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Research Progress on the Role of Immune Checkpoint Inhibitors in Liver Cancer Therapy

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Abstract: Globally, hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality and the sixth most common type of cancer, with pronounced therapeutic challenges in the Asia-Pacific region. Its progression is driven by an immunosuppressive tumor microenvironment (TME) linked to hepatitis B and C viruses (HBV/HCV) or metabolic-associated steatohepatitis (MASH).Immune checkpoint inhibitors (ICIs) are a breakthrough treatment for advanced HCC because they reverse T-cell exhaustion by targeting the PD-1/PD-L1 or CTLA-4 pathways. However, single-agent ICIs yield modest efficacy in second-line therapy (15-20% objective response rate [ORR], 12-15 months median overall survival [OS]), limited by TME-mediated immune evasion.Combination therapies now dominate clinical strategies: (1) Immune-targeted regimens (e.g., anti-angiogenics + ICIs) enhance TME immune infiltration, extending median OS to 19.2 months; (2) Dual checkpoint blockade (such as PD-1 + CTLA-4 inhibitors) boosts ORR to 36%, albeit requiring careful management of immune-related toxicities; (3) Immune-local therapy integration (e.g., ablation/radiation + ICIs) leverages antigen release to amplify systemic responses, achieving 90% disease control rates.Despite these advances, persistent hurdles include TME heterogeneity, drug resistance, and region-specific etiologies (e.g., HBV dominance in Asia). Future progress hinges on multi-omics profiling to decipher molecular drivers, development of predictive biomarkers, and personalized immunomodulatory approaches tailored to individual TME landscapes and etiological factors. Addressing these challenges may unlock more durable responses in this heterogeneous malignancy.

Keywords: immune checkpoint, liver cancer, gene expression, immune regulation

1. Introduction

In the world, liver cancer ranks third in terms of cancer-related deaths and is the sixth most frequent type of cancer.In 2022, there were about 865000 new cases and 758000 deaths worldwide[1]. Seventy-five percent of liver cancer cases and fatalities worldwide occur in the Asia-Pacific area, particularly in China, Japan, and South Korea. Among them, China accounts for 63.3 % of the burden of liver cancer in East Asia (197000 new cases and 172000 deaths in 2021). The primary culprits are still the hepatitis B virus (HBV) and the hepatitis C virus (HCV), accounting for 39.3 % and 29.3 % of global liver cancer cases, respectively. China and South Korea are dominated by HBV, while Japan is dominated by HCV. Metabolic risk factors such as metabolic-associated steatohepatitis (MASH), obesity, alcohol intake, and diabetes are rapidly increasing. Especially in

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China, the number of MASH-related liver cancer cases increased by 0.62 % annually. It is estimated that by 2046, the number of new cases of liver cancer worldwide will increase to 755000, with 707000 deaths, with the most significant increase in China.Hepatocellular carcinoma (HCC) accounts for about 75 % -85 %.Currently, liver transplantation, local ablation, and surgical resection are the main methods used to treat HCC.But early HCC has no obvious clinical symptoms, and the majority of patients are currently in the middle to late phases of their care. With the progress of the disease, the available treatment options are very limited.

Tumor immunotherapy controls and eliminates tumors by resuming and sustaining the tumor-immune cycle, which restores the body's natural anti-tumor immune response. The liver's unique immunosuppressive microenvironment lowers the immune response through down-regulation, lymphocyte imbalance, secretion of other immunomodulatory cytokines (like IL-10), and direct inhibition of lymphocyte ligand expression, the liver's unique immunosuppressive microenvironment lowers the immune response rate of tumor cells and promotes tumor immune escape. The introduction of immunotherapy offers a novel approach to treating HCC, with ICIs being the most popular. ICs are co-inhibitory signaling pathway molecules that maintain immune tolerance and reduce tissue damage caused by physiological immune responses, but tumor cells can use this molecule to achieve immune escape. By preventing ICs on the surface of immune or tumor cells from connecting to their ligands, ICIs can counteract tumor growth and restore the immunological response of anti-tumor cells. ICI has become another effective treatment for malignant tumors after radiotherapy, chemotherapy and targeted therapy. It enhances the body’s killing effect on tumor cells through the patient 's own immune system. Melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), and other conditions have all been treated with it. Through an analysis of pertinent literature, this paper seeks to explore the immunological mechanism of liver cancer and the use of immune checkpoint inhibitors for both single and combined therapy of liver cancer patients.

