Radioembolization in Patients with Progressive Gastrointestinal Stromal Tumor Liver Metastases Undergoing Treatment with Tyrosine Kinase Inhibitors

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ABSTRACT

Purpose: Gastrointestinal stromal tumors (GISTs) spread frequently to the peritoneum and the liver. If metastasectomy or tyrosine kinase inhibitors (TKIs) fail, interventional ablation techniques are considered. The purpose of this study is to assess the progression-free interval (PFI) of GIST liver metastases after radioembolization (RE).

Materials and Methods: Eleven patients with progressive GIST liver metastases undergoing TKI therapy were referred for RE; one was excluded because of a large hepatopulmonary shunt, and one was lost to follow-up. Depending on intrahepatic tumor distribution, one or both liver lobes were treated with RE. Contrast-enhanced magnetic resonance imaging, contrast-enhanced computed tomography (CT), and [^{18}F]fluorodeoxyglucose positron-emission tomography/CT were used for follow-up.

Results: In all, 16 liver lobes were treated with a mean activity of 1.06 GBq ± 0.37 (range, 0.55–1.88) per lobe. Three patients showed complete response, five showed partial response, and one showed stable disease. No patient showed progressive disease after RE. Median PFI was 15.9 months (range, 4–29 mo). Median survival was 29.8 months (range, 10–72 mo). No radiation-induced liver disease developed; however, one patient required surgery for persistent stomach ulcer.

Conclusions: RE offers a safe and effective treatment for patients with GIST liver metastases who do not show a response to TKIs. RE could be an option for earlier phases of therapy in patients with mutational status. The results might also challenge the notion that GISTs are resistant to radiation therapy.

ABBREVIATIONS

CR = complete response, CNR = contrast-to-noise ratio, GIST = gastrointestinal stromal tumor, PD = progressive disease, *PDGFRA* = platelet-derived growth factor receptor A, PET = positron-emission tomography, PFI = progression-free interval, PR = partial response, RE = radioembolization, SD = stable disease, SUV = standardized uptake value, TKI = tyrosine kinase inhibitor

Gastrointestinal stromal tumors (GISTs) cause liver metastases in 15.9% of all patients with GISTs (1). Lifelong treatment with a tyrosine kinase inhibitor (TKI) such as imatinib or sunitinib is mandatory, as tumors progress if treatment is interrupted (2).

Approximately 85%–90% of GISTs harbor a mutation in the *KIT* or *platelet-derived growth factor receptor A* (*PDGFRA*) gene that causes a tumor to develop. TKIs may competitively block the autophosphorylation produced by these mutations (3). However, additional secondary mutations in the *KIT* gene may promote resistance to TKI treatment (4). In addition, metastasectomy, in particular of progressive metastases (5), thermal ablation, or chemoembolization may aid in treating progressive liver metastases. However, ablative

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None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2015; 26:231–238

http://dx.doi.org/10.1016/j.jvir.2014.09.020

therapies are of limited usefulness in cases of multiple or very large metastases (6).

The results of radioembolization (RE) with yttrium-90 (^{90}Y) are promising for primary or secondary liver malignancy (7,8). In a transarterial approach, small radioactive particles are administered to the liver and accumulate in the metastases. In contrast to percutaneous radiation, radiation doses as high as 200 Gy can be applied to the area treated by using RE. The steep dose gradient of radiation spares toxicity to large parts of the normal liver parenchyma (9). The present study reports our initial experience in patients with progressive hepatic metastases of GISTs after treatment with standard drugs.

MATERIALS AND METHODS

Indication for Treatment

Between February 2008 and January 2013, 11 patients (six men and five women) with biopsy-proven liver metastases of GISTs were referred for treatment. The indication for treatment was progressive hepatic metastases not amenable to surgical resection and no further drug treatment available or thought to be indicated (**Table 1**). At least two lines of antiproliferative treatment had failed in all patients, with some patients having received as many as four lines of therapy. Four patients had extrahepatic metastases (**Table 2**) controlled by systemic treatment, and they continued with their drug treatment after RE. Chemoembolization, thermal ablation, or stereotactic percutaneous radiation therapy had not been performed for liver metastases in any patient. Bilirubin levels of more than 2.0 mg/dL, a more than fivefold increase in aminotransferase levels, and an International Normalized Ratio greater than 2.0 were considered contraindications for RE. The institutional review board gave approval for the retrospective data analysis.

Diagnostic Workup

Computed tomography (CT) or magnetic resonance (MR) angiography was used to plan the procedure and to locate any vessel variants. One week before RE, 150 MBq Technetium 99m (^{99m}Tc)–labeled macroaggregated albumin was administered to the right and left liver lobes in a transcatheter approach to rule out hepatopulmonary shunting. The distribution of the radionuclide in the lungs and liver was measured with conventional scintigraphy. If shunt volume was normal (< 10%), RE was performed within 1 week. For hepatopulmonary shunt volumes of 10%–20%, the dose needed to be reduced. A value of more than 20% was regarded as a contraindication (10). Consequently, one patient had to be excluded from therapy as a result of a hepatopulmonary shunt volume exceeding 20%. To prevent embolization of nontargeted radiation-sensitive organs, several

Table 1. Patient Age at RE, Diagnosis Date, and Chemotherapies Administered

Pt. No./Sex/Age (y)	Initial Diagnosis Date	Time to RE (mo)	Chemotherapy	
			Before RE	After RE
1/F/34	06/1999	104	Imatinib 400 mg, imatinib 600 mg + everolimus, sunitinib	Sunitinib, nilotinib, regorafenib
2/F/52	09/2006	22	Imatinib 400 mg, imatinib 600 mg + everolimus, sunitinib	Imatinib 800 mg, nilotinib, sorafenib
3/M/73	05/2005	50	Imatinib 400 mg, imatinib 800 mg, sunitinib, nilotinib	Sorafenib, everolimus
4/M/55	09/2003	70	Imatinib 400 mg, imatinib 600 mg, imatinib 800 mg	Sunitinib, imatinib 600 mg + everolimus
5/M/55	07/2007	26	Imatinib 400 mg, imatinib 800 mg, imatinib 1,000 mg, sunitinib	Sunitinib, nilotinib, sorafenib
6/M/61	03/2007	34	Imatinib 400 mg, sunitinib, sorafenib	Imatinib 800
7/M/58	06/2008	43	Imatinib 400 mg, sunitinib	Sorafenib
8/M/48	12/2004	85	Imatinib 400 mg, imatinib 800 mg, sorafenib	Nilotinib
9/M/74	08/2011	20	Imatinib, sunitinib	Pazopanib

RE = radioembolization.