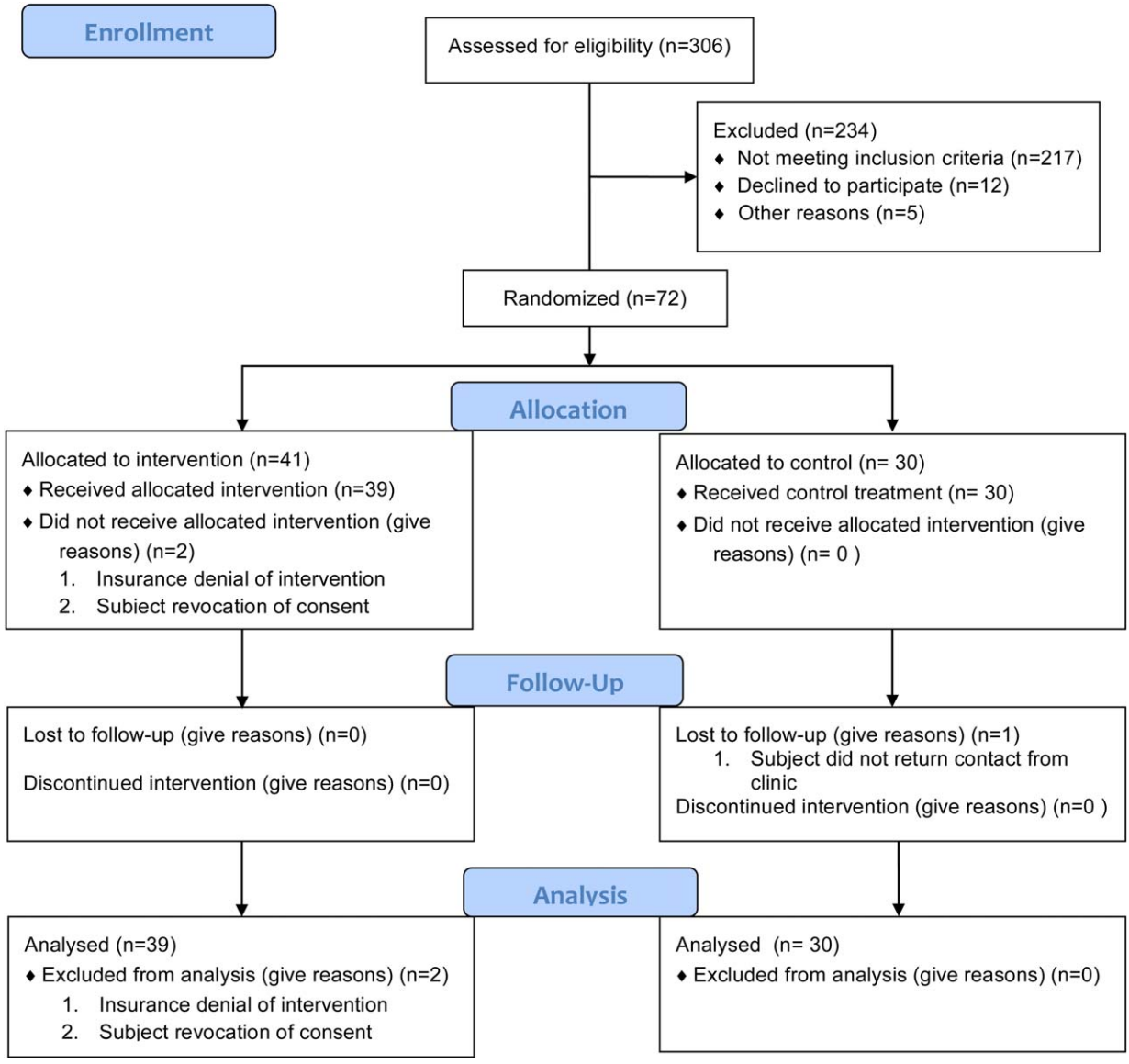

Figure 1. Consolidated Standards of Reporting Trials flow diagram of all patients screened and enrolled in the folinic acid, 5-fluorouracil, and oxaliplatin/irinotecan drug-eluting bead trial of chemotherapy-naive livers and liver-dominant metastatic colorectal cancer.

defined as target lesions. Nonhepatic, nontarget lesions were defined as any lesions outside the liver that were ≥1 cm in size (eg, portal lymph nodes and lung nodules). Surgical resectability was reassessed after each set of 4 cycles of systemic chemotherapy (ie, after the 4th, 8th, and 12th cycles). The decision for surgical resection was made by the treating surgeon on the basis of established criteria for resectability as reported.[14] A central assessment of the tumor response was performed for all patients by the principal investigator at the University of Louisville. When there was a discrepancy, the registry's principal investigator and the site's principal investigator reviewed the case again for concurrent agreement. Response rates were also calculated via a blinded, external review, which assessed the responses of both target liver lesions (up to 5) and nonliver, nontarget lesions with both RECIST 1.1[12,15] and Choi's criteria[16] to evaluate response rates.

