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Gastroduodenal Ulcerations in Patients Receiving Selective Hepatic Artery Infusion Chemotherapy

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Ninety-three patients with liver metastases underwent selective hepatic arterial infusion of chemotherapeutic agents through a surgically implanted hepatic artery catheter and pump. Fourteen patients who developed upper gastrointestinal symptoms at some time during the course of treatment were found to have gastroduodenal disease endoscopically. The severity of symptoms did not necessarily correlate with severity of endoscopic findings. There was no temporal relation between 5-fluoro-2′-deoxuridine infusion and symptoms; however, with mitomycin C, symptoms worsened in five of eight patients within 2 wk of the initial injection. Patients who received mitomycin C had more severe endoscopic findings and two of the 14 patients required partial or total gastrectomy. When biodegradable starch microspheres were coadministered with mitomycin C this was not associated with a higher incidence of gastroduodenal disease. The early experience with therapy using this system has been associated with a significant incidence of upper gastrointestinal symptoms. The presence of gastrointestinal symptoms in such patients should alert one to potentially serious disease.

INTRODUCTION

Percutaneous hepatic artery infusion with chemotherapeutic agents in patients with hepatic metastases has been associated with improved clinical responses and prolonged survival (1–4) compared to controls given conventional systemic chemotherapy.

However, numerous complications have been described in patients treated with percutaneous hepatic artery catheters (1–11), including arterial thrombosis, catheter displacement, abdominal pain, gastroduodenal ulcerations, and upper gastrointestinal bleeding.

In an effort to avoid some of these complications, catheters placed surgically into the splenic or gastroduodenal artery with ligation of vessels supplying the stomach or pancreas have been used for delivery of chemotherapeutic agents. This results in perfusion of both lobes of the liver without flow to the stomach or pancreas. Restricted hepatic perfusion with chemotherapeutic agents having a high hepatic extraction ratio permits delivery of large concentrations while theoretically reducing systemic toxicity.

Since surgically implanted hepatic artery catheters have been used only recently, the natural history of associated gastroduodenal complications has not yet been described. In our present study, we describe the spectrum of such complications observed in a group of patients receiving 5-fluoro-2-deoxuridine (FUDR) and mitomycin C.

MATERIALS AND METHODS

Patient population

Ninety-three of 110 patients who received selective hepatic arterial infusion of chemotherapy drugs were followed for more than 2 months. The remaining 17 patients either were lost to follow-up, withdrew voluntarily, or died within the first 2 months from cancer progression. Of the remaining 93 patients, 14 were referred to the gastrointestinal service for endoscopy. All 14 patients had persistent midepigastric pain, nausea with vomiting, or evidence of gastrointestinal blood loss. All patients had taken antacids or cimetidine without relief before endoscopy. Their ages ranged from 38 to 70 yr with a mean age of 60 yr. There were seven males and seven females. The patients had metastatic disease to the liver from colon (11 patients), bile ducts (one patient), breast (one patient), and pancreas (one patient). Celiac and superior mesenteric angiography was performed in all patients before laparotomy and surgical catheter placement. At surgery, the silastic catheter was placed via arteriotomy into the gastroduodenal artery (nine patients), splenic artery (four patients), or dorsal pancreatic artery (one patient). In three of these patients, catheters in two different arteries were required to assure perfusion of both hepatic lobes. Any visible branches of the hepatic artery not perfusing the liver were ligated. Before chemotherapy treatment, total hepatic arterial flow through the infusion catheter was determined by nuclear angiography with technetium labeled macro-aggregated albumin (^{99m}TcMAA) (12–14). All patients received cimetidine and/or antacids

