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Progress of Clinical Research on Immunotherapies for Liver Cancer

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Abstract: In recent years, immunotherapy has made a breakthrough in the treatment of liver cancer. Immunotherapy, as a novel precision-targeted treatment for tumors, is gaining significance in the clinical management of liver cancer. It not only substantially enhances patients' quality of life but also emerges as the most promising strategy for advanced hepatocellular carcinoma (HCC) when combined with other systemic or local therapies, owing to its ongoing application and development in this context. Several immunotherapy drugs have already entered large-scale clinical trials. This paper reviews recent developments in immunotherapy for liver cancer. The findings indicate that liver cancer treatment has progressed into a novel phase of immunotherapy. From the perspective of the entire process of tumor immunity, improving the cytotoxicity of immune cells and exploring the mechanism of cell death are expected to become key breakthrough areas in the next stage.

Keywords: Immunotherapy, liver cancer, advanced stage, antitumor immunity

1. Introduction

In China, the yearly incidence of new liver cancer cases and fatalities constitutes about 50% of the global total. According to the statistics released by the National Cancer Center (NCC) in February 2024, there were 367,700 newly diagnosed liver cancer cases in China in 2022, ranking fourth among all malignant tumors; moreover, the death toll reached up to 316,500, ranking second only to lung cancer. With the continuous and rapid development of China's market economy, the quality of life is improving rapidly. Enhanced healthcare access and the expanded HBV vaccine coverage have notably reduced virus-related liver cancer rates. The prevalence of alcoholic hepatitis, non-alcoholic fatty liver disease (NAFLD), and NAS

H-related liver cancer exhibits a yearly upward trend [1]. Abdominal hue Doppler ultrasonography, improved abdominal computed tomography (CT), alpha-fetoprotein (AFP) testing, and magnetic resonance imaging (MRI) are the primary modalities for the clinical diagnosis of liver cancer. With the successful application of immunotherapy in the clinical treatment of tumors, especially malignant tumors, liver cancer immunotherapy has become a central focus for liver cancer treatment. Immunotherapy activates and enhances the immune system, restarts and maintains the tumor-immune cycle, and realizes the roles of killing tumor cells and restoring the body's normal anti-tumor immune response, thus controlling and eliminating tumors. This anti-tumor treatment has garnered significant attention in recent years for its notable benefits, including sustained effects, effective tumor recurrence prevention, and potential curative outcomes. This paper discusses recent clinical trials and

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basic research on liver cancer immunotherapy through an extensive literature review, aiming to equip clinical practitioners and researchers with a deeper understanding of the latest advancements in this field.

2. Research status of immunotherapy for liver cancer

2.1. PD-1/PD-L1 inhibitors

Nivolumab. It is the first ICI applied in the clinical treatment of liver cancer globally, and research on it started early. The CHECKMATE 040 clinical trial indicated that the median overall survival (mOS) for Nivolumab was 15 months, with an objective response rate (ORR) of 15%, and its tolerability and safety were consistent with expectations [2]. In September 2017, the U.S. Food and Drug Administration (FDA) sanctioned Nivolumab as a second-line therapy for liver cancer subsequent to sorafenib, designating it as the inaugural immune checkpoint inhibitor (ICI) for liver cancer to obtain FDA approval. At present, Nivolumab is still the Child-Pugh Class B recommendation in the National Comprehensive Cancer Network (NCCN) guidelines for liver cancer diagnosis and treatment [3]. It has a lower incidence of adverse events, making it a viable treatment option for patients who are at high risk of complications from tyrosine kinase inhibitors. The phase III NADINA trial confirmed participants in the neoadjuvant therapy cohort who transitioned from MPR to neoadjuvant therapy and then received adjuvant Nivolumab or Dabrafenib in conjunction with Trametinib (for patients with BRAFV600E/K mutations) in a controlled study. The primary objective was event-free survival (EFS).

