Introduction

Fifty percent of patients with colorectal carcinoma can be expected to develop metastatic disease [1], while approximately 20% have isolated hepatic deposits as their index metastasis [1,2]. In those with hepatic lesions amenable to resection or surgical ablation, a 3-year survival of up to 60% can be obtained and a 5-year survival of 25–40% [1,3,4]. These figures compare with a 5-year survival of 1–3% and a mean survival of 7.5 months in untreated but apparently resectable hepatic disease [5,6].

Unfortunately, most patients with isolated hepatic metastasis are not candidates for resection due to widespread disease within the liver. Tumours larger than 3 mm are preferentially supplied by the hepatic artery in contrast to hepatic parenchyma [7,8]. Infusion of chemotherapy via the hepatic artery allows regional delivery of high doses of the agent without systemic toxicity. Meta-analysis and key randomised trials have demonstrated at least a doubling of response rate, significant survival advantage and improved quality of life when comparing hepatic intra-arterial chemotherapy to systemic chemotherapy or symptomatically treated controls [2,9,10–13].

The fluoropyrimidines floxuridine (FUDR) and 5-flourouracil (5-FU) have high first-pass extraction, allowing large doses to be infused via the hepatic artery with limited systemic effects. Placement of the arterial catheter is an operative procedure associated with minimal morbidity, but complications related to the toxicity of the agents infused are common and contribute to treatment failure [14].

Duodenal and gastric ulceration can complicate this type of therapy [15–17]. It has been ascribed to the delivery of chemotherapeutic agents to the gastroduodenum via aberrant vessels arising from the hepatic artery, distal to the infusing catheter [15,18]. The use of methylene blue injection into the hepatic artery catheter during upper gastrointestinal endoscopy has previously been described to detect unintended perfusion of the duodenum by these vessels [19,20] for evaluation of patients with pain following hepatic artery chemotherapy.

Background

Unintended perfusion of the gastroduodenum may complicate hepatic arterial chemotherapy leading to mucosal ulceration.

Patients and methods

In a review of 233 consecutive hepatic artery catheters placed, 61 patients were investigated for chemotherapy-related epigastric pain. Investigations included catheter imaging, upper gastrointestinal endoscopy with methylene blue injection via the hepatic artery catheter and angiography.

Results

Twenty patients (33%) demonstrated blue staining of the gastroduodenum. Angiography performed in 15 of these patients confirmed a misperfusing vessel in 13. The aberrant artery was successfully embolised and infusional chemotherapy recommenced in 11 patients. Forty-one patients had a negative dye test, of whom three had gastroduodenal ulcers, 14 had oesophagitis or gastroduodenitis, ten had catheter complications (leak \( n = 2 \), arteritis \( n = 5 \), pseudoaneurysm \( n = 1 \), sepsis \( n = 1 \)), three had liver collections, five had floxuridine cholangitis and one had myocardial ischaemia. No cause could be found in 8 patients. No patient with a negative dye test developed unintended perfusion on repeat investigation.

Keywords

gastroduodenal ulceration; hepatic arterial chemotherapy; unintended perfusion; pseudoaneurysm
We evaluated the investigation and management of patients presenting with pain following hepatic intra-arterial chemotherapy. In particular, methylene blue was injected via the hepatic catheter port during upper gastrointestinal endoscopy (methylene blue endoscopy or MBE) to diagnose unintended perfusion.

Patients and methods

The Liver Unit database was reviewed, containing prospective details of patients with hepatic tumours and endoscopy records. Two hundred and thirty-three hepatic catheters were placed at our institution for intra-arterial chemotherapy with either FUDR or 5-FU between September 1995 and December 1998. The 61 patients from this group investigated for epigastric pain or dyspeptic symptoms by MBE form the basis of this report. Fifty-nine had catheters placed either for treatment of unresectable hepatic colorectal metastasis or for adjuvant therapy in patients at high risk of recurrence following hepatic resection (n=12) or cryotherapy (n=13). Of the remaining patients, one had hepatocellular carcinoma and the other a neuroendocrine tumour. In addition, 9 patients underwent technetium-99m macro-aggregate albumin scintography after other investigations proved negative. Extensive attempts to establish the cause of pain were made in all patients. In those with demonstrated unintended perfusion, the results of attempted aberrant vessel embolisation were recorded, with the aim of recommencing hepatic arterial chemotherapy.

Hepatic artery catheterisation

The operative technique of catheter placement has been well described [15,21,22]. The right gastric artery is ligated and divided, the gastroduodenal artery is dissected out and controlled. Any arteries arising near the gastroduodenal origin are ligated, and the catheter is placed so that its tip lies just within the hepatic artery. Intraoperative perfusion of the liver and the absence of unintended perfusion are confirmed by injection of methylene blue via the catheter.

