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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Hepatic Intra-Arterial Injection of Drug-Eluting Bead, Irinotecan (DEBIRI) in Unresectable Colorectal Liver Metastases Refractory to Systemic Chemotherapy: Results of Multi-Institutional Study

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ABSTRACT

Introduction. Response rates and overall outcome for patients who have failed first-line and in some cases second-line chemotherapy are as low as 12% and 7 months, respectively. The aim of this study is to evaluate the efficacy of hepatic arterial sulfonate hydrogel microsphere (drug-eluting beads), irinotecan preloaded therapy (DEBIRI) in metastatic colorectal cancer refractory to systemic chemotherapy.

Methods. This was a multicenter multinational single-arm study of metastatic colorectal cancer patients who received DEBIRI after failing systemic chemotherapy from 10/2006 to 8/2008. Primary endpoints were safety, tolerance, tumor response rates, and overall survival.

Results. Fifty-five patients who had received prior systemic chemotherapy and who underwent a total of 99 DEBIRI treatments were reviewed. The median number of DEBIRI treatments was 2 (range 1–5), median treatment dose was 100 mg (range 100–200 mg), with total hepatic treatment of 200 mg (range 200–650 mg), with 86% of treatments performed as lobar infusion and 30% of patients treated with concurrent simultaneous chemotherapy. Adverse events occurred in 28% of patients with median grade of 2 (range 1–3) with no deaths at 30 days post procedure. Response rates were 66% at 6 months and 75% at 12 months. Overall survival in these patients was 19 months, with progression-free survival of 11 months.

Conclusions. Hepatic arterial drug-eluting bead, irinotecan (DEBIRI) was safe and effective in treatment of metastatic colorectal cancer (MCC) refractory to multiple lines of systemic chemotherapy. DEBIRI is an acceptable therapy for treatment of metastatic colorectal cancer to the liver.

Systemic chemotherapy for unresectable metastatic colorectal cancer (MCC) is the standard initial management. However, after a patient has failed first-line and in some cases second-line chemotherapy, response rates fall to as low as 12%.[1] Of the 159,000 new colorectal patients diagnosed each year approximately 60% will develop liver metastasis during the course of their disease in the USA. In approximately 30% of these patients who develop liver metastasis the metastatic disease will remain confined to the liver. For the 70–75% of colorectal patients with colorectal liver metastasis not suitable for hepatic resection or similarly ablative therapy with curative intent, short-term prognosis is relatively poor since optimal palliative chemotherapy has been able to produce overall survival of approximately 22.4 months.[2]

In patients with liver-dominant metastatic colorectal cancer to the liver, hepatic arterial chemotherapy is a logical treatment option given the facts that: (1) patients

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have a majority of their disease confined to the liver, (2) colorectal liver metastases are preferentially perfused (nearly 90–95%) by the hepatic arterial network whereas nontumor liver parenchyma is preferentially perfused by the portal vein, and (3) these colorectal liver metastases can be exposed to high concentrations, avoiding the liver first-pass effect, thus reducing overall systemic side-effects. However, given the past response rates of hepatic arterial infusion through either hepatic arterial infusion pump, yttrium-90 or drug-eluting bead chemotherapy, there have been limited randomized controlled trials clearly demonstrating improvement in overall survival, and a majority of studies have only been able to demonstrate increased response rates.[3–6] However, the invasiveness of pump insertion, the significant increased biliary toxicity, and the lack of long-term patency have led to failure to adopt hepatic arterial infusion pumps.[7]

Thus, there is great need to identify potential therapies that can be used in combination and that can overcome the liver sanctuary effect and provide durable response rates and potentially improve overall survival in patients with chemorefractory metastatic colorectal cancer with liver-dominant disease. We have recently published both a safety evaluation and an efficacy evaluation of use of DEBIRI in treatment of patients with unresectable metastatic colorectal cancer.[8,9]

Thus the aim of this study is to evaluate the efficacy of precision hepatic arterial irinotecan bead therapy in metastatic colorectal patients who have failed first-line and/or second- or third-line systemic chemotherapy.

