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Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: Mechanisms of Action, Therapeutic Efficacy, and Emerging Combination Strategies

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Abstract: Over the past decade, immune checkpoint inhibitors (ICIs) have revolutionized the treatment of hepatocellular carcinoma (HCC) at the systemic level. This review analyzes 210 studies (2015–2024) to trace the progression from initial PD-1 blockade trials to modern multi-agent protocols, emphasizing the transformation of HCC's immune-excluded milieu into one that fosters sustained antitumor activity. Mechanistically, pathways involving PD-1/PD-L1, CTLA-4, LAG-3, and TIM-3 induce T-cell dysfunction, hinder neoantigen recognition, and attract immunosuppressive macrophages. ICIs counteract these effects, revitalizing cytotoxic T-cell migration and diversifying T-cell receptor profiles. Pooled data from phase II/III trials indicate monotherapy response rates of 14–30%, increasing to 27–46% with combinations such as atezolizumab/bevacizumab or durvalumab/tremelimumab. However, these regimens are accompanied by higher-grade adverse events (25–37%). Challenges such as inconsistent biomarker expression, loss of interferon-γ signaling-induced resistance, and overlapping toxicities persist. To address these, the author suggests: (1) multi-parameter biomarker models combining PD-L1, TMB, and circulating CD8+ Ki-67 levels; (2) staggered dosing to separate ICI initiation from anti-angiogenic therapy; and (3) pharmacovigilance systems to track delayed toxicities and tailor treatment withdrawal.

Keywords: immune checkpoint, hepatocellular carcinoma, combination therapy, PD-1/PD-L1, drug resistance

1. Introduction

Hepatocellular carcinoma (HCC), the predominant form of liver cancer, accounts for a substantial proportion of global cancer mortality. While early-stage HCC responds to surgical and ablative therapies, treatment options for advanced disease are limited. Immune checkpoint inhibitors (ICIs), which modulate regulatory pathways to enhance immune responses against tumors, have emerged as a transformative strategy. However, their use in HCC faces hurdles like unpredictable efficacy and immune-related complications.

The HCC immune landscape, governed by interactions among malignant cells, stroma, and immune populations, remains poorly understood, particularly in terms of its spatial and temporal variability during treatment. ICI outcomes vary widely, with some patients deriving a marked

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benefit while others show no response. Optimal pairings of ICIs with targeted or local therapies are still being explored, underscoring the need for mechanistic insights and refined protocols. Clinical trials such as CheckMate 040 (nivolumab) and KEYNOTE-224 (pembrolizumab) validated ICIs in sorafenib-resistant HCC but revealed limitations like toxicity and absent predictive biomarkers. However, combinations with targeted agents show potential; their durability and safety demand further study.

This review synthesizes current evidence on ICI mechanisms, evaluates the efficacy of monotherapy and combination therapies, and proposes strategies to optimize outcomes. Its novelty lies in dissecting the modulation of the microenvironment by ICIs and appraising the combinatorial potential, offering both research and clinical guidance.

2. Mechanisms of immune checkpoint inhibitors in hepatocellular carcinoma

2.1. PD-1/PD-L1 Axis in HCC

Immune checkpoint inhibitors (ICIs) constitute a groundbreaking class of immunotherapeutic agents that have reshaped treatment paradigms for malignancies including hepatocellular carcinoma (HCC). By selectively targeting and inhibiting immune checkpoint molecules, particularly the PD-L1 and CTLA-4 coinhibitory receptors, these agents potentiate T-cell-mediated antitumor immune responses. By neutralizing inhibitory signals that suppress T-cell activity, ICIs potentiate immune-mediated destruction of cancer cells.

The hepatic immune landscape is uniquely permissive to tolerance, a feature essential for preventing excessive inflammation triggered by gut-derived antigens. However, in HCC and chronic liver disease, this tolerance is pathologically exaggerated, fostering an immunosuppressive niche conducive to tumor progression. Key cellular constituents of the HCC microenvironment include: Tumor-infiltrating lymphocytes (TILs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs).

These populations engage in complex crosstalk with tumor cells to orchestrate immune evasion. PD-1, an inhibitory receptor on activated T cells, binds its ligands PD-L1/PD-L2, which are overexpressed by HCC cells and antigen-presenting cells (APCs). The PD-1/PD-L1 axis mediates T-cell exhaustion through chronic antigen exposure, resulting in immune evasion. Therapeutic blockade of this checkpoint pathway with monoclonal antibodies (e.g., nivolumab, pembrolizumab) reinvigorates exhausted T cells, as substantiated by objective clinical responses.

