

Chemoembolization for Hepatic Malignancies

Michael C. Soulen, MD, Associate Professor of Radiology & Surgery, University of Pennsylvania, Philadelphia, PA

Objectives:

As a result of attending this session, attendees will be able to:

1. Identify patients suitable for local and regional therapies for liver malignancies.
2. Understand the physiological basis for regional therapy.
3. Perform chemoembolization, including pre-procedure assessment and peri-procedural care.
4. Provide peri- and intraprocedural care for patients undergoing regional cancer therapy, including pain control and prophylaxis and management of post-embolization syndrome.
5. Report the expected outcomes of regional therapy.

Hepatic metastases present one of the most challenging problems in clinical oncology. In the United States, metastases constitute the vast majority of hepatic malignancies (20-fold higher incidence than hepatoma). Among tumors metastatic to the liver, the most common is colorectal cancer, accounting for 155,000 new cases of liver malignancy and 60,000 deaths per year in the U.S. (1). Hepatic metastasis in colorectal cancer is associated with an extremely poor prognosis, carrying a median survival time of 6 months along with low (approximately 20%) response rates to 5-FU containing chemotherapy regimens (1). Other tumors frequently developing hepatic metastases include uveal melanoma, neuroendocrine tumors and gastrointestinal stromal tumors. As in colorectal cancer, hepatic dissemination of these malignancies is associated with resistance to chemotherapy and poor prognosis. Recently, alternative approaches to systemic chemotherapy have been developed to treat metastatic hepatic malignancies, including direct hepatic infusion of chemotherapeutic drugs via the hepatic artery or portal vein, selective tumor vessel embolization, percutaneous tumor ablation with various agents, as well as interstitial or intravascular administration of radiopharmaceuticals. All of these approaches seek to maximize tumor cell kill while minimizing toxicity to surrounding normal tissues.

Chemoembolization is a dual therapeutic approach involving concomitant hepatic artery embolization and infusion of a concentrated dose of chemotherapeutic drugs. This combined technique offers several advantages over either individual treatment modality. First, the addition of embolic agents slows efflux of drug from the hepatic circulation, allowing hepatic drug concentrations to reach levels 10-25 fold higher than those achieved by simple intra-arterial infusion (2, 3). Chemoembolization also appears to increase the duration of therapy effect, with measurable drug levels being detected as long as a month post-infusion (4, 5). Additionally, embolization of presinusoidal arterioportal shunts may facilitate selective drug delivery to the tumor, as the blood supply to normal liver is derived from the portal circulation while that supplying hepatic malignant cells is almost exclusively from the hepatic artery (6, 7). As a result, systemic toxicity is minimized even at high doses (8). Another advantage is that chemoembolization produces profound tumor ischemia at the time of drug administration. One physiologic consequence of ischemia, tumor hypoxia, is known to potentiate the effect of cytotoxic drugs such as doxorubicin by inhibiting intracellular P-glycoprotein pumps and increasing tumor cell uptake of drug (9). Hypoxia has also been associated with p53 stabilization, which should augment therapeutic efficacy by producing tumor cell apoptosis either directly or in combination with other ischemic stresses such as acidosis and hypoglycemia (10-12). For all

of these reasons, chemoembolization would appear to be a promising treatment strategy for hepatic metastatic disease.