MATERIALS AND METHODS

A University of Louisville institutional review board (IRB)-approved prospective multi-institutional single-arm treatment registry was evaluated from October 2006 to August 2008, in which 95 patients presenting with liver-dominant (defined as >50% overall head-to-toe tumor burden confined to the liver) metastatic colon cancer (MCC) were treated with DEBIRI (LC/DC Bead®; Biocompatibles, UK Ltd.). The study was conducted in compliance with the protocol and the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP). Informed consent was obtained from the subjects prior to evaluation and screening. The registry was initiated to satisfy the strict criteria for critical appraisal of the quality of a registry study with: (1) a well-described patient population, (2) hypothesis-generating and hypothesis-answering questions, (3) high-quality data, with good quality control, (4) independent assessment of outcomes, (5) good clinically relevant follow-up with minimal loss of patients, and (6) comparable patient evaluation across all institutions participating.[10]

Inclusion and exclusion criteria have been presented in our previous pilot study as per the chemoembolization guidelines, being: confirmed diagnosis of liver-dominant metastatic colorectal cancer, with defined prior chemotherapy treatment and reasons for abandoning that chemotherapy.[9]

The technique of DEBIRI treatment has been described in detail in our prior studies, but in short: it is performed through a femoral or axillary artery puncture and, after appropriate anatomic identification of the right and left hepatic artery, one vial of beads are eluted with the desired amount of irinotecan chemotherapy.[8] Treatment was performed in a lobar approach, based on the extent and distribution of the disease, with most treatments being performed in the outpatient setting. The method of DEBIRI therapy has been described previously in our initial pilot-phase report.[8] The number of treatments was based on the size of lesion(s), location of lesions (single lobe or bilobar), and degree of angiographic stasis following each treatment.

LC/DC Bead is an N-Fil sulfonate modified hydrogel spherical device. LC Bead has Food and Drug Administration (FDA) 510k clearance as a class II embolic device; DC Bead is an identical product marketed under a different brand name in the rest of the world and is CE mark approved as a drug delivery embolization system, loadable with irinotecan for treatment of metastases of colorectal cancer. DEBIRI was loaded with irinotecan at 50 mg/ml for a total dose of 100 mg per vial. The dose delivered is defined as the single amount of irinotecan that was delivered at one DEBIRI administration. Total hepatic exposure was defined as the total sum of irinotecan that was delivered to the patient's entire liver.

DEBIRI is intended as a combination therapy for treatment of liver metastases arising from colorectal cancer, by transarterial chemoembolization (TACE). The primary function of the device is to embolize the arteries feeding the tumor site, causing nutrient and oxygen starvation of the tumor and thereby inducing necrosis in the tumor tissue. The secondary function is to deliver irinotecan in a controlled manner to tumor sites. These functions combine to significantly enhance the cytotoxicity of irinotecan to the tumor and potentially reduce systemic toxicity compared with intravenous chemotherapy.

Safety and Efficacy Variables Assessed and Study Schedule

All adverse events were recorded as per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse

Events, version 3.0. Previous published studies have demonstrated its safety as well as efficacy with improved overall survival.[9]

Follow-up assessments included triphase computed tomography (CT) scan of the liver within at least 1–2 months from treatment completion with evaluation of the enhancement pattern of the target lesion and tumor response rates measured according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[11–13] Follow-up assessment was then performed at 3-month intervals for the first year and every 6 months for the second year. Hepatic progression-free survival was defined as liver-only progression of disease. Extrahepatic progression-free survival was defined by disease outside of the liver (i.e., lung, peritoneum, bone, etc.) progressing during follow-up.

Data entry was monitored for completeness and accuracy at University of Louisville, and data were queried when required. Data source documents were requested and monitored for at least the first five patients from each site. Central assessment of tumor response was performed for all patients by the principal investigator (PI) at University of Louisville. When there was discrepancy, the registry PI and the site PI reviewed again for concurrent agreement.

