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Review Article

Current role of systemic therapy in transarterial chemotherapy-refractory hepatocellular carcinoma patients

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A B S T R A C T

Transarterial chemotherapy (TACE) is the standard treatment for patients with intermediate-stage hepatocellular carcinoma (HCC), defined as large, unresectable, or multinodular HCC in patients with good functional performance. The definition of TACE refractoriness is not well established. Generally, TACE refractoriness is defined as an insufficient response after two or more consecutive TACE. An increase in the number of liver lesions, continuously elevated tumor markers, vascular invasion, and extrahepatic spread also suggest TACE refractoriness. Timely switching to systemic therapy for TACE refractoriness should be considered to improve the outcome. Although data are sparse, the combination of anti-angiogenic and immune checkpoint inhibitor therapies shows promise for TACE-refractory patients. In this article, we review the role of systemic therapy in TACE-refractory patients with HCC.

Keywords: Hepatocellular carcinoma; Refractoriness; Systemic therapy; Transarterial chemotherapy

Introduction

Transarterial chemotherapy (TACE) is the standard treatment for patients with intermediate-stage hepatocellular carcinoma (HCC).[1,2] The Barcelona Clinic Liver Cancer (BCLC) staging system defines intermediate-stage HCC as large, unresectable, or multinodular HCC in patients with good functional performance and Child–Pugh class A or B. Kudo et al[3] classified BCLC stage B into four subgroups according to tumor size and number: 1) patients with 4–6 nodules, a maximum tumor diameter of ≤ 3 cm, and a good response to conventional TACE (cTACE); 2) patients with < 6 nodules, a maximum tumor diameter of > 3–6 cm, and a good response to cTACE; 3) patients with up-to-7 criteria with multiple nodules (≥ 7) and a poor response to cTACE; and/or 4) patients with < 6 nodules, a maximum tumor diameter of > 6 cm, and a poor response to cTACE. Unlike the original BCLC staging system, the Asia-Pacific Primary Liver Cancer Expert consensus defines intermediate-stage HCC as (i) a single tumor with a maximum size of ≥ 5 cm in BCLC stage A or (ii) BCLC stage B.[3] That is, patients with intermediate-stage HCC can differ in terms of their liver function, tumor size and number.[3] Irrespective of this heterogeneity, TACE is the only guideline-recommended treatment for intermediate-stage HCC.

A complete radiologic response is rarely achieved after a single session of TACE, and most patients require repeat sessions. The overall response rate generally decreases with additional TACE sessions compared to the initial TACE.[4] The global OPTIMIS study, an international, prospective, and observational study, included 507 patients (31%) ineligible for TACE.[5] Complete and partial responses to the first TACE session were observed in 14% and 26% of the patients, respectively, and these rates decreased after the second (10% and 16%, respectively), third (10% and 15%, respectively), and fourth (8% and 17%, respectively) TACE sessions. The rate of progressive disease increased with the number of TACE procedures (18%, 21%, 25%, and 27% after the first, second, third, and fourth TACE sessions, respectively).

TACE is considered the first-line treatment in selected patients with advanced stage HCC.[6] However, not all patients with BCLC stage B or C HCC benefit from TACE. Therefore, clinicians consider the benefit and risk of TACE based on individual tumor characteristics and liver function. To decide whether patients will benefit from repeated TACE, an understanding of the concept

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of TACE refractoriness. Systemic therapy can be considered for TACE refarctoriness.[2] Sorafenib and lenvatinib are available for advanced HCC. Various molecular-targeted agents have been developed for patients with advanced HCC and preserved liver function.[7] Atezolizumab (anti-programmed death-ligand-1 antibody) and bevacizumab (anti-vascular endothelial growth factor [VEGF] therapy) were superior to sorafenib in a phase 3 randomized controlled trial.[8] The clinical efficacy of systemic therapy has been demonstrated in patients with intermediate-stage HCC.[9–11] Selecting suitable patients at the appropriate time for switching to systemic therapy is important for achieving a good prognosis in TACE-refractory patients.

In this article, we review TACE refractoriness and the role of systemic therapy for TACE-refractory patients with HCC.

When Should TACE be Stopped?

TACE can be performed several times for HCC patients with recurrence or intrahepatic metastasis. However, repeat procedures may decrease therapeutic efficacy and cause liver dysfunction. The indications for TACE are controversial and vary among centers and countries.[12] Generally, TACE is not beneficial for patients with TACE refractoriness or frequent deterioration in hepatic functional reserve to Child–Pugh class B in response to TACE.[3] In these situations, other treatment modalities should be considered.