2. The Basic Knowledge about Immune Checkpoints

By controlling the activation, activity, and tolerance of immune cells via signaling pathways, ICs, regulatory mechanisms inside the immune system, maintain immunological balance and self-tolerance, averting autoimmune assaults and excessive immune responses. Among these checkpoints are inhibitory receptors that are expressed on T cells, mainly programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). However, in pathological conditions, certain tumor cells or pathogens exploit immune checkpoints to evade immune attacks by suppressing immune cell activation, promoting tumor growth or persistent infections[2]. As a co-signaling inhibitory receptor, PD-1 is essential for controlling T cell activation and function. On the surface of tumor cells, its ligand PD-L1 is extensively expressed. When PD-L1 binds to PD-1, it recruits protein tyrosine phosphatase 2 (SHP-2) by activating the tyrosine phosphorylation site of the PD-1 receptor. This further inhibits important pathways including protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) by dephosphorylating downstream signaling molecules like phosphatidylinositol 3-kinase (PI3K) and spleen tyrosine kinase (Syk) [3]. This process directly suppresses T cell activation and effector molecule production, impairing anti-tumor responses and enabling tumor immune evasion.While PD-1/PD-L1 has traditionally been viewed as a T cell-centric checkpoint, recent studies highlight its role in modulating the phagocytic function of tumor-associated macrophages (TAMs). Moreno-Vicente et al demonstrated that the interaction between TAMs’ Fcγ receptors (FcγRs) and the Fc region of therapeutic antibodies may alter antibody distribution, half-life, or efficacy, potentially reducing treatment effectiveness. In some cases, TAM activation may even suppress anti-tumor immunity, enhancing tumor cell survival. Consequently, combining PD-1/PD-L1 blockade

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antibodies with engineered IgG variants that avoid FcγR binding or drugs inhibiting FcγR interactions could significantly enhance immunotherapy outcomes. This tactic increases T cell-mediated anti-tumor activity by reducing inadvertent contacts with immunosuppressive TAMs in the tumor microenvironment.By obstructing inhibitory signals, ICIs such as anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab), and anti-PD-L1 (atezolizumab) antibodies restore T cell tumor-killing ability. These treatments have improved survival rates and quality of life in people with melanoma, non-small cell lung cancer, renal cell carcinoma, bladder cancer, and lymphoma. Some patients have had long-lasting improvements. However, excessive immune activation may trigger autoimmune toxicity, necessitating a balance between efficacy and safety [4].

3. The Relationship between Immune Checkpoints and Liver Cancer

Immune checkpoints, such as CTLA-4 and PD-1/PD-L1, physiologically function to maintain immune homeostasis and prevent excessive immune responses. Hepatocellular carcinoma (HCC) cells, on the other hand, take advantage of these substances by overexpressing them in order to inhibit immune cells' cytotoxic action, allowing “immune escape”. For instance, PD-L1 overexpression on HCC cell surfaces binds to T cell PD-1, directly preventing T cell activation and enabling tumors to elude immune monitoring. According to recent research, one of the main causes of immune escape in HCC is hepatitis B virus (HBV) infection. The HBV-encoded HBx antigen activates the TGF-β signaling pathway, inducing tumor cells to secrete the long non-coding RNA HDAC2-AS2 within exosomes. CD8+ T cells absorb this RNA, which then breaks down the CDK9 protein, a crucial kinase controlling the cell cycle, preventing T-cell proliferation and cytotoxic activity and eventually impairing the immune response [5].This mechanism highlights an epigenetic regulatory pathway beyond classical immune checkpoints in HBV-associated HCC. Furthermore, by overexpressing PD-L1 and secreting inhibitory molecules like IL-10, myeloid-derived suppressor cells (MDSCs) in the HCC microenvironment support an immunosuppressive network. Research from Tongji Hospital demonstrates that HCC cells activate S100A9 secretion via the transcription factor ETV5, recruiting and polarizing MDSCs into an S100A9+ subtype. These MDSCs create a "ETV5-S100A9" positive feedback loop by enhancing the malignant phenotype of HCC cells via the ERK/NF-κB signaling pathway.The immune escape mechanisms in HCC are not limited to single checkpoints but involve dynamic multicellular and multipathway regulatory networks. The examples are included in the following.

