Radioembolization in Combination with Systemic Chemotherapy as First-line Therapy for Liver Metastases from Colorectal Cancer

Suzanne Kosmider, MBBS, Thean H. Tan, MBBS, Desmond Yip, MBBS, Richard Dowling, MBBS, BMedSc, Meir Lichtenstein, MBBS, and Peter Gibbs, MD

ABSTRACT

Purpose: To report clinical experience with radioembolization (RE) plus systemic chemotherapy as a first-line treatment for liver metastases from colorectal cancer (CRC).

Materials and Methods: Clinical outcomes were evaluated retrospectively among 19 patients with unresectable liver metastases from CRC who had a good performance status and a low burden of extrahepatic disease (EHD) and were eligible for RE. Most (74%) had disease confined to the liver. Concurrent treatment with 5-fluorourail/leucovorin (n = 7) or 5-fluorourail/leucovorin/oxaliplatin (FOLFOX; n = 12) was started 3–4 days before single treatment with RE.

Results: Overall response rate according to the Response Evaluation Criteria in Solid Tumors was 84% (two complete responses and 14 partial responses). Median progression-free survival (PFS) time was 10.4 months and median overall survival (OS) time was 29.4 months. For patients with disease confined to the liver, PFS improved (10.7 mo vs 3.6 mo; $P = .09$), with significant prolongation of OS (median, 37.8 mo vs 13.4 mo; $P = .03$) compared with those who had EHD. Nine patients, including three long-term (> 3 y) survivors, remained alive after a median follow-up of 18.6 months. Serious treatment-related toxicities included febrile neutropenia with concurrent FOLFOX treatment, a perforated duodenal ulcer, and one death from hepatic toxicity.

Conclusions: The present findings confirm the effectiveness of RE plus systemic chemotherapy for metastatic CRC. Patients with liver-confined disease derived the greatest benefit, with median survival times beyond 36 months. Larger datasets from ongoing phase III trials are needed to further define the safety and efficacy of RE in the first-line setting.

ABBREVIATIONS

CRC = colorectal cancer, EHD = extrahepatic disease, FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin, GDA = gastroduodenal artery, OS = overall survival, PFS = progression-free survival, RE = radioembolization, RECIST = Response Evaluation Criteria in Solid Tumors, RGA = right gastric artery

The liver is the most common site of metastatic disease in colorectal cancer (CRC). Radioembolization (RE) with yttrium-90 (^{90}Y) resin microspheres uses the well-characterized dual vasculature of the liver to selectively target tumors that are almost exclusively supplied by blood from the hepatic arterial branches while limiting the delivery to the normal liver parenchyma, which is supplied predominantly by the portal circulation (1). In most centers, RE is used as a salvage therapy for patients with liver-dominant metastatic disease (2–8). The clinical evidence from randomized controlled trials (9,10) suggest that benefits may be greater if used earlier and in combination with systemic chemotherapy. To date, two randomized studies (9,10) have reported significant benefits of combining RE with single-agent first-line chemotherapy, and more recently, encouraging outcomes were seen when RE was combined with 5-fluo-

From BioGrid Australia (S.K., P.G.), Level 6 North, Royal Melbourne Hospital, Grattan St., Parkville, Victoria 3050, Australia; Departments of Nuclear Medicine/Radiology (R.D., M.L.) and Oncology (P.G.), Royal Melbourne Hospital, Parkville, Victoria; and Department of Oncology (T.H.T., D.Y.), Canberra Hospital, Garran, Australian Capital Territory, Australia. Received October 13, 2009; final revision received January 31, 2011; accepted February 16, 2011. **Address correspondence to** S.K.; E-mail: suzanne.kosmider@mh.org.au.

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rouracil/leucovorin/oxaliplatin (FOLFOX) in a phase I dose-ranging study (11).

Here we report our early experience and long-term follow-up (to 78 mo after treatment) of patients with synchronous liver-dominant metastatic CRC who received RE combined with conventional intravenous chemotherapy as a first-line treatment.

