Chemoembolization in Conjunction with Bevacizumab: Preliminary Results

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ABSTRACT

Transarterial chemoembolization is an effective, minimally invasive therapy that is widely used for treatment of unresectable colorectal cancer liver metastases (CRC-LM). However, chemoembolization induces a hypoxic microenvironment, which increases neoangiogenesis and may promote early progression. For this reason, transarterial chemoembolization efficacy may be improved by combining it with an angiogenesis inhibitor, such as bevacizumab. This report shows that transarterial chemoembolization with irinotecan-loaded polyethylene glycol embolics and bevacizumab therapy was effective and well tolerated by 6 patients with CRC-LM, resulting in a disease control rate of 83% and an overall improvement in quality of life.

ABBREVIATIONS

CRC-LM = colorectal cancer liver metastases, FHSI-8 = 8-item FACT Hepatobiliary Symptom Index, OS = overall survival, PEG = polyethylene glycol

Transarterial chemoembolization is indicated for the treatment of patients with unresectable colorectal cancer liver metastases (CRC-LM), patients with disease refractory to systemic chemotherapy, elderly patients, and patients who have a poor performance status (1,2) and is usually performed using irinotecan covalently loaded onto microembolics (3). Several types of embolics made of different materials are currently available for chemoembolization, such as drug-eluting embolics (DC Bead; Biocompatibles UK Ltd, Farnham, United Kingdom), acrylic copolymer, tris-acrylic microspheres, and polyethylene glycol (PEG) microspheres (3,4). Drug-eluting embolics are delivered in the distal vascular bed of the tumor, where they slowly release the loaded drug (4), allowing the reduction of its systemic concentration. Although chemoembolization results in an objective response (4), it also creates a hypoxic microenvironment. Hypoxia induces and activates the hypoxia-inducible transcription factors (hypoxia-inducible factor-1 and hypoxia-inducible factor-2) that promote vascular endothelial growth factor expression and consequent neoangiogenesis. This may cause early relapse and progression, supporting the association of transarterial chemoembolization with a therapeutic inhibitor of angiogenesis, such as bevacizumab (5). This study reports the data on tumor response, quality of life, and adverse events of transarterial chemoembolization therapy followed by intravenous bevacizumab for the treatment of patients with CRC-LM that are refractory to systemic therapy.

MATERIALS AND METHODS

Patients

This prospective observational single-center study was approved by the institutional review board. Six patients with CRC-LM were included; written informed consent was obtained from all patients. The patients were treated with transarterial chemoembolization using irinotecan-loaded PEG embolics and intravenous administration of bevacizumab. Inclusion criteria were age > 18 years, diagnosis of unresectable CRC-LM that were refractory to standard chemotherapy, Eastern Cooperative Oncology Group status

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Table. Characteristics of Sample

Case	Age (y)	Site of LM	Size (cm)	No. Lesions	Previous Surgery	No. CHT Lines	Ras Status	Tumor Response		FHSI-8			Adverse Events	OS (mo)	TTP (mo)	PFS (mo)
								1 mo	3 mo	Baseline	1 mo	3 mo				
1	64	Left lobe	11	2	No	3	Wild-type	SD	SD	8	8	4	Transaminase rise (G2)	9	4	3
2	77	Left lobe	5	4	Metastasectomy	3	Wild-type	PR	CR	7	5	2	Pain (G2), transaminase rise (G2)	15		15
3	75	Left lobe	2.5	2	Metastasectomy	3	Mutated	PR	PR	8	6	2	Pain (G2), skin rush (G2)	7	3	3
4	78	Right lobe	9	2	Metastasectomy	4	Mutated	SD	PD	8	10	8	Fever (G2), pressure rise (G2)	9	3	3
5	74	Right lobe	3	1	No	3	Wild-type	CR	CR	8	6	2	Pain (G2), transaminase rise (G3), skin rush (G2)	12		12
6	69	Left lobe	4	2	No	3	Mutated	PR	PR	7	5	2	Transaminase rise (G2)	11		11

CHT = chemotherapy; CR = complete response; FHSI-8 = 8-item FACT Hepatobiliary Symptom Index; G2 = moderate adverse event; G3 = severe adverse event; LM = liver metastases; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; TTP = time to progression.

