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Exploratory Study of Hepatic Arterial Infusion Oxaliplatin With Systemic 5-Fluorouracil/Bevacizumab in Patients With Refractory Solid Tumor and Extensive Liver Metastases

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Abstract

Purpose—This pilot clinical trial explored the feasibility, safety, and efficacy of regional hepatic therapy combined with systemic anticancer agents in patients with refractory solid tumors and extensive unresectable liver involvement, including those with compromised hepatic function.

Patients and Methods—Six patients with colorectal (N = 3), ovarian (N = 2), and hepatocellular carcinoma (N = 1) received intra-arterial hepatic oxaliplatin followed by intravenous 5-fluorouracil, leucovorin, and bevacizumab every 2 weeks until disease progression. All had extensive liver metastases; four had elevated baseline serum total bilirubin. Median total bilirubin was 2.8 mg/dL (range, 0.2–5.2 mg/dL). Median Child-Pugh score was 7 (range, 5–10).

Results—Thirty treatments were delivered (2–7 per patient). Median age of patients was 57 years (range, 25–69 years). Three patients (1 with colorectal, 1 with hepatocellular, and 1 with ovarian cancer) attained partial responses. Two had failed previous oxaliplatin and cisplatin treatment. Some with elevated bilirubin at baseline had a significant drop in bilirubin with treatment (bilirubin 5.2 → 1 mg/dL, 4.8 → 1.1 mg/dL, and 5.2 → 1.8 mg/dL). The regimen was generally well tolerated; the most common side effects were grade 1 fatigue, anorexia, and/or hypertension. One patient died of enzyme-linked, immunoassay-confirmed, heparin-induced thrombocytopenia during the sixth cycle of therapy.

Conclusion—At doses tested, this regimen was safe and demonstrated antitumor activity in patients with advanced refractory malignancies involving the liver, including those with hepatic insufficiency. Further study is warranted.

Keywords

Pilot clinical trial; Regional therapy

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Introduction

The liver is a major site of involvement for patients with solid malignancies, including breast, ovarian, colorectal, and malignant melanoma. Liver involvement is an indicator of poor prognosis; few patients can undergo surgical resection at the time of presentation and attain long-term survival.

When surgical resection of liver metastases is feasible, adjuvant hepatic arterial infusion (HAI) therapy can prolong the survival of patients with colorectal cancer.¹⁻³ Hepatic arterial infusion, which also results in tumor responses, can sometimes improve quality of life.¹⁻³

Encouraging results from studies of hepatic oxaliplatin infusion in patients with colorectal cancer and advanced liver metastases⁴⁻⁸ prompted us to explore the safety and antitumor activity of oxaliplatin combined with intravenous (I.V.) bevacizumab and 5-fluorouracil in patients with refractory and unresectable solid tumors involving the liver.

Patients and Methods

Between November 2005 and June 2006, 6 patients with advanced solid tumors and metastases predominantly in the liver were treated. All patients provided written informed consent before therapy, and analysis of their medical records was approved by the MD Anderson Cancer Center Institutional Review Board.

Patient Evaluations

All patients underwent a baseline physical examination and blood work, including complete blood counts, serum chemistry, liver function, coagulation profile, and serum tumor markers. These studies were repeated before each course of therapy. Blood counts, serum electrolytes, and liver function tests were also monitored while patients were in the inpatient unit. Tumor assessment was carried out every 8 weeks with computed tomography (CT) scans of the thorax, abdomen, and pelvis following Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. A radiologist performed a formal review of all scans.