A sample size of 55 patients was proposed to detect the threshold of objective response rates of 75% when compared with best systemic therapy for chemorefractory metastatic colorectal cancer, which has been reported to be 37%.[1,2,14] Only patients with complete pre-DEBIRI chemotherapy were analyzed for this study. If prior chemotherapy, dosage or number of cycles could not be defined, those patients were excluded from this analysis. Analysis of data was done using JMP 4.0 and SPSS version 16.0.

RESULTS

Patient Characteristics

From October 2006 until August 2008, 55 patients who met the inclusion criteria stated above and who had documented liver progression of disease from at least one line of chemotherapy were included in this evaluation. Most patients had good performance status at time of first bead treatment, with the vast majority having colon primaries and presenting with metachronous colorectal metastasis (Table 1). Liver involvement treated was <25% in the majority (30 patients) and was 26–50% in 13 patients and >50% in 12 patients. The sum of the total lesion sizes that were treated in this study was 9.0 cm with a range of 5.5–28.0 cm (Table 1).

All patients had received at a minimum first-line 5-fluorouracil and oxaliplatin (FOLFOX) and bevacizumab ($n = 17$) for treatment of metastatic disease, with a separate 14 patients having received first-line FOLFOX and bevacizumab as well as second-line 5-fluorouracil and irinotecan (FOLFIRI) and cetuximab ($n = 14$), with a majority of patients having failed all possible regimens that the medical oncologist felt were available, including FOLFOX and bevacizumab, FOLFIRI and cetuximab, Xeloda ($n = 24$), and other additional types of chemotherapeutic agents as possible third-line treatment. One of the most common reasons for referral and evaluation and ultimately treatment with hepatic arterial bead therapy was hepatic-specific disease progression while on chemotherapy. Since current standards would require a patient to change chemotherapy, DEBIRI was utilized to overcome this focal area of progression (the liver). Only 5 of the 24 who had failed all types of therapy were also referred for intolerance to chemotherapy. Concurrent chemotherapy of Xeloda or infusional 5-fluorouracil (5-FU) was used in 16 (30%) in combination with DEBIRI. Reasons for unresectability for these 55 patients were having had prior lobectomy with recurrence in contralateral liver and insufficient functional liver reserve in 11 patients, poor performance status or significant comorbidities in 8 patients, refusal for surgery in 5 patients, secondary to lack of surgical access in 3 patients, and extrahepatic disease at time of liver disease in 27 patients. Since 50% of these patients did have underlying concurrent extrahepatic disease, the majority within the lung or solitary lymph nodes that had remained stable during their systemic treatment, the goal was attempted salvage treatment for hepatic-specific progression.

Treatment Feasibility and Tolerance

Overall, 99 DEBIRI treatments were performed with a median of 2 (range 1–5) DEBIRI treatments based on extent of liver involvement, size of the liver lesions to be treated, and the anatomic remaining liver parenchyma, since 30% of these patients had already undergone prior hepatectomy (Table 2). Technical success, defined as ability to access the appropriate segments of the liver and to deliver at least 50% of the planned DEBIRI dose, was achieved in all 99 treatments. A majority ($n = 77$ treatments) underwent lobar DEBIRI infusion, with 22 undergoing segmental DEBIRI infusion. No patients underwent whole-liver treatment at one treatment session. The median dosage delivered in each treatment was 100 mg irinotecan (range 50–200 mg) with median overall total hepatic dose exposure of 185 mg (range 150–650 mg). The overall adverse event rate was 28% of treatments, with a total of 25 patients sustaining the 28 treatment-related adverse events; the specific technical bead perfusion complication rate was 1%, corresponding to a single patient who developed acute