Patient selection criteria

The most important factor when considering patients for regional chemoembolization is whether their metastatic disease is confined to the liver. While this is highly desirable, patients with minimal or indolent extrahepatic disease may be candidates if the liver disease is considered the primary source of morbidity. Tolerance of chemoembolization also requires sufficient portal vein inflow to allow hepatic artery occlusion. Portal vein patency should be assessed at the time of angiography. Patients with portal vein thrombosis can safely undergo the procedure provided that sufficient hepatopetal collateral flow is present (13). Caution should also be exercised in patients with hepatic parenchymal disease, in which the normal liver will be more dependent upon hepatic arterial blood flow. In particular, a subgroup of patients has been identified who should be excluded from consideration because of the high risk of acute hepatic failure. The exclusion criteria include a combination of greater than 50% liver volume replaced by tumor, lactate dehydrogenase >425 IU/L, aspartate aminotransferase >100 IU/L and total bilirubin >2.0 IU/L (14, 15). Hepatic encephalopathy and jaundice are also absolute contraindications to chemoembolization. Biliary obstruction, even with a normal serum bilirubin, should be considered a contraindication due to the high risk of biliary necrosis of the obstructed segment(s) of the liver following arterial embolization. The presence of a bilioenteric anastomosis or biliary stent predisposes to Gram-negative bacteremia and liver abscess formation in almost all such patients, presumably due to colonization of the biliary tree with intestinal flora (16). Finally, there are the normal contraindications to angiography, which include severe anaphylactoid reactions to radiographic contrast media, uncorrectable coagulopathy, renal insufficiency, and severe peripheral vascular disease precluding arterial access, as well as contraindications to chemotherapy such as severe cytopenias and impaired cardiac function (17).

Procedure and Peri-procedural Care

Pre-Treatment Assessment

Preoperative evaluation for chemoembolization includes a tissue diagnosis, cross-sectional imaging of the liver, exclusion of extrahepatic disease, and laboratory studies including CBC, PT, PTT, creatinine, liver function tests, and tumor markers.

Patient Education

Before embarking on this fairly arduous palliative regimen, patients should be thoroughly informed of the side effects and risks. Eighty to 90% of patients suffer a post-embolization syndrome, characterized by pain, fever and nausea and vomiting. The severity of these symptoms varies tremendously from patient to patient, and can last from a few hours to several days. Other significant toxicities are rare. Serious complications occur after 5%-7% of procedures (see below). Given the significant discomforts, hazards, and expense of this treatment, its palliative role should be clearly understood.

Procedure

Patients fast overnight, and are admitted to the hospital the morning of the procedure. Sample admitting orders to an Interventional Radiology service are illustrated in Figure 1. A

Foley catheter is inserted, and vigorous hydration is initiated (NSS at 200-300 cc/hr). Prophylactic antibiotics (cephazolin 1 gram, metronidazole 500 mg) and antiemetics (ondansetron 24 mg, decadron 10 mg, diphenhydramine 50 mg) are administered intravenously. The benefit of antibiotic prophylaxis is unproven. Patients with a bilioenteric anastomosis or biliary stent should receive a two-day pre-procedure bowel prep with oral neomycin-erythromycin, and stronger antibiotic prophylaxis in the hospital such as intravenous levaquin.

Diagnostic visceral arteriography is performed to determine the arterial supply to the liver and confirm patency of the portal vein or the presence of hepatopetal flow through collaterals to the liver in patients with tumor thrombus in the portal vein. The origins of vessels supplying the gut, particularly the right gastric and supraduodenal arteries, are carefully noted in order to avoid embolization of the stomach or small bowel. Replaced hepatic arteries are common and must be catheterized beyond any gastric or mesenteric branches. The origin of the cystic artery should be noted. Chemoembolization of the right hepatic artery proximal to the origin of the cystic artery is safe, but causes a sterile ischemic and/or chemical cholecystitis. This is an independent determinant for the severity and duration of post-embolization syndrome (14). Therefore, catheterization beyond the origin of the cystic artery is preferable.

Once the arterial anatomy is clearly understood, a catheter is advanced superselectively into the right or left hepatic artery, depending upon which lobe holds the most tumor. A 4F hydrophilic cobra catheter used with a hydrophilic guidewire suffices for about half of cases. Use of a standard 0.035"-0.038" lumen catheter allows rapid injection of the viscous chemoembolic emulsion and is unlikely to clog with particles. However, the catheter should not be used in vessels less than twice its diameter, as the catheter will cause a partial occlusion of the vessel lumen, resulting in pseudo-stasis. Withdrawal of the catheter then results in return of flow to the tumor. Small vessels and branches unable to be accessed with a standard angiographic catheter can be catheterized with a variety of microcatheters designed for hepatic chemoembolization. These catheters differ from standard microcatheters in that they have a slightly larger inner lumen and shorter overall length, which makes the injection of viscous chemoembolic emulsions easier.

