

Synergistic PD-1/PD-L1 Blockade Strategies in Hepatocellular Carcinoma Management

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Abstract. Primary liver cancer ranks as the sixth most commonly diagnosed malignancy and the third leading cause of cancer-related mortality worldwide. Treatment at early stages primarily involves surgical resection; however, more than 70% of patients are diagnosed at intermediate or advanced stages according to the Barcelona Clinic Liver Cancer (BCLC) staging system. At these stages, curative-intent surgery is often precluded due to vascular invasion or extrahepatic metastasis. Immunotherapy, especially inhibitors targeting the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathway, has emerged as a promising therapeutic strategy. Nevertheless, its application is constrained by challenges such as immune-related adverse events (irAEs) and the development of acquired resistance to immune checkpoint inhibitors (ICIs). To overcome these limitations, combination therapeutic approaches—which target both the tumor microenvironment and the host immune system—have been extensively investigated. These regimens not only improve antitumor efficacy but also help mitigate resistance mechanisms. This review comprehensively summarizes recent advances in combination strategies for unresectable liver cancer, including immune-targeted, immune-radiotherapy, and immune-chemotherapy combinations, with the aim of providing valuable insights and clinical guidance for improving outcomes in this patient population.

Keywords: Hepatocellular Carcinoma, Tumor microenvironment, Immune checkpoint inhibitors, Immunotherapy, Combination therapy

1. Introduction

In China, liver cancer constitutes a major public health burden, claiming one life every three minutes. Hepatocellular carcinoma (HCC), representing approximately 75-85% of primary liver malignancies, is the predominant subtype. Epidemiological trends indicate rising HCC incidence and mortality, primarily driven by chronic HBV/HCV infections, aflatoxin exposure, alcohol misuse, and metabolic disorders including non-alcoholic fatty liver disease (NAFLD). A critical obstacle in managing HCC is its typically asymptomatic early stage, leading to frequent late detection. Consequently, over 70% of patients present at intermediate or advanced phases, precluding curative surgical resection.

Due to the constraints of conventional treatments, intense research focuses on novel therapeutic avenues. Central to this effort is the PD-1/PD-L1 immune checkpoint pathway, a key mechanism

enabling tumor immune evasion through T-cell suppression [1]. While PD-1/PD-L1 blockade reverses exhaustion in tumor-infiltrating T lymphocytes, their effectiveness as single agents remains limited, with objective response rates under 20%. This has spurred investigation into combination strategies, such as integrating checkpoint blockade with anti-angiogenic drugs, tyrosine kinase inhibitors, or locoregional therapies, aiming to synergistically amplify immune responses and enhance clinical outcomes. Such multimodal approaches hold significant promises for improving the prognosis of this lethal disease.

2. The immunological mechanisms of the tumor immune microenvironment in liver cancer

PD-1/PD-L1 blockade reactivate antitumor immune surveillance by blocking checkpoint signaling. Within TME, PD-L1 is expressed by both malignant and immunosuppressive cells. Its binding to PD-1 suppresses T cell function, facilitating tumor immune evasion. These agents disrupt PD-1/PD-L1 engagement, reversing T cell inhibition and amplifying cytotoxic activity. Concurrently, they revitalize antigen-presenting cell (APC) function, promoting the activation and infiltration of tumor-specific T lymphocytes. This cascade reprograms the immune milieu, instigating an antitumor response.

3. The efficacy of PD-1/PD-L1 blockade as monotherapy in HCC

Remains suboptimal, with objective response rates generally confined to 15-20%. This limitation stems principally from the complex immunosuppressive landscape of TIME, characterized by redundant mechanisms including TGF- β signaling and MDSC infiltration. To overcome therapeutic resistance, combination strategies have consequently become a foundational approach.