TABLE 1
Symptoms and Endoscopic Findings

Patient	Age/Sex	Symptoms	Drugs/Cumulative Dose	Microspheres with Mitomycin-C	Time from Initial Infusion to Symptoms/ to Endoscopy	Endoscopy Findings
CT	38/F	Anorexia, nausea, vomiting, epigastric discomfort	FUDR—515 mg Mitomycin—48 mg	Yes	8 days/4 mo	Diffuse gastric erosions, friability, focal hemorrhages which worsened in antrum and pylorus; duodenal edema and erosion
MM	66/F	Nausea, vomiting, wt loss	FUDR—1050 mg Mitomycin—20 mg	No	9 mo/15 mo	Diffuse gastric erythema; 2 × 2 cm antral ulcer along greater curve; 2 × 2 cm antral ulcer along posterior wall; pyloric channel ulcer; unable to enter duodenum
JW	66/M	Epigastric pain	FUDR—1275 mg Mitomycin—60 mg	Yes	2 mo/4 mo	Severe diffuse erosive gastritis
LB	49/F	Nausea, vomiting	FUDR—490 mg	No	7 days/53 days	Patchy gastric erythema
TW	65/M	Epigastric pain	FUDR—850 mg Mitomycin—60 mg	No	5 mo/9 mo	Antral ulcerations and severe duodenitis
RP	63/M	Nausea, vomiting	FUDR—375 mg Mitomycin—20 mg	No	Immediate/52 days	1.5 × 3.0 cm antral ulcer along lesser curve extending into pylorus
TN	70/F	Nausea, vomiting, abdominal pain	FUDR—650 mg	No	2 mo/3 mo	Erosive duodenitis
JR	53/F	Nausea, vomiting, epigastric pain	FUDR—1400 mg Mitomycin—15 mg	No	3 mo/3 mo	2.5 cm ulcer in fundus, just distal to gastroesophageal junction
FH	61/M	Nausea, vomiting, epigastric pain, anorexia, wt loss	FUDR—450 mg	No	12 days/19 days	Antral ulcer
LI	62/F	Epigastric pain	FUDR—680 mg Mitomycin—50 mg	No	50 days/21 mo	Antral gastritis
IF	70/M	Nausea, vomiting	FUDR—400 mg	No	Several days/13 days	Esophagus plus gastric ulcers
JM	70/M	Nausea, vomiting	FUDR—5500 mg	No	1 mo/19 mo	Antral erosions, erythema of body
RM	53/M	Anorexia	FUDR—670 mg Mitomycin—45 mg	Yes	4 mo/4½ mo	Linear esophageal erosions with friability; multiple gastric erosions
SB	52/F	Nausea, vomiting	FUDR—600 mg Mitomycin—10 mg	No	6 wk/3½ mo	Diffuse erosive gastritis with ulcerations and exudates along entire lesser curve; several discrete erosions along greater curve

immediately after surgery and throughout the treatment period.

Chemotherapeutic Agents

FUDR and mitomycin C were the two most commonly infused drugs. FUDR was given as a protracted infusion over 2 wk, alternating every 2 wk with normal saline. Mitomycin C was given either as a 1-min injection or 30-min infusion. All patients who were followed for more than 2 months received FUDR and 54 of 93 received mitomycin C. Of the 14 patients who underwent upper endoscopy, six received FUDR alone and eight received FUDR plus mitomycin C. Biodegradable starch microspheres were coadministered with mito-

TABLE 2
Patients Receiving Mitomycin

Patient	Cumulative Dose	Mitomycin-C with Microspheres	Worsening of Symptoms after Mitomycin Dose	Days to Endoscopy
	mg			
CT	16	Yes	Yes	35
MM	20	No	Yes	13
JW	30	Yes	Yes	8
TW	30	No	Yes	38
RP	20	No	No	52
SR	15	No	No	90
RM	80	Yes	Yes	15
SB	10	No	Yes	50

mycin C in three of 14 patients studied endoscopically, and in 37 of 93 overall. One patient received three separate infusions of starch microspheres with mitomycin C, one received two infusions, and one received only one infusion. In a fourth patient, pretesting with starch microspheres labeled with ^{99m}TcMAA demonstrated flow to the stomach and spleen, thus microspheres and mitomycin C were not coadministered.