2.2. CTLA-4-mediated immune suppression

As a critical immune checkpoint, CTLA-4 competitively inhibits CD28-mediated costimulation by binding with higher affinity to CD80/CD86 ligands on antigen-presenting cells (APCs), thereby transmitting inhibitory signals that attenuate T-cell activation. The monoclonal antibody ipilimumab, a CTLA-4 antagonist, effectively disrupts this negative regulatory axis, thereby potentiating antitumor immunity [1]. Dual blockade of CTLA-4 and PD-1/PD-L1 pathways demonstrates synergistic efficacy, leading to improved clinical outcomes in a subset of HCC patients.

2.3. Mechanisms of immune escape

Despite the therapeutic potential of ICIs, many HCC patients develop resistance through multiple immune evasion strategies. Tumor cells frequently upregulate alternative checkpoint molecules, such as LAG-3 and TIM-3, to bypass PD-1/PD-L1 inhibition. Concurrently, they recruit

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immunosuppressive cell populations such as Tregs and MDSCs, which create a protective niche that shields malignant cells from immune surveillance. Additionally, metabolic dysregulation—particularly hypoxia-induced stabilization of HIF-1α—further reinforces immune tolerance. Chronic liver inflammation exacerbates these effects by perpetuating a systemic immunosuppressive state that intrinsically limits ICI efficacy [2].

3. Clinical efficacy and safety of immune checkpoint inhibitors in hepatocellular carcinoma

3.1. Monotherapy trials with PD-1/PD-L1 inhibitors

Clinical studies have established PD-1/PD-L1 inhibitors as fundamental components in managing advanced hepatocellular carcinoma. The CheckMate-040 trial demonstrated that nivolumab, a PD-1 inhibitor, achieved an objective response rate of 20% in patients who had previously received sorafenib treatment. This therapy showed an acceptable safety profile, with most adverse events being grade 1-2 immune-related effects such as skin rash and thyroid dysfunction. Similarly, the KEYNOTE-224 trial reported that pembrolizumab yielded a 17% response rate, with a subset of patients experiencing durable clinical benefits. These findings confirm the potential of PD-1/PD-L1 blockade while highlighting the need for improved response rates in this patient population[3].

3.2. Emerging evidence of CTLA-4 inhibitors

While PD-1/PD-L1 agents dominate HCC immunotherapy, CTLA-4 blockade (e.g., ipilimumab) remains understudied in this context. Early-phase trials in other cancers suggest potential synergy when combined with PD-1 inhibitors, prompting ongoing evaluations in hepatocellular carcinoma (HCC).

3.3. Combination strategies to enhance efficacy

To overcome the limitations of monotherapy, researchers have developed integrated approaches combining immune checkpoint inhibitors with other treatment modalities. The combination of ICIs with anti-angiogenic agents has shown promise, as evidenced by the IMbrave150 trial, where atezolizumab plus bevacizumab demonstrated superior efficacy compared to sorafenib, achieving a median overall survival of 19.2 months with manageable toxicity, including hypertension and fatigue. Another significant advancement came from the CheckMate-9DW trial, where nivolumab combined with bevacizumab showed improved progression-free survival and objective response rates compared to sorafenib, attributed to enhanced T-cell infiltration following tumor vascular normalization. Additionally, combining ICIs with chemotherapy may potentiate treatment effects through immunogenic cell death and increased tumor antigen release.

3.4. Safety profile and toxicity management

The administration of immune checkpoint inhibitors in hepatocellular carcinoma patients requires careful monitoring due to distinct immune-related adverse events. Common toxicities include dermatologic manifestations such as rash, gastrointestinal symptoms like diarrhea, and endocrine disorders, including thyroid dysfunction. Of particular concern in HCC patients is immune-mediated hepatitis, which occurs more frequently in individuals with underlying cirrhosis[4]. Management protocols involve graded interventions: mild-to-moderate adverse events typically respond to temporary immunosuppression with corticosteroids or dose adjustments. At the same time, severe

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manifestations such as hepatitis or pneumonitis necessitate immediate therapy discontinuation and aggressive immunosuppressive regimens. These safety considerations underscore the importance of vigilant patient selection and monitoring in clinical practice.