Treatment Regimen

We modified the regimen described by Ducreux et al by adding I.V. bevacizumab after 5-fluorouracil infusions (Table 1).⁶

Therapy included an initial 2-hour continuous HAI of oxaliplatin at 100 mg/m² administered in the inpatient unit, followed by leucovorin at 200 mg/m² over 2 hours. 5-fluorouracil was then administered, starting with a bolus of 300 mg/m² and followed by a 500 mg/m² continuous 22-hour infusion. A second infusion of leucovorin and 5-fluorouracil was given at the same doses once the first set of infusions was completed. Bevacizumab I.V. was then administered at 7.5 mg/kg over 90 minutes. To prevent the arterial line from clotting, 5000 IU of standard unfractionated heparin was diluted in 1000 mL of normal saline and infused at 50 mL per hour. Once the oxaliplatin was reconstituted and started, 3000 IU of standard unfractionated heparin was added to the solution of 250 mL dextrose 5% and water (D5W) and oxaliplatin, and continuously infused via the hepatic artery over 2 hours. The treatment was repeated every 2 weeks until tumor progression or life-threatening toxicity, defined as a grade 3 or higher toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Supportive medications included prophylaxis against tumor lysis syndrome with allopurinol, antiemetics with palonosetron, and gastric protection with a proton pump inhibitor or H₂ antagonist. Incentive spirometry was encouraged during the hospital course. Patients

maintained absolute bed rest until the catheter's extraction at the termination of infusion. Manual pressure was then applied for 15 minutes and a sandbag was subsequently placed on top of the area of catheter insertion for the next 6 hours following institutional guidelines.

Results

In this initial pilot study, 6 patients with refractory solid tumors involving the liver and different clinical profiles received therapy (Table 2). Patients were referred to our Department of Investigational Cancer Therapeutics Phase I Clinic and did not meet eligibility for other clinical protocols. All patients had failed previous platinum-based therapy (patients 1, 2, and 6, oxaliplatin; patients 3 and 5, carboplatin). Platinum-free intervals ranged from 3 months to 2 years.

Toxicities

Treatment was well tolerated overall. There were no catheter- or procedure-related complications. Most observed toxicities (fatigue, mild myelosuppression) were tolerable, and few developed secondary toxicities from cumulative exposure to the agents tested. One patient developed a rapidly progressing and fatal thrombocytopenia, apparently related to heparin (Table 3).

Preliminary Antitumor Activity

Three patients attained partial responses (PRs): 1 patient with ovarian cancer, 1 with colorectal cancer, and 1 with hepatocellular cancer. Two other patients remained stable for 3-4 months. One patient with epithelial ovarian carcinoma experienced progression of disease after a very short-lived biochemical response (Table 2 and Figures 1, 2, and 3). One patient with hepatocellular cancer who attained a PR withdrew consent after 2 courses of therapy. However, his bilirubin dropped from a baseline of 5.2 mg/dL to 1.8 mg/dL. Two other PRs were achieved (ovarian and colorectal cancer). In addition, a 59-year-old male with advanced adenocarcinoma of the sigmoid colon metastatic to the liver and lungs received 6 courses of therapy with a slight decrease in hepatic and retroperitoneal lymph nodes (stable disease) and a decrease in bilirubin from 5.2 mg/dL to 1.0 mg/dL. Another patient with ovarian cancer also showed a decrease in bilirubin from 4.8 mg/dL to 1.1 mg/dL, with a decrease in liver metastases (Table 2). Of note, 2 of the patients who achieved a PR had failed a previous platinum treatment regimen, including oxaliplatin in one case, with the platinum-free interval ranging from 3 months to 2 years.

Discussion

Our pilot results suggest that regional HAI of oxaliplatin in combination with systemic 5-fluorouracil, leucovorin, and bevacizumab is well tolerated in patients with advanced malignancies involving the liver and various degrees of hepatic dysfunction. Despite its intensity, the most common toxicity of the treatment regimen was fatigue, most likely secondary to short treatment intervals.

Our findings suggest that this regimen can result in objective antitumor responses in patients with advanced solid tumors in addition to colorectal carcinoma who failed extensive previous systemic cytotoxic therapies, including platinum-based regimens. Three patients with extensive liver metastases had normalization or near-normalization of their bilirubin. Local regional infusions of anticancer agents might overcome cellular resistance by achieving higher tumor concentrations.⁹ Additionally, in vitro experiments with platinum-resistant cell lines demonstrate that oxaliplatin and cisplatin have a different spectrum of activity and low cross-resistance. Although the number of patients is small and the results

preliminary, our observations suggest that further study is warranted in patients with ovarian, breast, melanoma, lung, and other diseases for whom platinum-based therapies provide a substantial antitumor benefit.

