Transarterial Chemoembolilzation

Subjects: Others

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Transarterial chemoembolization (TACE) is widely recommended as a first-line treatment for intermediate-stage HCC. TACE is based on the predominantly arterial vascularization of HCC compared to the surrounding normal liver parenchyma, and aims to induce tumor necrosis by injecting chemotherapy agents with blockade of the arterial blood supply of tumor.

Keywords: Transarterial chemoembolization ; hepatocellular carcinoma ; Combination therapy

1. Introduction

Primary liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer mortality worldwide. Hepatocellular carcinoma (HCC) accounts for 75% to 95% of all primary liver cancer cases. HCC-related mortality continues to increase despite the overall declining trends in cancer incidence and death rates. Because of its global disease burden and poor prognosis, HCC is considered a major global health problem.

Prognosis of HCC patients is highly heterogeneous and depends on various factors such as tumor burden, baseline liver function, cancer-related symptoms represented by performance status, and treatment allocation. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, which has been commonly used in clinical practice and endorsed by international guidelines, transarterial chemoembolization (TACE) is the treatment of choice for intermediate-stage HCC, including unresectable multinodular HCC without extrahepatic spread. The BCLC system additionally recommends that TACE should be used when other recommended treatments are not feasible or unsuccessful in the early stages of HCC. In Asian countries, TACE tends to be more broadly recommended for various clinical situations. Although the clinical situations in which TACE is indicated differ slightly depending on the various staging systems, TACE is a well-established treatment for intermediate-stage HCC.

2. Application of TACE Outside of Intermediate-Stage HCC

2.1. Early-Stage HCC

TACE is primarily recommended for patients with intermediate-stage disease. For patients with early stage HCC, liver transplantation, surgical resection, or local ablation are generally recommended as curative treatments. However, some patients are not good surgical candidates due to several clinical factors such as old age, hepatic dysfunction, and severe comorbidities. Furthermore, the shortage of liver donors is a major limitation of liver transplantation. Although local ablation is considered a safer alternative to surgery in these situations, it is also not suitable for tumors with a subcapsular or dome location or in tumors located near the main bile duct, large vessels, or intestinal loops. Patients who cannot benefit from curative treatment, despite earlier stage disease, could be good candidates for TACE. This treatment stage-migration strategy is well established and recommended by international guidelines. Several studies have reported a high response rate and good outcomes after TACE in patients with early stage HCC for whom curative treatment is not feasible owing to various clinical factors. TACE can be used as neoadjuvant therapy before liver transplantation (LT). In such cases, TACE serves as a downstaging therapy, allowing a patient to become suitable for LT, or as a bridge therapy while the patient is on the waiting list. Several studies have demonstrated that TACE decreases the dropout rate from the waiting list of LT to 3–13%, especially when the expected waiting time for LT exceeds six months. Moreover, response to preoperative TACE has been confirmed to correlate with post-transplant tumor recurrence and OS.

2.2. Advanced-stage HCC

Advanced stage HCC (BCLC stage C) is characterized by cancer-related symptoms with/without vascular invasion or extrahepatic metastasis with preserved liver function and performance status. Sorafenib is the treatment of choice for advanced HCC, and lenvatinib has also been recommended as a first-line systemic treatment after its non-inferiority to sorafenib was demonstrated. More recently, the combination of atezolizumab and bevacizumab resulted in better OS and

progression-free survival (PFS) than sorafenib, and has been approved by the U.S. Food and Drug Administration for advanced HCC patients who have not received prior systemic therapy. For sorafenib-experienced patients, regorafenib, cabozantinib, ranucirumab, and nivolumab can be used as second- or third-line treatments. However, the population with advanced-stage disease is heterogeneous because the extent of portal vein tumor thrombosis (PVTT) and extrahepatic spread is not considered. Approximately 20–30% of the newly diagnosed HCC patients have PVTT; this proportion increases up to 42% in patients without HCC surveillance, and all of these patients are considered to have advanced-stage disease. The extent of PVTT can vary, ranging from the involvement of the small segmental branch to the main trunk and beyond, and it has been repeatedly reported that the extent of PVTT, not just the presence of PVTT, is an important determinant of survival. Nevertheless, according to most treatment guidelines, the presence of PVTT severely restricts treatment options, regardless of the extent of PVTT. Systemic chemotherapy with sorafenib or lenvatinib other than local treatment is the only proven standard treatment in such cases.

Despite the stipulated guidelines, TACE was implemented as the first-line treatment in nearly 50% of the cases of BCLC-C stage HCC in an international large-scale longitudinal cohort study that reflected real-world clinical practice. The rationale for the application of TACE in HCC with PVTT is that collateral vessel formation around the portal vein allows for the preservation of liver function, which in turn makes TACE possible in selected cases with segmental or subsegmental PVTT. The survival benefit afforded by TACE over that afforded by best supportive care has been demonstrated in various studies.

To summarize, TACE is recommended not only for intermediate-stage HCC, but also for early stage HCC as a stage-migration strategy and neoadjuvant treatment. Although TACE is not recommended as a standard therapy in most cases of advanced-stage HCC, it can be considered as a treatment option in selected patients with segmental PVTT and preserved liver function. Further study comparing TACE and systemic therapy as first-line treatment in selected patients is necessary.