Untreatable progression or insufficient response

Bruix et al[13] introduced the concept of "untreatable progression," defined as progression associated with a profile that prevents retreatment or, by this, failing to induce an objective response. Untreatable progression includes massive liver involvement, extrahepatic spread, vascular invasion, and minor intrahepatic progression with impaired liver function. Additionally, repeat TACE should not be considered for patients who have no significant tumor necrosis after two treatment sessions or in sites of tumor progression, or who have disease progression that prevents safe retreatment. Although assessment of TACE outcomes is challenging, patients with "untreatable progression" probably have TACE refractoriness.

The concept of TACE refractoriness was proposed by the Japan Society of Hepatology in 2010.[14] In the 2014 version, TACE refractoriness was defined as an insufficient response after two or more consecutive TACE procedures,[15] (i) an increase in the number of lesions in the liver, (ii) continuous elevation of tumor markers, (iii) vascular invasion, and/or (iv) extrahepatic spread. The detailed criteria include (i) an insufficient response of the tumor (viable lesion > 50%) after two or more consecutive TACE procedures, as assessed 1 to 3 months after the procedure by computed tomography (CT) or magnetic resonance imaging (MRI), despite a change in chemotherapeutic agents and reanalysis of the feeding artery; (ii) progression in liver tumor burden (increase in tumor number after TACE); (iii) continuously elevated tumor markers immediately after TACE; (iv) detection of vascular invasion; and/or (v) detection of extrahepatic spread. Although these criteria are not well recognized worldwide, they provide a definition of TACE refractoriness and help clinicians make a decision regarding TACE discontinuation.

The Expert Panel Opinion on Interventions in Hepatocellular Carcinoma and Taiwanese criteria state that TACE refractoriness occurs within 6 months after at least two or three on-demand TACE sessions.[16,17] An online survey conducted by Korean experts revealed that TACE refractoriness was expected in patients when recurrences were detected within 1 month, there were four to six tumors, the maximal tumor size was 3 to 5 cm, and when there was insufficient tumor necrosis despite three or more repeat TACE.[18] This indicates that, despite international effort, there is much controversy over TACE refractoriness.

Liver function deterioration after TACE

Another possible reason to consider discontinuation of TACE is deterioration of liver function. Repeated TACE can damage the hepatic artery and impair liver function, which contributes to a poor prognosis in HCC patients. In a European randomized controlled trial, TACE was repeated every 2 to 3 months unless contraindicated or disease progression occurred.[19] The TACE group received 192 courses of TACE, with a median of 4.5 courses per patient. A significant survival benefit was observed with TACE (relative risk of death: 0.49; 95% confidence interval [CI]: 0.29–0.81; $P = 0.006$). TACE was discontinued in patients with poor liver function (hepatic encephalopathy, uncontrolled ascites, variceal bleeding, serum bilirubin level > 50 μmoL/L, serum albumin level < 28 g/L, or prolonged prothrombin time > 4 seconds), serious adverse events, or disease progression. TACE was discontinued due to cancer progression, death, poor liver function, adverse events, patient refusal, arteriovenous shunt, and hepatic artery thrombosis. In a systematic review, TACE was performed at baseline, 2 months, 6 months, and every 6 months thereafter.[20] Treatment was discontinued based on patient preference or if the patient developed Child–Pugh class C, active gastrointestinal bleeding, encephalopathy, uncontrolled ascites, and/or vascular invasion. The major reasons for discontinuation were tumor progression, technical problems, severe adverse events, patient refusal, death, and liver failure. In patients with TACE refractoriness, deterioration of liver function may reduce the opportunities for systemic therapy. Therefore, a timely switch to systemic therapy is important for prolonging overall survival (OS). Several scoring systems can be used to determine when to repeat or stop TACE.

Scoring Systems That Evaluates the TACE Response

ART score

Several studies have been conducted to identify objective indicators of the need for repeat TACE procedures. Sieghart et al[21] investigated the effect of the first TACE procedure on liver function, tumor response, and OS. They developed the Assessment for Retreatment with TACE (ART) score, which includes a > 25% increase in the aspartate aminotransferase level (hazard ratio [HR] = 8.4; $P < 0.001$), increase in the Child–Pugh score of 1 point (HR = 2.0) or ≥ 2 points from baseline (HR = 4.4; $P < 0.001$), and absence of a radiological tumor response (HR = 1.7; $P = 0.026$). An ART score of ≥ 2.5 prior to the second TACE session predicts a dismal prognosis and suggests that patients may not benefit from further TACE.