Statistical Analysis

The statistical analysis of the data was performed with JMP 8.0. We estimated that the response rate in the intravenous chemotherapy group could be assumed to be 60%, and we estimated a response rate of 80% in the FOLFOX-DEBIRI group. The sample size of 70 patients (40 in the

TABLE 1. Baseline Preexisting Medical Conditions, Performance Status, and Initial Tumor Burden for Both Groups

Characteristic	Treatment Arm (n = 40)	Control Arm (n = 30)	*P*
Median age, y	57	60	.2
Sex: male/female, No.	24/16	21/9	.3
Race: African American/ white/Asian, No.	7/33	4/25/1	.7
Prior colon surgery, No. (%)	17 (43)	13 (45)	.9
Prior liver surgery, No.	2	1	
Past medical history, No.			
Cardiac	11	2	.1
Pulmonary	2	1	
Diabetes	3	3	
Alcohol	3	4	
Tobacco	11	5	
Past surgery, No.			NS
Cholecystectomy	9	4	
Prior liver resection	1	0	
CEA, median (range)	64 (1-12,600)	105 (1-16,381)	NS
ECOG performance status, No. (%)			.042
0	17 (44)	20 (68)	
1	20 (50)	9 (30)	
2	3 (6)	1 (2)	
Pretherapy pain score, No. (%)			
0	20 (50)	19 (65)	
1-3	9 (22)	7 (23)	
4-6	5 (13)	3 (10)	
>7	6 (15)	1 (1)	
Colon primary in place, No.	12	11	.3
Rectal primary in place, No.	9	6	
kRas mutation, No. (%)	20 (50)	10 (30)	.05
bRaf, No. (%)	6 (15)	2 (8)	NS
Presence of extrahepatic disease, No. (%)	22 (55)	9 (31)	.046
Extent of overall tumor in liver, No.			
100%	17	16	.08
90%-99%	9	8	
80%-89%	14	6	
Median liver involvement, %	30	30	NS
Bilobar disease, No. (%)	34 (85)	28 (93)	NS
No. of target lesions	5 (1-5)	5 (1-5)	NS
No. of nontarget lesions	6 (0-19)	4 (0-15)	
Cumulative sum of target lesions, cm	10.7 (3.5-46.2)	13.5 (4.4-37.2)	NS

Abbreviations: CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; NS, not significant.

treatment [FOLFOX-DEBIRI] group and 30 in the control [FOLFOX] group) provided 80% power for Fisher's exact test to detect the given difference between the assumed proportions at a significance level of .05.

RESULTS

Between June 29, 2009 and November 19, 2012, 70 patients from 9 institutions were enrolled in this prospective, randomized phase 2 clinical trial, which was coordinated through the University of Louisville and the James Graham Brown Cancer Center, and there was follow-up through March 30, 2014. Patient characteristics and primary disease sites are summarized in Table 1. A majority of the patients presented with synchronous colon or rectal disease at the time of presentation and enrollment (53% in the treatment arm and 57% in the control arm; P = not significant). All enrolled patients were chemotherapy-naive; however, the treatment group had a statistically significantly worse overall performance status (Eastern Cooperative Oncology Group performance status of 1 or 2, 56% in the treatment group vs 32% in the control group; $P = .04$). Similarly, there was a greater incidence of patients with liver-dominant disease (ie, the presence of extrahepatic disease) versus liver-only disease in the treatment arm (55%) versus the control arm (31%; $P = .05$). The remaining parameters of the tumor burden, bilobar disease, and numbers of target lesions were similar in the 2 groups (Table 1).

Forty patients in the treatment arm underwent a total of 115 DEBIRI treatments (Table 2). A majority of the patients received at least 2 DEBIRI treatments, with the median number of DEBIRI treatments being 4 (Table 2). The DEBIRI technique was a technical success in 84% of the 115 procedures. Tolerance of the DEBIRI treatment was similar for all patients, and there were minimal to no changes in the overall performance status (Table 2).