3. Combination Treatment with TACE

3.1. TACE with Radiofrequency Ablation

An RCT in patients with a solitary recurrent HCC lesion < 5 cm in diameter demonstrated that sequential therapy with TACE followed by radiofrequency ablation (RFA) significantly improved OS compared to the therapy with RFA alone. The one-, three-, and five-year survival rates were 94%, 69%, and 46% for the combination therapy, respectively, and 82%, 47%, and 36% for RFA alone (p = 0.037). In addition, sequential combination therapy resulted in significantly longer recurrence-free survival in patients with tumors larger than 3 cm in diameter. Another RCT demonstrated the superiority of the TACE-RFA combination therapy over RFA alone in patients with HCC lesions with a diameter of less than 7 cm in both OS (HR = 0.525; p = 0.002) and recurrence-free survival (HR = 0.575; p = 0.009). For small HCC lesions (2–3 cm in diameter), there was no significant difference in long-term therapeutic outcomes between TACE combined with RFA and surgical resection, which implies that the TACE/RFA combination therapy could be an alternative treatment for patients with a single small HCC lesion for whom surgical resection is unsuitable. Two meta-analyses reported that TACE combined with RFA was more effective than RFA alone, especially for intermediate- and large-sized HCC, and in younger patients with HCC.

3.2. TACE with Radiation Therapy

There has been mounting evidence regarding the efficacy of combination therapy of TACE and radiation therapy (RT) for treating patients with intermediate-stage HCC, as well as advanced-stage HCC with PVTT. According to an extensive meta-analysis involving 11 RCTs and 14 non-RCTs, treatment with TACE plus RT resulted in significantly improved response and survival rates compared to TACE alone in patients with unresectable HCC. In addition, TACE plus RT has shown a promising response rate and OS among HCC patients with macrovascular invasion in several observational studies. Based on these observational studies, a well-designed RCT was conducted, which demonstrated that first-line treatment with TACE plus RT was well tolerated and improved various treatment outcomes compared to those associated with sorafenib treatment among advanced-stage HCC patients with macrovascular invasion. This research provides a new treatment paradigm to treat patients with locally advanced HCC using a combination of TACE and RT.

2.3. TACE with Systemic Therapy

The anticancer mechanisms of TACE involve a tumor embolic effect leading to tissue necrosis, in addition to the local delivery of cytotoxic agents. TACE causes tissue hypoxia that results in the upregulation of vascular endothelial growth factor (VEGF), which may lead to tumor revascularization and local recurrence. In this regard, the combination of

antiangiogenic agents with TACE was expected to inhibit the revascularizing action of upregulated VEGF induced by TACE. Accordingly, the combination of TACE with anti-angiogenic agents may delay tumor progression or recurrence, and thus improve OS.

Several attempts have been made to combine TACE with other systemic agents whose main mechanism of action is anti-angiogenesis: The SPACE and TACE 2 trials compared TACE plus sorafenib and TACE alone, while the BRISK-TA study did the same with brivanib, and the ORIENTAL study with orantinib. Despite the plausible rationale for the combination strategy, all four RCTs evaluating the combination of TACE with systemic agents failed to show any clinical benefit compared to TACE alone. Kudo et al. presented several reasons for these repeated negative trials. They suggested that the duration of the study was too short to evaluate OS as a primary endpoint. In addition, post-trial treatments after progression likely affect OS, making it difficult to evaluate treatment outcomes using OS. The definition of time to progression or PFS also needs to be more standardized, and tailored to the specifics of TACE treatment. Based on the lessons from the previous trials, Kudo et al. demonstrated positive results of the TACTICS trial, a randomized phase II trial comparing TACE plus sorafenib with TACE alone. The use of TACE plus sorafenib resulted in a major improvement in PFS: 25.2 months in the TACE plus sorafenib group versus 13.5 months in the TACE alone group (p = 0.006). The improved outcomes observed in the TACTICS trial can be explained by the differences in the study protocol compared to those of the previous trials. The most distinctive difference is that new intrahepatic lesions were not regarded as progressive disease because they do not imply treatment failure based on the natural tumor biology of HCC. Progression in this trial was defined as untreatable (unTACEable) progression; e.g., > 25% of intrahepatic tumor progression, deterioration of liver function to Child-Pugh class C after TACE, macrovascular invasion, or extrahepatic spread. Treatment was continued until unTACEable progression, TACE refractoriness, or unacceptable toxicity. Sorafenib was started two–three weeks prior to the first TACE in this trial. As a result, patients in the TACTICS trial received sorafenib treatment for a much longer period than in previous trials, with a median of 38.7 weeks and 17.0 to 21.0 weeks, respectively. This new TACE-specific endpoint and protocol should be validated in future TACE combination trials.

Another approach being investigated is the combination of immune checkpoint inhibitors with TACE. Locoregional therapies, including TACE, activate the host immune system by promoting local inflammation and triggering the release of tumor antigens. When tumor antigens are released by TACE, subsequent administration of immune checkpoint inhibitors can prevent intrahepatic micrometastases, which are typically undetectable, and are the main cause of recurrence. One prospective study demonstrated that ablative therapies, such as RFA and TACE, induced a peripheral immune response and enhanced the efficacy of tremelimumab in patients with advanced-stage HCC. The combination of TACE and tremelimumab afforded favorable outcomes, with a partial response rate of 26% and OS of 12.3 months. At present, a phase III trial of combination therapy with TACE plus durvalumab and/or bevacizumab (the EMERALD-1 trial) is ongoing (NCT03937830).