Salvage Radioembolization of Liver-dominant Metastases with a Resin-based Microsphere: Initial Outcomes

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PURPOSE: The use of radioembolization of hepatic metastases with yttrium-90 (^{90}Y) microspheres is increasing. The present report describes the outcomes in a cohort of patients with metastatic liver tumors treated with a resin-based microsphere agent.

MATERIALS AND METHODS: Thirty patients with colon (n = 13), breast (n = 7), and other primary cancers (n = 10) were treated after the failure of first- and second-line therapy. Overall survival (OS), time to progression (TTP), and time to treatment failure (TTTF) were calculated from the first treatment. Response was measured according to Response Evaluation Criteria In Solid Tumors at interval follow-up imaging.

RESULTS: Thirty patients underwent 56 infusions of ^{90}Y, and 18 remained alive at the end of the study. Fourteen patients (47%) had a partial response or stable disease. OS (604 vs 251 days), TTP (223 vs 87 days), and TTTF (363 vs 87 days) were all significantly longer for patients who had a partial response or stable disease (P < .05). Median OS, TTP, and TTTF for patients with colorectal carcinoma were 357, 112, and 107 days, respectively, versus 638, 118, and 363 days in patients with other metastatic sources. Median survival was not reached for patients with breast carcinoma, and the TTP and TTTF were each 282 days. One patient (3%) experienced grade 3 toxicity (gastrointestinal ulceration).

CONCLUSIONS: ^{90}Y microsphere therapy produced promising survival rates compared with systemic salvage options, with minimal toxicity.

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Abbreviations: OS = overall survival, TTTF = time to treatment failure, TTP = time to progression

MORE than 60% of patients with metastatic breast or colorectal cancer will develop hepatic metastases (1,2). Although outcomes with newer chemotherapeutic and targeted antineoplastic regimens for patients with unresectable metastatic disease have improved during the past decade, long-term survival with these treatments remains poor. Disease progression after salvage therapy confers a dismal prognosis. Hepatic failure secondary to metastatic disease is the cause of death in 20% of all patients with breast cancer and 60% of patients with breast cancer with metastatic disease (3–5). The reported median survival times for patients with breast cancer with liver metastases vary widely, ranging from 3 to 16 months (6). Liver metastases from colon cancer are an even greater source of morbidity and mortality. Tumor-related liver failure causes as many as 90% of all deaths from metastatic colorectal cancer (7). First-line treatment of metastatic colorectal cancer has shown response rates between 30 and 55%, with rates precipitously decreasing for second-line therapy (5%–25%) (8). Median survival times for patients receiving second-line regimens with irinotecan or oxaliplatin for colorectal cancer are only 8–12 months (9–14). In patients with liver-dominant disease who have undergone failed polychemotherapy with or without targeted agents, therapies resulting in local control of liver disease may be the only option to provide symptomatic relief and potentially prolong survival (15).

Interventional radiology techniques such as hepatic artery chemoembolization and chemotherapeutic agent infusion have historically been used for salvage therapy in this patient group. These methods have demonstrated control of liver disease by limiting pro-

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gression, but have not demonstrated a survival benefit (16–20). Whereas nonselective external-beam radiation therapy to liver metastases is effectively tumoricidal at high doses (approximately 70 Gy), its use is limited by the lower tolerance of normal hepatic parenchyma (approximately 30 Gy) (21). This susceptibility of hepatic metastases to radiation and the concomitant dose limitation associated with normal tissue intolerance has led to investigation and development of two types of radioactive microspheres that are delivered via the hepatic artery. Currently, two types of yttrium-90 (^{90}Y) spheres are available for intraarterial infusion: SIR-Spheres (Sirtex Medical, Sydney, Australia) and TheraSphere (MDS Nordion, Kanata, Ontario, Canada). These microspheres emit pure β-radiation with a half-life of 2.67 days. Both types of microspheres have been shown to preferentially localize to abnormally vascularized liver tumors, where they exert intense localized radiation, while limiting radiation exposure to the uninvolved hepatic parenchyma (15,22,23).

