Transarterial Therapy for Patients With Hepatic Malignancy

Transarterial interventions continue to play a key role in managing patients with hepatic malignancy.

BY MICHAEL J. WALLACE, MD, AND RAVI MURTHY, MD

Primary and secondary hepatic neoplasms are some of the most common tumors worldwide. In Western countries, hepatic metastases are the most common malignant hepatic neoplasms, whereas worldwide, hepatocellular carcinoma (HCC) is the most common primary visceral malignancy in adults.

The liver is a unique organ with dual blood supply. It derives 70% to 80% of its supply from the portal vein and the remaining 20% to 30% from the hepatic artery. Malignant tumors in the liver receive nearly all their nourishment from the hepatic arterial supply, whereas the normal hepatocytes are predominantly nourished by the portal venous supply. These observations are the basis for the development of transarterial therapy for hepatic neoplasia while preserving normal hepatic function. Locoregional therapies are indicated in the treatment of hepatic malignancy in those patients with disease limited to the liver or liver-dominant disease for patients who are not candidates for resection.

Various forms of catheter-directed hepatic therapies are currently in use, including hepatic artery embolization (HAE), transarterial chemoembolization (TACE), and transarterial radioembolization (TRE). Local ablative therapies, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are additional techniques that are also currently used alone or in combination with TACE to treat hepatic malignancies. Hepatic artery infusion via surgically implanted pumps and percutaneously placed catheters demonstrated optimistic initial response rates within the liver but failed to improve survival and thus have fallen out of favor.

TRANSARTERIAL CHEMOEMBOLIZATION

Mechanism of Action

TACE is a technique in which intra-arterial infusion of chemotherapeutic agents is combined with arterial embolization of the vascular supply to the neoplasm. In addition to the direct effect of ischemia on the neoplasm by embolization, hypoxia increases vascular endothelial growth factor and vascular permeability factor. The occlusion prolongs the transit time through the tumor vascular bed, theoretically increasing the contact time between the infusate and the neoplastic cells to increase tumor cell kill and programmed cell death (apoptosis). Measurable levels of chemotherapeutic drugs can be present in the tumor up to a month after chemoembolization.[1,2] The increased local drug concentration in the tumor is enhanced by the increased tissue permeability caused by hypoxia.

Ischemia also produces paralysis of the cell membrane adenosine triphosphate-driven pumps, responsible for drug resistance, resulting in higher intracellular concentrations of the infusate. Intratumoral drug concentrations are 10 to 25 times higher[3,4] than those that can be achieved by intra-arterial infusion alone. The overall effect is cytotoxic not only to the neoplasm but also to the vessels being embolized and infused, compounding the vasculitis and occlusion. The systemic toxic effect may be reduced by metabolism of the drug during its passage through the infused organ, thereby confining the higher concentration to the target organ. Within the liver, 85% of the infusate remains and is retained, thereby reducing systemic toxicity despite high intra-arterial doses.[5]

