CLINICAL STUDY

Angiogenic Response following Radioembolization: Results from a Randomized Pilot Study of Yttrium-90 with or without Sorafenib

Robert J. Lewandowski, MD, Jessica M. Andreoli, MD, Ryan Hickey, MD, Joseph R. Kallini, MD, Ahmed Gabr, MD, Talia Baker, MD, Sheetal Kircher, MD, Riad Salem, MD, MBA, and Laura Kulik, MD

ABSTRACT

Purpose: To compare the regulation of serum angiogenic factors in patients with unresectable early hepatocellular carcinoma (HCC) treated with yttrium-90 (^{90}Y) radioembolization alone vs with sorafenib.

Materials and Methods: In a single-center pilot study, 23 patients with unresectable HCC awaiting orthotopic liver transplantation were prospectively randomized to receive radioembolization alone (n = 12) or radioembolization with sorafenib (n = 11). Serum angiogenic markers (angiopoietin-2 [Ang-2], hepatocyte growth factor, interleukin [IL]-6, IL-8, c-reactive protein, platelet-derived growth factor [PDGF], and vascular endothelial growth factor [VEGF]) were assayed at baseline and at 2 and 4 weeks after radioembolization (^{90}Y alone, n = 6; ^{90}Y plus sorafenib, n = 7).

Results: In the ^{90}Y-alone group, all growth factors were elevated above baseline levels at 2 and 4 weeks: VEGF increased 36% vs baseline at 2 weeks and 22% at 4 weeks, and PDGF increased 24% at 2 weeks and 3% at 4 weeks. In the ^{90}Y/sorafenib arm, Ang-2 and PDGF decreased at 2 weeks and the remainder increased. By 4 weeks, only PDGF remained below baseline levels. VEGF increased 49% at 2 weeks and 28% at 4 weeks, and PDGF decreased 31% at 2 weeks and 39% at 4 weeks. Differences were statistically significant for hepatocyte growth factor ($P = .03$) and PDGF ($P = .02$) at 2 weeks and for IL-6 ($P = .05$) at 4 weeks.

Conclusions: Radioembolization is associated with a mild increase in angiogenic markers. The addition of sorafenib blunts PDGF response; other factors such as VEGF remain unaffected. The predominant effect of sorafenib may be through downregulation of PDGF and not VEGF.

ABBREVIATIONS

Ang-2 = angiopoietin-2, HCC = hepatocellular carcinoma, IL = interleukin, OLT = orthotopic liver transplantation, PDGF = platelet-derived growth factor, VEGF = vascular endothelial growth factor, ^{90}Y = yttrium-90

Transcatheter intraarterial chemoembolization has been considered the standard of care for patients with unresectable hepatocellular carcinoma (HCC) based on prospective trials that demonstrated a survival benefit of this therapy versus best supportive care (1,2). However, embolization interrupts tumor blood flow, leading to hypoxia and subsequent induction of angiogenic growth factors (3). Therefore, although chemoembolization is effective at local tumor control, this procedure may initiate a cascade of events leading to increased angiogenesis that could promote disease progression. An increase in vascular endothelial growth factor (VEGF) following chemoembolization has been reported and found to correlate with worse outcomes (4–6).

From the Department of Radiology, Section of Interventional Radiology (R.J.L., J.M.A., R.H., J.R.K., A.G., R.S.), Department of Medicine, Division of Hematology/Oncology (R.J.L., S.K.), Department of Medicine, Division of Hepatology (R.S., L.K.), and Department of Surgery, Division of Transplant Surgery (T.B., R.S.), Northwestern University, 676 N. St. Clair St., Suite 800, Chicago, IL 60611. Received December 5, 2015; final revision received March 25, 2016; accepted March 28, 2016. **Address correspondence to** R.J.L.; E-mail: r-lewandowski@northwestern.edu

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There has been much interest in combining systemic and liver-directed therapies (eg, chemoembolization) given the potential for enhanced efficacy with inhibition of the angiogenic flair following embolization (7,8). Sorafenib (Bayer/Onyx, Leverkusen, Germany) is a multikinase inhibitor that targets several factors involved in angiogenesis and HCC proliferation (9). It is currently the only approved antiangiogenic agent for patients with advanced HCC, and has been established as standard of care for systemic treatment (10,11).