Tislelizumab. In June 2021, Tislelizumab was approved by the State Food and Drug Administration (SFDA) for the treatment of HCC after at least one systemic therapy. The ORR assessed by the RECIST v1.1 criteria was 13.3%; to be specific, the ORRs were 13.8% in second-line patients and 12.6% in third-line patients and above [4]. At the European Society of Medical Oncology Annual Meeting 2022 (ESMO 2022), Professor Masatoshi Kudo from the Affiliated Hospital of Kinki University School of Medicine, Japan, reported the final analysis of the RATIONALE 301 study in an oral presentation. Their findings suggested that Tislelizumab achieved a non-inferior OS to Sorafenib for the first-line treatment of unresectable liver cancer [5].

Camrelizumab. The SHR-1210-II/III-HCC research demonstrated that Camrelizumab conferred long-term advantages for patients with advanced liver cancer and significantly extended survival rates. A multicenter phase II clinical trial on second-line and subsequent treatments for HCC conducted in China indicated that the baseline condition of the recruited patients was suboptimal. The findings indicated that the objective response rate (ORR) for patients in the Camrelizumab cohort was 14.7%, the 12-month survival rate was 55.9%, and the median overall survival (mOS) was 14.2 months, reflecting substantial efficacy [6]. Camrelizumab monotherapy may therefore be a valuable treatment option for advanced liver cancer in second-line or later cases.

2.2. CTLA-4 blockers

CTLA-4 blockers, mainly including Lpilimumab and Tremelimumab (the only cytotoxic T lymphocyte antigen 4 used for the treatment of liver cancer), are applied to treat liver cancer at present. Ipilimumab was approved by the FDA for the treatment of advanced melanoma in 2011, and Nivolumab combined with Ipilimumab was approved for the second-line treatment of HCC in 2020. Ongoing studies on other immune checkpoints, such as TIM-3 and LAG-3, may help explore the effect of these ICIs in combination with PD-1/PD-L1 inhibitors on treating HCC.

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2.3. Chimeric antigen receptor T-cell immunotherapy (CAR-T)

As an anti-tumor immunotherapy with broad application prospects, CAR-T cell therapy has played an important role in the clinical treatment of hematological malignancies. The application of this treatment for solid tumors has emerged as a prominent research focus [7]. The basic principle of this therapy is to utilize the corresponding mechanism to achieve the targeted high expression of specific proteins on the tumor surface. Notably, the targeted research of Glypican3 (GPC3) has yielded a series of significant findings. GPC3 is not expressed in normal human tissues; however, in HCC patients, the high expression probability exceeds 70%, and its expression level is directly related to the prognosis of patients [8]. A large number of research results have sufficiently demonstrated the therapeutic effect of GPC3-CAR-T cells. With the help of biotechnology, CAR-T therapy genetically modifies the normal immune cells from the human body, so that the surface of T lymphocytes can express specific receptors for certain tumor antigens, which can then be used for the recognition of target tumor antigen ligands, thus killing tumor tissue [9]. The specific clinical efficacy of CAR-T therapy is directly affected by the selection of therapeutic targets. Generally, antigens that are overexpressed in tumor tissues, but are lowly or not expressed in the normal tissues are selected as the target antigens, such as GPC3, AFP, mucin1 (MUC1), and hepatocyte growth factor receptor. Relevant studies have become increasingly advanced, with numerous research findings emerging. For example, a study conducted by Zhai et al. confirmed that GPC3-CAR-T therapy had a positive effect in delaying disease progression in patients [10]. Similarly, the results of the Ori-CAR-001 trial also demonstrated that in advanced HCC and positively relapsed HCC, GPC3 not only attained the expected efficacy, but also had a satisfactory safety profile, with a disease control rate as high as 78% [11].

Based on the above research results, ACT has become the major immunotherapy strategy for cancers including HCC. However, it should be emphasized that the effect of this strategy is still unsatisfactory in the clinical treatment of solid tumors, and there is still a large room for improvement in the clinical effect of CAR-T immunotherapy on liver cancer. Further research and exploration are needed to enhance its efficacy.