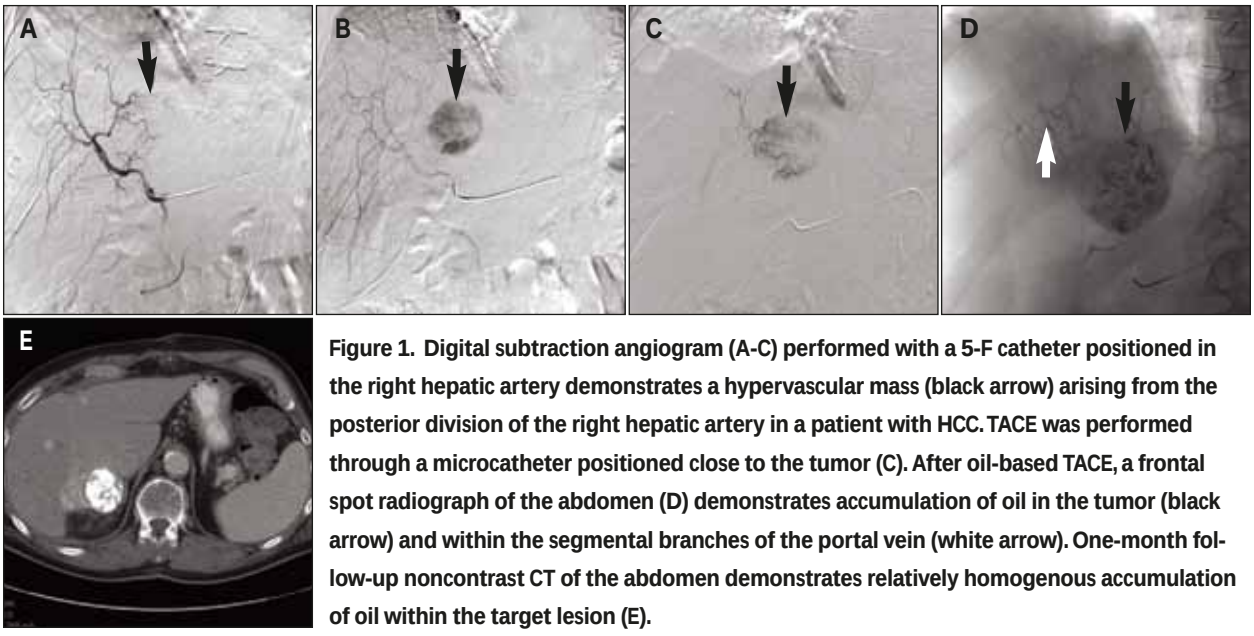

Figure 1. Digital subtraction angiogram (A-C) performed with a 5-F catheter positioned in the right hepatic artery demonstrates a hypervascular mass (black arrow) arising from the posterior division of the right hepatic artery in a patient with HCC. TACE was performed through a microcatheter positioned close to the tumor (C). After oil-based TACE, a frontal spot radiograph of the abdomen (D) demonstrates accumulation of oil in the tumor (black arrow) and within the segmental branches of the portal vein (white arrow). One-month follow-up noncontrast CT of the abdomen demonstrates relatively homogenous accumulation of oil within the target lesion (E).

Indications and Contraindications

Patient selection is critical to optimize tumor response and minimize complications to yield the best possible survival benefit. TACE is contraindicated in the presence of hepatic encephalopathy or jaundice. Patients at higher risk for acute hepatic failure after arterial embolization have (1) extensive hepatic replacement by tumor (>50%), (2) elevated lactic acid dehydrogenase (LDH) above 425 IU/L, (3) elevated transaminases with an aspartate aminotransferase above 100 IU/L, and (4) elevated total bilirubin >2 mg/dL.[6] Another subgroup at higher risk for postembolization complications includes patients with compromised portal venous blood flow. In the presence of hepatopetal flow, despite portal vein occlusion, TACE can be performed, with reasonable safety, utilizing superselective techniques to treat a smaller fraction of the liver with reduced doses of embolic materials and chemotherapeutic agents.[6]

Morbidity and Mortality

TACE does not appear to induce significant long-term worsening of liver function in patients with Child-Pugh class A or B cirrhosis,[7,8] but there is undoubtedly an increased local effect along with an acute increased toxicity and potential complications. Sakamoto et al reported an incidence of 102 (4.4%) complications in 2,300 TACE procedures for hepatic neoplasms. Of those related to the chemotherapeutic agents, 63 (1.8%) produced injury to the liver, including acute liver failure, liver abscess, intrahepatic biloma formation, liver infarction, and multiple intrahepatic aneurysms. Injury to extrahepatic structures, probably secondary to inadvertent TACE of adjacent arteries, occurred in 28 sessions (.09%), including severe cholecystitis, gallbladder and splenic infarction, gastrointestinal mucosal lesions (ulcer, especially along the lesser curvature of the stomach, from inadvertent right gastric TACE), pulmonary embolism or infarction, tumor rupture, and variceal bleeding. In 39 patients (1.7%), the complications were secondary to catheter or guidewire trauma leading to iatrogenic dissection, occlusion or vascular perforation.[9]

