Efficacy and safety of transarterial chemoembolization with 70- to 150- μ m drug-eluting beads alone or in combination with 100- to 300- μ m drug-eluting beads

Marco Cura, MD, FSIR^a, and Evans Heithaus, MD^b

^aDepartment of Radiology, Baylor University Medical Center and Texas A&M Health Science Center, Dallas, Texas; ^bDepartment of Radiology, University of Florida, Gainesville, Florida

ABSTRACT

To evaluate the safety and efficacy of transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma, a retrospective analysis of patients who underwent TACE utilizing up to one vial of LC BeadM1 (70–150 μ m) embolics with doxorubicin was performed. If tumor devascularization was not achieved, up to one additional vial of LC Bead (100–300 μ m) embolics with doxorubicin was subsequently administered. Ninety-four sessions of TACE were completed among 48 patients. After a mean follow-up of 182 days, complete response was achieved in 10 patients (21%), partial response in 19 (40%), stable disease in 8 (17%), and progressive disease in 10 (21%). Disease control was achieved in 79% of patients: 90% of patients treated with 70- to 150- μ m embolics alone vs. 70% of patients treated with both sizes of embolics ($P=0.47$). Pathologic examination revealed complete necrosis in 5 of 10 tumors in eight transplants. Overall survival at 3, 12, and 24 months was 100%, 94%, and 94%, respectively. The median progression-free survival was 282 days. In conclusion, drug-eluting bead TACE with 70- to 150- μ m embolics alone or in combination with 100- to 300- μ m embolics is safe and demonstrates good disease control, particularly with small, solitary tumors.

KEYWORDS: Chemoembolization; drug-eluting embolic; hepatocellular carcinoma; liver transplantation; mRECIST

Treatment for hepatocellular carcinoma (HCC) has evolved, improving survival and bridging patients to transplantation. The use of transarterial chemoembolization (TACE) has aided in achieving disease control, and the incorporation of drug-eluting beads (DEBs) into embolization regimens has proven to be better tolerated with fewer adverse events compared to conventional TACE.^{1,2} As the use of DEB has increased, smaller beads have been employed.³ Animal models have shown a more uniform, deep penetration with 70- to 150- μ m beads when compared to 100- to 300- μ m beads.⁴ Only a few studies utilizing the new 70- to 150- μ m beads have been published, with limited follow-up.^{5–7} To further evaluate the efficacy and safety of DEB-TACE with the new 70- to 150- μ m beads, we conducted a retrospective review of patients at our institution undergoing TACE

with 70- to 150- μ m DEBs alone or in combination with 100- to 300- μ m DEBs.

METHODS

Institutional review board approval was obtained, and consent was waived. Forty-eight consecutive patients were retrospectively examined. Patients who underwent DEB-TACE with 70- to 150- μ m beads for HCC were included. Chart review included examination of pretreatment and posttreatment imaging. Of the 48 patients reviewed, 47 had preoperative magnetic resonance imaging (MRI) and one had preoperative multiphase computed tomography (CT) due to the presence of a pacemaker. Tumor characteristics were recorded, including tumor size and number. Additionally, Barcelona Clinic Liver Cancer (BCLC) stage, age, gender, and transplantation status were recorded. Due

Corresponding author: Marco Cura, MD, FSIR, Department of Radiology, Baylor University Medical Center and Texas A&M Health Science Center, 3500 Gaston Avenue, Dallas, TX 75246 (e-mail: Marco.Cura@BSWHealth.org)

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to tumor size and vascularity, some patients underwent embolization with one vial of 70- to 150- μ m beads followed by up to one vial of 100- to 300- μ m beads.

All patients were evaluated at a multidisciplinary tumor board that included representatives from the fields of medical oncology, surgical oncology, radiation oncology, and interventional radiology. Patients with residual tumor or new tumor were continually re-evaluated by a multidisciplinary team prior to retreatment. All patients were evaluated for complications, including liver failure, liver abscess, surgical cholecystitis, biloma, dissection, and death within 30 days of the procedure.

Each vial of beads was loaded with either 50 or 75 mg doxorubicin by the pharmacy utilizing guidelines from the manufacturer. The doxorubicin dose was chosen by the interventional radiologist and medical oncologist preoperatively depending on tumor burden and hepatic reserve. Patients were given preoperative intravenous hydration and intravenous medications, including 3 g amoxicillin/sulbactam, 10 mg dexamethasone, 4 mg ondansetron, and 50 mg diphenhydramine. Patients were also given procedural sedation (fentanyl and lorazepam). Chemoembolization was carried out utilizing a 5-F base catheter and a coaxial microcatheter (2.8-F Rengade HI-FLO, Boston Scientific, Marlborough, MA, or 2.4-F Progreate, Terumo Europe, Leuven, Belgium) in a segmental or subsegmental fashion. Cone-beam CT was utilized in some cases to ensure superior target embolization.