In recent years, radioembolization with the local delivery of the isotope yttrium-90 (^{90}Y) on 20–60-μm microspheres has emerged as a treatment for patients with unresectable HCC. Unlike chemoembolization, in which 300–500-μm permanent embolic particles are used, radioembolization is a microembolic therapy that maintains hepatic artery patency. This mechanistic difference compared with chemoembolization could theoretically lead to a less robust angiogenic response following radioembolization.

The purpose of the present study was to assess the angiogenic response after glass microsphere radioembolization with or without sorafenib among patients with unresectable HCC awaiting orthotopic liver transplantation (OLT).

MATERIALS AND METHODS

Study Design

This is an analysis of serum angiogenic growth factor response among patients with unresectable HCC awaiting OLT enrolled in a single-center, unblinded prospective randomized pilot study of glass microsphere radioembolization with or without sorafenib. The study was approved by the institutional review board, in accordance with the Health Insurance Portability and Accountability Act, and compliant with the Consolidated Standards of Reporting Trials statement (12). Twenty-three patients fulfilled study inclusion/exclusion criteria, provided signed consent, and were enrolled during the study time period (February 2009 to October 2012). They were randomized at a 1:1 ratio to undergo Y^{90} radioembolization alone or in combination with sorafenib. Subjects were recruited through hepatology, interventional radiology, and pretransplantation clinics.

Inclusion and Exclusion Criteria

Inclusion criteria were HCC confirmed by histology or imaging criteria, Child–Pugh score < 8 and potential candidacy for OLT (meeting University of California, San Francisco, criteria [13]). Patients with extrahepatic disease, vascular invasion, Eastern Cooperative Oncology Group performance status > 2, or contraindications to sorafenib and/or ^{90}Y were excluded. Study stopping rules included self-withdrawal, deterioration of performance status to ≥ 3, > 12 months of sorafenib, or more than two ^{90}Y treatments. For the present analysis, patients from the study cohort were selected who had blood samples drawn before treatment and at 2 weeks and 4 weeks after radioembolization and subsequently underwent transplantation.

Randomization and Study Groups

A total of 23 enrolled patients were randomly distributed between the two groups by using a computer generated randomization schema www.randomization.com): 12 patients were randomized to receive ^{90}Y alone and 11 patients received ^{90}Y plus sorafenib. Three patients were initially excluded: one patient from the ^{90}Y arm died before treatment and, in the combination therapy group, one patient with unconfirmed HCC on angiography subsequently had a negative biopsy result and another self-withdrew. Twenty patients ($n = 10$ in each group) received ^{90}Y radioembolization with or without sorafenib. Eight patients from each group underwent OLT. Complete blood samples drawn at baseline and 2 weeks and 4 weeks after radioembolization were available from seven patients in the ^{90}Y group and six patients in the ^{90}Y/sorafenib group (Fig 1). These 13 patients constitute the present study cohort.

Patients

Patient characteristics are summarized in Table 1. There were seven male patients and six female patients. Hepatitis C virus was the most common etiology (78%). Seventy percent of patients had Child–Pugh class A disease. All patients exhibited portal hypertension. There were no differences in baseline characteristics between groups.

Yttrium-90 Treatment

Radioembolization treatment was preceded by a simulation procedure to estimate the degree of potential extrahepatic deposition. Technetium-99 macroaggregated albumin was injected into the hepatic arterial vasculature, simulating ^{90}Y microsphere distribution. When required, coil embolization of extrahepatic arteries was performed to avoid inadvertent deposition. Glass microspheres loaded with ^{90}Y (TheraSphere; Nordion, Ottawa, Ontario, Canada) were used per standard methodology (14,15). Volumetric analysis of the hepatic treatment sites were based on magnetic resonance (MR) imaging, and mass of the treatment volume was estimated assuming a hepatic density of 1.03 g/cm^3. Prescribed ^{90}Y microsphere activity and prescribed radiation dose to the treatment volume (in Grays) were calculated by using standard Medical Internal Radiation Dose assumptions. Radioembolization was performed by using 3–15-GBq vials of ^{90}Y microspheres. Median doses received were 123.84 Gy (range, 104.8–191.0 Gy) for the ^{90}Y-only arm and 81.51 Gy (range, 21.8–120.6 Gy) for the combination arm. Patients randomized to receive sorafenib underwent radioembolization after a minimum of 14 days receiving sorafenib.