Chapter 10
Minimally Invasive Therapies for Hepatocellular Cancer: Catheter-Directed Therapies

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Abstract Techniques have been developed for catheter-directed delivery of therapy for hepatocellular carcinoma (HCC) since the 1980s, and are still undergoing evolution. Currently, this involves embolization with particles, as well as delivery of chemotherapeutic agents with a variety of materials, and is referred to as transarterial chemoembolization (TACE). TACE is made both feasible and effective due to the dual blood supply of the liver. Advances in catheter and guide wire technology have been accompanied by the development of techniques for the superselective placement of catheters for the safe and effective delivery of therapeutic agents to hepatic tumors. TACE is recommended for patients with Intermediate Stage, multinodular HCC (Okuda Stage 1–2; Childs-Pugh Stage A-B; Performance Status 0). Combination therapy with RFA and TACE may lead to more extensive tumor necrosis than mono-ablative therapy and may be a more effective treatment for HCC. Further study will be needed to determine the effectiveness of combining RFA and TACE, and in which order. The combination of TACE with antiangiogenic agents, such as sorafenib, is under investigation as well. The use of sorafenib may curtail the post-TACE rise in VEGF-mediated signaling, and simultaneously target tumor foci distant from the site of treatment. Selection parameters and treatment outcomes for locoregional therapies, alone or in combination, such as thermal ablation and TACE, with or without systemic chemotherapy agents will eventually be factored in generating Digital Patient Models (DPMs) to facilitate diagnosis, prognosis, and treatment selection, i.e. Model Guided Therapy (MGT) and Predictive, Preventive and Personalized Medicine (PPPM).

Keywords Personalized medicine · Hepatocellular carcinoma · Locoregional therapy · Treatment · Transarterial chemoembolization (TACE) · Drug-eluting beads · Sorafenib

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10.1 Introduction

Techniques have been developed for catheter-directed delivery of therapy for hepatocellular carcinoma (HCC) since the 1980s, and are still undergoing evolution [1–4]. This has included bland embolization with particles, as well as delivery of chemotherapeutic agents, with a variety of materials, referred to as transarterial chemoembolization (TACE). (Radioembolization with Yttrium-90 microspheres is discussed in Chap. 11.)

10.1.1 Transarterial Chemoembolization for Hepatocellular Carcinoma

TACE is made both feasible and effective due to the dual blood supply of the liver. HCC derives 95% of its blood supply from the hepatic artery, whereas normal hepatic parenchyma is supplied 75 and 25% by the portal vein and hepatic artery, respectively. (These differences in arterial supply account for the detectability of early HCC on dynamic, contrast-enhanced computed tomography [CT] and magnetic resonance imaging [MRI] as described in Chaps. 3 and 4). Advances in catheter and guide wire technology have been accompanied by the development of techniques for the superselective placement of catheters for the safe and effective delivery of therapeutic agents to hepatic tumors.

As indicated by the Barcelona Clinic Liver Cancer (BCLC) Staging Classification and Treatment Schedule [5, 6] TACE is recommended in patients with Intermediate Stage (Okuda Stage 1–2; Childs-Pugh Stage A–B; Performance Status 0) with multi-nodular HCC. Relative contraindications to TACE, which are evolving as increasing experience is gained, have included: greater than 50% liver involvement (although patients may be consider for staged procedures); LDH > 425; AST > 100; total bilirubin > 2; biliary obstruction; stent; anastomosis; and portal vein invasion or occlusion. Childs-Pugh Class B and C cirrhotic patients, as well as patients with end stage HCC, are at an increased risk of liver failure and death and are not appropriate candidates for TACE [3].

Two different basic methodologies have developed over the years for the transcatheter delivery of chemotherapy to hepatocellular carcinoma.

10.1.1.1 Iodized Poppy Seed Oil

The first method utilizes iodized poppy seed oil, which is injected into the hepatic artery, and remains preferentially localized within the neovascularity of HCC. The oily substance serves as a vehicle for the delivery of cytotoxic agents to tumor sites in the liver. Cytotoxic agents which have been used include doxorubicin (Adriamycin), 5-fluorouracil, cisplatin, and mitomycin. The poppy seed oil, combined with embolic particles, causes ischemia and prolonged contact of the chemotherapeutic

agent with the tumor. The dose of doxorubicin typically ranges from 30 to 75/m^2, to a maximum of 150 mg, which is usually mixed with 5 to 20 mL of lipiodol [7].

10.1.1.2 Drug-Eluting Beads

The second method for transcatheter delivery of chemotherapy to HCC utilizes drug-eluting beads or particles (DEB-TACE) to carry and deliver the chemotherapeutic agent. At the time of this writing, particles in use include 100–300 μm alcohol-sodium acrylate microspheres (QuadraSphere microspheres) and polyvinyl alcohol (PVA) hydrogel that has been modified with sulphonate groups (DC Beads). For patients with single tumor < 5 cm, or multiple tumors (up to three, < 3 cm each), each single treatment should include a planned dose of 50 to 75 mg doxorubicin loaded into one vial containing 2 mL of DC Beads (loading dose, 25 to 37.5 mg doxorubicin/mL of beads). For patients with more advanced disease each single treatment should include a planned dose of up to 150 mg doxorubicin loaded into two vials of DC Beads. In huge or bilobar tumors, treatment typically includes separate sessions approximately 4 weeks apart, in the absence of complications that would require a longer time interval between the two sessions. Obtaining confirmation that the liver enzymes have returned to baseline before performing the second treatment session is recommended [7].