Another study showed the prognostic value of the ART score before the third and fourth TACE sessions.[22] The ART score before the third TACE session had prognostic value, and patients with a score of 0–1.5 points had a median OS of 28.1 months (95% CI = 21.7–24.4), while those with an ART score of 2.5 points had a median OS of 8.5 (95% CI = 7.4–9.6; $P < 0.001$). Similar results were observed for the ART score assessed before the fourth TACE session. The ART score was found to be a valid predictor of OS independent of the Child–Pugh score, C-reactive protein level, and tumor characteristics. Even among patients with a favorable ART

score (0–1.5 points) before the second TACE session, repeat ART score assessment before the third session identified a subgroup of patients with a dismal prognosis (median OS: 27.8 and 10.8 months, respectively; $P < 0.001$). This study demonstrated that sequential ART score assessment before TACE sessions may identify patients with a dismal prognosis to TACE retreatment.

A European study group proposed a new algorithm for TACE,[12] which suggests that the TACE program should be discontinued if severe adverse events or liver dysfunction occur after the first TACE session. In addition, sequential TACE should not be performed if disease progression is observed by CT or MRI at 4–6 weeks after the first TACE. In cases of stable or responsive disease, the ART score can be calculated to make treatment decisions a few days prior to the planned second or third TACE session. However, clinical use of the ART score is still limited to centers or clinicians who choose to use it.

ABCR score

In France, the ABCR (alpha-fetoprotein, BCLC, Child-Pugh, and Response) score was developed to decide the suitability of repeat TACE.[23] The ABCR score is a simple and clinically relevant index. In a multivariate analysis, four prognostic factors were associated with OS: the BCLC stage, baseline alpha-fetoprotein level (> 200 ng/mL), increase in Child–Pugh score by ≥ 2 from baseline, and absence of a radiological response. These factors were included in the ABCR score (range: –3 to +6), which is correlated with OS. The ABCR score was validated in two cohorts. Using cut-off scores of 0 and 4, the median OS rates were 37.8 months for an ABCR score ≤ 0, 17.1 months for an ABCR score of 1–3, and 7.5 months for an ABCR score ≥ 4. An ABCR score ≥ 4 prior to the second TACE session identified patients with a dismal prognosis who may not benefit from further TACE sessions. Compared with the ART score, the ABCR score had superior predictive value for OS. As with the AET score, its use is limited and further studies are needed.

Current Systemic Therapies

Among molecular targeted agents, sorafenib and lenvatinib are available as first-line agents. Regorafenib, cabozantinib, and ramucirumab are second-line agents.[24] Systemic therapies are associated with a survival benefit mostly in advanced HCC. Although phase 3 clinical trials included patients with intermediate-stage HCC who were refractory to TACE after multiple sessions, the data for systemic therapy alone for TACE refractoriness are sparse (Table 1). The available data are mostly on combination therapies. Pretreatment with systemic therapy improved the clinical outcomes of TACE by promoting vascular normalization; suppressing hypoxia inducible factor-1; upregulating VEGF, platelet-derived growth factor, and angiopoietin 2; and improving the distribution of lipiodol mixed with anticancer drugs.[25–28]

Sorafenib

Sorafenib is an oral multikinase inhibitor that targets VEGF, RAF and platelet-derived growth factor receptor, thereby exerting both antiangiogenic and antitumor effects. In Taiwan, an immediate switch to systemic treatment is recommended for TACE-refractoriness. Sorafenib can be reimbursed when used for the treatment of TACE-refractory intermediate-stage HCC.[24]

In the OPTIMIS study, only 9% of patients received sorafenib after developing TACE refractoriness.[5] Among 507 patients, the 47 (9%) who received sorafenib at the time of TACE ineligibility had longer OS. The OS of patients treated with sorafenib due to TACE refractoriness was prolonged in patients who received two or more consecutive ineffective TACE procedures compared with those who received three or more TACE procedures.[29]

The SPACE (NCT00855218) and TACE 2 (ISRCTN93375053) trials did not show any clinical benefit of sorafenib with drug-eluting beads using TACE (DEB-TACE) compared with DEB-TACE alone.[30,31] By overcoming the limitations of previous trials, the TACTICS trial (NCT01217034) showed a better clinical outcome

Table 1 Clinical Trials of Systemic Treatments for Patients with Intermediate or Advanced Hepatocellular Carcinoma

