Treatment of Liver Tumors with Transarterial Chemoembolization

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Liver cancer is the fifth most common cancer among men and the ninth most common cancer among women worldwide, and is the second most common cause of cancer mortality for men and women combined.¹ Moreover, liver cancer death rates currently have the most rapid rise of all cancer deaths among both sexes worldwide.² Chemotherapy treatment options have also been limited by general insensitivity to systemic chemotherapy.³

Transcatheter arterial embolization (TAE) was first reported in 1974 as a novel treatment for liver tumors.⁴ In the early 1980s, utilization of lipiodol allowed inclusion of chemotherapy and the practice of transarterial chemoembolization (TACE) became widespread.⁵ TACE combines conventional TAE with regional chemotherapy to selectively induce ischemia and chemotherapy effects within the tumor while minimizing damage to the untreated liver. It is currently indicated as the first-line treatment for patients with unresectable intermediate-stage hepatocellular carcinoma (HCC), for down staging patients to Milan's criteria for orthotopic liver transplant, as a bridging therapy to prevent transplant list drop off, and as a palliative treatment.^{6–8}

While different methods of embolotherapy are commonly used in the treatment of liver tumors, management is variable across medical centers. This article aims to provide insight into the factors the authors consider in their clinical practice when determining appropriate treatment for a patient.

Workup for Therapy

Guidelines currently recommend against using TACE when patients have limited life expectancy, severely compromised liver function (indicated by Child–Turcotte–Pugh [CTP] classification of late B or C),^{9,10} in the setting of diffuse or massive tumor involvement, significant portal vein invasion, extrahepatic spread, or main portal vein thrombosis.^{8–10} To maximize the success of TACE, it is important to have preserved liver function without significant tumor vascular invasion.

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Clinical Considerations

Laboratory tests and clinical examinations are critical to assess prior to performing liver-directed therapy (LDT). Patients are generally considered high risk if bilirubin ≥ 3 mg/dL, international normalized ratio (INR) > 1.5 , creatinine > 1.2 mg/dL, platelet count $\leq 60,000$ /mL, albumin < 3.5 mg/dL, ascites present, transjugular intrahepatic shunt (TIPS) present, CTP class B or C, model for end-stage liver disease score ≥ 15 , and Barcelona classification for liver cancer stage.¹⁰ That is not to say that therapy should be withheld in these circumstances; however, risk stratification is important for both informed consent and determination of ultimate eligibility for LDT. The authors integrate these data in conjunction with Eastern Cooperative Oncology Group to determine candidacy for TACE. These factors have variable weight on decision for therapy. The authors have safely treated patients with significantly elevated bilirubin or portal vein thrombosis; however, a native INR greater than 2.1 would be considered almost an absolute contraindication in the authors' practice.

Anatomic Considerations

Tumor extent and characteristics are best evaluated by preprocedural computed tomography (CT) or magnetic resonance imaging (MRI).⁹ For the best chance at obtaining a complete tumor response, diligent angiography and treatment of all vessels feeding the tumor are necessary. Untreated tumor supply virtually ensures incomplete response. The need for complete tumor embolization must be balanced with the amount of uninvolved parenchyma embolized and the patient's functional hepatic reserve. The decision on where to administer the chemoembolic agent is complex. More selective delivery is desirable when possible and may be better tolerated in terms of postprocedural symptoms or hepatic function, but runs the risk of incomplete tumor coverage. The authors have found cone beam CT (CBCT) invaluable in confirming complete tumor coverage; the authors routinely perform CBCT in all cases.

Identification of arterial tumor supply can be challenging. Patients with cirrhosis often have tortuous arteries and distorted segmental anatomy. Arterial overlap can be significant on 2D angiography, necessitating the use of multiple views or CBCT. Tumors can derive flow from more than one segment if they are in a "watershed" area, increasing the risk of incomplete response. It is often helpful to examine segmental arteries adjacent to the tumor, particularly in cases of incomplete response. Careful review of the preprocedural cross-sectional imaging can identify hepatic arterial variations and locations of tumors, and can often delineate arterial anatomy to the segmental level.