Song et al reported the incidence and predisposing factors for the development of postembolization liver abscess. In their series of 2,439 patients, a total of 6,255 chemoembolization procedures were performed. Fifteen abscesses occurred in 14 patients (0.2%) with an associated mortality rate of 13.3% (2 of 14). Abscesses developed in three of 987 (.03%) with portal vein obstruction, three of 114 (2.6%) with metastatic tumors, one of 49 (1.8%) with simple biliary obstruction, four of 55 (7.4%) with complex biliary abnormalities at risk for ascending infection, two of 18 (11.1%) for malignant gastrointestinal mucosal lesions, and nine of 2,108 (0.4%) for protocols including additional embolization with gelatin sponge particles.[10]

Technical Considerations

In Japan, the technique of TACE that has gained wide clinical application since 1983 is the use of embolic material mixed with chemotherapeutic agents and iodized oil (Lipiodol, Laboratoire Guerbet, Aulnay-sous-Bois, France) delivered into the arterial supply to a neoplasm followed by Gelfoam (Pfizer, New York, NY) or particulate embolization. The iodized oil acts as a contrast medium, an embolic agent, and as a vehicle or drug carrier. When injected

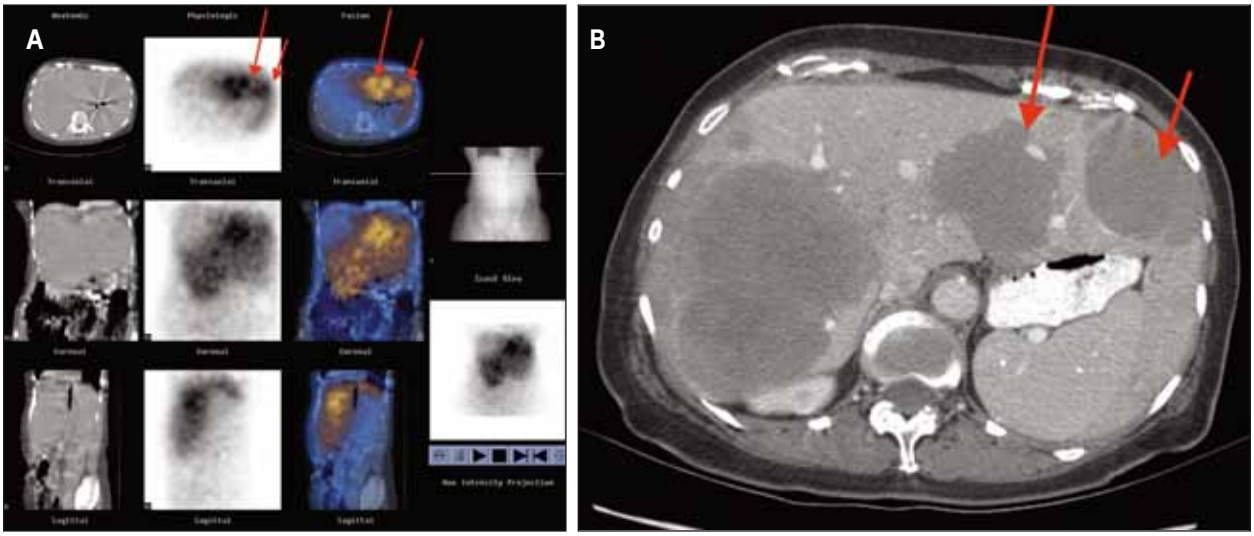

Figure 2. A 68-year-old woman with hepatic metastatic carcinoid malignancy. Thirty-five mCi of Y 90 microspheres was delivered via the left hepatic artery (A). SPECT-CT fusion Bremsstrahlung scans 36 hours after the treatment demonstrate preferential deposition within the metastases (arrows) that are more accurately depicted on the contrast-enhanced axial CT scan (B).

