Phase I Trial of Selective Internal Radiation Therapy for Chemorefractory Colorectal Cancer Liver Metastases Progressing After Hepatic Arterial Pump and Systemic Chemotherapy

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Abstract

This prospective, single-center phase I study assessed the safety and outcomes of selective internal radiation therapy (SIRT) for liver-predominant metastases of colorectal cancer in patients with progression after hepatic arterial and systemic chemotherapy. Of 19 patients, 3 experienced grade 3 toxicity. Median liver-progression-free, progression-free, and overall survival after SIRT were 5.2 months, 2.0 months, and 14.9 months, respectively.

Introduction: This prospective study assessed the safety and outcomes of selective internal radiation therapy (SIRT) using yttrium-90 (^{90}Y) resin microspheres as a salvage therapy for liver-predominant metastases of colorectal cancer in patients with documented progression after hepatic arterial chemotherapy (HAC) and systemic chemotherapy. **Patients and Methods:** We recruited 19 patients who had received a mean of 2.9 prior lines of chemotherapy and $\geq$ 1 line of HAC. Dose-limiting toxicities (grade 3 or higher) were catalogued using Common Terminology Criteria for Adverse Events version 3.0. At 4 to 8 weeks and 3 to 4 months post SIRT, responses were assessed by carcinoembryonic antigen (CEA), and quantitative imaging using Response Evaluation Criteria in Solid Tumors (RECIST) and PET Response Criteria in Solid Tumors (PERCIST). Liver progression-free survival (LPFS), progression-free survival (PFS), and overall survival (OS) were calculated using Kaplan-Meier methodology. **Results:** Median follow-up was 31.2 months after SIRT. Within 6 weeks of SIRT, 3 patients (15.8%) experienced grade 3 toxicity. There was no incidence of radiation-induced liver disease. Responses by RECIST, PERCIST, and CEA were, respectively, 0%, 20%, and 32% at 4 to 8 weeks and 5%, 33%, and 21% at 3 to 4 months post SIRT; 53% of patients had stable disease (by RECIST) at 3 to 4 months. Of 19 patients, 4 (21.1%) had liver ablation, 9 (47%) received additional HAC, and 17 (89%) received systemic chemotherapy after SIRT. Median LPFS, PFS, and OS after SIRT were 5.2 months, 2.0 months, and 14.9 months, respectively. **Conclusion:** SIRT was well tolerated and did not prohibit subsequent treatment, resulting in a median OS of 14.9 months in this heavily pretreated population.

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Introduction

Colorectal cancer (CRC) is the fourth most common malignancy and the second most common cause of cancer-related deaths.[1] Many patients will develop liver metastases (CLMs) during the course of their disease.[2] Although surgery is considered the gold-standard therapy, most CLMs are not resectable, because of

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excessive tumor burden, unfavorable location, or comorbidities.[2] The local infusion of chemotherapy directly into the hepatic artery takes advantage of the dual blood supply to the liver and preferentially targets the arterially fed tumor, delivering high-dose chemotherapy to the tumor arterial bed while sparing the normal liver and minimizing systemic toxicities.[3] Several small series have demonstrated that hepatic arterial chemotherapy (HAC) can improve progression-free survival (PFS) and patient survival.[4-6]

SIR-Sphere yttrium-90 (^{90}Y) microspheres (Sirtex Medical, Sydney, Australia) are an arterial brachytherapy device that has been approved by the Food and Drug Administration (FDA) for the treatment of unresectable CLM.[7] ^{90}Y is a beta radiation—emitting isotope, which decays to stable zirconium-90 with a half-life of 64.2 hours. The beta radiation of ^{90}Y has an average energy of 0.935 million electron volts (MeV) and an average penetration in tissue of approximately 2.5 mm.[7-10] To facilitate predictable delivery of the ^{90}Y within precapillary tumor vasculature, ^{90}Y is bound to nonbiodegradable resin[8,9,11-18] or glass[10,19,20] microspheres.

Selective internal radiation therapy (SIRT, or radioembolization), when administered concomitantly with chemotherapy, may extend time to liver progression and possibly overall survival (OS) when compared with chemotherapy alone.[17,21,22] SIRT has been used in combination with HAC as a first-line therapy,[21] as well as in combination with different lines of systemic chemotherapy,[23-25] with acceptable safety profiles. SIRT has also been used as a salvage treatment in patients with progression after different chemotherapy regimens, with acceptable safety profile.[10,13,16,19,23,24,26] However, the tolerability of SIRT in patients who have progressed following prior systemic chemotherapy and HAC is unknown. This prospective, phase I trial was designed to assess the safety and tolerability of ^{90}Y resin microspheres in heavily pretreated patients with documented CLM progression following at least 1 line of systemic chemotherapy and HAC. Secondary aims included evaluation of radiographic and laboratory response to treatment, liver PFS (LPFS), PFS, and OS.