Studies demonstrating outcomes of ^{90}Y radioembolization therapy for liver metastases are limited. Our group has treated a number of patients with SIR-Spheres (Sirtex Medical) for chemotherapy-refractory liver metastases. The primary aim of the present study is to evaluate overall survival (OS) and time to progression (TTP) in this cohort of patients.

MATERIALS AND METHODS

This retrospective study was approved by our local institutional review board. All patients treated with ^{90}Y radioembolization for metastatic disease at our institution were included. All were seen at the interventional radiology and radiation oncology clinics before treatment. Eligibility criteria included liver-dominant metastases in the setting of failed standard polychemotherapy regimens, a tumor burden that was too great to be treated by thermal ablation (based on size, number, or location), Eastern Cooperative Oncology Group performance status of 0–2, compensated liver disease with a bilirubin level less than 2 mg/dL, adequate renal function with a creatinine level less than 1.8 mg/dL, and adequate coagulation parameters. Failure of chemotherapy regimens was defined by progressive disease according to standardized criteria after standard first- and second-line therapy drugs. Exclusion criteria were limited tumor burden that was treatable with thermal ablation, life expectancy of less than 2 months, Eastern Cooperative Oncology Group performance status of 3 or higher, and greater than 20% lung shunting on macroaggregated albumin scan (as described later).

Mapping Angiography

Study procedures were performed on an outpatient basis, and technical details have been described elsewhere (8). The gastroduodenal artery was empirically embolized in all patients. The right gastric artery was targeted based on selective angiography of the common hepatic artery and was embolized in 15 patients.

Activity Calculation

The total administered activity was calculated on the basis of radiation dose to normal liver according to a manufacturer-provided algorithm incorporating ideal liver size based on body surface area (see Eq 1) or by direct computation of mean normal liver activity from computed tomography (CT) data (see Eq 2, which is derived from the partition model) (24). The method that provided the lower treatment activity was used.

Method 1.—Body surface area in square meters was calculated from weight and height tables as follows:

$$\text{Body surface area} = 0.20247 \times ([\text{height in } m]0.725) \times ([\text{weight in kg}]0.0425)$$

The fraction of tumor involvement of the lobe to be treated was determined as the volume of tumor divided by the total volume of liver including the tumor.

$$\text{Total administered activity in BGq} = (\text{body surface area} - 0.2) + \text{fraction of tumor involvement} \quad (1)$$

Method 2.—The alternative calculation of total administered activity in GBq was as follows:

$$\text{Total administered activity in GBq} = 0.8 \times \text{mass of liver in kg, including tumor deposits} + (0.5 \times \text{mass of tumor deposits in kg}) \quad (2)$$

Use of these equations was designed to set the mean dose to uninvolved liver to 40 Gy, assuming the least favorable tumor–to–normal liver uptake ratio of 1.5. Liver tumors were estimated from volumes contoured on CT or magnetic resonance (MR) imaging and assuming a water equivalent density of 1 kg/L. The total administered activity was no greater than the lesser of Eqq 1 and 2. In most cases, Eq 2 was lower. Further activity reduction was planned for patients with pulmonary shunting in excess of 10%; however, none had shunting this severe. For patients undergoing separate right and left lobar infusions, the target activity was divided by the percentage volumes to the right and left lobes. In patients receiving whole-liver infusions from the proper hepatic artery, two treatments were administered, with half the total activity administered at each session.

Treatment

One to 2 weeks after mapping angiography, patients returned for initial radioembolization. Patients were premedicated with 30 mg of lansoprazole and 10 mg of dexamethasone. If disease was confined to one lobe, a single treatment was performed. In the setting of bilobar disease, separate lobar infusions or whole-liver infusions were performed with the treatment sessions separated by 3–6 weeks. Whole-liver infusions were performed in the setting of separate origins of the segmental branches of the left hepatic artery to allow treatment of all tumor-bearing liver in two visits. The first 18 patients were observed overnight and discharged the following morning. Given the lack of symptoms after therapy, the radioembolization procedures were then done on an outpatient basis with admission reserved as an option after the procedure in cases of nausea and/or abdominal pain. One patient with post-