MATERIALS AND METHODS

Study Design and Inclusion Criteria

The aim of our analysis was to assess retrospectively the clinical outcomes (overall response rate, progression-free survival [PFS], and overall survival [OS]) as well as the safety and tolerability of RE combined with systemic chemotherapy as first-line therapy among patients with synchronous liver metastases from CRC. We conducted a retrospective analysis of consecutive patients who were treated between January 2002 and October 2008 at one of two institutions. Institution review board approval was not required for this retrospective audit.

Patients with unresectable liver metastases from CRC, good performance status, and low burden of extrahepatic disease (EHD) at diagnosis (ie, limited pulmonary nodules or abdominal lymphadenopathy) were assessed as possible candidates for RE. Patients were encouraged to consider RE if a clinical trial option was not available, and aggressive therapy was indicated because of the bulk of disease or younger age of the patient. An unknown number of patients given the option of RE did not pursue this treatment option. All patients eligible for RE were required to have adequate renal function (ie, creatinine level < 1.5 times normal value or creatinine clearance > 50 mL/min) and hemopoietic function (ie, leukocyte count $> 1{,}500/mm^3$ and platelet count $> 100{,}000/mm^3$) and sufficient liver function to tolerate RE (ie, absence of ascites or synthetic liver dysfunction, total bilirubin level < 1.75 mg/dL [< 30 μmol/L], and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels each less than four times the upper limit of normal).

Treatment Planning and RE

A detailed account of the two-stage treatment protocol has been previously published (12). It comprised initial mapping angiography, branch coil embolization where indicated, and macroaggregated albumin scan. Typically, 2 weeks later, eligible patients underwent treatment of one or both sides of the liver by selective injection into the right and/or left hepatic arteries to avoid named or unnamed collateral vessels to the pancreaticoduodenal arcade or gastric arcades, or within the proper hepatic artery if no such collateral vessels were identified, as a single procedure with ^{90}Y resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). The amount of microspheres administered was calculated based on an empiric or body surface area method as determined by the treatment center.

Chemotherapy

Patients were given oxaliplatin-based or 5-fluorouracil chemotherapy at clinician discretion and according to local protocols. RE was given on day 3 or 4 of cycle 1. Chemotherapy was continued for a maximum of 6 months unless toxicity or disease progression necessitated treatment cessation.

Assessments and Study Endpoints

Patients were assessed by computed tomography (CT) of the chest, abdomen, and pelvis for tumor response at 8 weeks and every 2 months thereafter until disease progression was noted. The overall response rate was determined by Response Evaluation Criteria in Solid Tumors (RECIST) at the time of the best response recorded in the liver after RE. The durations of response and PFS were determined from the date of administration of RE until documented progression or, in those without disease progression, last review. OS was determined from the date of initiation of chemotherapy with RE to the documented date of death or last review for patients who were still alive.

Toxicities were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3. Adverse events were recorded from the time of the initiation of chemotherapy until the end of follow-up, documentation of disease progression, or voluntary withdrawal from the study.

The recently reported phase I dose-escalation trial of RE combined with increasing systemic doses of oxaliplatin (11) reported significant rates of grade 3/4 neutropenia. Given this, it recommended an initial dose reduction of oxaliplatin to 65 mg/m^2 (11). Many of the patients in the present study were treated before the study findings with full-dose oxaliplatin (85 mg/m^2) were reported (11), so we specifically examined the rates of neutropenia in the first three treatment cycles for these patients.

Statistical Analysis

Kaplan–Meier survival analyses were applied, and comparisons were carried out by using the log-rank test. Data were analyzed using Stata software (version 10.0; Stata, College Station, Texas).

RESULTS

Patient Characteristics and Treatment

Nineteen patients received RE plus systemic chemotherapy and were included in the present analysis (**Table 1**). One patient had received 12 cycles of adjuvant FOLFOX chemotherapy for node-positive colon cancer with a relapse-free interval of 16 months before the development of liver metastases. All other patients had stage IV disease at initial presentation.

Median metastatic liver involvement, as determined by the treating clinician based on CT imaging, was 40%