into the hepatic artery, the iodized oil rapidly enters the portal vein primarily through the peribiliary plexus, arteriolar-sinusoidal twigs, vasa vasorum, or by direct anastomoses, and passes through the sinusoids, into the hepatic veins and general circulation.[11] This results in a dual embolization (ie, the hepatic artery and portal vein) (Figure 1). There is temporary vascular and sinusoidal occlusion and congestion. Removal of the iodized oil is accomplished by re-establishment of arterial flow and phagocytosis of the oil by the Kupffer cells. Hypervascular hepatic neoplasms respond more favorably to TACE than lesions that are hypovascular.

Preliminary diagnostic celiac and superior mesenteric angiography is performed to assess the hepatic arterial supply (Figure 1A-C) and to document the patency of the portal vein. In addition to the identification of variant hepatic arterial anatomy, identification of the arterial supply to the gastrointestinal tract (left and right gastric, cystic, gastroduodenal, supraduodenal arteries, etc.) is also important to recognize and avoid in order to reduce the risk of nontargeted embolization. Portal vein evaluation is often satisfactorily demonstrated on preprocedural cross-sectional imaging. Portal venous investigation from the angiographic approach is only crucial when portal vein occlusion is encountered on pre-embolization imaging.

Once the appropriate target vessel is selected, the chemoembolic suspension can then be delivered until a reduction in arterial flow is accomplished. Some investigators advocate reducing arterial inflow to near stasis, and several different techniques and regimens for accomplishing this latter step have been described, including (1) delivery of particulate material followed by the chemotherapeutic agent, (2) suspension of particulate material in the chemotherapeutic agent, (3) incorporation of the chemotherapeutic agent into particulate form (microencapsulation, nanoparticles), (4) "emulsification" of lipiodol/ethiodol and the chemotherapeutic agent with or without subsequent particulate embolization, and (5) emulsification/suspension of iodized oil and the chemotherapeutic agent, and particulate material. Patients are usually admitted for 3 to 5 days after the procedure and given supportive care (hydration, pain control, and antiemetics) until they are able to tolerate oral intake. Follow-up sessions are scheduled at 4- to 6-week intervals until the entire liver or target region is treated.

TRANSARTERIAL RADIOEMBOLIZATION

Mechanism of Action

This relatively new therapy is now FDA approved for use in the US. Two products are commercially available—TheraSphere (MDS Nordion, Ottawa, Canada), and SIR-Spheres (Sirtex Medical, Australia), consisting of glass and resin microspheres, respectively. Classified as devices, they possess the pure high-energy beta-emitter Yttrium-90 (Y 90) as the active moiety that delivers tumoricidal radiation. When millions of these microspheres measuring between 20 µm and 40 µm in diameter are injected via the hepatic artery, they are preferentially distributed to the peritumor vasculature plexus wherein they are immediately trapped (ie, become embolized).[12] Y 90 has a half-life of 64.2 hours, and most of the effective radiation is delivered in the first week after administration. Both microspheres

are biocompatible and remain within the liver permanently. The device can be infused via appropriately positioned hepatic arterial ports or catheters. In the US, most patients are being treated on an outpatient basis.

Indications and Contraindications

Similar to TACE, patient selection is paramount to prevent adverse outcomes. At the time of this writing, intense investigations are underway to define the patient population that is most likely to benefit. Generally speaking, patients who are considered to be candidates for TACE, employing similar delivery techniques, would also be considered candidates for TRE.

Morbidity and Mortality

TRE and TACE are associated with a similar spectrum of toxicities with three exceptions: TRE can be associated with radiation pneumonitis, gastroduodenitis/ulcerations, and hepatitis.