Extrahepatic supply is also common and further complicates complete angiography. Previously identified predisposing factors for extrahepatic supply include prior embolization, large tumors, or particular tumor locations. In the authors' practice, gastroduodenal arteriography is performed for tumors located in segment 2, 4, 5, or 8. There can be gastroepiploic supply even in a tumor that has not been treated previously. Right or left phrenic supply is often identified in lesions abutting the diaphragm. Supply to tumors can also be noted from renal, adrenal, intercostal, internal mammary/superior epigastric, and superior mesenteric arteries among others. For embolization of extrahepatic tumor supply, the authors tend to use bland particles or lipiodol, as extrahepatic deposition tends to be more significant, less avoidable, and the authors feel that the addition of chemotherapy adds to the overall risk. Review of the CT/MRI can be helpful to increase the yield of extrahepatic angiography.

While not necessarily as severe as with radioembolization, extrahepatic deposition of chemoembolic material can have

adverse consequences. Arterial–hepatic venous shunting can be challenging to quantify without a dedicated macroaggregated albumin (MAA) study, as one would do in the planning stages of radioembolization treatment. Examining hepatic venous opacification on preprocedural arterial phase imaging or CBCT can provide some estimate of pulmonary shunting. Initially delivering larger particles may be helpful to occlude the shunts and decrease amount of embolic delivered to the lungs. Chemical cholecystitis (cystic artery), diaphragm paralysis (phrenic artery), skin ulceration (falciform artery), and gastrointestinal ulceration (numerous, most common right gastric) have all been reported following chemoembolization. In situations where extrahepatic deposition is unavoidable by adjusting catheter position or coil embolization, usage of bland embolization and lipiodol rather than particles may be safer.

Angiographic Considerations

Careful and thorough angiography is important both to assure that all vascular supply to tumor is addressed and to simplify treatment planning for subsequent therapy. Single treatment with TACE is the exception, not the norm. Common hepatic angiography with either a left anterior or right anterior oblique to offset anterior and posterior branches of the right hepatic artery is important to demonstrate anatomy. The authors routinely perform angiography of the gastroduodenal artery in every case, as the gastroepiploic artery can be a source of tumor supply in many cases, even in patients without previous treatment (→ Fig. 1). Tumors in segments 4, 8, and 2 are most likely to present with gastroepiploic supply. After embolization

Fig. 1 Patient treated with transarterial chemoembolization. (a) Initial CT demonstrating hypervascular lesion (arrow). (b) Initial treatment at an outside hospital via a phrenic artery demonstrates partial hypervascularity. (c) Follow-up CT demonstrating residual disease (arrow). (d) Subsequent common hepatic angiography did not show the significant perfusion and as such (e) selective angiography of the GDA was performed. This demonstrated a branch of the gastroepiploic supplying the inferior margin of the tumor (arrow). This was embolized and (f) subsequent follow-up demonstrated lipiodol staining (arrow) but no residual enhancement.

of a tumor, it is important to assess potential collateral supply of a tumor as recollateralization will result in incomplete response. It is important to routinely assess vessels adjacent to a treated tumor, as collateralization will leave portions of the tumor perfused and not treated, decreasing response rate. It is common for tumors near the dome of the liver to develop supply from phrenic or intercostal arteries after prior TACE treatments.

Technical Considerations

Lastly, the local imaging environment should be considered. In medical centers with CT subtraction algorithms available, follow-up imaging of conventional TACE is less problematic. In the absence of these methods, drug-eluting beads (DEB) may be easier to assess tumor response with CT.

