Complications of reservoir hepatic arterial infusion chemotherapy.

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Learning objectives

To learn the several toxic effects of hepatic arterial infusion chemotherapy with their imaging findings. Because most of those complications are accompanied with hepatic artery stenoses or occlusions, repeat DSA via a reservoir is essential for early diagnosis of the arterial injuries and the prevention of the subsequent severe complications.
Background

In general, systemic chemotherapy is usually selected for colorectal cancer with distant metastases [1]. Recently, the standard regimens such as FOLFILI (5-FU plus leucovorin with oxaliplatin) and FORFOX (5-FU plus leucovorin and irinotecan) are used, and the median survival after FOLFILI and FORFOX has been reported to be 12.6-21.5 months [2].

On the other hands, the totally implantable drug infusion pump became clinically available in 1981 and provided a facile, dependable means of delivering chemotherapeutic agents. Hepatic arterial infusion (HAI) of antineoplastic drugs has been shown to be effective in the treatment of intrahepatic metastases, especially those from colorectal cancer. The use of an implantable pump permits continuous delivery of a high concentration of chemotherapeutic agent directly to the dominant focus of disease with little systemic toxicity. In 60%-70% of patients who have never undergone treatment for colorectal cancer metastatic to the liver, clearcut reduction in tumor mass occurs with HAI chemotherapy. In 30%-40% of patients in whom tumor masses progress after systemic chemotherapy, HAI results in tumor mass reduction. In a randomized study in which systemic administration was compared with HAI of fluoropyrimidines, the response rate following HAI was significantly greater (50% for HAI vs. 20% for systemic administration) [3]. In Japan, good results have been also reported after intermittent hepatic arterial infusion of a high dose of 5-FU: the response rate is reportedly 78% and the median survival time is 25.8 months [4].

Unfortunately, if not carefully monitored, local toxicity can limit the efficacy of HAI chemotherapy. Although initial results were very encouraging, it soon became obvious that such therapy was not without complications. Accordingly, we undertook a retrospective analysis of the medical records and imaging studies for 55 patients who received Fluorouracil via an HAI pump. In this article, we describe the rates and types of complications encountered in our series of 55 patients, and present illustrative cases, and discuss the efficacy and limitations of HAI chemotherapy.
Procedure Details

Between October 2006 and September 2010, 55 patients (59 procedures) with unresectable liver metastases from colorectal cancer underwent radiological placement of port-catheter systems at our institution. All procedures for the placement of port-catheter systems were performed by interventional radiologists in the angiography suite with the patients under local anesthesia. The procedure was performed as follows. All patients underwent angiography before catheter placement, which was performed using a 4 Fr angiographic catheter (Cathex, Japan) inserted from the femoral artery to allow arterial mapping and to prevent extrahepatic influx of the anticancer agents. The extrahepatic arteries branching from the hepatic artery, such as the right gastric artery, posterior superior pancreatoduodenal artery, and superior duodenal artery, were embolized with microcoils (Tornado; Cook, Bloomington, IN, USA) through a microcatheter inserted coaxially [5, 6]. In patients with more than two hepatic arteries, these arteries were converted into a single arterial supply by microcoil embolization so that drugs could be distributed to the entire liver using a single indwelling catheter [5]. Next, an indwelling catheter (Anthron P-U catheter; Toray Medical, Tokyo, Japan or W spiral catheter; PIOLAX, Yokohama, Japan) with a side hole was inserted using the catheter exchange method. The catheter tip was inserted into the deep segment of the gastroduodenal artery so that the side hole was placed into the common hepatic artery. The gastroduodenal artery around the tip of the indwelling catheter was embolized using microcoils through a microcatheter inserted coaxially via the 5 Fr indwelling catheter side hole (GDA coil method). When this method is failed, the indwelling catheter tip was directly placed into the proper hepatic artery (HA method). Finally, the proximal end of the indwelling catheter was connected to a port implanted in the subcutaneous pocket created usually above inguinal ligament. Digital subtraction angiography and C-arm CT were performed during injection of contrast medium through the implanted port-catheter system to confirm that the catheter was not dislodged and that the entire liver was perfused adequately.