Chemotherapy

Patients with a subcutaneous port received two-weekly infusional chemotherapy with 5-FU via an external pump, which delivered 4 g over 4 days, in conjunction with oral folinic acid 15 mg tds. Patients with implanted pumps (Infusaid) were given FUDR at 0.18 mg/kg/day (range 0.1–0.3).

Gastroscopy and methylene blue test (MBE)

MBE was performed on all patients presenting with pain whilst undergoing hepatic infusional chemotherapy. After examination of the stomach and duodenum, 5 ml methylene blue was injected into the port over a 15–20 second interval. The port was then heparinised. A positive result is determined by instantaneous staining of an area of duodenum or stomach. Common areas of unintended perfusion include the first part of the duodenum, antrum, and lesser curve of the stomach.

Results

There were 233 patients in whom hepatic catheters were placed during this period for intra-arterial chemotherapy with either FUDR (63) or 5-FU (170). Sixty-one patients (26%) developed pain related to chemotherapy infusion and underwent MBE. There were 43 men and 18 women, with a mean age of 59 (37–79) years. Twenty of these patients had rapid blue staining of the stomach or duodenum at endoscopy (Table 1). Seven with positive MBE had ulceration at endoscopy. Fifty-five had catheter contrast radiology (portocathogram) before endoscopy, but in only one patient was unintended perfusion suggested by this investigation.

Fifteen patients with a positive MBE underwent subsequent hepatic artery angiography, confirming an aberrant artery supplying the gut in 13; two patients had no significant vessel demonstrated. The identified vessels were successfully embolised in 11 of the 13 patients, and chemotherapy was recommenced after repeat MBE without recurrence of gastroduodenal toxicity. Repeated embolisation attempts in 2 patients were unsuccessful due to technical inaccessibility of the misperfusing vessel. The 2

<table>
<thead>
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<th>Table 1. Outcome of patients with positive methylene blue endoscopy (MBE)</th>
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<tr>
<td><strong>Positive MBE</strong></td>
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<tr>
<td>20 blue staining endoscopy</td>
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<td>13 aberrant vessels causing unintended perfusion</td>
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<tr>
<td>11 successfully treated by angiography/embolisation</td>
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<td>14 of 20 recommenced chemotherapy</td>
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<td>6 of 20 did not restart chemotherapy</td>
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patients with vessels that could not be embolised had early recurrence of pain despite changing chemotherapeutic agents. The location of the aberrant vessels is listed in Table 2. Eight of these vessels were located beyond the scope of our dissection, but could have been found by skeletonisation of the hepatic artery.

Of the remaining 5 patients with a positive MBE, three had leakage of methylene blue directly into the duodenum related to erosion of the catheter into the duodenal wall. One had partial hepatic artery thrombosis secondary to arteritis causing retrograde flow of dye along the hepatic artery. On re-examination 6 weeks later the arteritis had resolved, and a subsequent MBE failed to demonstrate unintended perfusion; chemotherapy was recommenced successfully. The final patient, who was undergoing chemotherapy for neuroendocrine metastasis, had disease progression and was changed to octreotide.

Forty-one patients had a negative MBE, of whom 17 had other pathology detected at endoscopy. Three patients had ulcers without unintended perfusion, one associated with an underlying inflammatory collection from extravasation of the chemotherapy agent. Of 4 patients with oesophagitis at endoscopy, one had candidiasis and the others had additional non-endoscopic pathology (catheter sepsis, biloma collection, arteritis). Ten patients had gastritis/duodenitis, and two of these had other concurrent pathology (catheter sepsis, arteritis).

Of the 24 patients without positive findings at endoscopy, most had pathology determined by other investigations. Ten patients had catheter problems consisting of leak (n = 2), arteritis (n = 6), pseudoaneurysm (n = 1) or sepsis (n = 2). Three patients had liver collections, five had sclerosing cholangitis secondary to FUDR, one had ischaemic chest pain from 5-FU and a final patient had pain secondary to involution of hepatic metastases. In 8 patients no cause for the symptoms was established. No patients with an initial negative MBE went on to develop unintended perfusion, despite repeat endoscopy.

Operative findings
Approximately one third of the 61 patients in this series had aberrant arterial anatomy demonstrated at operation (eight accessory right and 11 accessory left hepatic arteries), but none of these patients developed unintended perfusion postoperatively. Of the 9 patients (15%) with unintended perfusion of the duodenum demonstrated intraoperatively, seven had successful ligation of the offending vessel. One patient went on to have subsequent embolisation of a small artery not located during operation before starting on chemotherapy, while the other developed pain and ulceration during the first course of chemotherapy due to a residual misperfusing vessel.