RESULTS

The most common upper gastrointestinal symptoms were nausea, vomiting, and epigastric pain, which occurred in 13 of the 14 patients who were endoscoped (Table 1). The interval between the initial dose of chemotherapy and the development of symptoms was variable, ranging from several days to 9 months. In addition, the time for initiation of drug therapy to endoscopy varied from 13 days to 21 months.

The total dose of FUDR infused on an intermittent schedule in the 14 patients ranged from 375–5500 mg. Excluding the one patient who received 5500 mg over 19 months, the average cumulative dose of FUDR was 716 mg. One patient, RP, noted symptoms within 4 days of initiating a 2-wk infusion of FUDR (375 mg). A gastric ulcer was demonstrated endoscopically 2 wk after infusion of FUDR. The variability in interval before onset of symptoms may result from the difficulty of separating them from those commonly associated with the underlying metastatic disease (Table 1). In no patients who received FUDR alone were symptoms immediately worsened after infusion.

Mitomycin C was infused in eight patients. Cumulative doses ranged from 10–60 mg, with an average dose of 10–30 mg per infusion (Table 2). Five of the eight patients receiving mitomycin C developed symptoms within 2 wk of initial injection of the drug. Reinfusion with mitomycin C was associated with worsening of symptoms. All of the patients who received microspheres fell into this category. The time interval from infusion with mitomycin C to endoscopy ranged from 8–90 days.

A number of patients were taking drugs that are known to be gastric irritants. Four patients were administered prednisone, which was usually given as an initial dose of 60 mg, with rapid tapering. One patient was ingesting aspirin infrequently.

The endoscopic findings are depicted in Table 1. Gastric lesions were found in all patients and included patchy gastric erythema, diffuse erosions, and discrete ulcers. The two most severe cases, CT and SB, showed diffuse edema, with ulcerations involving the greater and lesser curves. Erosions and ulcers were seen in the duodenum in one patient and in the esophagus in another.

CASE REPORT

CT, a 39-year-old white woman underwent a modified left radical mastectomy for intraductal breast carcinoma. Three of 15 nodes were positive for metastasis. Breast tumor estrogen receptors were positive. While receiving systemic chemotherapy with prednisone, liver metastases were discovered. Because the patient failed on systemic therapy and because distant metastases were limited to the liver, a hepatic artery infusion catheter and pump (via the splenic artery) were surgically implanted and prednisone infusion initiated. A postoperative nuclear angiographic study with ^{99m}TcMAA showed perfusion of the liver but no other organs. After two 2-wk courses of FUDR totaling 515 mg shrinkage of the liver metastases was observed, but bone metastases developed. The third treatment consisted of 16 mg of mitomycin C coadministered with biodegradable starch microspheres infused via the hepatic artery over a 1-min period. During the last 30 s of infusion, the patient experienced burning epigastric discomfort. Because of persistent anorexia, she was begun on hourly antacids and Cimetidine with meals and at bedtime. Prednisone dose was tapered to 20 mg daily. Two weeks later she complained of persistent nausea, vomiting, and epigastric pain. Repeat liver spleen scan showed diminution in the size of the liver metastases. The same dose of mitomycin C and microspheres was infused over a 1-min period with the patient vomiting at the end of the infusion. Two weeks later a third dose of mitomycin C was infused. She was admitted to the University Hospital 3 wk later for evaluation of hematesesis which began 1 day before admission. Her other symptoms had persisted. Upper endoscopy revealed marked mucosal edema with erosions, focal hemorrhages, and fresh blood, predominately in the gastric fundus, with confluent ulcers and narrowing in the antrum. Multiple pyloric channel and duodenal bulb erosions were observed. For the next 4 wk, nausea, vomiting, and upper gastrointestinal bleeding persisted.

The patient required 19 U of blood. Upper endoscopy performed 1 month later showed minimal esophageal erythema and decreased distensibility of the fundus and body with extensive erosions and ulcerations overlying necrotic tissue. Despite discontinuing the selective hepatic chemotherapy, fibrosis and narrowing of the antrum had progressed to the point that a GIF-P_2 gastroscope could not be passed into the duodenum. The next day she underwent total gastrectomy with esophagojejunostomy. Subsequently, no further gastrointestinal bleeding occurred but the patient died 15 months later with extensive spinal metastases and sepsis.