Another consideration for future studies is the possibility of reverting physiologic organ dysfunction in patients with mild-to-moderate liver involvement (Child-Pugh scores A and B). It might also be of interest to evaluate this regimen in earlier stages of liver involvement when the feasibility of rendering patients surgically resectable is more realistic.

Conclusion

Extrahepatic tumor progression remains challenging. Our pilot study suggests that antitumor activity can be seen in this regimen in patients with liver metastases, even in the presence of hyper-bilirubinemia, a setting in which few therapeutic alternatives are available. However, determining response rates and effect on progression-free and overall survival will require larger and/or randomized trials.

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References

1. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med*. 2005; 352:734–5. [PubMed: 15716576]
2. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med*. 1999; 341:2039–48. [PubMed: 10615075]
3. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol*. 2006; 24:1395–403. [PubMed: 16505413]
4. Barber FD, Mavligit G, Kurzrock R. Hepatic arterial infusion chemotherapy for metastatic colorectal cancer: a concise overview. *Cancer Treat Rev*. 2004; 30:425–36. [PubMed: 15245775]
5. Kern W, Beckert B, Lang N, et al. Phase I and pharmacokinetic study of hepatic arterial infusion with oxaliplatin in combination with folinic acid and 5-fluorouracil in patients with hepatic metastases from colorectal cancer. *Ann Oncol*. 2001; 12:599–603. [PubMed: 11432616]
6. Ducreux M, Ychou M, Laplanche A, et al. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol*. 2005; 23:4881–7. [PubMed: 16009952]
7. Mancuso A, Giuliani R, Accettura C, et al. Hepatic arterial continuous infusion (HACI) of oxaliplatin in patients with unresectable liver metastases from colorectal cancer. *Anticancer Res*. 2003; 23:1917–22. [PubMed: 12820479]
8. Fiorentini G, Rossi S, Dentico P, et al. Oxaliplatin hepatic arterial infusion chemotherapy for hepatic metastases from colorectal cancer: a phase I-II clinical study. *Anticancer Res*. 2004; 24:2093–6. [PubMed: 15274406]
9. Collins JM. Pharmacologic rationale for regional drug delivery. *J Clin Oncol*. 1984; 2:498–504. [PubMed: 6547166]

Figure 1. Drop in Serum Tumor Marker CEA After Treatment

A 59-year-old male with colorectal cancer metastatic to the liver achieved stable disease by RECIST, with a 10% decrease in tumor load. After 4 courses, overall performance status, liver function (bilirubin decreased from baseline level of 5.2 mg/dL to posttreatment level of 1 mg/dL), and serum tumor marker (CEA decreased from baseline level of 2493 ng/mL to posttreatment level of 439 ng/mL) were substantially improved. Unfortunately, a fatal hemorrhagic complication developed secondary to heparin-induced thrombocytopenia after the sixth course of treatment.

Abbreviations: CEA = carcinoembryonic antigen; RECIST = Response Evaluation Criteria in Solid Tumors

Figure 2. Computed Tomography Scans of Patient With Metastatic Colorectal Cancer Before and After Treatment

A 68-year-old male with colorectal carcinoma metastatic to the liver, peritoneum, and pelvic lymph nodes presented with tumor progression after extensive cytotoxic and biologic therapy with cetuximab and bevacizumab. Baseline serum bilirubin was 0.8 mg/dL; ALK, 316 IU/L; AST, 41 IU/L; ALT, 31 IU/L; LDH, 3210 IU/L; albumin, 3.9 g/dL; and CEA, 890 ng/mL. Comorbidities included type 2 diabetes mellitus, chronic renal insufficiency, hyperlipidemia, and chronic depression. The patient received 6 courses of therapy with a 1-month break between the fourth and fifth courses because of pulmonary emboli. There was overall improvement in performance status and tumor marker (CEA decreased from baseline level of 890 ng/mL to posttreatment level of 38.9 ng/mL). Extrahepatic tumor progression in periportal nodes and lung nodules was documented after 4 months. The CT scans show the liver at baseline (left) and after 4 courses of therapy (right). Imaging sections correspond to largest tumor diameters per RECIST guidelines. White arrows indicate tumor implants. (CT scan cuts were selected to capture largest dimension of lesions depicted). Abbreviations: ALK = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CEA = carcinoembryonic antigen; CT = computed tomography; LDH = lactate dehydrogenase; RECIST = Response Evaluation Criteria in Solid Tumors