The endpoint of embolization was slow flow just short of stasis. All patients were first treated with the 70- to 150- μ m beads, receiving up to one vial per TACE session. If adequate tumor devascularization was not achieved with one vial of 70- to 150- μ m beads, then up to one additional vial of 100- to 300- μ m beads was administered. The maximum dose of beads to the patient was two vials total in one session of TACE (one vial of 70- to 150- μ m beads and one vial of 100- to 300- μ m beads). Patients were subsequently monitored overnight following the procedure.

Patients were evaluated with pre- and posttreatment MRI for diagnosis of HCC and grading of treatment response, respectively. Multiphase CT was used in one patient who could not undergo MRI due to a pacemaker. Tumor response was categorized as complete response, partial response, stable disease, or progressive disease based on modified response evaluation criteria in solid tumors (mRECIST).⁸ Disease control was defined as complete response + partial response + stable disease. In patients who underwent liver transplantation immediately following TACE, follow-up imaging was not available. Pathological examination of the explanted livers was utilized in these patients to determine tumor response. Tumors with total necrosis were classified as complete response and those with >50% necrosis was categorized as partial response. Patients whose tumors demonstrated minimal or no necrosis were categorized as stable disease. If new

tumors were discovered at follow-up or the tumor had grown in size, the patient was classified as progressive disease.

RESULTS

Ninety-four sessions of TACE were completed for 48 patients (median age, 63; male, 75%; hepatitis C virus, 52%; BCLC stage A, 65%; stage B, 31%; large tumor [≥ 3 cm], 42%; multifocal tumor, 48%) (Table 1). There were eight transplants with a total of 10 lesions, and pathological examination of the explanted livers was available for all 8 patients.

Table 1. Demographic and tumor characteristics of 48 patients undergoing TACE for hepatocellular carcinoma

Patient characteristics	Mean value (range or percentage)	70- to 150- μ m DEBs	70- to 150- μ m plus 100- to 300- μ m DEBs
Age (years)	62 (31–81)	50 (41–69)	65 (31–81)
Sex			
Male	36 (75%)	15 (71%)	21 (78%)
Female	12 (25%)	6 (29%)	6 (22%)
BCLC stage			
A	31 (65%)	15 (70%)	16 (59%)
B	15 (31%)	5 (25%)	10 (37%)
C	2 (4%)	1 (5%)	1 (4%)
Childs-Pugh			
A	27 (56%)	10 (47%)	17 (62%)
B	19 (39%)	9 (42%)	10 (37%)
C	2 (4%)	2 (10%)	0
Liver disease etiology			
Ethanol	6 (12%)	4 (19%)	2 (7%)
HBV	2 (4%)	1 (5%)	1 (4%)
HCV	25 (52%)	12 (57%)	13 (48%)
Other	15 (31%)	4 (19%)	11 (41%)
Tumor characteristics			
Small (<3 cm)	28 (58%)	15 (71%)	13 (48%)
Large (≥ 3 cm)	20 (42%)	6 (29%)	14 (52%)
Focal disease (1 tumor)	25 (52%)	12 (57%)	13 (48%)
Multifocal disease	23 (48%)	9 (43%)	14 (52%)
TACE (mean no.)			
Small	1.9	1.1	2.7
Large	1.8	1.3	2.2
Focal	1.6	1.2	2
Multifocal	2	1	2.9

TACE indicates transarterial chemoembolization; DEBs, drug-eluting beads; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus.

One patient was lost to follow-up after the first session of TACE. Thirty patients underwent more than one session of TACE, with an overall average of 1.9 TACE sessions per patient. Both bead sizes were used in 27 of the 48 patients. In these patients, a combination of both beads was used in 13 of the 74 TACE sessions in this patient cohort. The other 21 patients received only the 70- to 150- μ m beads during 20 sessions of TACE.

Tumor response by mRECIST is outlined in [Table 2](#). Median follow-up was 182 days (range, 35–940 days).

Tumor response	Number (%)	70- to 150- μ m DEBs	70- to 150- μ m plus 100- to 300- μ m DEBs
Complete response	10 (21%)	5 (25%)	5 (18%)
Partial response	19 (40%)	8 (40%)	11 (41%)
Stable disease	8 (17%)	5 (25%)	3 (11%)
Progressive disease	10 (21%)	2 (10%)	8 (30%)
Tumor response (CR + PR)	29 (62%)	13 (65%)	16 (59%)
No response (PD + SD)	18 (38%)	7 (35%)	11 (41%)
Disease control (CR + PR + SD)	37 (79%)	18 (90%)	19 (70%)
Small tumors	26/27 (96%)	14/14 (100%)	12/13 (92%)
Large tumors	11/20 (55%)	4/6 (66%)	7/14 (50%)
Focal disease	23/24 (96%)	11/12 (92%)	12/12 (100%)
Multifocal disease	14/23 (61%)	7/8 (88%)	7/15 (46%)

TACE indicates transarterial chemoembolization; DEBs, drug-eluting beads; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

Greater disease control was achieved in solitary tumors than in multifocal disease (96% vs 61%; $P = 0.04$). Similarly, disease control was greater in small tumors than in large tumors (96% vs 55%; $P = 0.0009$). Seventeen of the 48 patients (35%) had small, solitary tumors.