2.4. Tumor vaccines

Tumor vaccines are therapeutic vaccines targeting tumor-associated antigens, which can effectively kill tumor cells by stimulating the human body to produce specific cellular and humoral immune responses. Polypeptide vaccines, DC vaccines, and oncolytic virus vaccines are currently receiving wide concern.

Polypeptide vaccines. Polypeptide vaccines are prepared from relevant polypeptides distributed on the tumor surface or inside the tumor. After entering the human body, they can induce related tissues to produce specific T lymphocytes, thus effectively strengthening the anti-tumor immune response of the human body. Glypican3 (GPC3), a proteoglycan on the cell membrane, is not normally expressed in healthy tissues but is highly expressed in liver cancer cells. Sawada et al. conducted a long-term follow-up study on patients vaccinated with the GPC3 vaccine and discovered that patients vaccinated and treated with surgical treatment not only had a much lower recurrence rate than the control group but also had a significant survival advantage [12]. Some research also found that multi-drug resistance related protein 3 polypeptide vaccine effectively improved the quality of life of advanced HCC patients [13]. Meanwhile, in the study conducted by Butterfield et al., the effectiveness of the alpha-fetoprotein (AFP) polypeptide vaccine was determined through clinical trials, and the proportion of patients with immunogenicity was up to 83.33%. Moreover, it was found that the vaccine had a strong stimulating effect on the activation of antigen-specific T lymphocytes,

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indicating the good application potential of the AFP polypeptide vaccine in the clinical treatment of HCC [14].

DC vaccines. Dendritic cells (DCs) represent a kind of powerful antigen-presenting cells. Through the co-culture of the isolated DCs with tumor antigen extracts, DC vaccines sensitized to various tumor antigens produced specific immune responses. Studies suggested that DC vaccines increased the number of CD8+T lymphocytes and the serum level of interferon-γ (IFN-γ) in HCC patients, thereby prolonging the overall survival (OS) of patients [15]. In 2005, a clinical study on DC-based immunotherapy for liver cancer showed that DC vaccines had good safety and definite efficacy in the treatment of HCC [16]. In 2023, Joonsu Han reported a simple metabolic labeling method, which could specifically regulate the adoptive transfer of DCs and was used to develop enhanced DC vaccines. The research indicated that metabolic glycan labeling diminished the membrane mobility of dendritic cells (DCs), thereby stimulating DCs and enhancing their antigen presentation and subsequent T cell activation properties. Moreover, metabolic glycan tagging can augment the anti-tumor efficacy of dendritic cell vaccinations [17].

2.5. Combination therapy

With the continuous development of cancer immunotherapy, exploring the combination therapy strategies has become a mainstream research trend. These strategies not only efficiently reduce drug resistance but also significantly improve overall clinical outcomes. Currently, the mainstream combination therapy schemes mainly include dual-ICI combination therapy, ICI combined with local therapy, molecular targeted drug therapy and radiotherapy.

Dual-ICI combination. Currently, dual-ICI combination therapy has been widely applied in the clinical treatment of HCC, demonstrating clear therapeutic efficacy and a high response rate. In the past, the combination of PD-1/PD-L1 inhibitors and CTLA-4 inhibitors has achieved remarkable results in the treatment of melanoma, which has thereby become an important direction of HCC research. The CheckMate040 cohort study used Nivolumab combined with Ipilimumab in treating patients receiving Sorafenib treatment, and the results showed that the ORR and DCR of the dual-ICI combination therapy were 31.1% and 48.6%, respectively [18]. The trial on the combination of Durvalumab and Tremelimumab for the treatment of unresectable HCC reported an overall response rate (ORR) of 24.0% among patients [19]. In March 2020, the FDA authorized the PD-1 antibody Nivolumab from BMS in conjunction with the CTLA-4 inhibitor Ipilimumab for the treatment of HCC patients who have previously undergone Sorafenib therapy. In Check-in Mate 040 (NCT01658878), the phase I/II study on dual-ICI combination immunotherapy, the ORR was 32% [20]. The Nivolumab combined with Lpilimumab (anti-CTLA-4) combination therapy scheme has a controllable safety profile, good ORR, and durable response, with a mOS of 22.8 months [21].