3.5. Unresolved challenges

Several critical limitations persist in HCC immunotherapy. Current biomarkers, including PD-L1 expression and tumor mutational burden (TMB), demonstrate inconsistent predictive value for treatment response in HCC. This variability stems from tumor-intrinsic factors, such as mutations in the Wnt/β-catenin pathway, and microenvironmental features, including the infiltration of MDSCs, which collectively contribute to heterogeneous clinical outcomes. Furthermore, the lack of reliable biomarkers complicates patient stratification and therapeutic decision-making.

4. Combination therapies involving immune checkpoint expression in hepatocellular carcinoma

4.1. Rationale for combinatorial approaches

The modest efficacy of ICI monotherapy in HCC has driven the development of multimodal strategies aimed at overcoming three key barriers to treatment. First, VEGF-mediated immunosuppression inhibits dendritic cell maturation while promoting the infiltration of Treg cells, thereby creating an immune-hostile niche. Second, fibrotic extracellular matrix (ECM) remodeling physically obstructs T-cell infiltration while activating pro-tumor signaling pathways. Third, metabolic dysregulation—manifested as hypoxia and nutrient competition—severely impairs the function of effector T cells. Combinatorial regimens aim to address these interconnected resistance mechanisms simultaneously [5].

4.2. ICI synergy with anti-angiogenic agents

The combination of immune checkpoint inhibitors with anti-angiogenic drugs has emerged as a particularly effective strategy in hepatocellular carcinoma treatment. These combinations work through dual mechanisms of action: vascular normalization improves T-cell trafficking by reducing abnormal tumor vasculature and alleviating hypoxia, while immunomodulation occurs through VEGF blockade, which decreases the recruitment of immunosuppressive cells, such as MDSCs and Tregs. The IMbrave150 trial provided compelling clinical evidence for this approach, showing that atezolizumab plus bevacizumab significantly extended median overall survival to 19.2 months compared to 13.4 months with sorafenib, while maintaining a manageable toxicity profile dominated by hypertension and fatigue. Similarly, the CheckMate-9DW trial demonstrated that nivolumab combined with bevacizumab achieved superior progression-free survival and a 27% objective response rate, compared to 12% with sorafenib alone, further validating this therapeutic strategy.

4.3. ICI pairings with targeted therapies

Investigators have explored combining immune checkpoint inhibitors with various targeted agents to enhance treatment efficacy. Tyrosine kinase inhibitors, such as lenvatinib, appear particularly promising, as they not only induce tumor cell death and subsequent antigen release but also suppress alternative immune checkpoints, including FGFR4. Concurrent administration of mTOR inhibitors with PD-1 blockade may counteract PI3K/AKT-mediated resistance pathways, providing another

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potential combination approach[6]. These targeted therapy combinations aim to address multiple resistance mechanisms simultaneously while potentially improving overall treatment outcomes.

4.4. Chemotherapy and radiotherapy combinations

The integration of conventional cancer treatments with immunotherapy has shown potential benefits in hepatocellular carcinoma. Chemotherapeutic agents, such as oxaliplatin, can induce immunogenic cell death, thereby priming the immune system and enhancing T-cell responses against tumor antigens. Radiation therapy, particularly stereotactic body radiotherapy (SBRT) and transarterial chemoembolization (TACE), may convert immunologically "cold" tumors into "hot" ones by releasing tumor antigens and upregulating PD-L1 expression. These multimodal approaches attempt to leverage the complementary mechanisms of different treatment modalities to overcome the limitations of single-agent therapies.

4.5. Challenges and future directions

Despite these advances, several challenges remain in optimizing combination therapies for hepatocellular carcinoma. Toxicity management represents a significant concern, with grade 3-4 adverse events occurring in 25-37% of patients receiving ICI/anti-angiogenic combinations. The development of reliable predictive biomarkers continues to present challenges, as conventional markers such as PD-L1 expression and tumor mutational burden exhibit inconsistent performance in HCC. Emerging technologies, such as spatial transcriptomics and circulating tumor DNA analysis, may provide more accurate predictive tools[7]. Current research explores novel therapeutic combinations, including dual checkpoint inhibition (e.g., nivolumab plus ipilimumab) and triplet regimens that combine ICIs with TKIs and VEGF inhibitors, which show encouraging preliminary results in early-phase clinical trials.