Radiation pneumonitis is related to the embolization of radioactive microspheres into the terminal pulmonary arterial branches. Microspheres reach the pulmonary interstitium when they are injected via the hepatic artery by virtue of their passage through pathologic tumor-associated arteriovenous shunts that are of larger diameter than the microsphere. Fortunately, the presence of such shunts can be detected prior to delivery of Y 90 microspheres by utilizing technetium 99m macroaggregated albumin (Tc 99m MAA) as a surrogate. When Tc 99m MAA is injected via the hepatic artery, a quantitative analysis of their distribution that mimics the ultimate Y 90 microsphere distribution can be obtained scintigraphically. Radiation exposure to the lung exceeding 30 Gy will lead to clinically apparent, treatment-recalcitrant radiation pneumonitis. However, by extrapolation and adjusting the dose of Y 90 microspheres to maintain the lung exposure below this threshold, one can avoid this devastating complication.[13] As a testament validating this approach, in more than 1,500 treatments delivered to date in the US, there have been no reported cases of this entity.

Varying degrees of severity of radiation-related gastroduodenal injury can occur from the deposition of Y 90 microspheres into the gastrointestinal submucosal arterioles via nontarget delivery. The reported incidence is between 0% and 12%. Prevention is either by empiric fibered-coil embolization of the right gatric, gastroduodenal, and other unnamed branches supplying this region, or by infusion distal to such vessels or via a combination of both techniques.[14] Radiation hepatitis, more properly described as radiation-induced liver disease, is a forme fruste of hepatic veno-occlusive disease. It is a rare complication that is heralded clinically by the development of anicteric ascites resulting in varying degrees of hepatic decompensation. Treatment with steroids is generally ineffective at ameliorating the natural history of this entity.

HCC

HCC is the most frequent tumor worldwide, with an estimated 1 million deaths per year. In the US, between 6,000 and 9,000 new cases present each year. The presence and degree of liver dysfunction and cirrhosis, along with the presence of multifocal disease, can limit the utility of surgery, and thus less than 25% of patients with HCC are operative candidates. For patients who undergo resection, the overall 5-year survival rates range from 35% to 50%.[15-18] Orthotopic liver transplantation has become an additional surgical alternative when patients are not candidates for partial hepatectomy. The best survival rates for transplantation have been achieved in patients who fall within the Milan criteria (solitary HCC <5 cm in diameter, multiple HCC ≤ 3 tumors that are each <3 cm in diameter),[19] with 1- and 2-year survival rates of 90% and 85%, respectively.[20]

Systemic chemotherapy for HCC is disappointing due to the low response rates (20% to 30%) and lack of substantial improvements in overall survival. Although not currently considered the mainstay of transarterial therapy, HAE using particulate agents alone has demonstrated 1- and 2-year survival rates of 50% and 33%, respectively.[21] TACE is currently the most widely used primary treatment for unresectable HCC. Depending on the size (<3 cm) and tumor location, direct intralesional ablation therapy (PEI and RFA) can be utilized as a stand-alone approach or in combination with TACE. These locoregional therapies can also be utilized in liver transplant candidates awaiting transplantation as a means to prevent tumor progression.[22]

Results

The more common TACE regimens include doxorubicin, cisplatin, and/or mitomycin C. Despite the significant experience with TACE, early randomized controlled trials in the 1990s[2-27] failed to demonstrate a statistically significant survival benefit in patients treated with transarterial therapy compared to conservative therapy. Recent randomized clinical trials have shown significant survival advantage in patients treated with TACE compared to those treated conservatively.[28,29] A systematic review by Llovet et al[30] also demonstrated a significant survival benefit with TACE compared to conservative management. Oil-based regimens have produced 1-, 2-, 3-, and 4-year survival rates of up to 64%, 38%, 27%, and 27%, respectively.[31-33] The best results reported to date are from a study reported by Matsui et al[34] in which subsegmental TACE was used in 82 patients with nodular HCC (<4 cm in

diameter, Childs-Pugh classes A and B). The 1-, 2-, 3-, and 4-year survival rates were 100%, 92%, 78%, and 67%, respectively.

