International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 16, No. 2, 2026

Research Progress on TACE Combined with Targeted and Immunotherapy in the Comprehensive Treatment of Massive Hepatocellular Carcinoma

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Abstract: Massive hepatocellular carcinoma (HCC) is characterized by large tumor volume, strong invasiveness, high propensity for vascular invasion and intrahepatic dissemination. Consequently, most patients lose the opportunity of radical surgical resection at initial diagnosis. Monotherapy with conventional transarterial chemoembolization (TACE) is associated with low remission rate, high risk of recurrence and metastasis, and poor long-term survival. In recent years, the rapid development of targeted therapy and immunotherapy has provided novel systemic therapeutic approaches for advanced liver cancer. The comprehensive regimen of TACE combined with targeted and immunotherapy has gradually become a research hotspot for massive hepatocellular carcinoma. This article comprehensively reviews the mechanism and clinical application of TACE combined with targeted and immunotherapy in the treatment of patients with massive HCC, aiming to provide a reference for optimizing clinical treatment strategies for such patients.

Keywords: Massive Hepatocellular Carcinoma; Transarterial Chemoembolization; Targeted Therapy; Immunotherapy.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide. China bears a high incidence of liver cancer, with the annual number of new cases and deaths accounting for nearly half of the global total, resulting in a severe disease burden. Massive hepatocellular carcinoma is generally defined as HCC with a maximum tumor diameter ≥ 5 cm or occupying most of the liver lobe. It exhibits aggressive biological behaviors including strong invasiveness, active proliferation, high tendency of portal vein and hepatic vein invasion, and frequent intrahepatic micrometastasis. Most patients are diagnosed at the intermediate and advanced stages, making radical treatments such as surgical resection and liver transplantation rarely feasible.

Transarterial chemoembolization (TACE) is currently the standard locoregional therapy for unresectable intermediate and advanced HCC. Its mechanism lies in embolizing the tumor feeding arteries and perfusing chemotherapeutic agents locally, thereby inducing ischemic injury of tumor tissues and achieving tumor shrinkage and volume reduction. This article summarizes the latest research advances, and elaborates on the mechanism, clinical application, improvement strategies and existing challenges of TACE combined therapy, so as to provide theoretical basis for clinical practice and further research.

2. Synergistic Mechanism of TACE Combined with Targeted and Immunotherapy

2.1. Regulation of Tumor Immune Microenvironment and Antigen Release Effect of TACE

As a locoregional interventional therapy, TACE not only directly kills tumor cells and reduces tumor volume, but also remodels the tumor immune microenvironment and activates immunogenicity, thereby laying a foundation for subsequent targeted and immunotherapy.

Tumor tissues of massive hepatocellular carcinoma are generally in an immunosuppressive state, characterized by sparse intratumoral lymphocyte infiltration, increased regulatory T cells and myeloid-derived suppressor cells, high expression of PD-L1, and activation of immune checkpoint-related pathways. This forms a "cold tumor", resulting in poor efficacy of immunotherapy alone.

By embolizing tumor-feeding arteries, TACE induces acute ischemia and hypoxia in tumor tissues and leads to tumor cell necrosis and apoptosis. Meanwhile, a large number of tumor-associated antigens, damage-associated molecular patterns, and inflammatory factors are released, such as ATP, HMGB1, IL-1β, TNF-α and so on. These substances can activate peripheral innate immune cells, promote the maturation and migration of dendritic cells, and initiate antigen presentation. Furthermore, they effectively activate effector immune cells such as $CD8^+$ cytotoxic T lymphocytes and NK cells, converting immunosuppressive "cold tumors" into immunogenic "hot tumors"[1].

2.2. Dual Effects of Vascular Regulation and Immune Enhancement by Targeted Drugs

Anti-angiogenic targeted agents are the main systematic therapeutic drugs for massive hepatocellular carcinoma, including tyrosine kinase inhibitors and anti-VEGF monoclonal antibodies. They exert vital dual roles in vascular regulation and immune enhancement during TACE combined targeted-immunotherapy [2].

Massive hepatocellular carcinoma is characterized by abundant and structurally disordered tumor neovasculature, with overexpression of pro-angiogenic factors such as VEGF and PDGF. Ischemia and hypoxia after TACE can sharply upregulate VEGF expression, accelerate angiogenesis in

residual tumor tissues, and further induce tumor recurrence and metastasis. In this context, targeted drugs can specifically interfere with signaling pathways such as VEGF/VEGFR, inhibit the formation of tumor neovascularization, block compensatory angiogenesis after TACE, thereby strengthen the local therapeutic effect of TACE and reduce the risk of tumor recurrence [3].

2.3. Systemic Immune Activation and Long-term Response Maintenance of Immunotherapy

Immune checkpoint inhibitors block immunosuppressive pathways such as PD-1/PD-L1 and CTLA-4, thereby relieving tumor-induced immunosuppression of T cells, activating and expanding tumor-specific T cells, and exerting durable and systemic anti-tumor immune effects. They serve as the core guarantee for achieving long-term disease control in TACE combined targeted-immunotherapy [4].