A total of 613 chemotherapeutic doses were delivered to the patients (Table 3). There was a significant increase in any type of dose delay, which was defined as dose administration more than 24 hours later than the planned dose, in the treatment group (25%) versus the control group (14%; $P = .0002$), with the most common reasons being scheduling, neutropenia, and pancytopenia. There was no significant difference in dose delays when hematologic reasons were evaluated. There was no difference in dose-limiting toxicity, with equal percentages of patients having dose-limiting toxicity that required them to have more than 21 days between their FOLFOX dosing schedules (treatment dose-limiting toxicities: 3.5% of doses in the treatment arm vs 3.0% of doses in the control arm). There were similar rates of oxaliplatin and 5-fluorouracil dose reductions in the 2 arms (Table 3).

The adverse event profiles of both arms are demonstrated and summarized in Table 4. There was a significantly greater incidence of grade 3/4 toxicities in the treatment arm, predominantly because of device-related serious adverse events (Table 4). Device-related serious adverse events were recorded if a patient had to stay in the hospital longer than 23 hours or was re-admitted to the hospital after DEBIRI

TABLE 2. Summary of DEBIRI Therapy in 40 Patients Receiving 115 DEBIRI Treatments

DEBIRI treatments, No.	
1	40
2	37
3	18
4	13
5	4
6	3
Delay in DEBIRI, No.	2 (patient discretion and scheduling delay)
Level of infusion: lobar, %	100
Treatment location, No.	
Right	65
Left	50
Fluoroscopy time, median (range), min	9.35 (4-42)
Radiation dose, median (range), rad	18.24 (1.34-109)
Procedure duration, median (range), min	55 (24.5-130)
Volume of contrast added, median (range), mL	5 (3-11)
Total volume of contrast and beads, median (range), mL	8 (5-15)
Bead size of 100-300 micron, %	100
Angiocatheter size	5F (89%)
Dose delivered, median (range), mg	100 (50-100)
Technical failure of DEBIRI	Early arterial spasm, catheter cannulation not possible (left)
Technical success (≥75 mg), No. (%)	96 (83)
Reason for failure, No.	
Early stasis	10
Change from Bevacizamab	2
Other	7
Degree of arterial stasis (right), %	
None	66
Partial	33
Degree of stasis (left), %	
None	57
Partial	36
Total	7
Length of stay, median (range)	23 h (23 h to 3 d)
ECOG performance status during DEBIRI, median (range)	0 (0-1)
Worst pain score during DEBIRI, median (range)	4 (0-9)
Systolic blood pressure, median (range), mm Hg	123 (89-200)
Diastolic blood pressure, median (range), mm Hg	81 (60-137)
Heart rate, median (range), bpm	77 (52-120)
Post-DEBIRI hematologic change, median (range)	
Creatinine, mg/dL	0.7 (0.4-1)
Total bilirubin, mg/dL	0.4 (0.2-1.6)
AST, U/L	32 (14-385)
ALT, U/L	30 (10-126)
INR	1.1 (1.0-1.4)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DEBIRI, irinotecan drug-eluting beads; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio.

TABLE 3. Chemotherapy Administration in Both the Treatment Arm and the Control Arm for Chemotherapy-Naive Metastatic Colorectal Cancer to the Liver

	FOLFOX-DEBIRI (40 Patients, 346 Doses)	FOLFOX (30 Patients, 267 Doses)	*P*
Median cycles of chemotherapy, No.			
Cycle of chemotherapy, No. of patients	10	9	
Dose 1	40	30	
Dose 2	40	29	
Dose 3	39	28	
Dose 4	37	28	
Dose 5	32	24	
Dose 6	30	24	
Dose 7	28	23	
Dose 8	25	23	
Dose 9	21	16	
Dose 10	20	15	
Dose 11	17	14	
Dose 12	15	14	
Bevacizamab use			
No. of patients (%)	28 (70)	27 (90)	<.0001
% of doses	44	56	
Reason for no Bevacizamab., No. of doses			
Stroke history	4	0	.0001
Rectal bleeding	25	0	
Hypertension	3	1	
Recent PE	1	0	.0001
Recent surgery	22	9	
Physician discretion	96	20	
Other	4	15	
Any dose delay, %	25	14	.0002
Reason for any delay, No. of doses			
Neutropenia	27	10	
Pancytopenia	12	1	.29
Thrombocytopenia	23	12	
Failure to thrive	3	1	
Electrolytes	2	0	
Other	15	9	
Surgery	6	3	
DLT, % of doses	3.5	3	.9
Reason for DLT, No. of doses			
Neutropenia	2	1	
Other	2		
Oxaliplatin dose reduction, No. of doses	21	10	
50%	5	6	
20%	16	4	
25% 5-FU dose reduction, No. of doses	9	6	
Bevacizamab dose reduction, No. of doses	1	0	