When the catheter is positioned for treatment, it is important to perform an arteriogram to confirm the anatomy before injecting any chemotherapy. Microcatheters can be power injected at 2.5-4.0 cc/sec after lowering the pressure threshold on the injector to 300 psi. This superselective injection may reveal findings not depicted on the celiac or SMA injection, such as cystic, right gastric, or falciform arteries arising from the target hepatic artery, or guidewire-induced spasm in the target artery (Figure 2).

The chemoembolic mixture is injected until nearly complete stasis of blood flow is achieved. In our institution, we use 100-150 mg cisplatin, 50 mg doxorubicin, and 10 mg mitomycin-C dissolved in 10 cc of radiographic contrast and 10 cc of iodized oil. We typically emulsify 5 cc aliquots (2.5cc of chemo solution with 2.5 cc oil) at a time, and add 150-250 μ m polyvinyl alcohol particles to later aliquots once flow starts to slow. The patient receives intraarterial lidocaine (30 mg boluses up to 200 mg total) before and after each aliquot as well as intravenous Fentanyl and morphine to alleviate pain during the embolization. The endpoint is a "tree in winter" appearance, with elimination of the tumor blush, but preservation of flow in the lobar and segmental arteries, in order to allow repeat treatment in the future. Excessive embolization is probably the most common technical error. Typically catheters hold 1.0-1.5cc of emulsion, so the final flush of the catheter can convert a desired endpoint to complete stasis.

After the procedure, vigorous hydration (NSS 3L/24 hrs), intravenous antibiotics, and antiemetic therapy (ondansetron and decadron) are continued. Narcotics, perchlorpromazine, and acetaminophen are liberally supplied for control of pain, nausea, and fever. The patient is discharged as soon as oral intake is adequate and parenteral narcotics are not required for pain control. About half of patients are discharged in one day, most in two days. Oral antibiotics are continued for another five days, as well as antiemetics and oral narcotics if needed. The patient returns for a second procedure directed at the other lobe of the liver 3-4 weeks later. Depending upon the arterial anatomy, two to four procedures are required to treat the entire liver, after which response is assessed by repeat imaging studies and tumor markers.

Pitfalls

Scrupulous attention to hepatic arterial anatomy, variants, and non-target branches is necessary in order to avoid potentially devastating complications. A few other pitfalls should be kept in mind. Hypervascular tumors can create a sump effect, reversing flow in the gastroduodenal artery (GDA). Thus an SMA injection will fill the hepatic artery via an enlarged GDA, which sometimes is mistaken for a replaced right hepatic. Celiac injection will fail to opacify the GDA because of the flow reversal. This may be mistaken for an occluded GDA. After embolization of the tumor, the flow will revert to antegrade in the GDA. Thus it is important to have the catheter tip distal to the origin of the GDA in order to avoid non-target embolization after the direction of flow normalizes.

Stenosis or occlusion of the celiac axis or common hepatic artery may occur due to the median arcuate ligament of the diaphragm, tumor compression, prior surgery, pump therapy, or atheroma. Typically the liver tumor will be fed by reversed flow up the GDA. It is usually possible to catheterize the liver from the SMA via this route and treat the tumors despite occlusion of the celiac.

Hypervascular tumors near the periphery of the liver may parasitize blood supply from extrahepatic collaterals. Prior embolizations of the hepatic arteries can predispose to this, as the remaining viable tumor seeks other sources of blood. Clues to the presence of extrahepatic collateral supply include failure to completely opacify the entire tumor during hepatic angiography, or evidence on follow-up cross-sectional imaging of residual or recurrent viable zones in the tumor periphery. Extrahepatic collaterals can originate from inferior phrenics, intercostals, lumbar, internal mammary, mesenteric, epiploic, splenic, pancreatic, cystic, and gastroduodenal arteries. Flush aortography and selective injection of these vessels can identify collateral supply to the tumor. Chemoembolization can be performed through such collaterals if a sufficiently superselective catheter position can be obtained to avoid perfusion of the non-target tissue normally supplied by these vessels (18) (Figure 3).