Figure 1. Tumor response at 1, 3, and 6 months after first transarterial chemoembolization. CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

0 or 1, measurable tumor size by modified Response Evaluation Criteria in Solid Tumors (6), ≤ 40% liver involvement, life expectancy of at least 3 months, and blood biochemistry within the normal range. Patient exclusion criteria were contraindication for angiographic catheterization, extensive extrahepatic disease, pregnancy or breastfeeding, and other severe clinical contraindications (eg, liver failure, ascites, cardiovascular diseases, chronic obstructive pulmonary disease).

From January 2016 to December 2017, 16 patients with CRC-LM were treated with transarterial chemoembolization, using irinotecan-loaded PEG embolics; 6 of these patients agreed to participate in this study. Patients received 2 rounds of transarterial chemoembolization therapy followed by intravenous bevacizumab administration. Baseline data for each patient included detailed medical history, weight and height, blood pressure, performance status, blood tests and routine blood chemistry, and cancer antigen 19.9 and carcinoembryonic antigen levels. Tumor response was assessed with computed tomography imaging at 1, 3, and 6 months, applying modified Response Evaluation Criteria in Solid Tumors criteria (6). Progression-free survival and time to disease progression were also evaluated. Patient quality of life was assessed monthly using the 8-item FACT Hepatobiliary Symptom Index (FHSI-8) questionnaire (0–32 maximum score). FHSI-8 is a shorter version of the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Subscale. This 8-item symptom index evaluates the severity of symptoms reported by patients with liver metastases (7), including pain (3 items), fatigue (2 items), nausea (1 item), weight loss (1 item), and jaundice (1 item).

The sample included 3 (50%) men and 3 (50%) women (**Table**). Median age was 75 years (range, 64–77); baseline Eastern Cooperative Oncology Group status was 1 in 4 (67%) patients and 0 in 2 (33%) patients; median tumor size was 4 cm (range, 0.5–11 cm) at baseline. Five (83%) patients had multinodular disease with a median of 2 nodules (range, 1–4); only 1 (17%) patient had a single

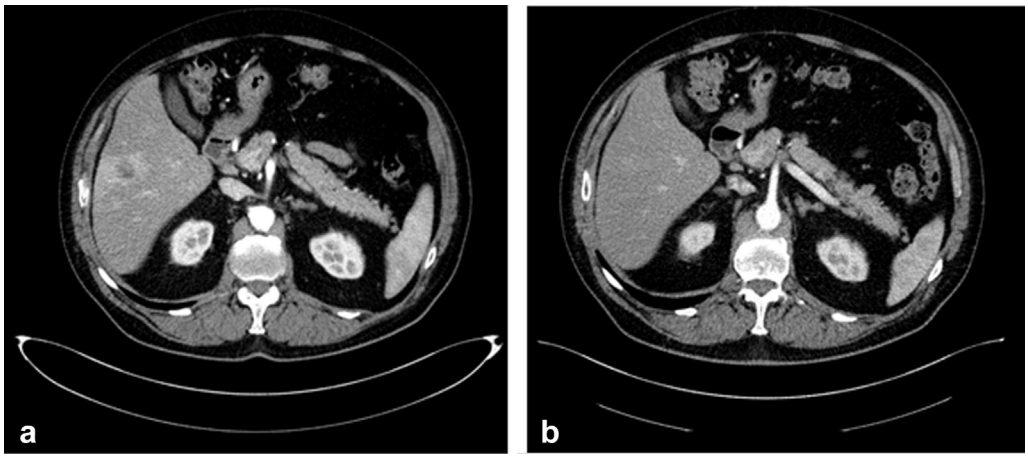

Figure 2. Computed tomography imaging of case 5. **(a)** Image of 3-cm tumor in the right lobe before treatment. **(b)** Image obtained after transarterial chemoembolization and bevacizumab therapy showing complete disappearance of the lesion.

lesion. One patient had concomitant lung metastases. All patients had primary tumor resection, and 2 had also undergone metastasectomy (33%). All patients were refractory to systemic chemotherapies (> 3 lines), including intravenous or oral fluoropyrimidine, oxaliplatin, and irinotecan alone or in combination with the biologic drugs bevacizumab or cetuximab.

