Toxicities after Radioembolization with Yttrium-90 SIR-Spheres: Incidence and Contributing Risk Factors at a Single Center

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ABSTRACT

Purpose: To report the incidence of liver function test (LFT) toxicities after radioembolization with yttrium-90 (^{90}Y) SIR-Spheres and review potential risk factors.

Materials and Methods: Patients receiving ^{90}Y for radioembolization of primary or metastatic liver tumors had follow-up LFTs 29–571 days after treatment. The incidence and duration of bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) toxicities were documented using common terminology criteria. Factors that were assessed included previous intra-arterial (IA) therapy, systemic chemotherapy, low tumor-to-normal liver tissue ratio at mapping angiography, vascular stasis, and higher prescribed ^{90}Y doses.

Results: There were 81 patients who underwent 122 infusions and had follow-up LFTs. Of 122 infusions, 71 (58%) were associated with toxicity. One patient died with radiation-induced liver disease. Grade 3 or greater toxicities occurred in seven (7%) patients after nine procedures. The median durations of laboratory elevations for bilirubin, AST, and ALT were 29 days, 29 days, and 20 days. Toxicity developed after 51 (71%) of 72 infusions with previous IA therapy versus 20 (40%) of 50 infusions in treatment-naïve areas ($P = .0006$). Absence of previous systemic therapy was associated with greater risk of toxicity versus previous chemotherapy (47% vs 66%, $P = .03$). Other factors were not associated with increased toxicity.

Conclusions: Mild hepatotoxicity developed frequently after infusion of SIR-Spheres using the body surface area method, with normalization of LFTs in most patients. Grade 3 or greater toxicities were seen in $< 10\%$ of infusions. Toxicity was strongly associated with previous IA therapy.

ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, IA = intra-arterial, LFT = liver function test, ^{90}Y = yttrium-90

Radioembolization with yttrium-90 (^{90}Y) microspheres for liver dominant tumors is rapidly expanding in clinical practice (1–5). Two types of ^{90}Y microspheres are available in the United States: a glass-based agent (TheraSphere; MDS Nordion, Ottawa, Ontario, Canada) and a resin-based agent (SIR-Spheres; Sirtex Medical, Wilmington, Massachusetts). These microspheres are inherently quite different in terms of relative radiation activity/sphere and embolic effect. All oncologic therapies are associated with toxicities. Many series have evaluated the incidence of biochemical hepatotoxicities with ^{90}Y therapy. The greatest amount of research has focused on glass microspheres (6–12). Limited investigations into toxicity have been performed with resin microspheres for treatment of both primary and metastatic liver disease (1,3,4,13,14). Most reports on resin microspheres consist of relatively smaller sample sizes except for a single multicenter review reporting outcomes with varying dose calculation methods and infusion techniques (1).

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Given the difference in these agents, hepatotoxicities resulting from use of glass microspheres should not be assumed to be similar to hepatotoxicities with resin microspheres. The primary purpose of this article is to report the incidence of hepatotoxicities after resin ^{90}Y microsphere infusion for liver dominant primary or metastatic tumors. A secondary goal was to determine potential contributing factors to development of hepatotoxicities after therapy.

MATERIALS AND METHODS

This study was approved by the institutional review board and compliant with the Health Insurance Portability and Accountability Act. From January 2007 through June 2010, 87 patients underwent 161 resin microsphere infusions at our institution. All infusions were done off-label and without intra-arterial (IA) fludarabine. After each infusion, patients were given a prescription for weekly liver function tests (LFTs) over the first month. Of this group, 81 patients undergoing 122 infusions were compliant with the ordered follow-up LFTs. These patients constituted the study group. Follow-up imaging was obtained 4 weeks after treatment. After that point, LFTs were obtained every 3 months with follow-up imaging unless continued elevations were identified and the treating physicians desired more rapid follow-up.

Yttrium-90 Treatment

Baseline cross-sectional imaging was obtained based on the primary tumor etiology. All patients underwent mapping arteriography with side-branch embolization performed and technetium-99m macroaggregated albumin infusion as previously described (15,16). Based on satisfactory outcomes, the first treatment was 10–21 days later. The prescribed dose was based on the body surface area method (1). Patients who had previously received either systemic chemotherapy or IA liver-directed therapy (chemoembolization or immunoembolization) had a 25% dose reduction. Patients were treated with lobar or whole-liver infusion based on anatomy and tumor burden. If untreated liver remained or if patients underwent whole-liver therapy in multiple fractions, the second treatment was performed 4–6 weeks after the initial infusion.

Data Collection

Toxic values of the LFTs including the duration of elevation were tracked using the common terminology criteria for adverse events version 3.0 (CTCAE v3) (**Table 1**) (17). Potential contributing factors were identified, and relationships were tested with either Fisher exact or *t* tests. Identified potential contributing factors included infusion in a territory that had been previously treated with IA therapy such as chemoembolization or immunoembolization versus a treatment-naïve zone, previous systemic chemotherapy versus no previous systemic therapy, a lower tumor-to-normal uptake ratio at mapping angiography in patients with toxicity versus patients without toxicity, a greater rate of development of arterial stasis during ^{90}Y infusion in patients with toxicity versus patients without toxicity, higher dose prescription for patients developing toxicities, and location of infusion (left lobe, right lobe, or whole liver).

Table 1. Reference Values for CTCAE v3 Toxicity Grades for Liver Function Tests

Laboratory Value/Grade	Upper Limit of Normal	Calculation of Grade
Total bilirubin	1.2 mg/dL	
Grade 1		1.2–1.8 mg/dL
Grade 2		1.8–3.6 mg/dL
Grade 3		3.6–12 mg/dL
Grade 4		> 12 mg/dL
AST	42 IU/L	
Grade 1		42–126 IU/L
Grade 2		126–210 IU/L
Grade 3		210–840 IU/L
Grade 4		> 840 IU/L
ALT	45 IU/L	
Grade 1		45–135 IU/L
Grade 2		135–225 IU/L
Grade 3		225–900 IU/L
Grade 4		> 900 IU/L

ALT = alanine transaminase; AST = aspartate aminotransferase.

RESULTS

Demographics

There were 81 patients treated with 122 infusions who had follow-up LFTs. Six treated patients who did not complete LFT follow-up all were alive and seen in clinic at follow-up. These patients were not included even with laboratory values at that time point because possible transient LFT toxicities may have already resolved. The group of 81 patients consisted of 54 women and 27 men 23–90 years old. Disease etiologies included uveal melanoma (n = 48), colorectal carcinoma (n = 17), hepatocellular carcinoma (n = 7), breast carcinoma (n=3), neuroendocrine carcinoma (n = 2), adenoid cystic carcinoma (n = 1), gastric carcinoma (n = 1), Merkel cell carcinoma (n = 1), and prostate carcinoma (n = 1). The patients underwent one to three infusions (mean 1.8 ± 0.6, median 2); 42 patients had one infusion, 37 patients had two infusions, and 2 patients had three infusions. Of the infusions, 105 (86%) of 122 were lobar, and the remainder were whole-liver infusions. Of the whole-liver infusions, 6 (36%) of 17 were unfractionated with the entire liver dose of ^{90}Y microspheres given via a single proper hepatic artery infusion. The remaining 11 (64%) of 17 whole-liver infusions were fractionated with the entire liver dose given from the proper hepatic artery divided over two infusions separated by 4–6