Complications

Major complications of hepatic embolization include hepatic insufficiency or infarction, hepatic abscess, biliary necrosis, tumor rupture, surgical cholecystitis, and non-target embolization to the gut. With careful patient selection and scrupulous technique, the incidence of these serious events collectively is 3%-4%. Other complications include periprocedural cardiac events, renal insufficiency, and anemia requiring transfusion, with incidences of <1% each. Thirty-day mortality ranges from 1%-4%.

Patients may undergo chemoembolization many times, particularly those with neuroendocrine tumors who may live with their disease for several years. Repeated high dose

fluoroscopy over the right upper quadrant can achieve a cumulative dose high enough to cause radiation burns to the skin (18). Avoiding prolonged use of magnification, and periodically altering the beam entry angle helps to diminish this risk.

Results in specific diseases

The effectiveness of chemoembolization was initially demonstrated in nonrandomized retrospective studies involving unresectable hepatoma, where 1-year survival rates following chemoembolization were superior to both hepatic artery embolization alone and systemic chemotherapy (4, 19-23). Chemoembolization has subsequently become the standard of care for unresectable hepatoma, and more recent studies have explored its potential effectiveness in metastatic liver disease.

Colorectal metastases

Phase II studies for metastatic colorectal cancer have been conducted by several centers in the United States. Chemoembolization has generally been considered a last resort for patients with liver-dominant disease, and most patients enrolled in these studies have failed systemic and/or intraarterial infusion chemotherapy. In a study from L.S.U., a combination of superselective segmental and selective lobar injections of a doxorubicin-iodized oil emulsion was used on 46 patients (24). 59% of patients achieved stabilization or regression of disease, while 17% had a complete response. Actuarial survival was 68% at one year and 37% at 2 years. At the Boston Center for Liver Cancer, forty patients were chemoembolized with 5-FU, mitomycin-C, oil and gelatin sponge (25). 63% had partial or minor tumor morphologic responses and 62% had a decrease in CEA level greater than 50%. Median survival from first chemoembolization was 10 months. A number of prognostic factors were identified, including ECOG performance status (median survival 24 months for PS 0-1 vs. 3 months for PS 2) and absence of extrahepatic disease (median survival 14 months vs. 3 months if extrahepatic disease present). Among patients with good performance status and no extrahepatic disease, actuarial survival was 73% at one year and 61% at 2 years. Alkaline phosphatase or LDH levels more than three-fold above normal, as well as AST elevation above normal all predicted worse survival. At Northwestern, 30 patients were chemoembolized with cisplatin, doxorubicin, mitomycin-C (CAM) and bovine collagen (26). 95% of patients had a greater than 25% decrease in CEA level, 63% had a radiologic response defined as tumor necrosis or greater than 25% decrease in size by CT imaging. Median survival was 8.6 months from first chemoembolization and 29 months from diagnosis. At the University of Pennsylvania, 51 patients were chemoembolized with CAM, iodized oil and polyvinyl alcohol (PVA) (27). Morphologic stabilization or regression occurred in 72% of patients; CEA stabilized or decreased in 90%, median duration of response was 12 months. (Figure 4) Actuarial survival from diagnosis with metastatic disease was 86%, 55% and 23% at one, two and three years respectively, with a median of 24 months. While these results appear promising, it is important to remember that high rates of early response do not necessarily translate into improved rates of survival. The American College of Radiology Imaging Network (ACRIN) is currently funding a prospective multicenter randomized trial of systemic chemotherapy with or without chemoembolization for hepatic colorectal metastases to determine if chemoembolization provides a survival benefit.