Drug	Mechanism	Combination	Trial identifier	Phase
Sorafenib	A protein kinase inhibitor	Sorafenib + DEB-TACE vs DEB-TACE alone	NCT00855218	2
		Sorafenib + DEB-TACE vs DEB-TACE alone	ISRCTN93375053	3
		Sorafenib + TACE vs TACE alone	NCT01217034	2
		Sorafenib + HAIC	NCT03722498	2
Brivanib	VEGFR2 inhibitor	Brivanib after TACE vs TACE alone	NCT00908752	3
Orantinib	VEGFR inhibitor	Orantinib + TACE vs TACE alone	NCT01465464	3
Camrelizumab + Apatinib	Anti-PD-1 immune checkpoint inhibitor + Tyrosine kinase inhibitor	Camrelizumab + Apatinib + TACE	NCT04479527	2
Tremelimumab	A monoclonal antibody against CTLA-4	Tremelimumab + RFA or TACE	NCT01853618	1/2
Durvalumab + Tremelimumab	Anti-PD-1 antibody + A monoclonal antibody against CTLA-4	Durvalumab + Tremelimumab after DEB-TACE	NCT01853618	1/2
Durvalumab + Bevacizumab	Anti-PD-1 antibody + Anti-VEGF antibody	Durvalumab + Bevacizumab + DEB-TACE	NCT03937830	2
Nivolumab	Anti-PD-1 antibody	Nivolumab + DEB-TACE	NCT03143270	1
		Nivolumab + TACE	NCT03572582	2
Pembrolizumab	Anti-PD-1 antibody	Pembrolizumab after TACE	NCT03397654	1/2
Immune killer cells	Immune killer cells	Immune killer cells + TACE vs TACE alone	NCT03592706	2/3

DEB-TACE, drug-eluting beads using transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; VEGFR, vascular endothelial growth factor receptor; anti-PD-1, anti-programmed cell death protein-1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; RFA, radiofrequency ablation; anti-VEGF, anti-vascular endothelial growth factor.

with sorafenib followed by TACE in patients with intermediate-stage HCC patients.[32] Median progression-free survival based on untreatable progression (defined as the inability of the patient to further receive or benefit from TACE) was significantly longer in the combination group than in the TACE-alone group (HR = 0.570; 95% CI = 0.33–0.99; P = 0.04).

Lenvatinib

Lenvatinib is a multikinase inhibitor that targets VEGF receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor alpha, rearranged during transfection, and KIT.[33–36] The REFLECT trial included advanced-stage HCC patients and showed non-inferiority of lenvatinib compared with sorafenib in terms of OS (13.6 and 12.3 months, respectively). Additionally, lenvatinib showed a significant improvement in progression-free survival (7.4 and 3.7 months, respectively), time to progression (8.9 and 3.7 months, respectively), and the objective response rate (ORR) (24% and 44%, respectively) compared with sorafenib.[9] More evidence is needed, but lenvatinib is expected to maximize treatment efficacy in cases of TACE refractoriness with high HCC burden.

Lenvatinib showed a better ORR (61.3%) in patients with BCLC B stage compared with TACE (42%) or OPTIMIS study (52%).[37] For TACE-unsuitable patients, lenvatinib is the only first-line agent associated with better OS compared with TACE in TACE-naïve patients with up-to-7 criteria out nodules.[38] After propensity-score matching, a comparison of outcomes showed a significantly higher ORR (73.3% and 33.3%, respectively; P < 0.001) and longer median progression-free survival (16.0 and 3.0 months, respectively; P < 0.01) in patients treated with lenvatinib (n = 30) than in those treated with cTACE (n = 60). Lenvatinib significantly prolongs OS compared with cTACE alone (37.9 and 21.3 months, respectively; P < 0.001). The albumin–bilirubin (ALBI) score worsened over time in the cTACE group compared with the lenvatinib group. The ALBI score from baseline to the end of treatment changed from −2.61 to −2.61 in the lenvatinib group (P = 0.254) and from −2.66 to −2.09 in the cTACE group (P < 0.01). By the end of treatment, the ALBI score did not improve in the TACE group, whereas it returned to baseline in the lenvatinib group. In that study, almost 70% of the patients underwent TACE after receiving lenvatinib in the lenvatinib group. Four patients in the lenvatinib group achieved a drug-free status after a complete response, which may be explained by the initial lenvatinib administration followed by selective TACE in patients exceeding the up-to-7 criteria.