TACE induces the release of tumor antigens, and targeted drugs improve immune cell infiltration, which jointly establish a favorable microenvironmental foundation for immunotherapy. In turn, immunotherapy amplifies and consolidates the anti-tumor immune response, forming a closed-loop mechanism of **local therapy initiating immunity–targeted therapy enhancing immunity–immunotherapy sustaining immunity**.

For massive hepatocellular carcinoma, due to its low tumor immunogenicity and markedly immunosuppressive microenvironment, the objective response rate of single-agent immunotherapy is generally unsatisfactory [5].

3. Current Clinical Application Status of TACE Combined with Targeted and Immunotherapy

3.1. Breakthroughs in Clinical Efficacy of First-line Combined Regimens

With the clarification of the mechanism underlying TACE combined targeted-immunotherapy, prospective multicenter clinical trials have been successively launched. Relevant studies have confirmed that this combined model presents prominent efficacy advantages in the first-line treatment of massive hepatocellular carcinoma, breaking the efficacy limitations of conventional TACE monotherapy.

At present, the mainstream first-line combined clinical regimens mainly include two categories: TACE combined with anti-angiogenic TKI plus PD-1 inhibitors, and TACE combined with anti-VEGF monoclonal antibody plus PD-L1 inhibitors. Both regimens yield superior benefits in objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) compared with TACE alone. A number of phase III clinical studies have demonstrated that for unresectable hepatocellular carcinoma with intermediate to high tumor burden, the combined regimens provide significantly longer median progression-free survival and higher objective response rate than single TACE treatment. For patients with massive tumor lesions complicated by vascular invasion, such combination therapy can achieve longer disease control duration and lower recurrence ris[6].

3.2. Application Value and Clinical Significance in Conversion Therapy

Due to the large tumor size and frequent concomitant vascular invasion or intrahepatic dissemination, the initial resectability rate of massive hepatocellular carcinoma is less than 20%. Conversion therapy has become an important approach to acquire the opportunity of radical treatment. With the advantage of rapid tumor regression, TACE combined with targeted and immunotherapy has emerged as the primary option for conversion therapy of unresectable massive HCC, with increasingly prominent clinical significance [7].

Compared with conventional TACE or single targeted-immunotherapy conversion regimens, triple combination therapy can rapidly and effectively reduce tumor volume and downstage tumor staging, form a clear boundary between the tumor and large blood vessels, control tumor thrombus and micrometastatic lesions, and create favorable conditions for subsequent surgical resection. Clinical research data show that the conversion resection rate of TACE combined with targeted and immunotherapy for massive hepatocellular carcinoma can reach 20%–35%, which is markedly higher than that of traditional conversion strategies. Moreover, patients with successful conversion achieve postoperative recurrence-free survival and overall survival comparable to those of early-stage HCC after surgery, enabling long-term survival and even clinical cure [8].

3.3. Application as Salvage Therapy after Recurrence and Metastasis

Hepatocellular carcinoma is associated with a high postoperative recurrence and metastasis rate. Due to its aggressive biological characteristics, massive hepatocellular carcinoma carries an even higher risk of recurrence and metastasis. Once recurrence occurs, it mostly presents as multiple intrahepatic metastases, repeated vascular invasion or distant metastasis, resulting in great therapeutic difficulty.

TACE combined with targeted and immunotherapy has achieved favorable efficacy in the salvage treatment of recurrent and metastatic massive hepatocellular carcinoma, serving as an important alternative therapeutic modality after disease recurrence. For locally recurrent massive intrahepatic lesions after surgery, TACE enables precise control of local recurrent foci, and combined targeted and immunotherapy inhibits the potential systemic metastasis, thereby achieving the goal of delaying disease progression.

For recurrent patients with extrahepatic metastasis, TACE controls intrahepatic primary lesions, while targeted and immunotherapy exert systemic anti-tumor effects. This realizes synergistic regulation of both intrahepatic and extrahepatic lesions, improves clinical symptoms and prolongs patient survival.

Clinical studies have shown that for recurrent and metastatic massive HCC treated with TACE combined targeted–immunotherapy as salvage therapy, the objective response rate reaches 30%–45%, the disease control rate exceeds 70%, and the median survival time is significantly superior to that of chemotherapy or targeted monotherapy. Meanwhile, the combination regimen exhibits favorable safety and improves patients' quality of life.

4. Optimization and Individualized Strategy of TACE Combined with Targeted-Immunotherapy

4.1. Optimization of Treatment Timing and Sequential Mode

The combination timing and sequential regimen of TACE combined with targeted-immunotherapy are directly related to the synergistic efficacy and safety profile, serving as a core direction for therapeutic regimen optimization. Currently, three major clinical models are commonly adopted: **TACE followed by sequential targeted-immunotherapy**, **targeted-immunotherapy induction followed by TACE**, and **concurrent** combination therapy, each with unique advantages and applicable clinical scenarios.

