Early Experience with 70-150 μm Irinotecan Drug-eluting Beads (M1-DEBIRI) for the Treatment of Unresectable Hepatic Colorectal Metastases

OLAGUOKE AKINWANDE[1], CHARLES SCOGGINS[2] and ROBERT C.G. MARTIN[2]

[1]*Department of Radiology, Division of Interventional Radiology, The Johns Hopkins Hospital, Baltimore, MD, U.S.A;*
[2]*Department of Surgery, Division of Surgical Oncology, University of Louisville, James Graham Brown Cancer Center, Louisville, KY, U.S.A.*

Abstract. *Aim: To report our early experience on the feasibility and safety of 70-150 μm drug-eluting beads loaded with irinotecan (M1-DEBIRI) for treating unresectable hepatic colorectal metastases. Patients and Methods: An Institutional Review Board-approved, prospectively maintained, multi-institutional registry was evaluated from 2/2009 to 8/2013. Fifteen consecutive patients presenting with liver-dominant metastatic colorectal cancer were treated with M1-DEBIRI. Kaplan–Meier statistics was used to evaluate hepatic progression-free-survival and overall survival. Results: Fifteen patients underwent 32 DEBIRI treatments. The mean prescribed dose was 100 mg of irinotecan (range=100-200 mg). In 75% of treatments (n=24), 100% of the prescribed dose was delivered before complete stasis. In 97% of treatments (n=31), at least 50% (median 100 mg, range 25-150 mg) of the prescribed dose was delivered. There was grade 2 abdominal pain after one treatment (3%). In another patient, increased total bilirubin (1.1 to 3.1 mg/dl) was seen after one treatment. There was 42% reduction in median carcinoembryonic antigen level and 33% (5/15 patients) with Response Evaluation Criteria in Solid Tumors (RECIST) objective response (complete and partial). Modified RECIST and European Association for the study of the Liver (EASL) objective response rates were both 73% (11/15 patients). The disease control rate was 93% (14/15 patients). Hepatic progression-free-survival and overall survival were 8 and 13 months respectively. Disease in one patient was down-staged to resection (6%). Conclusion: M1-DEBIRI appears to be safe and feasible in the treatment of metastatic colorectal cancer. Smaller beads also provide efficient irinotecan dose delivery. Larger studies are needed to validate these findings.*

Correspondence to: Robert C.G. Martin, MD, Ph.D., Professor of Surgery, Division of Surgical Oncology, Department of Surgery, University of Louisville School of Medicine, Louisville, KY 40292, U.S.A. Tel: +1 5026293355, Fax: +1 5026293030, e-mail: robert.martin@louisville.edu

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The standard of management for the treatment of unresectable metastastic colorectal cancer (mCRC) is systemic chemotherapy (*i.e.* folinic acid, 5-fluorouracil, oxaliplatin – FOLFOX). Unfortunately, patients eventually fail therapy and run out of treatment options. Locoregional therapy (radioembolization and chemoembolization) can be beneficial for the treatment of liver dominant metastatic disease from colorectal cancer because liver disease typically dictates the prognosis (1-6). A recent randomized control trial reported that combination of first-line chemotherapy and radioembolization (yttrium-90) can improve liver tumor response and hepatic progression-free survival over chemotherapy alone (7). Studies on the use of chemo-embolization for mCRC have also shown promise in recent years. In particular, chemoembolization using drug-eluting beads (DEBs) loaded with irinotecan (DEBIRI) may provide palliation and disease control patients with mCRC after failure of systemic chemotherapy (8-12). A recently published randomized control study showed that DEBIRI in combination with first-line systemic chemotherapy (FOLFOX) can be particularly effective in down-staging non-resectable cases to resection (13).