Abbreviations: 5-FU, 5-fluorouracil; DEBIRI, irinotecan drug-eluting beads; DLT, dose-limiting toxicity; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; PE, pulmonary embolism.

treatment. When we evaluated only chemotherapy-associated adverse events, there were no differences in the treatment and control arms among patients evaluated for chemotherapy-specific adverse events (Table 4).

The most common adverse events are outlined in Table 4. A summary of the grade 3/4 adverse events is outlined in Table 4, which shows similar percentages for the treatment (DEBIRI) arm and the control arm.

TABLE 4. Adverse Events in Both the Treatment Arm and the Control Arm for Chemotherapy-Naive Metastatic Colorectal Cancer to the Liver

Adverse Events	DEBIRI Arm (40 Patients)	Control Arm (30 Patients)	*P*
All adverse events, No.	973	459	
Grade 3 or 4 adverse events, No.	144 (32 patients)	36 (18 patients)	
Serious adverse events, No.	57	15	.03
Expected	2	1	
Unexpected	23	1	
Stopped trial	8	15	
Device-related adverse events, No.	19	NA	NA
Chemotherapy-related adverse events, No.	38	21	.08
Device-related serious adverse events, No.			
Abdominal pain	7	NA	
Acute renal failure	1		
Ascites	1		
Cholecystitis	2		
Pulmonary	1		
Hypertension	4		
Pancreatitis	1		
Emesis	3		
CTCAE version 3, No. (%)			
1. Mild	540 (55)	316 (69)	0.15
2. Moderate	289 (30)	107 (23)	
3. Severe	135 (14)	33 (7)	
4. Life-threatening	9 (1)	3 (1)	
Chemotherapy-associated adverse events, No. (%)			
1. Mild	282 (54)	206 (66)	
2. Moderate	169 (33)	73 (24)	
3. Severe	67 (13)	29 (9)	
4. Life-threatening	1 (1)	2 (1)	

Grade 3/4 Adverse Events (>10% of Patients)	DEBIRI Arm	Control Arm, No. (%)
Neutropenia, No. (%)	5 (13)	6 (21)
Abdominal pain, No. (%)	5 (13)	1 (3)
Procedural hypertension, No. (%)	5 (13)	0 (0)
Neutrophil count decrease, No. (%)	4 (10)	0 (0)
Hypertension, No. (%)	5 (13)	2 (7)

Specific Adverse Events	Adverse Events in DEBIRI Arm (n = 973)	Grade 3 or 4 Adverse Events in DEBIRI Arm (n = 144)	Adverse Events in Control Arm (n = 459)	Grade 3 or 4 Adverse Events in Control Arm (n = 36)	*P*
Blood/lymph, No. (%)	90 (9)	24 (17)	27 (6)	10 (28)	.14
Anemia	11	3	3	0	
Neutropenia	40	17	13	8	
Thrombocytopenia	43	7	7	0	
Cardiac, No. (%)	10 (0.1)	0	2 (0.1)	0	NS
Gastrointestinal, No. (%)	206 (21)	26 (18)	120 (26)	9 (25)	.12
Abdominal pain	37	10	9	1	
Constipation	16	0	12	0	
Diarrhea	24	1	17	0	
Nausea	42	0	23	3	
Emesis	21	2	15	3	

TABLE 4. *Continued*

Adverse Events	DEBIRI Arm (40 Patients)		Control Arm (30 Patients)		*P*
Hepatobiliary, No. (%)	13 (1)	5 (3)	2 (0.4)	0	NS
Biliary dilation	1	0	0	0	
Cholecystitis	1	1	0	0	
Hemobilia	1	1	0	0	
Hepatotoxicity	2	1	0	0	
Hyperbilirubinemia	8	2	2	0	
Infections, No. (%)	27 (3)	5	10 (2)	1	NS
Pulmonary, No. (%)	46 (5)	0	35 (6)	2	NS
Skin, No. (%)	37 (4)	1	28 (6)	1	NS
Vascular, No. (%)	38 (4)	7	12 (2)	3	NS
Nervous system, No. (%)	75 (7)	4	58 (11)	1	NS

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DEBIRI, irinotecan drug-eluting beads; NA, not applicable; NS, not significant.