Figure 3. Computed Tomography Scans of a Patient With Ovarian Cancer Before and After Treatment

Computed tomography scans of the liver of a 54-year-old woman showing platinum-refractory epithelial ovarian carcinoma at baseline (left panels) and after 6 courses of therapy (right panels). White arrows indicate tumor implants. (CT scan cuts were selected to capture largest dimension of lesions depicted). The patient had recurrent liver disease 14 months after her first course of therapy and further control of the liver implants was attained with a different hepatic-directed therapy.

Abbreviation: CT = computed tomography

Table 1

Treatment Regimen

Chemotherapeutic Agent	Route	Dose	Day
Oxaliplatin	Intra-arterial	100 mg/m ² over 2 hours	1
5-fluorouracil	Intravenous	Initial bolus 300 mg/m ² followed by a continuous infusion for 22 hours at 500 mg/m ²	2 and 3
Leucovorin	Intravenous	200 mg/m ² over 2 hours	2 and 3
Bevacizumab	Intravenous	7.5 mg/kg over 60-90 minutes	4

Table 2

Characteristics of Treated Patients

Patient	Diagnosis	Age, Years	Sex	Previous Treatments	Baseline Serum Bilirubin, mg/dL	Posttreatment Serum Bilirubin, mg/dL	Child-Pugh Score	Courses (N)	Response	Duration of Response, Months	Comments
1	Colorectal	59	M	FOLFIRI FOLFOX Irinotecan + Cetuximab Capecitabine	5.2	1.0	8 (B)	6	SD	4	Died of heparin-induced thrombocytopenia
2	Colorectal	68	M	FOLFOX FOLFIRI + Bevacizumab Irinotecan + Cetuximab	0.8	0.3	6 (A)	6	PR	4	Extrahepatic progression
3	Ovarian	69	F	Paclitaxel + Carboplatin Paclitaxel Azacytidine + Carboplatin	4.8	1.1	10 (C)	3	PD	–	–
4	HCC	25	M	5-Fluorouracil + Interferon	5.2	1.8	9 (B)	2	PR	1	Withdrew consent
5	Ovarian	54	F	Paclitaxel + Carboplatin Intraperitoneal Cisplatin and FUDR Topotecan Carboplatin + Gemcitabine Liposomal Doxorubicin Docetaxel Bevacizumab + Cyclophosphamide	0.5	0.3	5 (A)	6	PR	3	Increase in CA-125 leading to change in hepatic treatment
6	Colorectal	40	M	FOLFOX/FOLFOX + Bevacizumab Irinotecan + Cetuximab	0.2	0.2	5 (A)	7	SD	4	–

Abbreviations: FOLFIRI = 5-fluorouracil/leucovorin/irinotecan; FOLFOX = 5-fluorouracil/leucovorin/oxaliplatin; FUDR = floxuridine; HCC = hepatocellular carcinoma; PD = progression of disease; PR = partial response; SD = stable disease

Table 3

Clinical Toxicities Experienced by Patients

Adverse Event	Severity				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	3	1	1	0	0
Anorexia	2	0	0	0	0
Nausea	1	0	0	0	0
Vomiting	1	0	0	0	0
Constipation	1	0	0	0	0
Hemorrhage	0	0	0	0	1 ^a
Hypertension	2	0	0	0	0
Neuropathy	1	0	0	0	0

^a Heparin-induced thrombocytopenia (documented by ELISA with detection of anti-PF4 platelet antibodies).