DEBIRI, when delivered through the hepatic artery, provides continuous release of irinotecan while embolizing the vessels supplying the metastatic neoplastic tissue (*i.e.* colorectal cancer metastases) (14). Although DEBIRI has been determined to be safe and efficacious, the technical aspects of the procedure, such as the size of the DEBs, are still debated. DEBs comes in various sizes, commonly 100-

300 μm, 300-500 μm and 500-700 μm beads. Recently, 70-150 μm beads (LC/DC M1 Bead; Biocompatibles UK Ltd, Farnham, Surrey, UK) have been introduced into the market which can be loaded with doxorubicin (M1-DEBDOX) or irinotecan (M1-DEBIRI).

The premise for the use of smaller beads is that smaller beads penetrate deeper (compared to larger beads) into the tumor bed, which may improve the therapeutic index of the loaded drug. In addition, deeper penetration may also delay early stasis, resulting in the ability to deliver a higher proportion of the bead–drug complex (15, 16). Finally, smaller beads can provide more homogenous drug delivery compared to larger beads (14), potentially leading to more uniform tumor response. Comparative studies between bead sizes are limited, comprising a few non-randomized studies. Within limitations, these studies suggest there are fewer adverse events with the use of smaller beads (17, 18). Recent single-arm human studies have demonstrated that the use of 70-150 μm beads (M1-DEBDOX) for chemoembolization is safe (19, 20); however, those studies were performed on the hepatocellular cancer population or a heterogeneous (pooled) population.

To our best knowledge, no study has reported specifically on the feasibility and safety of M1-DEBIRI for the mCRC population. Thus, the aim of this study was to report our early experience on the feasibility and safety of 70-150 μm beads loaded with irinotecan (M1-DEBIRI) for the treatment of unresectable mCRC.

Patients and Methods

Patient entry criteria. An Institutional Review Board-approved, prospectively maintained, multi-institutional treatment registry was retrospectively evaluated from 2/2009 to 8/2013. Our database was assessed retrospectively. Fifteen consecutive patients presenting with liver-dominant (defined as >50% tumor burden confined to the liver) mCRC were treated with M1-DEBIRI. This study was performed in compliance with the protocol and principles laid down in the Declaration of Helsinki. Informed consent was obtained prior to screening and evaluation.

Patients included were at least 18 years old, with radiological or histological proof of disease metastatic to the liver. Patients had to be able to give informed consent. Life expectancy >3 months, Eastern Cooperative Oncology Group (ECOG) performance status score <2, and without pregnancy (with continuous use of contraceptives in premenopausal women) were also inclusion criteria. Exclusion from intra-arterial therapy included contraindication to angiography, severe cardiac comorbidities, significant extrahepatic disease with imminent life-threatening outcome, >75% hepatic parenchymal involvement and severe liver dysfunction. Patients with prior intra-arterial locoregional treatments were excluded.

Pre-therapy evaluation of patients with metastatic disease included a three-phase abdominopelvic computed tomography (CT) <1 month prior to treatment. All CT scans were performed with and without contrast with image acquisitions in the arterial, portal-venous and delayed phases. This was to establish a pre-treatment baseline and to confirm liver dominant disease.

DEBIRI technique. Our technique for hepatic arterial DEBIRI administration has been reported previously (21, 22). In brief, the procedure consisted of a celiac and superior mesenteric angiogram from a femoral arterial approach. Liver tumor burden was important in determining the number of treatments required and the appropriate placement of the delivery catheter. The treatment consisted of a minimum of two dosing schedules of at least 100 to 200 mg of irinotecan loaded in one-two LC/DC bead vials depending on the tumor size and extent. The dose delivered was defined as the single amount of irinotecan that was delivered at one DEBIRI administration. If stasis was reached prior to administration of the prescribed dose, that was our endpoint. If stasis was not reached after delivery of the prescribed dose, then the angiographic endpoints were stratified. Angiographic endpoints used were classified according to increasing degree of stasis: No stasis, partial stasis, near stasis and complete stasis. This scale was originally adapted from the Subjective Angiographic Chemoembolization Endpoint classification scheme by Lewandowski *et al*. (23), as modified for DEBIRI administration by Akinwande *et al*. (16). Treatment was performed in a lobar or segmental fashion, based on the distribution and extent of the disease.