After a median follow-up of 19 months (range, 17-38 months), the overall response rates, as measured with the modified RECIST criteria, were statistically significant superior at 2 ($P = .01$), 4 ($P = .03$), and 6 months ($P = .05$) in the treatment arm versus the control arm, predominantly because of enhanced complete and partial responses (Fig. 2A). There were similar statistically significant improvements in 2- ($P = .02$), 4- ($P = .03$), and 6-month response rates ($P = .05$) for just the target lesions in the treatment arm versus the control arm (Fig. 2B).

Enrolled patients then underwent a blinded radiologic review with the established RECIST 1.1 criteria or Choi's criteria. According to RECIST, there was a nonsignificant improvement in the overall response at 2, 4, and 6 months in the treatment arm versus the control arm (88% vs 89%, 97% vs 95%, and 92% vs 89%, respectively). For target lesions, according to RECIST, the treatment and control groups were similar at 2 (100% vs 95%, respectively), 4 (100% vs 90%, respectively), and 6 months (98% vs 91%, respectively).

There was a significant improvement in the 2-month overall response (98% for the DEBIRI group vs 82% for the control group; $P = .01$), and there were nonsignificant improvements in the 4- (100% for the DEBIRI group vs 89% for the control group; $P = .09$) and 6-month overall response (95% for the DEBIRI group vs 92% for the control group; $P = .12$) according to Choi's criteria. The overall durability of the response or the greatest response was also significantly greater in the DEBIRI treatment arm (12-month response with FOLFOX-DEBIRI, 50%) versus the control arm (12-month response, 24%; Fig. 1).

After a median follow-up of 24 months, there was a nonsignificant improvement in progression-free survival in the control arm (median, 15 months; range, 10.4-20 months) versus the treatment arm (median, 12 months; range, 9-15.4 months; $P = .18$). In an evaluation of liver-target progression-free survival, neither median survival was reached with significant response rates out to 24 months. In an evaluation of liver nontarget liver-only progression-free survival, there was an improvement in the DEBIRI treatment arm (median, 21 months; range, 12-28 months) versus the control arm (median, 15 months; range, 10.8-24 months; $P = .68$). There was a statistically significant improvement in liver progression-free survival in the treatment group (median, 17 months; range, 12-23 months) versus the control group (median, 12 months; range, 11-24 months; $P = .05$). Overall extrahepatic progression-free survival was similar in the 2 groups: the treatment median was 13.7 months (range,