Time to symptoms
Most patients with unintended gastroduodenal perfusion by chemotherapy presented with pain within 6 months of catheter placement.

Discussion
Of the many potential complications following hepatic arterial chemotherapy, gastroduodenal ulceration secondary to unintended perfusion is important as a potentially avoidable cause of morbidity. Most patients presenting with symptoms suggestive of ulceration have another cause for pain, but endoscopy remains a central part of their evaluation, 37 (61%) of patients in this series having an endoscopic diagnosis. The occurrence of gastric or duodenal ulceration following hepatic artery infusional chemotherapy has been well described, but its relationship to aberrant arterial anatomy has not. In this series, patients with aberrant vessels perfusing the duodenum were able to avoid further gastroduodenal toxicity following successful embolisation. Those with failed embolisation suffered recurrent symptoms and ulceration.

Preoperative angiography is not performed routinely in our unit. Although some feel that detailed knowledge of anatomic variants is important before operation, we feel that the anatomy becomes clear during dissection or after methylene blue injection. Larger misperfusing or aberrant vessels can be dissected out and ligated intraoperatively.

<table>
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<th>Table 2. Aberrant vessels causing unintended perfusion</th>
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<tr>
<td><strong>Origin of vessel</strong></td>
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<tr>
<td>3 proximal to GDA origin</td>
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<tr>
<td>5 around GDA origin or hepatic artery</td>
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<tr>
<td>5 around or distal to hepatic artery bifurcation</td>
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<tr>
<td><strong>Comment</strong></td>
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<tr>
<td>Proximal reflux occurs with secondary vasculitis distal to catheter insertion</td>
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<tr>
<td>These branches should be ligated during routine dissection</td>
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<tr>
<td>Due to limited yield, dissection distal to hepatic artery not routine</td>
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<td>GDA = gastroduodenal artery.</td>
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In this series only five misperfusing vessels arose from near the gastroduodenal origin, within the scope of normal operative dissection. In addition, our work indicates that a negative intraoperative methylene blue test does not exclude the possibility of postoperative unintended perfusion.

Patients with misperfusing vessels arising proximal to the catheter insertion (n=3) demonstrate reflux into the common hepatic artery as an alternate cause of unintended perfusion. Increased distal resistance to flow from arteritis would seem a likely initiator of reflux. In our patients hepatic arteritis is a common phenomenon since most receive 5-FU infusions. In other published series of hepatic artery chemotherapy FUdR is usually the agent of choice, and complications related to arterial toxicity appear to be less common.

We have also noted the tendency of patients receiving 5-FU to present earlier with unintended perfusion than those receiving FUdR. In addition, some patients with misperfusing vessels do not develop ulceration despite prolonged infusion with FUdR. These findings support our belief that the greater tissue toxicity of 5-FU leads to more rapid development of ulceration than FUdR, but a larger series would be required to demonstrate statistically significant differences.

No patient with an initial negative MBE went on to develop unintended perfusion at a later stage, although many patients had multiple endoscopies (average 2, range 1–5). This fact establishes the reliability of the test as an initial investigation. Of 20 patients with a positive MBE, 14* had unintended perfusion due to aberrant vessels. As no patient was subsequently found to have unintended perfusion on later investigation by other modalities, the sensitivity of methylene blue endoscopy was 100% with a positive predictive value of 70%. The specificity (true negative rate) was 87%. False-positive MBE was due to overly rapid injection of dye in 2 patients, but in 3 patients it was due to catheter erosion through the wall of the duodenum while in another it was due to distal vessel obstruction by vasculitis.

During the study period several patients (n=6) presented with upper gastrointestinal haemorrhage. Hepatic artery chemotherapy has a recognised association with bleeding [21,24], but the mechanism has not been described. It can occur as a result of unintended perfusion-induced ulceration, but in this series only 1 patient with unintended perfusion presented with bleeding. In 5 patients bleeding was related to hepatic artery pseudoaneurysm (HAPA) or erosion of the catheter through the hepatic arterial wall, with subsequent fistulation into either duodenum or bile duct.

The relationship between unintended perfusion and pseudoaneurysm formation, the most serious complication of hepatic artery chemotherapy, is not known. In the present series only 3 of 14 patients with unintended perfusion went on to develop a pseudoaneurysm. Clearly the outcome may have been different if embolisation had not been performed. It is certainly possible that pseudoaneurysms are not related to unintended perfusion but to localised chemotherapy leaks with adjacent tissue injury.

In conclusion, our policy (Figure 2) for investigation of pain associated with hepatic infusional chemotherapy is:

*Includes one patient with neuroendocrine tumour who did not require angiography.
1. Portacathogram to exclude leakage from the catheter tip – usually into a localised collection
2. Methylene blue endoscopy
3. Hepatic arteriogram to exclude arteritis.

References