Peri-procedural medications, including antibiotic prophylaxis, intra-arterial lidocaine/morphine, corticosteroids, pain medications and proton pump inhibitors, were all administered at the discretion of the physician.

Assessment and follow-up. The primary outcome measures were feasibility and safety. Feasibility included the technical success (ability to deliver therapy in the culprit hepatic artery) and the proportion of the prescribed dose that was delivered. Our intent was to deliver at least 50% of the prescribed dose before complete stasis. Regarding safety, patients were followed-up for treatment-related adverse events immediately after treatment and for 90 days thereafter. 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 (24). Given the lack of consensus as to the optimal objective response assessment method, image-based tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST) and European Association for the Study of the Liver (EASL) criteria (25-27). Standard follow-up protocol included tri-phase CT scan of the liver (with and without contrast) at 3 months post-treatment. Biochemical response was monitored using carcinoembryonic antigen (CEA).

Secondary outcome measures were hepatic-specific progression-free survival (HPFS) and overall survival (OS). HPFS was defined as the time between the start of DEBIRI treatment and image-based disease progression in the liver or death from any cause. OS was defined as the time between the start of DEBIRI treatment and death from any cause.

All statistics were calculated using JMP software (SAS Institute Inc., Cary, NC, USA). Kaplan–Meier statistics was performed for survival analysis.

Results

Patients' characteristics. Fifteen patients met the inclusion criteria mentioned above (Table I). The median age was 63.5 years, and patients had a good performance status (median Karnofsky score, 100%; ECOG 0). Overall, seven out of 15 patients had had prior surgery or ablation. All patients had

Table I. *Clinical demographic and prior chemotherapy data in patients treated with M1-DEBIRI.*

Characteristic	M1-DEBIRI (n=15)
Median age, (range), years	63.5 (44-75)
Gender, n (%)	
Male	9 (60%)
Female	6 (40%)
Median Karnofsky performance score (range)	100% (90-100%)
Prior liver surgery or ablation, n (%)	7 (47%)
Hepatic resection, n	3
Ablation, n	1
Resection and ablation, n	3
Extent of liver involvement, n (%)	
<25%	8 (53%)
26-50%	6 (40%)
51-75%	0 (0%)
>75%	0 (0%)
Not recorded	1 (7%)
Number of liver lesions, n (%)	
Patients with countable lesions, n (%)	14 (93%)
Median number of lesions, range	2 (1-15)
Patients with innumerable lesions, n (%)	1 (7%)
Median total size of target, cm (range),	5.7 (3-9.8)
Extrahepatic metastasis, n (%)	5 (33%)
Median no. of lines of prior chemotherapy (range)	1 (0-2)
Prior systemic chemotherapy, n (%)	
None	4 (27%)
1	4 (27%)
2	7 (47%)
Concurrent chemotherapy, n (%)	8 (53%)
FOLFOX-Bev, n	1
FOLFIRI-Bev, n	2
FOLFOX, n	1
Capecitabine, n	1
XELIRI, n	1
Cetuximab, n	1
Capecitabine, n	1
Prior locoregional therapy, n (%)	0 (0%)

M1-DEBIRI: 70-150 μm Drug-eluting beads loaded with irinotecan; FOLFOX: folinic acid + flourouracil + oxaliplatin; FOLFIRI: folinic acid +flourouracil + irinotecan; BEV: bevacuzimab; XELIRI: capecitabine (Xeloda) + irinotecan.