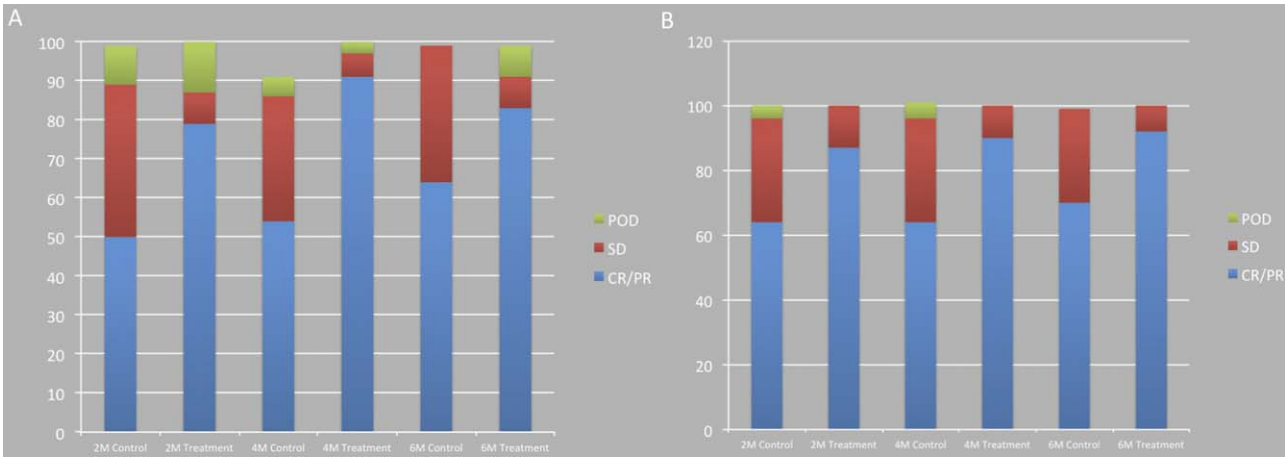

Figure 2. (A) The modified Response Evaluation Criteria in Solid Tumors demonstrated statistically significantly superior 2M ($P = .01$), 4M ($P = .03$), and 6M overall response rates ($P = .05$) in the treatment arm versus the control arm, predominantly because of enhanced CR and PR rates. (B) There were similar statistically significant improvements in the 2M ($P = .02$), 4M ($P = .03$), and 6M response rates ($P = .05$) for just the target lesions in the treatment arm versus the control arm. 2M indicates 2 months; 4M, 4 months, 6M, 6 months; CR, complete response; POD, progression of disease; PR, partial response; SD, stable disease.

9-38 months) for the treatment group and 16 months (range, 10-38 months) for the control group ($P = .35$).

DISCUSSION

The FOLFOX-DEBIRI trial is the first randomized trial to our knowledge to evaluate the treatment effect of hepatic artery therapy with DEBIRI in combination with an oxaliplatin-containing regimen for first-line treatment in patients with liver-dominant metastatic colorectal cancer. In patients with liver-dominant disease, we demonstrated superior 2-, 4- and 6-month response rates (Figs. 1 and 2) and similar progression-free survival in patients receiving FOLFOX-DEBIRI and patients receiving FOLFOX alone. The FOLFOX-DEBIRI arm also demonstrated a significant improvement in best overall response rates, regardless of the follow-up time interval, and we believe that this is important because systemic chemotherapy alone may have a slower time to an optimal response in comparison with DEBIRI. Even with this combination of hepatic artery therapy (DEBIRI), we did not see any type of augmentation of adverse events or severe adverse events and, more importantly, did not see any type of augmentation of chemotherapy-associated adverse events (Table 4). These similar adverse events were expected from our previous phase 1 clinical evaluation, which demonstrated minimal to nonexistent systemic exposure to irinotecan when it was administered through drug-eluting bead technology via the hepatic artery.[8]

The improvement in response rates did correlate with a significant improvement in downsizing to resection in the FOLFOX-DEBIRI arm (35%) versus the FOLFOX-alone control arm (6%; $P = .05$). There were 2 main reasons for the downsizing to resection in this group of patients. The first indication occurred when extrahepatic disease, which was the reason that the patient was unresectable at enrollment, was eradicated or disappeared. The second indication occurred with the complete response of contralateral liver lesions, which had caused the patient to be unresectable at enrollment. Similarly, in that subset of patients who were downsized to resection, a statistically significant improvement in progression-free survival after resection was also seen with the FOLFOX-DEBIRI combination in comparison with the control arm.

These results for the FOLFOX-DEBIRI arm, compared with previously published results for the use of conventional chemoembolization, demonstrate a significant improvement in the response rate, progression-free survival, and overall survival in comparison with these historical controls.[13,14,17] Sanz-Altamira et al[14] reported an overall median survival of 10 months from the date of first chemoembolization. The 1 unique difference in this study was the use of concurrent systemic chemotherapy, which historically has not been used when hepatic artery therapy is being evaluated. These preliminary results also demonstrate similar tolerance, adverse event rates, progression-free survival, and downsizing to surgical resection in patients who were treated with combination systemic chemotherapy and hepatic artery infused pumps.[18] The potential advantage of using DEBIRI is that this spares the patient a surgical procedure, which is

required for hepatic artery infused pumps. However, the current study does not allow us to make any type of direct comparison to other liver-directed therapies.