Embolization Types

Bland Transarterial Embolization

Bland embolization is defined as hepatic arterial blockade using gelatin sponge (GS), lipiodol without chemotherapy, or engineered particles, aiming at pure tumor ischemia.¹¹

GS was first reported clinically in 1964 as an embolic agent used to treat traumatic carotid cavernous fistula.¹² It has since been used for several tumors and bleeding conditions.¹¹ It is available as a biodegradable 40 to 60 μm powder or a sheet/sponge, and is regarded as an absorbable or temporary embolic agent.¹¹

Polyvinyl alcohol (PVA) particles were first reported as embolic agents in 1974,¹³ and have been used to treat several tumors and hemorrhagic conditions.¹¹ PVA beads range in size from 50 to 1,200 μm and are suspended in contrast media. The PVA particles adhere to the vessel walls, forming an intravascular lattice to which platelets aggregate. TAE with PVA particles is typically considered to be permanent, although it is possible for capillary proliferation to recanalize.¹¹ Microspheres were introduced in the 1990s to overcome the disadvantages of nonspherical PVA.¹¹ The spherical beads have a smooth hydrophilic surface, are compressible, and do not clump together as readily as PVA. Moreover, they can easily pass through a microcatheter and reach distal blood vessels.¹¹ Commercially available particles are generally 40 μm or larger; sizes smaller than 40 μm may shunt to the lungs. This means that the spheres will not penetrate to the level of the direct hepatic arterial–portal venous connections that average 15 μm in diameter, and as such they cannot block direct hepatic arterial to portal venous connections. This results in increased portal inflow, with the portal vein partially compensating for the loss of arterial flow.¹⁴ Although there is less pressure and venous blood flowing to the tumor, the tumor is still prevented from becoming completely hypoxic, as the tumor is able to extract oxygen from the portal vein.

Conventional Transarterial Embolization with Lipiodol

Lipiodol has the characteristics necessary to embolize small blood vessels as well as carry and localize chemotherapeutic

agents inside tumors.⁹ Because of its hydrophobic properties, lipiodol forms small micelles when mixed with aqueous solution, which can be driven into the sinusoids in the liver (**Fig. 2**). In general, lipid micelles as small as 10 μm can routinely be generated.⁹ The lipiodol in the sinusoidal spaces at this size allows interruption of both arterial and portal vein inflow. Lipiodol is removed from the liver via Kupffer cells and lymphatics. Since Kupffer cells are absent in HCC and the lymphatics are disorganized and ineffective, lipiodol selectively remains in tumor nodules at a high concentration from several weeks to more than a year. This has both diagnostic and therapeutic potential in HCC.

When performing bland embolization, the authors tend to start with lipiodol micellized between 2:1 and 4:1 ratios of lipiodol to contrast, which decreases the rate at which lipiodol is removed from the liver. This also allows occlusion of both small vessels and more proximal larger vessels not occluded with pure lipiodol. The lipiodol is driven directly in the portal venules to increase effectiveness of treatment like cTACE. With initial infusion of lipiodol, the hepatic venous outflow is carefully monitored. Properly micellized, no contrast should be seen in the outflow if there is no significant arteriovenous shunting. If significant shunting is observed, embolization with lipiodol is stopped and large particles are injected to prevent the intrahepatic shunts. Careful digital subtracted angiography is performed to assess for shunting of large particles. Lipiodol is infused until second or third order portal radicals are identified, at which time particles are injected to arterial stasis. Lipiodol embolization can often require greater patience than particles, as the lipid can often continue to progress forward despite greater than 5 beat stasis by angiography.

Conventional Transarterial Chemoembolization

TACE occurs when TAE is combined with chemotherapeutic agents. Anticancer drugs that are used include doxorubicin, epirubicin, aclarubicin, 5-fluorouracil, mitomycin, cisplatin, and styrene maleic acid neocarzinostatin, with doxorubicin and cisplatin being the most common.⁹ The chemotherapeutic agents suspended in aqueous contrast media are vigorously mixed with lipiodol by pumping the mixture between two syringes to prepare an emulsion. This should be done a minimum of 30 times to create more uniformly sized ($\sim 15 \mu\text{m}$) micelles so that the lipiodol can enter the sinusoids in the liver (**Fig. 3**). The ratio of lipiodol to doxorubicin that yields the best pharmacokinetics is two to four parts lipiodol to one part doxorubicin/aqueous solution.^{9,15} The excess volume of lipiodol results in water-in-oil emulsions with increased tumor uptake of doxorubicin while minimizing nontumor or lung uptake, compared with an oil-in-water type emulsion, with the secondary benefit of systemic concentrations of doxorubicin six times lower than with oil-in-water emulsions.¹⁵ The authors use 2:1 lipiodol: doxorubicin. The usual dose for doxorubicin is 10 to 70 mg per session, which can be dissolved in $<5 \text{ mL}$ of iohexol⁹; however, some investigators use up to 150 mg for a single

