Safety and Efficacy of Drug-eluting Bead Chemoembolization for Hepatocellular Carcinoma: Comparison of Small-versus Medium-size Particles

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ABSTRACT

Purpose: To compare safety and imaging response with 100–300 μm and 300–500 μm doxorubicin drug-eluting bead (DEBs) to determine optimal particle size for chemoembolization of hepatocellular carcinoma (HCC).

Materials and Methods: DEB chemoembolization using 100–300 μm (n = 39) or 300–500 μm (n = 22) LC beads loaded with 50 mg of doxorubicin was performed in 61 patients with HCC. Patient age, sex, etiology of liver disease, degree of underlying liver disease, tumor burden, and performance status were similar between the groups. All treatments were performed in a single session and represented the patient's first treatment. Toxicities and imaging response in a single index tumor were analyzed using World Health Organization (WHO) and European Association for the Study of the Liver (EASL) criteria.

Results: There was a significantly lower incidence of postembolization syndrome and fatigue after treatment in the 100–300 μm group (8% and 36%) versus the 300–500 μm group (40% and 70%) (100–300 μm group, $P = .011$; 300–500 μm group, $P = .025$). Mean change in tumor size was similar between the two groups based on WHO and EASL criteria and similar rates of objective response, but there was a trend toward a higher incidence of EASL complete response with 100–300 μm beads versus 300–500 μm beads (59% vs 36%; $P = .114$).

Conclusions: In DEB chemoembolization for treatment of HCC, 100–300 μm doxorubicin DEBs are favored over 300–500 μm doxorubicin DEBs because of lower rates of toxicity after treatment and a trend toward more complete imaging response at initial follow-up.

ABBREVIATIONS

CR = complete response, DEB = drug-eluting bead, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, PR = partial response, WHO = World Health Organization

Hepatocellular carcinoma (HCC) is diagnosed in > 0.5 million people worldwide, including approximately 20,000 new cases in the United States annually (1). Catheter-directed therapy in the form of transarterial chemoembolization has become the standard of care for well-compensated patients with HCC not amenable to resection or ablative techniques (2). In a multicenter, prospective comparison of conventional chemoembolization using ethiodized oil and doxorubicin versus chemoembolization with drug-eluting beads (DEBs), response rates were similar (3). Since then, chemoembolization with doxorubicin DEBs has become more common (4).

The published literature has described the use of 100–300 μm and 300–500 μm sized particles when performing embolization with DEBs (3,5,6). Despite the

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None of the authors have identified a conflict of interest.

From the SIR 2012 Annual Meeting.

J Vasc Interv Radiol 2013; 24:301–306

http://dx.doi.org/10.1016/j.jvir.2012.11.023

recommendation that small particles be used (7), comparative data between particle sizes are limited to a single analysis of pooled registry data (8). Although the study concluded that the use of smaller particle sizes resulted in fewer adverse events, the inherent limitation of strong selection bias limited the usefulness of its conclusions. The purpose of this study was to compare the safety and efficacy of DEB chemoembolization between 100–300 μm and 300–500 μm particles in patients with HCC.

MATERIALS AND METHODS

A retrospective study was conducted at a single institution by querying the hospital's patient information system to identify all patients who underwent DEB chemoembolization and follow-up for HCC between January 1, 2010, and June 30, 2012. These data were collected into a database in compliance with regulations of the Health Insurance Portability and Accountability Act and approved by the hospital's institutional review board.

All patients with a diagnosis of HCC were presented at the institution's multidisciplinary liver tumor board, whose members included physicians from interventional radiology, diagnostic radiology, hepatology, surgical oncology, transplant surgery, medical oncology, and pathology. Patients were considered for transarterial chemoembolization if all of the following criteria were met: (*a*) curative procedure (eg, immediate transplantation, surgical resection, ablation) was not an option, (*b*) Child-Pugh cirrhosis A or B, (*c*) absence of portal vein thrombosis, (*d*) absence of extrahepatic disease, and (*e*) a performance status 0–2 (Eastern Cooperative Oncology Group [ECOG] score). Baseline demographic data were collected, including sex, age, etiology of cirrhosis, stage of cirrhosis, and performance status. Baseline tumor characteristics were tabulated using the following criteria: size and number of tumors, presence or absence of portal vein thrombosis, and Barcelona Clinic Liver Cancer tumor stage.

Transarterial chemoembolization was performed by one of seven board-certified interventional radiologists. Antibiotic prophylaxis (1g of cefazolin and 500mg of metronidazole) was provided, and the procedures were performed under moderate sedation. After diagnostic angiography of the superior mesenteric artery and celiac trunk with a 4-F or 5-F catheter, selective catheterization of the hepatic arteries supplying the tumor was performed with a 2.8-F coaxial microcatheter (Progreat; Terumo Medical Corporation, Somerset, New Jersey, or Renegade HI-FLO; Boston Scientific, Natick, Massachusetts). Superselective arterial catheterization was performed whenever possible. If multiple feeding arteries to a tumor were present, embolization was performed proximally to cover the entire perfused territory. C-arm computed tomography (CT) was performed at the discretion of the radiologist to identify feeding arteries. The degree of selectivity did not differ between the two treatment groups.

Embolization was performed with doxorubicin drug-eluting LC Beads (Biocompatibles, Oxford, Connecticut). Particle size of 100–300 μm versus 300–500 μm was chosen by the interventional radiologist performing the chemoembolization. Preparation of the doxorubicin DEBs was done according to a standardized protocol similar for both sizes of beads. A 50-mg doxorubicin vial was reconstituted with 2 mL of sterile water. The saline from the LC bead vial was removed. The reconstituted doxorubicin solution was directly added to the LC bead vial. The total mixture was diluted with nonionic iodinated contrast material (20–30 mL). After delivery of the particles, angiography was performed. Complete stasis of the feeding artery was avoided to allow for repeat treatment in the future if necessary. Patients were admitted for overnight observation and pain and nausea control. Degree of nausea, pain, and vomiting was recorded by nurses in the hospital who are familiar with the effects of chemoembolization.

Follow-up outpatient clinic visits and imaging (multiphase CT or magnetic resonance [MR] imaging) were scheduled for 1 month after chemoembolization. Telephone follow-up occurred if an actual clinic visit was not logistically possible. Chemoembolization was repeated if follow-up imaging showed persistent enhancement of tumors (ie, incomplete necrosis). Toxicity was assessed at follow-up and retrospectively tabulated according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (9). Baseline and follow-up scans were independently analyzed by two board-certified radiologists with subspecialty in abdominal imaging. Both radiologists were blinded to the treatment arm. The primary index tumor was defined as the largest tumor and was considered the most appropriate target for the first round of therapy. This primary index tumor was assessed to determine response to chemoembolization. Tumor response was interpreted according to both World Health Organization (WHO) sizing criteria and European Association for the Study of the Liver (EASL) criteria (10,11).

Continuous measurements were summarized as mean and median [interquartile range]. Tumor size and enhancement changes from treatment to the initial follow up scan were expressed as percent changes by both the WHO and the EASL criteria. Tumor changes were also classified according to WHO and EASL criteria as complete response (CR), partial response (PR), stable disease, and progressive disease. Incidences of each category were compared between the 100–300 μm and 300–500 μm groups using Fisher exact test. Overall tumor response in each group was summarized as mean percent change, and the responses were compared between groups using the Mann-Whitney U test. Symptoms related to toxicity and biochemical abnormality grades were recorded and compared between the 100–300 μm and 300–500 μm groups using Fisher exact test. All statistical calculations were performed using R 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).