Our study was also unique in the ability to concurrently use systemic chemotherapy and regional hepatic-directed therapy and not need to rely on alternating therapy, as has been reported in the past.[19] This concurrent use, we believe, is essential, especially for the treatment of liver-dominant disease, and this was demonstrated by acceptable and similar extrahepatic progression-free survival in the 2 groups in this study: a median of 13.7 months (range, 9-38 months) for the treatment group and a median of 16 months (range, 10-38 months) for the control group ($P = .35$). This was surprising because of the significantly higher percentage of extrahepatic disease at the time of enrollment in the treatment group (55% vs 31% in the control group; $P = .046$). These results suggest synergistic activity and benefits from the addition of full-dose, active systemic chemotherapy to regional hepatic artery therapy when we consider the similar proportion of patients developing extrahepatic progression in comparison with the control arm. However, because this study was a phase 2 evaluation, the confirmation of these results with larger numbers of patients in a prospective trial will be required to ascertain a benefit from the addition of systemic chemotherapy. A challenge with concurrent use can be the scheduling of interventional radiology and systemic chemotherapy administration, as demonstrated in our study, which required a subset of the patients to be treated outside the 7-day window (± 1 day). Our study does appear to demonstrate an improvement in the time to progression and overall survival in comparison with previously published hepatic conventional chemoembolization studies in colorectal cancer that did not use systemic chemotherapy.[13,14] However, whether the activity of concurrent systemic chemotherapy and hepatic artery therapy delays the progression of extrahepatic metastases or whether localized liver-directed therapy with systemic therapy reduces the intrahepatic progression of disease cannot be definitively proven in this phase 2 trial. Nevertheless, the signal for prolonged intrahepatic disease control does produce enthusiasm for a larger study evaluation.

Key to any trial that involves a combination of local therapy and systemic therapy is the ability to deliver both therapies easily without accentuating the toxicity of either therapy. We were able to demonstrate the safety and tolerability of the FOLFOX-DEBIRI treatment, with minimal dose delays and similar dose delivery of the systemic chemotherapy in the 2 arms (Table 3). More importantly, we did not see an accentuation of systemic therapy–related adverse events or severe adverse events in either arm, and this demonstrated that localized DEBIRI therapy does not induce systemic toxicity in a majority of patients and, more importantly, does not induce an accentuation of liver toxicity in patients undergoing systemic FOLFOX and concurrent DEBIRI delivered with this technique.

It has been well established and proven that the evaluation of the radiographic response by the standard RECIST criteria is not adequate for liver-directed therapy chemoembolization studies.[20,21] For these well-established reasons, we chose to evaluate responses according to both the modified RECIST criteria[22-24] and Choi's criteria.[16,25] These response criteria have been used before in a recent prospective randomized control trial of sorafenib and doxorubicin drug-eluting beads.[26]

These modified RECIST criteria, which define a response as a loss of arterial enhancement from the baseline, have been similarly used in studies of hepatic artery therapy in metastatic colorectal cancer.[21,27-29] Continued high-quality triphasic computed tomography scanning is necessary for all follow-up to evaluate the maximal effect on the tumor volume because the evolution of these lesions continues to demonstrate sharper demargination and diminishing size over time.

Future prospective randomized clinical trials of hepatic artery therapy will continue to be a challenge because of the intrinsic clinical heterogeneity of patients with hepatic tumors, which is based on 1) the extent of liver involvement, 2) liver-only tumors versus liver-dominant tumors, 3) the kRas mutation status, 4) the prior use of adjuvant therapy (ie, FOLFOX), and 5) established definitions for stopping chemotherapy in patients with unresectable disease. However, future trials are needed with primary endpoints of downsizing to possible resection, improvements in the quality of life, and overall survival. We have established a simplified DEBIRI technique, which does not require these procedures to be performed in specialized centers but can be performed in both community and academic facilities safely and effectively.[30,31] The procedure-associated morbidities with DEBIRI have been well established and can be avoided with these types of technical modifications, which differ from conventional transarterial chemoembolization. We have validated a generally less technically complex DEBIRI procedure that does not require hospitalization, uses a minimal percentage of patient controlled anesthesia (PCA), and, therefore, represents a less toxic, less expensive, and more convenient treatment alternative to other regional hepatic artery therapies.

In conclusion, we believe that simultaneous mFOLFOX6 with bevacizumab and DEBIRI via the hepatic artery is safe, does not cause chemotherapy delivery delays, and does not increase chemotherapy toxicity. Simultaneous use of FOLFOX and DEBIRI leads to improved overall response rates, improved hepatic progression-free survival, and more durable overall progression-free survival in patients downsized to resection.

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CONFLICT OF INTEREST DISCLOSURES

Robert C. G. Martin II is a consultant for BTG/Biocompatibles. William S. Rilling reports working as a consultant for BTG, Cook Medical, Terumo, Guerbet, and B. Braun and receiving grants from BTG, B. Braun, Sirtex, Guerbet, and Siemens. Christopher J. Laing reports trial expenses from the University of Louisville.

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