Fig. 2 (a) Rabbit liver tissue with sinusoids demonstrating lipiodol. Spiculated brown material in clear area (*small arrows*) is iodine from lipiodol as the lipid is removed by the fixation process. (b) Birefringence of iodine. (c) Tumor surrounded by micelles. (d) Magnification view. Arrows on the left of the image demonstrating tumor.

session.¹⁶ In the authors' clinical practice, 50 mg of doxorubicin dissolved in 5 mL of contrast is used for standard patients and 25 mg of doxorubicin is used in patients with significant liver decompensation and 5 mL of contrast to allow a 2:1 emulsion.

Transarterial Chemoembolization with Drug-Eluting Beads

TACE with DEB (DEB-TACE) can also be used when the microspheres themselves act as the drug carriers. The authors use 100 to 300 μm beads routinely, except in cases of significant hepatic arterial–venous shunting visible on CT prior to treatment. In this situation, larger particles are utilized (500–700 μm). Smaller particles (40–150 μm) are also available, with the theoretical benefit of more distal tumor penetration. The concentration of doxorubicin that can be locally deposited is significantly higher with DEB-TACE than with cTACE; however, in all cases the particles are too large to penetrate to the level of hepatic arterial–portal venous connections. It is also of note that the systemic dose of doxorubicin is significantly lower in DEB-TACE than in cTACE, allowing safe treatment in patients with significant cardiac dysfunction or patients who have reached their

lifetime maximum dose of doxorubicin. Drug-eluting beads can only bind positively charged chemotherapy of appropriate morphology that presently includes only doxorubicin, epirubicin, and irinotecan. When loaded with chemotherapy, the beads swell and are 30% larger than their calibrated size. As it is lactic acid released from the hypoxic tumor that facilitates drug release, lipiodol should never be utilized in conjunction with DEB-TACE, as the hydrophobic lipiodol shields the beads from contact with hydrogen ions from lactic acid, and prevent release of chemotherapy.

Pros/Cons to Different Methods

One major benefit to TACE is that the vascular embolization minimizes arterial blood flow to the tumor while also preventing the washout of the chemotherapeutic drugs from the tumor. This results in lower systemic drug levels/less toxicity and a high objective response rate compared with systemic chemotherapy.⁹ It is important to note that, to date, there is no evidence of superiority of any single chemotherapeutic agent in TACE or TAE versus TACE.^{11,17,18}

The most common complications of TACE are reversible elevations of hepatic transaminases and serum bilirubin without impacting overall prognosis, although it is possible

Fig. 3 Micelles in lipiodol after creating emulsion by pumping mixture between two syringes: (a) 5 times. (b) 10 times. (c) 20 times. (d) 30 times.

to see irreversible hepatic dysfunction.¹⁰ Postembolic syndrome resulting in transient fever and abdominal pain occurs in 60 to 80% of patients, and ischemic cholecystitis, hepatic abscesses, and biliary strictures occur in less than 10% of patients.⁹ Bile duct injury has been reported in 0.5 to 2% of cases,⁹ and gastrointestinal complications can arise if there is efflux of anticancer drugs into the gastrointestinal organs.¹⁰

Risk factors for hepatic failure after TACE include portal vein obstruction, biliary tract obstruction, a previous history of bile duct surgery, high doses of chemotherapeutic agents and lipiodol, high basal level of bilirubin, a prolonged prothrombin time, hepatic artery occlusion due to repeated or nonselective TACE, and advanced CTP class.^{9,10} In the authors' experience, TIPS or elevated INR have the highest correlation with significant liver dysfunction following TACE.

