Yttrium-90 Radioembolization as a Salvage Treatment following Chemoembolization for Hepatocellular Carcinoma

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ABSTRACT

Purpose: To determine safety and efficacy of yttrium-90 (^{90}Y) transarterial radioembolization (TARE) in patients who have undergone chemoembolization for hepatocellular carcinoma.

Materials and Methods: A retrospective study identified 40 patients (median age 61 y; range, 44–84 y) who underwent ^{90}Y mapping angiography and had undergone $\geq$ one prior chemoembolizations. There were 4 (10%) patients in Barcelona Clinic Liver Cancer stage A, 7 (17.5%) in stage B, and 29 (72.5%) in stage C; 28 (70%) were Child-Pugh class A and 12 (30%) were class B. Median tumor diameter was 4.2 cm (range, 1–11.6 cm). The most common indications for changing to TARE were tumor progression (35/40; 86%) and development of portal vein thrombus (15/40; 37.5%).

Results: Of 40 patients, 29 (72.5%) underwent TARE; the most common reasons for not undergoing TARE were attenuated hepatic arteries (5/11), high pulmonary shunt (4/11), and poor arterial flow (2/11). Patients who underwent $\leq$ 4 chemoembolizations to the TARE target tended to be more likely to undergo TARE after mapping than patients who had $>$ 4 chemoembolizations ($P = .056$). Most common grade $\geq$ 3 toxicities were fatigue (9/29; 31%) and biochemical alterations (bilirubin [3/29; 10.3%], albumin [4/29; 13.8%], aspartate aminotransferase [5/29; 17.2%]). Of 27 patients treated with TARE with follow-up, responses were 11 (41%) complete response, 5 (19%) partial response, 2 (7%) stable disease, and 9 (33%) progressive disease. Median progression-free survival and overall survival were 90 days and 257 days.

Conclusions: TARE is safe and effective salvage therapy in patients after chemoembolization. In patients who have undergone $>$ 4 chemoembolizations to the ^{90}Y target, feasibility of TARE tends to be decreased.

ABBREVIATIONS

BCLC = Barcelona Clinic Liver Cancer, HCC = hepatocellular carcinoma, TARE = transarterial radioembolization, ^{90}Y = yttrium-90

Transarterial chemoembolization continues to be the most widely accepted therapy for patients with unresectable hepatocellular carcinoma (HCC) who meet appropriate criteria (1,2). Although yttrium-90 (^{90}Y) transarterial radioembolization (TARE) has gained increasing acceptance, it is often reserved for patients with advanced disease (3). Repeat chemoembolization is performed for patients when an optimal response is not initially achieved or in cases with tumor recurrence. However, at some point, a salvage therapy may become necessary if chemoembolization is no longer viable because of tumor progression, portal vein invasion, technical inability to deliver a chemoembolic agent secondary to arterial changes resulting from prior chemoembolization, poor patient tolerance, or progression of underlying liver disease (4,5). Further therapeutic options may be

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limited, with systemic agents showing limited tolerance and benefit (6). In this setting of exhaustion of chemoembolization options, TARE could be considered as a salvage treatment. However, the use of this therapy in the salvage setting has not been evaluated. The purpose of this study was to assess the safety and efficacy of ^{90}Y TARE in patients who previously underwent chemoembolization for HCC.