ICI combined with molecular targeted drug therapy. Molecular targeted drugs against tumor angiogenesis can inhibit tumor angiogenesis, improve the local immunosuppressive microenvironment of the tumor, and enhance the sensitivity to tumor cell immunotherapy [22]. It was reported that in advanced unresectable HCC patients, the therapeutic efficacy of the Atezolizumab combined with Bevacizumab group was significantly superior to that of the Sorafenib group. The ORR of patients in the combined treatment group reached 27% [23]. In another KEYNOTE-524 study, the ORR of Pembrolizumab combined with Lenvatinib in the treatment of advanced HCC was 60.0% and the DCR reached up to 93.3% [24].

ICI combination therapy. Radioimmunotherapy involves the introduction of radionuclide-labeled tumor-specific monoclonal antibodies (McAb) into the patients via various routes. These McAbs can induce double damage through the specific cytotoxic effects mediated by antigen-antibody interactions and the ionization radiation effects of radionuclides, thereby targeting tumor cells. Bian et al. found that the 1-year and 2-year recurrence rates of HCC patients receiving (131) I-Metuximab

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combined with radiofrequency ablation were significantly lower than those in patients receiving radiofrequency ablation alone, indicating that McAb-mediated radioimmunotherapy will play an important role in the comprehensive treatment of liver cancer [25]. The recent outcomes of the Notable-HCC phase 1b clinical trial signify significant advancement. This study is the inaugural investigation into the safety and efficacy of the neoadjuvant PD-1 inhibitor Tislelizumab in conjunction with Stereotactic Body Radiotherapy (SBRT) for early resectable HCC patients, offering a novel treatment strategy for liver cancer and holding significant milestone importance [26].

Although the results obtained from the above studies all demonstrate that combination therapy can improve therapeutic efficacy and bring significant survival benefits for patients with advanced liver cancer, the optimal combination therapy strategy still needs to be explored in clinical studies with larger sample sizes.

3. Discussion

A systematic review of recent research on HCC immunotherapy reveals that HCC is highly heterogeneous due to its complex molecular mechanisms, such as genomic complexity and epigenetic diversity, which means that most HCC patients do not benefit from immunotherapy. Nonetheless, the lack of reliable biomarkers makes it difficult to diagnose HCC at an early stage and predict treatment outcomes. Consequently, it is essential to establish novel diagnostic and prognostic biomarkers for liver cancer to aid in clinical diagnosis and forecasting. Overall, ICI-based immunotherapy still faces challenges like the low response rate, drug resistance, and potential systemic side effects. Future research should focus on identifying tumor-specific antigens or antigen peptides unique to liver cancer, and developing vaccines based on these targets. Such advancements could significantly enhance the effectiveness and specificity of anti-tumor immune responses in liver cancer patients.

4. Conclusion

Immunotherapy for liver cancer, encompassing immune checkpoint inhibitors (ICIs) such as PD-1, PD-L1, and CTLA-4 antibodies, as well as adoptive cell transfer therapies like CAR-T, CAR-NK, and TCR-T, aims to address the challenges of tumor cell detection and immune cell activation. However, it remains uncertain whether the immune cells within the tumor or the adoptive immune cells are capable of eliminating all the numerous, complex, and heterogeneous tumor cells. Additionally, the clinical application of ICIs is associated with obvious adverse reactions and is greatly affected by individual differences, and related research has stalled. The biggest problems with adoptive cell transfer therapy, represented by CAR-T, lie in cytokine release syndrome (also known as cytokine release storm, CRS) and neurotoxicity. Therefore, when considering the entire process of tumor immunity, improving the cytotoxic capacity of immune cells and exploring the mechanisms of cell death are expected to be key areas of breakthrough in the next stage. HCC treatment has entered a new era of immunotherapy. Although liver cancer immunotherapy is still in its early stages compared to other cancers, HCC is both immunogenic and immunosuppressive, which plays a crucial role in advancing immunotherapeutic strategies for liver cancer. The achievements of ICIs and combination therapy are encouraging, and the prospects are slowly emerging.

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