Combination Therapy

Several investigators have looked at combining TACE with percutaneous ablation. TACE + PEI has been reported to be more effective than each therapy alone,[35-37] with 1-, 2-, and 3-year survival rates of 100%, 85%, and 85%, respectively, for patients with solitary lesions larger than 3 cm.[35] Koda et al demonstrated a significant decrease in recurrence rate in patients that underwent combination therapy (TACE + PEI) compared to PEI alone.[37] TACE + RFA is a relatively new concept that lacks sufficient long-term follow-up data to make any assessment on survival or recurrence.

One recent article by Yamakado et al demonstrated overall 1- and 2-year survival rates of 100% and 93%, respectively, and 1- and 2-year recurrence rates of 15% and 43%, respectively, in 64 patients undergoing TACE-RFA.[38] In general, RFA is best suited for patients with Child-Pugh class A or B cirrhosis and a single, nodular-type HCC <5 cm or ≤ 3 HCC lesions, each lesion <3 cm when surgical resection or transplantation is not suitable. RFA performed after hepatic artery balloon occlusion, HAE, or TACE has been reported to increase the volume of coagulation necrosis, thus expanding its ability to treat larger lesions.[39-41]

Results With TRE

Historical data regarding the utility of Y 90 microspheres in the treatment of HCC comes principally from Hong Kong and Canada, with more recent published data available from the US. Independently, these studies demonstrated a favorable toxicity profile for the device and distinct dose-response[42,43] and dose-survival relationships;[42-44] patients who receive >100 Gy have a survival rate that is similar to that historically achieved with TACE.[45] In a large meta-analysis that included North American patients, several variables that prognosticated patients into a high-risk category for treatment included elevated serum bilirubin, presence of ascites, and elevated levels of serum transaminases.[46,47] Following TRE, patients have become resectable and have successfully undergone liver transplantation.[48] TRE has been safely performed in patients with segmental portal vein thrombosis.[49]

HEPATIC METASTASIS

Colorectal Metastasis

Colorectal cancer is the third leading cause of death in Western countries, behind lung and breast cancer. Nearly 40% to 50% of patients with colorectal cancer will develop hepatic metastases. Hepatic resection is the only potentially curative therapeutic option available for patients with isolated liver metastases. Recurrent disease occurs in up to 60% of patients, with 5-year survival rates ranging from 25% to 40%.[50-52] Despite 31% to 50% higher response rates with hepatic artery infusion therapy in patients with unresectable disease, there has been no significant improvement in survival.[53]

TACE for colorectal hepatic metastases has also been reported to provide no significant improvement in response or survival.[54] At the M.D. Anderson Cancer Center, we currently do not perform TACE in patients with metastatic colorectal carcinoma because the survival rates have not improved compared to the less-aggressive approaches. However, Lang and Brown,[55] and Pentecost et al[56] are encouraged by their results for TACE of hepatic metastases from colorectal cancer, and they believe that the technique can be recommended as palliative treatment. More recently, Pajkos et al treated 41 patients with metastatic colorectal carcinoma to the liver with chemoembolization consisting of doxorubicin, mitomycin C, cisplatin or carboplatin, lipiodol, and starch microspheres every 6 weeks, as well as systemic 5-fluorouracil and leucovorin. The response rate was 68% with a median survival time of 15 months.[57]

In this patient population, TRE has produced significant responses and clinical benefits that are augmented with chemotherapy. In the Australian phase III trial that led to FDA approval, an increase in time to tumor progression from 9.7 to 15.9 months (P=.01) was considered clinically relevant when a single dose of Y 90 microspheres was administered along with intra-arterial floxuridine.[58] More recently, a phase II randomized trial incorporating the administration of a single dose of Y 90 microspheres with a standard regimen of 5-fluorouracil/leucovorin demonstrated, among others, a survival benefit in the combination arm (29.4 vs 12.8 months).[59] Phase I trials combining irinotecan and oxaliplatin demonstrates that Y 90 microspheres are compatible with these agents in the dose ranges currently used in practice, paving the way for integration of these agents into the current therapeutic armamentarium.[60,61]