Pathologic examination was available for 10 tumors in eight transplant patients. Complete tumor necrosis was seen in 5 of the 10 tumors. An additional four lesions showed partial necrosis. Overall survival at 3, 6, and 12 months was 100%, 94%, and 94%, respectively. Median progression-free survival was 282 days. Median time to progression was 189 days for large tumors and 254 days for multifocal tumors.

Adverse events are outlined in [Table 3](#). Most patients (90% of the 94 TACE sessions) were discharged within 24 hours of the procedure. Nine sessions of TACE (10%) required hospitalization for >24 hours, but no hospital stay exceeded 48 hours. Additionally, there were no readmissions. In 10 sessions of TACE, 100% of each vial of the 70- to 150- μ m and 100- to 300- μ m beads was used. Of these 10 sessions, two resulted in hospitalization for >24 hours due to abdominal pain in two separate patients. Both patients were discharged within 48 hours. One patient experienced proper hepatic artery dissection prior to chemoembolization. The dissection was promptly treated with stenting, and embolization was carried out following stent placement. A short course of aspirin and clopidogrel was prescribed, and the patient underwent subsequent sessions of TACE therapy without further complication. There were two patient deaths, neither of which were related to the procedure or occurred within 30 days of TACE. No postprocedural hepatic abscess or biliary injury was encountered.

DISCUSSION

DEB-TACE with the new 70- to 150- μ m beads serves as a safe and effective treatment modality for patients with

Adverse event	Number (%)	70- to 150- μ m DEBs	70- to 150- μ m plus 100- to 300- μ m DEBs
Discharged within 24 hours	85 (90%)	31 (97%)	54 (87%)
Discharged within 48 hours	9 (10%)	1 (3%)	8 (13%)
Hospital stay >48 hours	0	0	0
Abscess (intact sphincter of Oddi)	0	0	0
Abscess (biliary enteric anastomosis)	0	0	0
Surgical cholecystitis	0	0	0
Biloma requiring drainage	0	0	0
Iatrogenic dissection preventing treatment	0 ^a	0	0
Death within 30 days	0	0	0

TACE indicates transarterial chemoembolization; DEBs, drug-eluting beads.
^aOne dissection; embolization was carried out following stenting.

intermediate-stage HCC. In our experience, the smaller beads were well tolerated with no serious adverse events. Additionally, disease control was achieved in a majority of patients, with eight patients being bridged to transplant. Treatment of advanced-stage (BCLC stage C) patients has been demonstrated to be safe,⁹ but larger tumors tend to need more than one session of TACE and tend to recur more frequently.^{10,11} In our experience, greater disease control was achieved in smaller tumors compared to large tumors and in focal disease compared to multifocal disease. Additionally, pathologic analysis showed total necrosis in half of the treated lesions, which appears to be in line with previous studies.¹²

Limited toxicity with few adverse events likely reflects the use of segmental and subsegmental embolization techniques. The judicious use of an embolic agent and the endpoint of slow flow or near stasis may also decrease toxicity. The recorded toxicity is similar to previously published studies.^{5,6} A study by Deipolyi and colleagues also reported similar rates of adverse events and length of hospital stay but a greater number of delayed hepatobiliary events, potentially accounted for by the difference in chemoembolization techniques and amount of embolic material used.

The current study has several limitations. First, the study did not provide a direct comparison of 70- to 150- μ m beads with other bead sizes; rather, the 100- to 300- μ m beads were used in conjunction with 70- to 150- μ m beads (13 of 94 sessions of TACE). The retrospective nature of this study did not allow for patient randomization and head-to-head comparison of outcomes with different bead sizes, and patient outcomes can be attributed to both bead sizes.

Second, no specific follow-up laboratory evaluation was performed unless repeat chemoembolization was required, limiting the consistent postembolization evaluation of liver function and changes in bilirubin levels. Third, eight patients in our study underwent liver transplantation following chemoembolization without additional follow-up imaging. In these patients, tumor response was determined by degree of necrosis at the time of resection.

In conclusion, the use of 70- to 150- μ m beads for DEB-TACE was well tolerated in our patient population, with adverse event rates comparable to those reported in previous studies. These beads, when used alone or in combination with 100- to 300- μ m DEBs, result in good disease control, particularly in small, solitary tumors.

ORCID

Evans Heithaus <http://orcid.org/0000-0001-7949-0150>

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