3.1. Trans arterial chemoembolization (TACE)

Integrated TACE and PD-1/PD-L1 blockade yields synergistic antitumor activity in intermediate- to advanced-stage HCC management. While TACE induces tumor necrosis and activates immune responses, the resultant hypoxic microenvironment triggers upregulation of PD-L1 and VEGF, facilitating immune escape. PD-1/PD-L1 blockade counteracts T-cell suppression, thereby enhancing anti-tumor immunity. This combined strategy holds promise for overcoming the high recurrence rates associated with TACE monotherapy [2]. Studies indicate that adding anti-VEGF agents improves the tumor microenvironment and promotes T-cell infiltration. A global Phase III trial involving 616 HCC patients compared three regimens: TACE + durvalumab + bevacizumab, TACE + durvalumab, TACE + placebo. Key outcomes revealed: The TACE+durvalumab+bevacizumab arm demonstrated significantly prolonged median progression-free survival (mPFS) at 15.0 months versus 8.2 months for placebo (HR 0.77; 95% CI 0.61–0.97; $p=0.032$), while the TACE+durvalumab cohort achieved 10.0 months mPFS. Objective response rate (ORR) reached 44% in the dual-combination group vs. 30% with placebo. Duration of response (DoR) extended to 22.1 months, indicating sustained clinical benefit [2]. Multiple Phase II studies report ORRs of 35%–50% for TACE combined with PD-1 inhibitors, with median overall survival (OS) extending to 16–24 months (Table 1) [3]. Notably, some patients achieved tumor downstaging

through combination therapy, enabling curative resection – particularly those with large HCC tumors or portal vein tumor thrombosis [4].

3.2. Lenvatinib

Lenvatinib, a multi-targeted kinase inhibitor, exerts dual effects by blocking VEGFR/FGFR pathways: it suppresses angiogenesis to remodel the tumor microenvironment while simultaneously enhancing immune cell infiltration and function. Its synergistic mechanism with PD-1/PD-L1 inhibitors involves alleviating immunosuppression, improving drug delivery, and reversing T-cell exhaustion, creating complementary antitumor effects [5].

In phase III trials, first-line lenvatinib-pembrolizumab therapy for unresectable hepatocellular carcinoma resulted in a 46% ORR (mRECIST), 22-month overall survival, and 9.3-month median PFS [6]. Based on these results, the U.S. FDA granted accelerated approval to lenvatinib plus pembrolizumab for advanced HCC in 2021. Subsequent data demonstrated: median OS: 21.2 months (combination) vs. 19.0 months (lenvatinib monotherapy) (HR=0.84, $p=0.0227$). Though OS improvement did not meet prespecified statistical significance thresholds, ORR was higher with combination therapy (26.1% vs. 17.5%) [6]. A Chinese multicenter Phase II trial (ASCO 2023) reported first-line lenvatinib-sintilimab therapy yielded a 34.3% ORR, 85.7% DCR, and 20.1-month mOS. (Table 1) [7]. The lenvatinib plus PD-1/PD-L1 inhibitor regimen demonstrates significant clinical benefits in HCC: rapid tumor shrinkage (observable within 3 months), durable responses DoR: 12-18 months, downstaging potential enabling curative resection in 15%-20% of initially unresectable patients.

3.3. Hepatic Artery Infusion Chemotherapy (HAIC)

HAIC delivers high-dose cytotoxic agents (e.g. FOLFOX), eliciting dual effects: induction of tumor necrosis with subsequent tumor-associated antigen (TAA) release, activating DC-T cell immunity; TME remodeling through aberrant vasculature reduction, Treg/MDSC depletion, and enhanced CD8⁺ T/NK cell infiltration. Synergistic interaction with PD-1/PD-L1 inhibitors operates via complementary mechanisms: HAIC provides "antigenic fuel" for immune initiation, while checkpoint blockade sustains response momentum by eliminating inhibitory signals [8]. This establishes a positive feedback loop: "Antigen Release → Immune Activation → Checkpoint Blockade" [9]. Clinical Evidence: retrospective Study (n=38, intermediate/advanced HCC): combination therapy (TACE-HAIC + Lenvatinib + PD-1 inhibitor) yielded: ORR: 63.16%, DCR: 86.84%, median PFS: 9.1 months, 21.05% of patients achieved downstaging to curative resection. DurHope Study (HCC with severe PVTT): durvalumab + HAIC resulted in: ORR: 47.4%, median PFS: 5.5 months, superior intrahepatic disease control (Median intrahepatic PFS: 6.8 months), complete responses (CR) observed in some patients (Table 1) [8].

Synergistic HAIC and PD-1/PD-L1 blockade induces dramatic tumor regression within 3 months, with some patients achieving radiographic CR and significant declines in AFP levels. The regimen of mFOLFOX-HAIC + Lenvatinib + PD-1 inhibitor for advanced HCC achieves a median OS of 20 months, surpassing outcomes with traditional therapies.