The beads are allowed to remain in a container with the chemotherapeutic agent prior to administration, to allow the agent to be absorbed by the beads. After catheter delivery, the particles remain lodged in the injected hepatic arterial branches, so that the cytotoxic agent is eluted over a prolonged period of time (7–10 days) to tumor sites in the liver. As stated above, at the current time, the cytoxic agent most commonly employed is doxorubicin (Adriamycin). The drug-eluting particles produce tumor ischemia and prolonged contact of the chemotherapeutic agent with the tumor.

Compared with TACE performed with poppy seed oil, TACE performed with drug eluting beads is reported to have a more standardized methodology, to be more reproducible, and to offer improved response and a significantly better safety profile [7, 8]. The improved safety profile is related to the decreased levels of cytotoxic agent found in the system circulation found with drug eluting particles.

10.1.2 Indications for TACE

Current indications for TACE include: (1) primary treatment for those patients with intermediate stage HCC who are not eligible for liver transplantation, patients and cannot receive RFA due to comorbidities or tumor locations; and (2) for downstaging of tumor prior to transplantation [3]. A recent meta-analysis of 7 trials including 545 patients undergoing treatment for unresectable HCC showed a survival benefit at 2 years for those who were treated with TACE compared to controls [9].

In a small trial of 30 patients with tumor burden that exceeded transplantation criteria, 21 (70%) were down-staged to within UCSF transplantation criteria by using TACE [10]. Although data supports TACE as an effective method to down-stage tumors, post-transplant outcomes from patients who have undergone TACE down-staging are largely unknown [3].

TACE is a relatively safe procedure in a carefully selected population. Patients without portal blood flow may be at risk for extensive tumor and nontumor liver necrosis after TACE which can result in liver failure. Therefore, TACE has not been recommended for patients with portal vein invasion by HCC according to the Barcelona Clinic Liver Cancer (BCLC) Staging System [5, 6]. However, more recent studies have shown that TACE is safe and beneficial in patients with both peripheral portal vein invasion, as well as central portal vein invasion, if there is sufficient collateral flow [11].

Adverse events associated with TACE are seen in approximately 10% of patients with a patent portal vein and include hepatic failure, pulmonary embolism, acute renal failure, infection, biliary infarction, and gastrointestinal bleeding [12]. Post-embolization syndrome which consists of fever, abdominal pain, and intestinal obstruction is seen in greater than 50% of patients and usually resolves completely within 48 h.

10.1.3 Combination of RFA and TACE

Combination therapy with RFA and TACE may lead to more extensive tumor necrosis than mono-ablative therapy and may be a more effective treatment for HCC [13]. A randomized controlled trial (RCT) of 291 patients, predominantly with hepatitis B and with >3 cm lesions from a single center in China have shown a mortality benefit from combination therapy with when compared to TACE alone or RFA alone (median survival 37 vs. 24 vs. 22 months respectively) [14]. There was no significant difference in complication rates among the three groups of patients in this study. Further study will be needed to determine the effectiveness of combining RFA and TACE in different patient populations, as well as the order in which these locoregional treatments are to be administered.

10.1.4 Chemoembolization and Portal Vein Embolization Prior to Surgical resection

Portal vein embolization is a catheter-directed technique with an entirely different purpose than TACE. Techniques were developed to embolize the contralateral lobe of the liver, prior to surgical resection of the hepatic lobe harboring the HCC. This was performed to induce compensatory hypertrophy of the embolized, tumor-free lobe, and thereby increase hepatic function, following surgical resection of the diseased lobe.

However, it is currently felt that PVE and pre-operative TACE prior to surgical resection offers no benefit [15–17]. It has also been suggested that malignant hepatocytes may also respond to the proliferative stimulus and this could result in uncontrolled tumor progression. In addition, portal vein obstruction may induce an acute increase in portal pressure and result in variceal bleeding. RCTs are needed to define the benefits and risks of these procedures [18].

10.1.5 Sorafenib and DEB-TACE

A high rate of tumor recurrence has been observed following TACE for HCC. It has been suggested that by interrupting blood flow to the tumor, TACE induces necrosis at the site of disease but may create conditions that permit or even encourage angiogenesis elsewhere in the liver [19]. Surrogate markers of tissue hypoxia have been reported to increase after TACE including hypoxia inducible factor 1α and both plasma and hepatic vascular endothelial growth factor (VEGF). Thus, it has been suggested that the combination of TACE with antiangiogenic agents may curtail the post-TACE rise in VEGF-mediated signaling, and simultaneously target foci distant from the site of treatment [19].

Investigation of this possible synergistic treatment has been studied in a phase 2 randomized double-blind placebo-controlled trial: SPACE study (Sorafenib or Placebo in Combination with DEBTACE for Intermediate-Stage HCC) [20]. The objective of the study was to evaluate the efficacy and safety of sorafenib in combination with DEB-TACE in patients with intermediate stage HCC. The study demonstrated an improved time to progression (TTP) of disease supporting the premise that Sorafenib may reduce the associated angiogenesis, although the results still need to be confirmed with phase 3 trials.

Conclusion

The methods, indications, and results of TACE, alone and in combination with other forms of therapy for HCC, have been reviewed in this Chapter. The selection parameters and treatment outcomes for TACE, as well as other locoregional therapies, alone or in combination, such as thermal ablation, with or without systemic chemotherapy agents will eventually be factored in generating Digital Patient Models (DPMs). It is hoped that diagnosis, prognosis, and treatment selection for patients with HCC will thereby be facilitated by Model Guided Therapy (MGT) and Predictive, Preventive and Personalized Medicine (PPPM).

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