Table II. *Technical outcomes of therapy with 70-150 μm drug-eluting beads loaded with irinotecan (M1-DEBIRI).*

	M1-DEBIRI
*Total number of treatments	32
Number of treatments per patient	2 (1-3)
Median dose prescribed (range)	100 mg (100-200 mg)
Median dose delivered (range)	100 mg (25-150 mg)
Angiographic endpoint, n (%)	
No stasis	1 (3%)
Partial stasis	15 (47%)
Near complete stasis	8 (25%)
Complete stasis	8 (25%)
Total hepatic dose exposure	200 mg (85-300 mg)
Lobar treatment, n (%)	21 (66%)
Segmental treatment, n (%)	11 (34%)

*In two treatments (for one patient) the data were not recorded.

Table III. *M1-DEBIRI Tumor response to therapy with 70-150 μm drug-eluting beads loaded with irinotecan (M1-DEBIRI) per patient (N=15) by Response Evaluation Criteria in Solid Tumors (RECIST), modified (m)RECIST, and European Association for the Study of the Liver (EASL)*

	Number (%)		
Outcome	RECIST	mRECIST	EASL
Complete response	0 (0%)	1 (7%)	1 (7%)
Partial response	5 (33%)	10 (67%)	10 (67%)
Stable disease	9 (60%)	3 (20%)	3 (20%)
Progressive disease	0 (0%)	0 (0%)	0 (0%)
Death from disease	0 (0%)	0 (0%)	0 (0%)
Death from other cause*	1 (7%)	1 (7%)	1 (7%)

*Patient died from chemotherapy toxicity.

less than 50% of the liver parenchyma involved with neoplastic disease; five had extrahepatic disease. Eleven patients (73%) had failed one or more lines of systemic chemotherapy and eight patients (53%) were on concurrent chemotherapy.

Feasibility of treatment. There were 32 M1-DEBIRI treatments in 15 patients (Table II). Technical success was achieved in all patients. The mean prescribed dose was 100 mg (100-200 mg). In 75% of treatments (n=24), we were able to deliver 100% of the prescribed dose before complete stasis. In 97% of treatments (n=31), we were able to deliver at least 50% of the prescribed dose before complete stasis. The median delivered dose in patients overall was the same as the prescribed dose (100 mg; range=25-150 mg). The majority of treatments were lobar treatments (66%) and the remaining were segmental treatments (34%). The median cumulative overall total hepatic drug exposure was 200 mg (85-300 mg) in a median of two treatments per patient.

Safety and efficacy of treatment. Grade 2 abdominal pain was experienced after one treatment (3%). Elevated bilirubin level (from 1.1 to 3.1 mg/dl) was seen after another treatment (3%) in a different patient. There were no high-grade adverse events. The median hospital stay was under 23 h, with the longest hospital stay being 3 days. There was a 42% reduction in median CEA after embolization (from 77 to 45 ng/ml). There was also a 33% objective response [complete response

(CR): 0%, partial response (PR): 33%] according to RECIST and 73% objective response according to mRECIST (CR: 7%, PR: 67%) and EASL (CR: 7%, PR: 67%) (Table III). The disease control rate, which comprises responders and those with stable disease, was 93% according to all three response criteria. One patient was down-staged to resection (6%). HPFS and OS were 8 and 13 months, respectively.

Discussion

In treating liver cancer with chemoembolization, the ideal size for DEBs has always been up for debate, with the most popular sizes being 100-300 μm, 300-500 μm and 500-700 μm beads. A few comparative studies have reported that smaller beads may be less toxic than larger beads in the treatment of hepatocellular carcinoma (HCC) (17, 18), as a result, smaller and smaller beads have been endorsed (28-31). One preclinical study showed that larger particles (300-500 μm) were distributed at a greater distance from the tumor compared to smaller beads (100-300 μm) (15). The authors reported that small beads were more likely to penetrate the target lesion compared to larger beads. Based on their findings, an inference can be made that 70-150 μm (M1) beads will penetrate even deeper. A subsequent preclinical study by Dreher *et al*. (14) confirmed that 70-150 μm beads did indeed not only travel further into the target tissue, but also created better spatial resolution and greater/more homogenous drug administration. The increased penetration and improved distribution of smaller beads are expected to provide better delivery of the chemotherapeutic agent. Interestingly, the lower drug-to-bead ratio found with smaller beads did not compromise drug pharmacokinetics (14).