3.1. The Interaction between Peritumoral Macrophages and Cytotoxic T Lymphocytes

Research by Kuang Dongming’s team found that CD103+ cytotoxic T lymphocytes (CTLs) in HCC tissues predominantly accumulate around the tumor periphery rather than infiltrating the core. Peritumoral macrophages are activated via the "perforin-calcium flux" signaling pathway, secreting pro-inflammatory factors that paradoxically suppress antitumor immunity within the tumor core. This spatial heterogeneity suggests that immune checkpoint inhibition may indirectly mediate immunosuppressive effects through intercellular communication in the microenvironment.

3.2. The Dysfunction and Novel Checkpoint Axes of NK Cells

Although NK cells are essential innate immunological elements in the liver, HCC significantly impairs their ability to infiltrate and function. A University of Hong Kong study, using single-cell sequencing, identified the TIGIT-NECTIN2 axis formed by the binding of NECTIN2 on HCC cells to TIGIT on T cells, which suppresses T-cell activity [6]. Blocking this axis restores T-cell cytotoxicity and reverses the immunosuppressive microenvironment. Moreover, it has been demonstrated that NK cells and type 1 innate lymphoid cells (ILC1) cannot infiltrate or perform

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cytotoxic functions when the IL-27R signaling pathway is activated. IL-27 downregulates NKG2D ligands (e.g., Raet1, H60b) on tumor cells, reducing activation signals for NK cells and thereby promoting immune escape.

4. The Application of Immune Checkpoint Inhibitors in HCC

Historically, there have been few alternatives for treating HCC, the most prevalent primary liver cancer, especially when it has progressed. With PD-1/PD-L1 and CTLA-4 inhibitors showing encouraging efficacy either as monotherapy or in combination regimens, the introduction of immune checkpoint inhibitors (ICIs) has completely changed the treatment of HCC [7]. Below is a comprehensive overview of key agents, clinical trial outcomes, and approved therapies in this field.

4.1. Monotherapy with PD-1/PD-L1 Inhibitors

Nivolumab (Anti-PD-1): Nivolumab was a breakthrough treatment for advanced HCC, according to the CheckMate 040 trial. An ORR of 15–20% and a median OS of 15 months were reported in this phase I/II research. Notably, a subset of patients showed persistent responses, and the disease control rate (DCR) rose to 58%. The U.S. FDA gave nivolumab rapid approval as a second-line treatment for advanced HCC following sorafenib failure in light of these findings.

Pembrolizumab (Anti-PD-1): Pembrolizumab was tested in patients with sorafenib-refractory HCC in the KEYNOTE-224 study; the results showed a median OS of 12.9 months, an ORR of 17%, and a DCR of 44%. The succeeding KEYNOTE-240 phase III trial, however, did not achieve its primary OS target, underscoring the need for predictive biomarkers and the variation in patient responses. Despite this, pembrolizumab remains FDA-approved for HCC under its accelerated approval pathway.

4.2. CTLA-4 Inhibitors as Monotherapy

Tremelimumab (Anti-CTLA-4): Tremelimumab showed minimal efficacy in early studies for advanced HCC, with a median OS of 12.3 months and an ORR of about 10%. While its single-agent activity is limited compared to PD-1 inhibitors, tremelimumab has shown unique antiviral effects in hepatitis-related HCC, likely due to its ability to reduce immunosuppressive regulatory T cells (Tregs) and enhance T cell activation [8].

4.3. FDA-Approved ICIs for HCC

Currently, two PD-1 inhibitors—nivolumab and pembrolizumab—are approved for HCC treatment in the U.S. Both agents are indicated as second-line therapies after sorafenib failure. Their approval underscores the role of PD-1/PD-L1 blockade in overcoming tumor immune evasion, though durability of response remains variable.

5. The Combined Treatment Strategy with Immune Checkpoint Inhibitors

Translation and Synthesis of Immune Checkpoint Inhibitor Combination Strategies in Hepatocellular Carcinoma (HCC) Treatment.

5.1. Immune-Targeted Combination Therapy

The combination of anti-angiogenic drugs (e.g., VEGF inhibitors) with immune checkpoint inhibitors (ICIs) is one of the most established strategies. This approach leverages the dual mechanism of VEGF inhibitors: increasing the effectiveness of ICI by inhibiting tumor

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angiogenesis and reversing the immunosuppressive tumor microenvironment (TME) by decreasing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Key Clinical Studies are shown in the following.

"A+T" Regimen (Atezolizumab + Bevacizumab): With a median overall survival (mOS) of 19.2 months17 and an objective response rate (ORR) of 30%, it was the first first-line combination therapy for advanced HCC to be approved.