Transarterial Chemoembolization plus Bevacizumab Procedure

Diagnostic angiography was performed to assess tumor arterial perfusion before chemoembolization. Transarterial chemoembolization was performed using 2 mL of PEG microspheres (LifePearl; Terumo Europe NV, Leuven, Belgium) of 100-μm diameter that had been loaded with irinotecan (100 mg) diluted in 5 mL of nonionic contrast solution and 5 mL of distilled water. Infusion of microspheres was performed at a fixed speed of 1 mL/min for a median time of 12 minutes (range, 8–16 minutes). A second transarterial chemoembolization was performed after 30 days. Transarterial chemoembolization was considered successful when flow was completely or partially stagnated. Bevacizumab (5 mg/kg) therapy was initiated 15 days after the first transarterial chemoembolization and was repeated every 2 weeks for a total of 8 cycles.

Statistical Analysis

Data analysis of the whole sample was performed using the median for continuous data. Proportions are expressed in percentage.

RESULTS

At 1 month after transarterial chemoembolization and bevacizumab treatment, complete response was observed in 1 (17%) patient, stable disease was observed in 2 (33%) patients, and partial response was observed in 3 (50%) patients (Fig 1). At 3 months, 2 (33%) patients showed complete response (Fig 2a, b), 2 (33%) patients showed partial response, 1 (17%) patient showed stable disease, and 1 patient (17%) showed progressive disease. The last-mentioned patient had advanced-stage disease, and transarterial chemoembolization was the fourth line of treatment. Disease control rate was 83%. Median follow-up was 12 months (range, 7–16 months). A 30% decrease in carcinoembryonic antigen levels was observed in 3 (50%) patients. Median overall survival (OS) was 10 months (range, 7–15 months), median time to progression was 3 months (range 2–5 months), and median progression-free survival was 7 months (range, 3–15 months).

No complications were observed during transarterial chemoembolization. Adverse events were of mild to moderate intensity and were related to postembolization syndrome. Three patients (50%) reported pain (G2: moderate), which resolved in 2–5 days. One patient (17%) reported fever (G2), and 3 patients (50%) had elevated levels of transaminase (G2 and G3: severe). Bevacizumab-related adverse events included blood pressure increase (G2) in 1 (17%) patient, which resolved with β-blockers, and skin rash (G2) in 2 (33%) patients. Thromboembolic effects were not observed in any patient. FHSI-8 score showed an improvement in quality of life for 4 patients (67%) and stabilization in quality of life for 2 patients (33%).

DISCUSSION

The induction of vascular endothelial growth factor expression as a consequence of transarterial chemoembolization was previously reported in hepatocellular cancer (8), and intravenous bevacizumab administration following transarterial chemoembolization was well tolerated in a pilot study and reduced neovascularization in patients with hepatocellular cancer (8). The present observational, single-center, prospective study assessed transarterial chemoembolization followed by bevacizumab therapy in a small cohort of 6 patients with CRC-LM that were refractory to chemotherapy. The results of the study suggest that the combination of

transarterial chemoembolization followed by intravenous bevacizumab is effective, feasible, well tolerated, and associated with mainly G1 (mild) and G2 (moderate) adverse events that resolved in a few days, in agreement with previous studies (9,10). This treatment also improved the quality of life in 66% of the patients studied.

A median OS of 10 months was observed in this study. This is less than the median OS of 14 months (range, 1.3–25 months) that was previously reported for patients with CRC-LM treated with transarterial chemoembolization alone (10). However, the patients included in this study received > 3 lines of systemic chemotherapy before enrollment; thus, they were already in advanced stage of disease, and this may have reduced their life expectancy. A disease control rate of 83% at 3 months was observed, which is comparable to 78% that was reported by Martin et al (10), who treated patients with CRC-LM with transarterial chemoembolization and folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX).

The main limitations of this report are as follows: single-center study, small cohort study, absence of control group, and no randomization. Further randomized multicenter studies with a larger number of patients are necessary to confirm these preliminary results on the therapeutic application of angiogenesis inhibitors with transarterial chemoembolization to counteract potential hypoxia-dependent, early relapse and progression in patients with CRC-LM that are refractory to systemic chemotherapy.

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