Given the promising characteristics of smaller beads, more and more Institutions have adopted smaller beads for locoregional treatment (16, 20, 32). Spreafico *et al*. reported that the use of 70-150 μm beads (M1-DEBDOX) in HCC was well tolerated, with a 2% rate of grade 3-4 adverse events and 77.7% objective response rate (19). Odisio *et al*. reported on the use of M1-DEBDOX/M1-DEBIRI in a mixed treatment population [HCC and metastatic disease (melanoma, squamous cell carcinoma, colorectal cancer, leiomyosarcoma)] (20). They reported a high rate of symptomatic all-grade adverse events (67.4%), but a low rate of severe adverse events (2%). Another study reported on the use of even smaller beads (30-60 μm beads loaded with doxorubicin; HepaSphere, Merit) for the treatment of HCC. This study reported a 68.9% objective tumor response rate with acceptable safety profile.

Although there is growing literature supporting the safety of small beads for the treatment of HCC, there are no data specifically reporting on the feasibility and safety of M1-DEBIRI. We report a 6% adverse event rate (in 32 treatments) using M1-DEBIRI for the treatment of non-resectable mCRC, without high-grade adverse events. M1-DEBIRI appears to be safe for use in a pretreated patient population and for those on concurrent chemotherapy. Given that the median hospital stay was less than 23 hours in this study, this procedure can potentially be performed on an outpatient basis or with a short inpatient observation period. The dogma of the increased risk of liver abscess/infarction when embolizing with smaller particles is not demonstrated in this small-scale study and also not supported by any of the previous studies.

Smaller beads may provide delayed angiographic stasis, allowing the ability to deliver a higher fraction of the prescribed dose (16, 18). Early stasis is linked to proximal deposition of particles, which is minimized by the deeper penetration of smaller beads. We were able to deliver the entire prescribed dose of DEBIRI in 75% of treatments, and 50% of the prescribed dose in 97% of treatments. These data are important because efficient dose delivery may translate to better treatment efficacy.

There was a 42% reduction of median CEA, 33% rate of RECIST response and 73% mRECIST/EASL response after treatment with M1-DEBIRI. The disease control rate was remarkably high at 93%. We were also able to downstage one patient (6%) to curative therapy. The constellation of findings show that M1-DEBIRI is effective in the treatment of unresectable mCRC. However, the relative effectiveness compared to larger beads cannot be extrapolated based on our findings.

The limitations of this study are many. Firstly, the study population was small therefore its power is limited. However, this study could provide the building blocks and point of reference for other future studies on M1-DEBIRI. SecondIy, given the design of the study, time-dependent assessment bias and selection bias are inevitable. Thirdly, our adverse event rate is lower than that of many of the published studies using 100-300 μm DEBIRI beads. While this may potentially be attributed to an improved safety profile, we cannot make that claim given the size of the study population. It is quite possible for the rate of adverse events to increase with a larger sample size. Fourthly, most of the patients in this study had small-volume disease and a sizable proportion (47%) had had previous surgery. Therefore, it is possible that our study may not be truly representative of the typical treatment population. Fifthly, the use of peri-procedural medications such as intra-arterial lidocaine and proton pump inhibitors may have confounded our safety observations. Lastly, this study probably does not have enough power to make a meaningful conclusion about the observed OS and HPFS.

In conclusion, this study shows that M1-DEBIRI is feasible and safe for the treatment of non-resectable hepatic mCRC. Smaller beads also provide efficient irinotecan dose delivery. Further studies are, however, needed to confirm these findings.

Conflicts of Interest

All Authors declare that they have no conflict of interest.

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