Ocular melanoma

Approximately two-thirds of patients with ocular melanoma develop rapidly progressive hepatic metastases, the appearance of which is associated with a median survival of two to six months (28). These metastases generally do not respond to systemic chemotherapy (4-5% response rate), making chemoembolization a viable option. M.D. Anderson Cancer Center reported on thirty patients treated by serial chemoembolizations with cisplatin and PVA (29). Complete tumor regression was observed in one patient, while a 50% or greater reduction in tumor cross-sectional measurement was observed in 46% of patients. (Figure 5) Median survival was 11 months, with an actuarial survival of 33% at one year. Subsequent chemoembolization series have been less promising, with response rate and median survival ranging from 0-36% and 6-7 months respectively, neither of which is significantly better than systemic chemotherapy (30, 31).

Neuroendocrine tumors

Hepatic metastases develop in approximately 50-75% of patients with neuroendocrine tumors (32). Hepatic artery embolization has an established role in the palliation of these hypervascular tumors, typically producing symptom-free intervals of 5-10 months in 90-100% of patients (33, 34). Chemoembolization has been explored in the hope of obtaining a more durable therapeutic response. Several reports have examined chemoembolization of metastatic neuroendocrine tumors (35-38). These studies consistently demonstrated relief from carcinoid symptoms (flushing, diarrhea, wheezing) in 90-100% of patients, decreased hormone levels in 90% of patients and reduced tumor burden in 60-80% of patients. (Figure 6) Median survival following chemoembolization was approximately two years. One of the studies compared chemoembolization to hepatic artery embolization and showed that, although response rates were comparable between the two modalities, patients receiving chemoembolization had a shorter hospital stay and less therapy-associated morbidity (liver enzyme elevation and reported pain) (37). In a recent study from Italy, twelve patients with metastatic pancreatic endocrine tumors underwent chemoembolization as an adjuvant to primary tumor resection (39). Median survival was 35.4 months, suggesting that this combined approach merits further investigation. An important palliative role for chemoembolization may be to relieve symptoms in metastatic carcinoid patients who are refractory to medical therapy with somatostatin analogs. One study from Vanderbilt focusing on this group reported symptomatic relief in greater than 50% of patients following chemoembolization, as well as radiologic evidence of tumor necrosis or shrinkage in 85% of patients (40). While these data suggest therapeutic benefit, a prospective randomized trial is necessary to determine if there is enough additive benefit from chemoembolization to justify the additional risk and cost.

Sarcomas

Most sarcomas metastasizing to the liver are gastrointestinal leiomyosarcomas, which are notoriously resistant to chemotherapy. M.D. Anderson Cancer Center reported major regression of metastatic gastrointestinal leiomyosarcoma in 70% of patients with cisplatin/gelfoam chemoembolization followed by a two hour vinblastine infusion into the hepatic artery, with a median duration of response of one year (41). A similar response was observed at the University of Pennsylvania, where 69% of patients treated with CAM/oil/PVA exhibited a response at 30 days post-procedure, with extensive tumor necrosis on CT in all cases (42). Three tumors became resectable, The survival benefit was marked, with a median survival of 20 months and a

three year actuarial survival of 40%. Additionally, three tumors became surgically resectable following chemoembolization.

Hepatoma

Among combined series of 800 patients with unresectable hepatocellular carcinoma treated palliatively with chemoembolization in the Orient, Europe, and in the United States, response rates as measured by decreased tumor volume and decreased serum alpha-fetoprotein levels were 60-83% (3, 15-20). Cumulative probability of survival ranged from 54%-88% at one year, 33%-64% at two years, and 18%-51% at three years, with the best results obtained by repeated embolizations with a combination of iodized oil, gelfoam, and chemotherapeutic drugs. Survival varies directly with oil uptake and retention, and inversely with tumor volume, stage, and Childs class.

Despite the large volume of single-institution experiences with chemoembolization of hepatoma published over the past decade, few controlled trials have been reported. A metaanalysis published in *Radiology* in 2002 suggested a survival benefit from bland or chemoembolization over supportive or chemotherapy (43). A randomized controlled trial of chemoembolization with doxorubicin, Lipiodol, and Gelfoam versus supportive care for nonsurgical candidates from Barcelona in 2002 also showed a survival benefit from treatment (43). Similar results were reported from Asia this year as well (44).

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