MATERIALS AND METHODS

Patient Selection

A retrospective study was conducted at a single institution by querying the hospital's patient information system to identify all patients who underwent a ^{90}Y mapping angiogram for HCC from January 2011 through December 2014 and had at least one prior chemoembolization. This study was approved by the hospital's institutional review board, with waiver of informed consent. The initial diagnosis of HCC was based on established criteria (2). Baseline demographic data were collected at the time of the initial mapping angiogram. Data included etiology of cirrhosis, Child-Pugh score, Eastern Cooperative Oncology Group performance status, and Barcelona Clinic Liver Cancer (BCLC) tumor stage. There were 40 candidates for TARE; median age was 61 years (range, 44–84 y); 4 (10%) were BCLC stage A, 7 (17.5%) were stage B, and 29 (72.5%) were stage C; 28 (70%) were Child-Pugh class A, and 12 (30%) were class B. Median tumor diameter was 4.2 cm (range, 1–11.6 cm). Multifocal disease was present in 28 patients (70%). Portal vein thrombosis involving one main portal vein, seven lobar branches, and nine segmental portal vein branches was present in 17 patients (42.5%). Baseline patient characteristics and reasons for changing therapy from chemoembolization to radioembolization are shown in **Table 1**.

Transarterial Chemoembolization

Treatment was based on the conclusion of a multidisciplinary liver tumor board. Patients who had undergone chemoembolization were not considered to be candidates for surgical resection or thermal ablation. All patients had Child-Pugh A or B cirrhosis, Eastern Cooperative Oncology Group performance status of 0–2, and tumors confined to the liver without vascular invasion.

Chemoembolization was performed by one of seven board-certified interventional radiologists with 2–25 years of experience. Superselective arterial catheterization was performed if possible. Chemoembolization was performed either with an oil-based mixture or with drug-eluting embolic agents. Oil-based chemoembolization was performed using a single drug (doxorubicin) or combination of drugs (cisplatin, mitomycin C, doxorubicin) mixed with ethiodized oil. The oil-based mixture was followed by embolization with particles (300–500 μm *tris*-acryl gelatin microspheres [Embosphere; Merit Medical Systems, Inc, South Jordan, Utah]). Drug-eluting embolic chemoembolization was performed with doxorubicin-eluting LC Beads (Biocompatibles, Inc, Oxford, Connecticut). The drug-eluting embolic agents were prepared according to a standardized protocol (7). Embolic particle size (100–300 μm or 300–500 μm) used for chemoembolization was at the discretion of the interventional radiologist. There were 106 prior chemoembolizations in 40 patients; 53 of 106 (37.2%) chemoembolizations used drug-eluting embolic agents, and the remaining chemoembolizations were oil-based. Embolic particle size was 100–300 μm for 36 of 53 (67.9%) chemoembolizations with drug-eluting embolic agents and 300–500 μm for the remaining chemoembolizations. Oil-based chemoembolizations used only doxorubicin, with the exception of cisplatin added to doxorubicin in 10 of 106 (9.4%) chemoembolizations and a triple-drug regimen used in eight of 106 (7.5%) chemoembolizations.

Radioembolization

Radioembolization was performed according to a standardized protocol (8,9). Coil embolization of extrahepatic vessels (eg, gastroduodenal artery, right gastric artery) was performed at the discretion of the interventional radiologist. At the conclusion of the mapping procedure, technetium-99m macroaggregated albumin was injected into the target hepatic artery for estimation of lung shunt fraction.

After mapping angiography, a determination was made regarding whether to proceed with TARE based on angiographic findings (**Fig 1**), lung shunt fraction, and any change in clinical status of the patient between mapping and treatment. Dosimetry calculations were based on perfused liver volume, with an intended dose of 120 Gy to the perfused tissue. Patients who underwent treatment to a single Couinaud segment were treated with a higher dose (10). ^{90}Y glass microspheres (TheraSphere; BTG International, Ottawa, Ontario. Canada) were used in all treated cases.

Follow-up

Follow-up visits and imaging (multiphase computed tomography or magnetic resonance imaging) took place 1 month after the procedure and every 3 months thereafter. Toxicity was assessed at follow-up and tabulated according to Common Terminology Criteria for Adverse Events, version 4.0 (11). Major adverse events were categorized according to Society of Interventional Radiology (SIR) Standards of Practice Committee classification (12). Tumor response on imaging was assessed by measuring the index tumor and categorizing change in tumor size into four categories (complete response, partial response, stable disease,