"Double Ai" Combination (Camrelizumab + Apatinib): In the CARES-310 study, this regimen demonstrated an mOS of 23.8 months and an ORR of 25%, with efficacy observed even in hepatitis B virus (HBV)-related HCC patients.

These regimens promote "vascular normalization", improving immune cell infiltration into the TME, and are now cornerstone first-line therapies.

5.2. Dual Immune Checkpoint Inhibitor Combination

Dual ICI tactics increase T-cell activation by blocking different checkpoints (such as PD-1 and CTLA-4). Traditional treatments like lenvatinib (mOS 13.8 months) were greatly outperformed by nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor), which together produced an ORR of 36% and a mOS of 23.7 months, according to the CheckMate 9DW study. Although immune-related adverse events (e.g., hepatitis, rash) are more frequent, dose adjustments and stratified management ensure safety. This regimen is now recommended for second-line treatment in unresectable HCC711.

5.3. Immune-Local Therapy Combinations

Local therapies (e.g., transarterial chemoembolization, TACE) synergize with ICIs by inducing tumor necrosis and antigen release, priming the immune system.

TACE + ICIs: TACE and the "Double Ai" regimen (camrelizumab + apatinib) dramatically extended progression-free survival (PFS) and produced a disease control rate (DCR) of about 90%, according to a phase III trial.

Radiotherapy + ICIs: Early data on yttrium-90 (Y90) radioembolization combined with ICIs suggest improved local control and survival, though optimal dosing and timing require further validation [9].

5.4. Triple Therapy: Targeted-Immune-Chemotherapy Integration

To address the rapid progression of HCC in Chinese patients, a "triple therapy" model combining ICIs, anti-angiogenic agents, and oxaliplatin-based chemotherapy has emerged. This approach offers: Rapid Tumor Control: Chemotherapy delays progression, buying time for slower-acting immunotherapies. Enhanced Antigen Exposure: Oxaliplatin induces immunogenic cell death (ICD), exposing tumor antigens. TME Remodeling: Chemotherapy suppresses MDSCs and Tregs, synergizing with ICIs. Phase II trials reported an ORR of 35–40% and a DCR of 90%, with manageable toxicity.

5.5. Emerging Strategies and Future Directions

Novel Targets: A study by Tongji Hospital identified the ETV5-S100A9-MDSC axis as a key driver of immunosuppression. Blocking S100A9 with monoclonal antibodies enhanced PD-L1 inhibitor efficacy in preclinical models [10].

Personalized Biomarkers: Biomarker-driven approaches Multi-omics profiling and tumor mutation burden (e.g., PD-L1 expression) are essential for improving patient selection.

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6. Conclusion

The immunotherapy of liver cancer, especially the application of immune checkpoint inhibitors (ICIs), marks a major innovation in the treatment paradigm of HCC. Although traditional treatments like surgical excision and targeted drugs have a certain effect in early HCC, the survival rate of advanced patients has stagnated for a long time.ICIs have brought breakthrough survival benefits to patients with advanced HCC by reversing the immunosuppressive state of the tumor microenvironment (TME). However, the high heterogeneity of HCC, complex immune escape mechanisms, and regionally specific etiologies pose multidimensional challenges to treatment strategies. Based on the existing research, the following summarizes the key progress and unsolved problems from four aspects: therapeutic breakthrough, mechanism exploration, joint strategy optimization and future direction. Single-agent ICIs (such as nivolumab and pembrolizumab) obtained a second-line treatment objective response rate (ORR) of 15%–20%, and the median overall survival (OS) was increased to 12–15 months. But their efficacy was limited by the immunosuppressive network of TME. In order to overcome the limitations of single drug, combination therapy has become the core strategy, mainly including immune-targeted combination, double immune checkpoint blockade, immune-local treatment integration and other programs. Although the combination therapy significantly improves the efficacy, the following problems need to be solved: accurate analysis of TME heterogeneity, development and verification of biomarkers, toxicity management and drug resistance mechanisms, and regional adaptive treatment strategies.Immune checkpoint inhibitors reshape the treatment pattern of advanced HCC, and the combined strategy significantly prolongs patient survival through multi-mechanism synergy. However, the improvement of efficacy is accompanied by complex challenges. It is necessary to analyze the dynamic characteristics of TME, develop new targets, optimize the combination regimen and individualized strategies through the deep integration of basic and clinical research.

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