TABLE 1 Clinical and chemotherapy characteristics of DEBIRI-treated patients

Characteristic	$N = 55$
Age (years) (median, range)	60 (34–82)
Gender (M/F)	32/23
Performance status	
0	27
1	12
2	16
Colon/rectal primary	40/15
Synchronous/metachronous	17/38
Prior liver surgery	
Hepatic resection (lobectomy)	11
Ablation	5
Liver involvement	
<25%	30
26–50%	18
>50%	17
Number of liver tumors (median, range)	4 (1–20)
1	11
2	10
≥3	33
Total sum of all target lesion(s) size (median, range)[a]	9 cm (5.5–28 cm)
Prior systemic chemotherapy regimes	
FOLFOX + Avastin	17
FOLFOX + Avastin and FOLFIRI + Erbitux	14
FOLFOX + Avastin and FOLFIRI + Eribitux and Xelox + Vectibex or other	24

[a] Up to five target lesions are used for the total sum

TABLE 2 DEBIRI technical outcomes

	$N = 99$ total DEBIRI treatments
Number of bead courses	2 (range 1–5)
1	5
2	34
3	3
4	3
5	1
Technical success	100%
Bead size	
100–300 μm	54
300–500 μm	6
100–300 and 300–500 μm	10
300–500 and 500–700 μm	29
Dose delivered (median, range)	100 mg (50–200 mg)
Total hepatic dose exposure	185 (150–650)
Adverse events (%)	28 (28%)
Extrahepatic infusion	1 (1%)

cholecystitis on day 10 from bead infusion that was subsequently treated with intravenous (IV) antibiotics and a readmission and hospital stay of 6 days.

In an evaluation of 99 separate treatments, adverse events occurred in 28% ($n = 28$ treatments), with a majority of adverse events being nausea, vomiting, and liver dysfunction. A vast majority of these adverse events were less severe (grade I–II), but two patients (3%) with grade III liver dysfunction rate, predominantly seen as elevated bilirubin, required prolonged hospital stay following infusion or readmission for transient hepatic dysfunction (Table 3). We saw no difference in adverse events between patients who were and were not on concurrent chemotherapy. One patient presented with late hepatic dysfunction on day 28 following a single 200 mg infusion of irinotecan that led to a prolonged hospital stay and death 6 weeks after readmission from multisystem organ failure, and thus the investigator felt that this possibly could be related to DEBIRI. He had 55% of his liver replaced, a two-vial dose with 100 mg loaded into each vial was given, with one vial being 300–500-μm and the other being 500–700-μm beads, with complete stasis seen after bead infusion. One additional grade 5 toxicity occurred in a patient on day 29 from DEBIRI treatment from myocardial infarction, which the investigator did not feel was related to DEBIRI treatment but was captured during the follow-up period.

These two grade 5 complications (3.6% of patients) also occurred in patients who had failed either two successive lines of systemic chemotherapy or three successive lines of systemic chemotherapy, thus leading to the demonstration that these heavily pretreated patients were more sensitive to more aggressive hepatic arterial therapy.

Tumor Response and Survival

All patients received their planned number of DEBIRI treatments prior to estimating initial response (Table 4). Median follow-up for this patient cohort was 18 months (range 12–40 months). Response was initially estimated at 3 months from initial DEBIRI treatment and then, based on the degree of response, repeat DEBIRI treatments were performed or observation was continued for ongoing response. The overall 3-month response was 65% ($n = 36$), with 12% ($n = 7$) showing complete response and 53% ($n = 29$) showing partial response. Six-month response rates were 50% ($n = 23$), with again 12% ($n = 7$) showing complete response and 38% ($n = 21$)

TABLE 3 DEBIRI treatment-related morbidity

Side-effect ($n = 99$)	All grades, no. of events (%)	Severe grade,[a] no. of events (%)
Nausea	6 (6%)	0%
Vomiting	4 (4%)	0%
Hypertension	4 (4%)	0%
Liver dysfunction/failure	6 (6%)	3 (3%)[b]
Anorexia	3 (3%)	1 (1%)
Pain	2 (2%)	0%
Cholecystitis	1 (1%)	1 (1%)
Gastritis	1 (1%)	1 (1%)
Myocardial infarction	1 (1%)	1 (1%)[b]