The authors generally have the highest complete response rates with cTACE. This may be related to greater hypoxia as well as treatment of the portal venous side of tumor where tumors are most likely to metastasize.^{9,19} Conventional TACE with smaller effective particle size can be driven into the sinusoidal space and portal vein (► **Fig. 4**), increasing hypoxia and treating small portal metastases which may decrease the rate of recurrence.¹⁴

Miyayama et al reported local recurrence rates of 85.7, 24.8, and 7.9% at 12 months and 85.7, 38.9, and 17.7% at 24 months, in no staining, staining of the portal vein adjacent to the tumor,

and staining of the portal veins in the entire embolized area of the tumor, respectively.¹⁴ Portal staining can be achieved if the micelles are made small enough ($<15\ \mu\text{m}$) to ensure that the lipiodol can enter the sinusoids, and this can only be achieved using a liquid embolic agent. For cTACE to be most effective,

Fig. 4 A patient demonstrating portal vein staining after transarterial chemoembolization. Portal vessels (arrows) are recognized by size relative to adjacent hepatic arteries and lack of continuity with hepatic arteries.

patience is required to allow the material to continue to wash in after stasis is achieved, allowing greater chemoembolic delivery and increase the success rates of portal staining. Moreover, occlusion catheters, such as the Scepter balloon and Surefire device catheters, can also be used. Since lipiodol is so easy to visualize, it also improves imaging in patients for whom ablation is used following TACE as the best clinical option.

Previous treatment with chemotherapy should be taken into consideration when choosing the method of TACE. For example, a patient who has had breast cancer or who has had significant doxorubicin for another malignancy can reach lifetime maximum recommended dose of doxorubicin. If this is the case, drug-eluting beads can be as the drug elutes slowly and keeps systemic levels of chemotherapy low enough not to be considered part of the patient's lifetime maximum dose of doxorubicin. Larger beads can also be considered in the setting of significant shunting of a tumor. It is also the authors' practice that if a patient has been treated unsuccessfully with TACE of one type (conventional or DEB), than the other type of TACE can be used for a subsequent treatment.

Beads loaded with epirubicin (the prodrug for doxorubicin, converted only in hepatocytes) can be used in patients with cardiomyopathy or in those receiving multiple TACE procedures. There is progressive cardiac toxicity with doxorubicin that does not occur with epirubicin. This relies on the tumor remaining differentiated enough to retain the metabolic apparatus to convert epirubicin to doxorubicin, and hence does involve some uncertainty in therapy.

If the patient is a transplant candidate, this may influence whether the authors pursue combination TACE/ablation in an attempt to cure disease or pursue primarily a bridging strategy until transplant.

Due to the absence of chemotherapeutic drugs, TAE results in lower toxicity than TACE,¹¹ and as such remains very useful in a robust interventional practice. Questions persist about the efficacy of TACE relative to TAE, and as such both should be considered effective modalities. One setback to using TAE with PVA beads is that the nonspherical beads tend to aggregate easily and occlude vessels more proximally than intended. In some cases, they can even cause microcatheter obstruction.¹¹ Because of the inconsistencies and issue of bead aggregation, the authors prefer microspheres and lipiodol. Caution is important with the small microspheres, as fatal pulmonary embolism has been reported in these cases where small microspheres were used for large HCC, due to the significant incidence of hepatic artery to hepatic vein shunting.¹¹

In performing TAE, the authors generally start with lipiodol micellized with contrast to improve small vessel occlusion. This is then followed with spherical particles to stasis. Beginning with lipiodol is beneficial as lipiodol can occlude sinusoids and small hepatic arterioles and portal venules improving hypoxia, with washout prevented by the particle embolization following lipiodol. Shunting is very easily identified with lipiodol and will favor the use of much larger particles to follow. Lipiodol is also cleared from the lungs without permanent small vessel occlusion. This results in a better safety profile than using small particles. The endpoint for TAE is stasis, preferably with visible staining of the portal vein from lipiodol.

Conclusion

Embolization remains the standard of care for HCC; however, careful technique can change response rates significantly. Careful procedural protocol and an understanding of the physiology of HCC are vital to maximize response to therapy.

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