DISCUSSION

Most patients treated with hepatic artery infusions have already failed systemic chemotherapy and thus have a poor prognosis. However, although no prospective, randomized study has been reported, response and survival rates appear to be improved after percutaneous or surgically implanted hepatic artery infusion chemotherapy (1–4, 7). Certain technological advances including surgical placement of silastic catheters and reliable infusion pumps for outpatient treatment make this mode of therapy more practical. As more physicians use this treatment, the potential for complications increases. Persistent upper gastrointestinal symptoms should alert one to potentially severe gastroduodenal disease.

Fourteen of our 93 patients (15%) were shown to have gastric or duodenal pathology. Undoubtedly this number underestimates the prevalence of gastrointestinal pathology since only those patients referred to the gastroenterology service were evaluated extensively.

The dose and time from initial infusion of FUDR to symptoms varied tremendously in the 14 patients. In contrast, symptoms worsened soon after initial infusion of mitomycin C. In all but one patient endoscopy was performed within 2 months after treatment with mitomycin C, because of worsening symptoms. Since all patients who received mitomycin C had also previously received FUDR, it may be the combination of drugs that is responsible for the pathology. Gastrointestinal symptoms developing after infusion of chemotherapy should not be confused with nonspecific systemic effects of the drug, until gastroduodenal disease is excluded since they can progress to severe complications including gastric outlet obstruction or massive hemorrhage.

Several possible mechanisms may be responsible for the development of the gastrointestinal lesions. The chemotherapeutic agents may be directly toxic to the gastric cells, causing cell death or alterations of the acid mucosal barrier. Preliminary evidence using tomography during hepatic arteriography has shown a small amount of blood flow to the distal stomach, which was not seen during HAPS scanning. This is consistent with the direct toxicity mechanism and explains the predominant antral involvement at endoscopy. Since these drugs are inhibitors of cell replication, and the gastrointestinal mucosa requires rapid cell turnover for maintenance of its integrity, it is possible that the resistance to injury is markedly diminished. These problems may be augmented by decreased gastric mucosal blood flow which may result from ligation of all branches of the hepatic artery not supplying the liver.

Many clinical studies have been performed using percutaneous hepatic artery infusion with mitomycin C, FUDR, or 5-Fluorouracil. Gastrointestinal toxicity reported in these studies include stomatitis, abdominal pain, nausea, and vomiting (16, 17). Less attention has been directed toward defining the cause of the symptoms or documenting gastroduodenal disease by endoscopy or barium studies. Four recent studies have observed gastric or duodenal ulcerations in patients undergoing percutaneous hepatic artery infusion with various drugs (1–4). In one study a patient developed gastric ulceration after accidental perfusion of the left gastric artery with mitomycin C and FUDR. Massey *et al.* (2) described duodenal ulceration in one of 40 patients after infusion with 27 g of 5-Fluorouracil over 21 days. Of 109 patients followed by Reed *et al.* (3), five developed gastric or duodenal ulcers during chronic percutaneous hepatic artery infusion with FUDR, with two deaths from ulcer perforation. Petrek and Minton (4) described six cases of upper gastrointestinal bleeding (three severe, three mild) in a group of 52 patients treated with percutaneous hepatic artery infusion with various chemotherapeutic agents. "Stress" gastritis and duodenal ulcer disese were found in their patients with severe disease.

The true incidence of gastroduodenal disease during hepatic arterial infusion with chemotherapeutic agents is unknown. Since damage is predominantly mucosal and the absence of symptoms may not exclude upper gastrointestinal disease, gastrointestinal endosopy is the preferred method of evaluation. Currently we are conducting a prospective, controlled trial in patients with liver metastasis from colon cancer to determine the true incidence of gastrointestinal lesions in patients undergoing hepatic artery chemotherapy.

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