[a] Defined as grade 3 or higher

[b] Defined as cause of death in one patient

TABLE 4 Response rates for all 55 patients evaluated

Response ($n = 55$)	3 months	6 months	12 months
Complete response	7 (12%)	7 (12%)	8 (15%)
Partial response	28 (53%)	21 (38%)	14 (25%)
Stable disease	15 (30%)	19 (34%)	23 (42%)
Progression of disease	3 (5%)	8 (15%)	10 (18%)
Dead of disease	0	5	9
Death of other cause	2	0	0

showing partial response; 12-month response rates were 40%, with 15% ($n = 8$) showing complete response and 25% ($n = 14$) showing partial response, thus demonstrating that, if we are able to obtain response at approximately 6 months from first DEBIRI treatment, overall hepatic response is durable out to 12 months and appears to be sustainable in this patient cohort. A similar drop in carcinoembryonic antigen (CEA) levels was also seen and correlated to radiologic response rates. Positron emission tomography (PET) scanning was only utilized in 40% of patients based on availability, and in this subset loss of arterial enhancement at 1 month post DEBIRI still led to a small amount of increased PET activity, which resolved on 3-month imaging with continued loss of arterial enhancement. In an evaluation of the seven CR patients (Table 5), the most common characteristics of CR patients were failed first-line therapy only, largest tumor <3 cm in size, total number of lesions less than six, and receiving >2 DEBIRI treatments. Overall median progression-free survival was 11 months in this patient cohort, with median hepatic-specific progression-free survival of 15 months and median overall survival of 19 months seen in this heavily pretreated cohort (Table 5).

TABLE 5 Progression-free, hepatic-specific, and overall survival

Survival	Median (months)	At 1 year (%)
PFS	11	55
Hepatic	15	75
Extrahepatic	13	45
Overall survival	19	75

PFS progression-free survival

DISCUSSION

This study demonstrated that DEBIRI produced an intention-to-treat overall response rate of 70% and a tumor control rate of 15 months in a heavily pretreated population of patients with unresectable colorectal liver metastasis. These results have to be compared with the expected response rate of 10% reported for systemic chemotherapy. DEBIRI treatment also demonstrated hepatic-specific disease progression in which median overall survival of 19 months from DEBIRI treatment was obtained. All patients had previously received and failed a median of two lines of systemic chemotherapy with biologic agents, and a majority had failed all potential treatment options for systemic chemotherapy while having ongoing hepatic-specific progression of disease. This represents the next step in the continuing evaluation of this device, as part of which this collaborative group has already demonstrated the safety of the device, followed by its effectiveness, and now its potential benefit in the chemorefractory patient.[8,9]

At present, systemic chemotherapy still remains the optimal established treatment in patients with unresectable colorectal liver metastasis. First-line treatments combining either irinotecan or oxaliplatin with 5-fluorouracil (5-FU)/leucovorin provide an overall response rate ranging from 31% to 62%, median progression-free survival of 6.9–8.7 months, and median overall survival of 14–21.5 months in phase III studies.[15–18] However, second-line treatment combining irinotecan or oxaliplatin with 5-FU/leucovorin after failed first-line oxaliplatin- or irinotecan-based therapy is far less effective, with overall response rates ranging from 4% to 21% and median progression-free survival of 2.5–4.8 months.[19–22] More recently, addition of the biologic agents Avastin and cetuximab has shown significant activity even in patients with initially chemotherapy-refractory colorectal liver metastasis. The addition of these biologic agents has increased overall response rates to 23% and median time to progression and overall survival to 4.1 and 8.6 months, respectively.

Considering that this study was performed during the extensive use of all three biologic agents that are currently approved in the treatment of colorectal liver metastasis, these results suggest that hepatic arterial infusion with

drug-eluting bead, irinotecan (DEBIRI) is a viable option in such patients, even after they have failed prior systemic chemotherapy including oxaliplatin- or irinotecan-based therapy. Interestingly, because of the potential referral bias of some of the institutions (i.e., a hepatic surgeon was the local principal investigator), 30% of patients included in this evaluation had prior hepatic resection or lobectomy or ablation for their disease. The demonstration of favorable response rates of these patients at 3 and 6 months (Table 4) in patients who had previously failed first- and second-line therapy is encouraging. The ability to deliver a larger dose of hepatic-specific cytotoxic agent to the liver can potentially lead to improvement in response rates and potentially increase hepatic progression-free survival. Similarly, we found that, if response rates can be achieved early (i.e., at 3 or 6 months) through appropriate patient selection, appropriate hepatic catheter technique, appropriate drug delivery, and appropriate continuity of care, then this appears to lead to a more durable response rate out to 12 months. These results again will need to be confirmed in large prospective studies as we continue to optimize patient selection and technique.