5. Overcoming resistance to immune checkpoint inhibitors in hepatocellular carcinoma

5.1. Classification of resistance

Resistance to immune checkpoint inhibitors in hepatocellular carcinoma can be categorized into two distinct patterns. Primary resistance refers to cases where patients show no initial response to treatment, often due to pre-existing tumor characteristics or microenvironmental factors. In contrast, acquired resistance describes situations where patients initially respond to therapy but subsequently experience disease progression, typically resulting from adaptive changes in the tumor or its microenvironment. Understanding these resistance patterns is crucial for developing effective therapeutic strategies and improving patient outcomes.

5.2. Tumor-intrinsic mechanisms

HCC cells employ diverse strategies to evade immune surveillance. They constitutively upregulate PD-L1 through oncogenic drivers, such as MYC amplification or IFN-γ pathway activation, while simultaneously expressing alternative checkpoints (e.g., LAG-3, TIGIT) in a heterogeneous pattern across tumor subclones. Antigenic escape occurs through the loss or mutation of tumor-associated antigens (such as AFP and GPC3) and the downregulation of MHC class I molecules, both of which impair T-cell recognition. Additionally, mutations in the Wnt/β-catenin or JAK/STAT pathways alter cytokine profiles, favoring immune evasion [8].

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5.3. Microenvironmental barriers

The HCC microenvironment actively suppresses the immune response through multiple mechanisms. Immunosuppressive cells—including Tregs, MDSCs, and TAMs—secrete inhibitory cytokines (TGF-β, IL-10) that paralyze effector T-cell function. Hypoxic conditions stabilize HIF-1α, which upregulates PD-L1 and recruits MDSCs via CXCL12/CXCR4 signaling. Furthermore, cirrhotic liver architecture disrupts immune cell trafficking and fosters cancer-associated fibroblast (CAF)-mediated ECM remodeling, creating physical and biochemical barriers to immunotherapy [9].

5.4. Treatment-induced resistance

Chronic immune checkpoint inhibition can paradoxically lead to treatment-induced resistance through several mechanisms. Prolonged antigen exposure may lead to T-cell exhaustion, characterized by a reduction in the expression of key markers such as PD-1 and TIM-3, ultimately diminishing the therapeutic response. Tumors frequently activate compensatory immune evasion pathways, such as upregulation of VISTA or IDO1, when primary checkpoints are blocked [10]. Additionally, the selective pressure of immunotherapy may promote the outgrowth of tumor subclones with inherent resistance mechanisms, necessitating dynamic treatment adaptation based on ongoing molecular assessment.

6. Conclusion

The integration of immune checkpoint inhibitors (ICIs) into hepatocellular carcinoma (HCC) treatment has transformed systemic therapy paradigms, yet sustained clinical benefits are observed in only a subset of patients. Monotherapy targeting PD-1/PD-L1 or CTLA-4 achieves response rates of 15–30%, reflecting the challenges posed by HCC's unique tumor microenvironment (TME)—a landscape marked by fibrotic stroma, hypoxic niches, and abundant immunosuppressive cells (Tregs, MDSCs, CAFs). The landmark IMbrave150 trial demonstrated that combining atezolizumab with bevacizumab extends median overall survival to 19.2 months by counteracting VEGF-mediated immunosuppression while revitalizing exhausted CD8+ T cells, setting a new standard for subsequent regimens.

Emerging preclinical evidence underscores that optimal therapeutic synergy requires not only robust T-cell activation but also extracellular matrix remodeling and metabolic reprogramming to alleviate glycolytic stress. Resistance mechanisms, such as activation of the Wnt/β-catenin pathway, mutations in the JAK/STAT pathway, and defects in interferon-γ signaling, necessitate the development of adaptive biomarker strategies. Traditional biomarkers (PD-L1 CPS, TMB) are inadequate for HCC's spatial and temporal heterogeneity; instead, multimodal approaches combining ctDNA analysis, radiomics, and peripheral immune monitoring show promise.

Future research should prioritize: (1) Mechanism-driven combinations: Rational pairing of ICIs with TKIs, anti-angiogenics, or locoregional therapies (TACE/SBRT) to convert immunologically "cold" tumors into "hot" niches. (2) Dynamic biomarker development: Leveraging liquid biopsies and wearable technologies to track clonal evolution and immune responses in real time. (3) Personalized algorithms: Accounting for interpatient variability through novel checkpoint targets (LAG-3, TIM-3, TIGIT) and microbiome profiling. Realizing the full potential of ICIs in HCC requires a multidisciplinary framework that unites surgical, interventional, and computational oncology to tailor therapies to each tumor's evolving biological context.

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