An intraarterial pump (SFA-501W; Nipro, Tokyo, Japan) was connected to the implanted reservoir with a percutaneous needle. Infusion was performed at 0.3 mL/min continuously. Fluorouracil, 1750 mg/35 mL, was infused into the balloon of the intraarterial pump as a 7-day dose of the solution, and it was prepared so that the total volume would be 50 mL by adding dexamethasone palmitate emulsion (Limethason; Welfide, Osaka, Japan), which contains 4.0 mg of dexamethasone palmitate, including 2.5 mg of dexamethasone, as well as physiologic saline solution [7]. Heparin was not used. The balloon of the pump was changed every week, and the infusion was continued without off-period, if the toxicity was well tolerated [8].

Imaging Findings
During the implantation, arterial injuries (3%) [Fig. 1 on page], coil migrations (3%) [Fig. 2A on page, 2B-F on page], or catheter mislodgments (5%) [Fig. 3A-B on page, 3C on page] occurred. As early complications, puncture site hematoma (2%) [Fig. 4A-C on page], abscess (10%), aneurysm formation (2%) [Fig. 4D-E on page], and subsequent DVT (2%) were observed. In the late phase, hepatic arterial stenosis (10%) [Fig. 5 on page], occlusion (20%) [Fig. 6A on page, 6B on page, 6C on page, 7A-B on page, 7C-D on page], aneurysm (5%) [Fig. 8 on page, 9 on page], arterio-duodenal (7%) [Fig. 10 on page, Fig. 11A-B on page, 11C on page, 11D on page, 11E on page, 11F-G on page, 11H on page] and arterio-biliary (3%) [Fig. 12A on page, 12B-D on page] fistula, biliary stenosis (5%) [Fig. 13A-B on page], biliary-duodenal fistula (2%) [Fig. 13C-D on page, 13E on page], liver abscess (2%) [Fig. 14 on page], and breakdown of catheter [Fig. 15B-D on page] followed by skin necrosis (2%) [Fig. 15A on page] were identified. Embolization using coils etc., covered or bare stents, or open surgery were followed depending on the situations. Two patients (3%) caused massive bleeding from gastroduodenal artery into duodenum immediately after retrieval of catheters and required urgent embolization via collaterals. Totally 44 patients (80%) caused complications to terminate HAI.

Most of these serious complications accompanied with hepatic artery stenoses or occlusions. Thus, the authors speculate our continuous regimen may cause forceful injection of the drugs into the hepatic artery, resulting in direct tissue destruction around the hepatic artery. The other possibility to cause duodenal injuries is the toxicity of the drug to the gastrointestinal mucosa. It was thought that biliary elimination may bring the duodenal mucosa in contact with high concentrations of the drug, but there is little evidence that biliary metabolites are active or cytotoxic [3, 9, 10]. Because the blood supply to the upper common bile duct arises from branches of the hepatic artery [11], biliary injuries may result from direct perfusion of the bile ducts by high, local concentrations of the drugs [12]. Imaging studies in the region of the porta hepatis are usually compromised by the presence of metallic coils used at the time of catheter implantation. Thus the diagnosis of biliary and duodenal injuries associated with the hepatic artery may be better established by means of other methods such as magnetic resonance imaging. We encountered one case with liver abscess in this series, and spontaneous liver abscesses associated with massive tumor necrosis were reported in a previous series [13]. However, development of an intrahepatic abscess is an unusual complication of HAI chemotherapy. As the metastatic lesion outgrows its blood supply, central tumor necrosis provides a susceptible substrate for infection.

The toxicity of HAI chemotherapy is the major limiting factor. Our series, as compared with other major series reporting complications, yields a similar frequency of toxicity. HAI chemotherapy yields higher response rates than systemic therapy, but its impact on overall survival remains to be determined. In order to justify this procedure the drastic reduction of complications should be required. New drugs [14], radionuclides [15], DC
beads [16], and monoclonal antibodies [17] are being investigated in their potential combination with HAI (25,26) in the future.
Conclusion

Our survey of the toxic effects of HAI chemotherapy correlates with data published by other authors. The severity of these effects, the inability to predict and control them, and the morbidity due to systemic disease progression limit overall efficacy of this treatment modality. Because most of these serious complications accompanied with hepatic artery stenoses or occlusions, Repeat DSA via a reservoir is essential for early diagnosis of the arterial injuries and the prevention of the subsequent severe complications. In the future, it is hoped that, with the advent of new therapeutic agents, the current toxicity profile of HAI will be lessened and will no longer be the limiting factor of this treatment modality.
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