Analysis Conclusions: 1. synergy Principle: All combinations leverage complementary mechanisms—local therapy (TACE/HAIC) or TKIs modulate the TIME/release antigens, while ICB sustains adaptive immunity; 2. efficacy: Triple combinations (e.g., TACE+ICB+Anti-VEGF,

HAIC+TKI+ICB) generally yield superior ORR and PFS vs dual therapy or monotherapy;3.clinical Impact: Key benefits include high response rates, tumor downstaging enabling resection in initially unresectable patients (15-21%), and durable responses (DoR 12-22+ months);4.optimal Selection: Choice depends on tumor burden, vascular involvement (PVTT), liver function, and treatment goals (disease control vs. downstaging). HAIC-based regimens show particular promise for bulky tumors or severe PVTT.

Table 1. Comparison of combined drug therapy

Therapy Combination	Key Synergistic Mechanism	Representative Efficacy Outcomes	Notable Advantages
TACE + PD-1/PD-L1 ± Anti-VEGF	TACE releases antigens & causes hypoxia → Hypoxia upregulates PD-L1/VEGF → Blockade counters escape	HR:0.77; 95% CI: 0.61–0.97; p=0.032; ORR: 44%; DoR: 22.1 mos; ORRs:35%–50%; OS:16–24 mos	Overcomes TACE-induced immune suppression; High ORR; Potential downstaging
Lenvatinib + PD-1/PD-L1	Lenvatinib inhibits VEGF/FGFR → Normalizes vasculature → Improves immune cell infiltration/drug delivery → ICB reverses exhaustion	ORR (mRECIST): 46%; Median PFS: ~9.3 mos Median OS: 20-22 mos; ORR:34.3%; DCR:85.7%; mOS:20.1-month	Rapid tumor shrinkage (≤3 mos); Durable responses; Downstaging in 15-20% of unresectable
HAIC + PD-1/PD-L1 ± TKI	HAIC provides potent "antigenic fuel" → Activates DC-T cell axis → ICB sustains response → HAIC remodels suppressive TME	ORR: 63.16%; DCR: 86.84%; Median PFS: 9.1 months; Median PFS: 5.5-9.1 mos	Strong antigen release; Effective TME modulation; High response rates; CR observed
Common Advantage	Overcomes primary/secondary resistance to monotherapy by targeting complementary pathways within the TIME	NA	Provides viable treatment options for advanced/unresectable HCC

4. Conclusion

Combination therapies demonstrate a favorable safety profile. The primary grade 3-4 adverse events include hypertension (6%), anemia (5%), and acute kidney injury (4%), with overall manageable incidence. Notably, irAEs such as thyroid dysfunction and rash occur at consistently low rates. The combination regimens do not appear to significantly exacerbate the unique risk profile associated with immunotherapy.

From a clinical practice perspective, while PD-1/PD-L1 inhibitor-based combinations have demonstrated robust anti-tumor activity, opportunities remain for optimizing combination strategies. Key parameters requiring further investigation include dosing sequence, schedule adjustments, and dose optimization.

Persistent Challenges and Future Directions: tumor Heterogeneity & Resistance, tumor heterogeneity and immunosuppressive mechanisms drive suboptimal responses to ICIs in certain HCC patients. Furthermore, established predictive biomarkers—particularly PD-L1 expression and tumor mutational burden (TMB)—demonstrate limited reliability in this malignancy. necessitating the development of more precise patient stratification strategies; local-Ablative Therapy Integration: optimizing the synergy between ablation and ICIs requires defining optimal ablation energy parameters, timing of ICI administration (neoadjuvant vs. adjuvant settings), efficacy of triplet regimens combining ablation, ICIs, and anti-angiogenic agents. Technological Innovation: Developing multimodal image-guided smart ablation systems could expand the ablation zone while

minimizing complication risks. Novel Combination Approaches: neoantigen-based vaccines combined with ICIs, offering tailored therapy for low-TMB tumors; establishing comprehensive HCC treatment paradigms integrating ablation, ICIs, targeted therapies, and cellular therapies.

The therapeutic paradigm for hepatocellular carcinoma is evolving towards molecularly stratified, multi-modal precision approaches. Adaptive, and AI-driven approaches. Achieving the leap from local control to systemic cure will require robust interdisciplinary collaboration.

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