The sequential model with TACE as the first-line treatment is the most widely used clinical strategy. After initial TACE treatment, combined immunotherapy is initiated within 1–2 weeks postoperatively, when liver function recovers and tumor necrosis as well as antigen release reach their peak. This regimen can rapidly reduce tumor burden, alleviate the immunosuppressive effect induced by high tumor antigen load, and lower the risk of liver injury caused by early concurrent systemic therapy after TACE, demonstrating favorable safety. It is particularly suitable for patients with massive nodular hepatocellular carcinoma characterized by **moderate liver reserve function and extremely high tumor burden**[9].

4.2. Individualized Drug Selection and Dose Adjustment

The selection of targeted agents and immune checkpoint inhibitors, as well as their dose modulation, constitute an essential part of optimizing the TACE combined targeted-immunotherapy regimen.

In terms of targeted drugs, lenvatinib exerts potent inhibitory effects on the VEGF pathway and can induce tumor regression. It can also inhibit compensatory angiogenesis after TACE, making it the preferred TKI for combination therapy in patients with massive hepatocellular carcinoma.

Bevacizumab is an anti-VEGF monoclonal antibody. It presents favorable synergistic effects when combined with PD-L1 inhibitors and shows a good safety profile, which is suitable for patients with Child-Pugh B liver function or those intolerant to TKI treatment.

As for immune therapeutic agents, both **PD-1 inhibitors** and **PD-L1 inhibitors** are widely applied in clinical practice. PD-1 inhibitors achieve a slightly higher overall response rate, while PD-L1 inhibitors are associated with a lower incidence of immune-related adverse events. Clinically, individualized selection should be made based on patients' previous immune status, underlying comorbidities, and the risk of adverse reactions [10].

4.3. Expansion of Combined Local Therapy and Upgrading of Combination Modes

To further improve the therapeutic efficacy of massive hepatocellular carcinoma (HCC), multimodal comprehensive treatment combining TACE plus targeted-immunotherapy with other local therapies is adopted to upgrade and optimize the therapeutic strategy.

For massive lesions with residual tumor or uncontrolled local lesions after TACE, combined local thermal ablation therapies such as radiofrequency ablation and microwave ablation can precisely eradicate residual cancerous tissues, further reduce tumor burden, and elevate the local control rate.

For patients with massive HCC complicated by portal vein tumor thrombus and hepatic hilar invasion, combined stereotactic body radiation therapy (SBRT) or yttrium-90 resin microsphere internal radiotherapy can effectively control tumor thrombus, shrink tumor lesions, ameliorate vascular invasion, and enhance tumor immunogenicity, thereby producing a synergistic effect with targeted and immunotherapy.

In addition, on the basis of TACE combined with targeted-immunotherapy, the addition of iodine-125 seed implantation can deliver sustained local radiotherapy to massive lesions, inhibit tumor growth, and activate immune responses. This approach is suitable for patients with poor tumor blood supply and unsatisfactory response to TACE.

A number of clinical studies have demonstrated that the quadruple or quintuple regimen of "TACE + targeted-immunotherapy + X" can further improve the objective response rate and conversion resection rate, prolong overall survival, and provide a more effective therapeutic option for unresectable massive hepatocellular carcinoma.

Meanwhile, with the advancement of interventional techniques, novel TACE modalities including precise TACE and drug-eluting bead TACE have been incorporated into combined regimens. These techniques can increase local drug concentration, prolong drug action time, reduce systemic adverse reactions of chemotherapeutic agents, and consequently improve the efficacy and safety of combination therapy.

5. Conclusion

TACE combined with targeted-immunotherapy represents a novel therapeutic strategy relying on the synergistic effect of local and systemic treatment for massive hepatocellular carcinoma (HCC). It breaks the efficacy bottleneck of conventional monotherapy, and exhibits prominent clinical significance in improving the objective response rate, prolonging survival time and promoting tumor conversion and downstaging. At present, it has become the mainstream treatment modality for massive HCC.

With the in-depth advancement of clinical research and the progress of therapeutic technologies, this combined therapeutic model has been continuously optimized, with gradually expanded applicable indications and increasingly standardized safety management. It brings hope of long-term survival and even radical cure to numerous patients with unresectable massive hepatocellular carcinoma.

In the future, further efforts should be made to clarify the synergistic mechanism, explore reliable biomarkers, optimize therapeutic regimens, standardize safety management, conduct more high-quality prospective clinical studies, and refine individualized treatment strategies. These measures will accelerate the precision and standardization of TACE combined with targeted-immunotherapy, improve the overall therapeutic efficacy for massive HCC, and bring greater survival benefits to patients with liver cancer.

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