Neuroendocrine Metastases

Islet cell carcinoma and carcinoid tumors are rare neoplasms that account for less than 1% of all malignant disorders in the US. The incidence in the US is estimated to be one to two cases per 100,000 people.[62] The majority of patients present with metastases and a resulting 5-year survival of only 10%, with a mean survival rate of 24 months.[63,64]

Both embolization and chemoembolization strategies have been utilized with success in the management of

hepatic involvement. There has been no randomized comparison between these two techniques to demonstrate any clear advantage of adding a chemotherapeutic agent.

Moertel et al have chronicled their 10-year experience in 111 patients with neuroendocrine hepatic metastases, usually hypervascular, receiving vascular occlusion therapy by a variety of methods.[65] Seventy-one patients also received subsequent alternating chemotherapy regimens. Objective regression rates of 60% with vascular occlusion alone and 80% with sequential therapy of vascular occlusion and chemotherapy were observed. A median survival time of 37 months was experienced in patients with islet cell carcinoma, whereas the median survival in patients with carcinoid hepatic metastases was 49 months. Repeated embolizations were preferred.

Gupta et al recently reported the M.D. Anderson Cancer Center experience in 123 patients with carcinoid (n=69) and pancreatic islet cell carcinoma (n=54) metastasis who underwent either hepatic embolization or TACE. Patients with carcinoid tumors demonstrated a higher response rate (66.7% vs 35.2%) and longer progression-free survival (22.7 vs 16.1 months) compared to patients with islet cell carcinoma. Additionally, carcinoid patients treated with embolization had a higher response rate than those treated with chemoembolization. Islet cell carcinoma patients treated with chemoembolization demonstrated a prolonged survival (31.5 vs 18.2 months) and improved response (50% vs 25%) compared with patients treated with embolization.

The benefits of TRE in this patient population are yet to be determined. Preliminary studies have demonstrated that the therapy is tolerated well in patients who are not optimal candidates for, or who have experienced excessive toxicities from TAE or TACE.

Ocular Melanoma

Ocular melanoma can arise from various structures within the eye and accounts for 70% of all primary malignancies of the eye. At the time of diagnosis, metastases are uncommon but appear in 19% to 35% of patients within 5 years. Unlike cutaneous melanoma, metastases from uveal melanoma are most commonly found within the liver in more than 50% of patients,[66] followed by lungs, bone, and skin. Cutaneous melanoma preferentially spreads to lymph nodes, lung, and brain rather than the liver. Metastatic uveal melanoma has a poor prognosis, with a >50% mortality rate within 5 months.

Cisplatin-based chemoembolization for hepatic metastases from ocular melanoma produced a response rate of 46% and a median survival period of 11 months.[67] The longest survivor was 5 years from the initial chemoembolization. In a larger series, Bedikian et al reported 201 cases of uveal melanoma with hepatic involvement that were treated at M.D. Anderson Cancer Center over a period of 2 decades. Cisplatin-based chemoembolization regimens yielded a 36% rate of response compared to systemic therapies that only produced a 1% response rate.[68]

Leyvraz et al[69] reported a 40% response rate in 30 patients undergoing intra-arterial chemoinfusion therapy with fotemustine. The median survival of treated patients in their series was 13 months, with three patients (10%) surviving more than 20 months.[69]

CONCLUSION

Despite the multitude of endovascular and percutaneous locoregional treatment options for unresectable liver cancer, there is no one approach that reigns supreme for all patients. A treatment plan must be tailored to the individual patient and to the size, location, distribution, and type of malignancy to yield the best chance for improving survival. Prospective studies comparing these approaches as stand-alone or combination therapies will be required to determine the best treatment algorithm. ■

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