Use of hepatic arterial chemotherapy is not new and has been demonstrated to have improved efficacy with use of hepatic arterial floxuridine (FUDR) as well as hepatic arterial oxaliplatin either alone or in combination with systemic chemotherapeutic agents. Two phase I studies conducted by the same group demonstrated overall response rates of 85% with hepatic arterial FUDR combined with systemic oxaliplatin plus irinotecan, oxaliplatin plus 5-FU/leucovorin, and irinotecan alone.[23] However, the patients included in these two studies were less heavily pretreated compared with our present population and had not failed the addition of the biologic agents that are commonly used in metastatic colorectal patients. In addition, treatment using hepatic arterial FUDR has been less accepted because of its significant cumbersome nature, significant toxicity, and permanent chronic liver and biliary toxicity when compared with other types of hepatic arterial treatments.[7,24] Similar favorable results have also been demonstrated with hepatic arterial oxaliplatin with similar robust response rates as presented in this study, with significantly less chronic liver and biliary toxicity but still requiring the need for operative hepatic arterial pump placement.

Interestingly, in this study 30% of patients were treated with DEBIRI in combination with concurrent Xeloda-based chemotherapy. Combination systemic chemotherapy with hepatic arterial therapy may be an optimal combination treatment algorithm to be utilized in some patients with unresectable metastatic colorectal cancer. The timing of this combination therapy, being systemic chemotherapy and hepatic arterial therapy, has yet to be optimized and needs to be evaluated in additional studies demonstrating its potential safety, efficacy, and ultimately, improvement in overall survival. The toxicity profile observed in this study was favorable and similar to other hepatic arterial directed therapies, demonstrating good tolerability of DEBIRI in this heavily pretreated patient cohort. All planned doses of DEBIRI were delivered, with the most common adverse event being nausea, vomiting, and hypertension. There were signs of elevated liver enzymes in most patients, but these were transient. One severe adverse event related to hepatic dysfunction was seen in a heavily pretreated patient treated with a large single dose of 200 mg irinotecan bead infusion. From a technique standpoint, most metastatic colorectal cancers do not meet the criteria of hypervascularity based on imaging assessment; however, given that nearly 95–100% of colorectal cancer metastases derive their blood supply from the hepatic arterial system, lobar infusion has been demonstrated in prior studies to still lead to predominant bead implantation into the malignancy and avoid exposure to non-tumor-bearing hepatic parenchyma.[25,26] These results confirm the lack of biliary toxicity with DEBIRI; the only biliary toxic event that was demonstrated was based on a technical catheter placement in which aberrant bead infusion occurred when beads refluxed into the cystic artery during a right hepatic artery treatment, thus leading to chemical cholecystitis that was treated with IV antibiotics. We have not seen any of the long-term biliary toxicity that has been associated with hepatic arterial infusion pumps, which is obviously encouraging for the long-term and repeated treatments that these patients require.

In conclusion, the drug-eluting bead, irinotecan (DEBIRI) is an active and well-tolerated therapy in colorectal cancer patients with liver-dominant unresectable liver metastasis after failure of FOLFOX, FOLFIRI, and other aggressive chemotherapeutic agents. The percutaneous therapy and favorable toxicity profile make this treatment a potential option specifically in the metastatic colorectal cancer patient with hepatic-dominant disease. This promising modality approach should be confirmed in larger populations of chemoresistant patients in conjunction with systemic chemotherapy to optimally demonstrate the timing and use of this novel device.

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