Patients and Methods

Study Design

This was a single-center, prospective phase I dose-escalation study approved by our institutional review board and the FDA prior to recruitment. The study was audited for compliance and monitored semiannually by the institution's data and safety monitoring committee. Patients with liver-predominant CRC and documented progression following prior chemotherapy and HAC were recruited serially to 3 groups that received SIRT at 70%, 85%, or 100% of an individualized calculated activity (as described in the Radiation Source and Dosimetry section). All patients referred as potential candidates for SIRT were fully informed of the nature of the study and eligibility requirements, and each patient gave written and oral informed consent prior to study entry. Chemotherapy was withheld for 2 to 4 weeks prior to SIRT administration to avoid combined toxicity.

Eligibility Criteria

All patients completed a prescreening clinic visit, which consisted of a physical examination, a review of treatment history, and radiologic and laboratory tests. Adult patients ($\geq$ 18 y) with Eastern Cooperative Oncology Group performance status 0 to 1, with histologically confirmed primary adenocarcinoma of the colon or rectum, with a life expectancy of at least 3 months, and with unequivocal radiologic imaging of unresectable or unablatable liver metastases refractory to at least 1 line of prior systemic chemotherapy and HAC were eligible for enrolment. Laboratory tests were required to be within the following range: white blood cell count $>$ 1.5×10^9 cells/L, platelet count $> 100 \times 10^9$ cells/L, creatinine level $\leq$ 1.5 mg/dL, and bilirubin level $\leq$ 1.5 mg/dL.

Exclusion criteria were (1) prior radiotherapy to the liver, (2) evidence of severe cirrhosis (Child-Pugh class B or C), portal hypertension with gastroesophageal varices, ascites, or liver failure as determined by clinical, radiologic, or laboratory assessment, (3) any of the following contraindications to the use of SIRT: (a) technetium-99m labeled macroaggregated albumin (^{99m}Tc-MAA) hepatic arterial perfusion scintigraphy demonstrating extrahepatic shunting to the gastrointestinal tract that could not be corrected by angiographic and embolization techniques or (b) $>$ 20% shunting of ^{99m}Tc-MAA to lungs by planar gamma camera scintigraphy after the intra-arterial injection of ^{99m}Tc-MAA.[12]

Radiation Source and Dosimetry

Pretreatment work-up with rotational and computed tomography (CT) arteriography was always performed in a combined CT-angiography suite with conventional digital subtraction angiography, to map the visceral and hepatic arterial anatomy. Any vessel that could potentially allow the nontarget delivery of the ^{90}Y resin microspheres was coil embolized. Once the desired location of SIRT administration was determined, ^{99m}Tc-MAA was injected and patients were transferred for gamma camera imaging. Planar images were acquired in 2 fields of view to encompass the entire liver and lungs. The images were converted to geometric mean images and regions of interest were drawn around the liver and separate regions of both lungs. The shunt fraction was defined as the total activity in the lung divided by that in the lung and liver. To evaluate for extrahepatic perfusion, a single-photon emission CT (SPECT/CT)(Philips Healthcare, Andover, MA) was also performed with the liver centered in the field of view. All images were reviewed by the molecular imaging and therapy faculty (N.P.T. or J.A.C.). Hepatic lobar and sublobar CT arteriography was used to define anatomy, and in combination with preprocedure CT, was used to calculate the tumor and liver volumes for the radiation-activity calculations. Liver volumes and tumor burden calculations were performed on a workstation (General Electric, Advantage Workstation version 4.2) using source images from a contrast-enhanced triple-phase CT obtained prior to the hepatic arteriography. The entire liver was first segmented by manually tracing the edge of the liver on each axial slice and then summating the volumes. Once the liver volume was calculated, the liver was further subdivided, into right and left hepatic lobes, by manually tracing according to the lobar anatomy defined during hepatic lobar CT arteriography. Within each targeted lobe or liver segment, tumor volumes were measured by manually tracing the tumors on axial slices and then adding the volumes. Whenever possible, preprocedure positron emission tomography-CT (PET-CT) imaging was obtained to identify regions of fluorodeoxyglucose (FDG)—avid tumors.