Lenvatinib showed favorable results in TACE-resistant tumors, such as poorly differentiated, confluent multinodular, or infiltrative tumors.[39,40] Also, TACE plus lenvatinib had a higher median time to progression (4.7 vs 3.1 months, P = 0.029) compared to TACE plus sorafenib in patients with advanced HCC and portal vein thrombosis.[41]

Other therapeutic considerations

Phase 3 clinical trials of brivanib (NCT00908752) and TSU-68 (orantinib, NCT01465464) in patients with intermediate-stage HCC reported no significant improvement in the OS of patients with unresectable HCC.[42,43]

According to ClinicalTrials.gov (updated on September 30, 2021), several clinical trials of TACE-refractory HCC patients are underway. A phase 2 trial is investigating the efficacy and safety of apatinib (VEGF receptor-2 inhibitor) combined with TACE in patients with TACE-refractory HCC (NCT03510416) with a primary outcome of progression. Apatinib is administered 4 to 7 days after TACE, and TACE is performed after apatinib is discontinued for 4 days. Each cycle lasts for 28 days. The trial will include BCLC B or C patients who progressed after at least two TACE sessions.

Another phase 2 trial is evaluating the safety and efficacy of combined hepatic arterial infusion chemotherapy with oxaliplatin, 5-fluorouracil, leucovorin, and sorafenib in patients with TACE-refractory HCC (NCT03722498). The primary and secondary outcomes are progression-free survival and OS. TACE refractoriness is defined based on the Japanese criteria, including vascular invasion or two or more consecutive insufficient responses of the intrahepatic lesion.

The effectiveness and safety of PD-1 antibodies, camrelizumab and apatinib, combined with TACE for the treatment of advanced HCC are being evaluated (NCT04479527). That study includes patients with tumors who cannot undergo surgical resection or local ablation and BCLC B or C tumors with at least seven nodules or nodules > 5 cm. Camrelizumab is used to treat patients with relapsed or refractory classic Hodgkin lymphoma who have received second-line chemotherapy. Camrelizumab (200 mg) was administered intravenously over 30 minutes, every 3 weeks. Apatinib (250 mg/time) was administered once a day.

Although immunotherapy failed to improve OS in phase 3 trials involving patients with advanced HCC,[44,45] immune checkpoint inhibitors, such as nivolumab (anti-programmed cell death protein-1 [PD-1] antibody) or pembrolizumab (anti-PD-1 antibody), are alternative treatments for TACE refractoriness. Tremelimumab (a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4, CTLA-4) in combination with ablation or TACE was evaluated in advanced HCC (NCT01853618).[46] Patients were given tremelimumab intravenously at doses of 3.5 and 10 mg/kg) every 4 weeks for six doses, followed by 3-monthly infusions. The combination of TACE and tremelimumab showed favorable outcomes, with a partial response rate of 26.3% and OS of 12.3 months. Also, durvalumab in combination with tremelimumab after DEB-TACE (NCT03638141), nivolumab with TACE (NCT03143270, NCT03572582), pembrolizumab after TACE (NCT03397654), immune killer cells with TACE (NCT03592706), and durvalumab, bevacizumab with DEB-TACE (NCT03937830) are under investigation.[47]

Future Perspectives

Atezolizumab (anti-PD-L1 antibody) plus bevacizumab (anti-VEGF antibody) showed better OS and progression-free survival compared with sorafenib alone for advanced HCC.[48] Atezolizumab plus bevacizumab showed a better ORR compared with standard treatment without systemic therapy according to the response evaluation criteria in solid tumors (27% and 12%, respectively; P < 0.0001) and the modified response evaluation criteria in solid tumors v1.1 (33% and 13%, respectively; P < 0.0001). Thus, atezolizumab plus bevacizumab may be a treatment option for patients with TACE refractoriness.

The treatment paradigm in HCC is shifting dramatically with the advent of new treatment options. Clinical trials of various combinations including immune checkpoint inhibitors are ongoing and include all stages of HCC, such as the adjuvant setting or in combination with TACE.[49] These changes in treatment paradigm are expected to improve the prognosis of patients with HCC and a high tumor burden, who are difficult to treat.

Conclusion

TACE is the standard treatment for patients with intermediate-stage HCC, defined as large, unresectable, or multinodular HCC in patients with good functional performance. Although there is some controversy, TACE refractoriness can be defined as an insufficient response after two or more consecutive TACE. An increase in the number of liver lesions, continuously elevated tumor markers, vascular invasion, and extrahepatic spread also suggest TACE refractoriness. Because repeated TACE may worsen liver function, a timely switch to systemic therapy for TACE refractoriness is important for prolonging OS. Scoring systems such as the AST or ABCR score can assist determination of when to repeat or stop TACE in patients with TACE refractoriness. Although evidence is limited, combination treatments with anti-angiogenic agents or immune checkpoint inhibitors show promise for TACE-refractory patients. Further studies on the efficacy, safety, and appropriate timing of switching to systemic therapy for TACE-refractoriness are needed.

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Conflicts of Interest

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