Scientific
Research
Publishing

Advances in Research on Immunological Checkpoint Inhibitors in Immunotherapy of Liver Cancer

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Abstract

The current treatments of liver cancer in China are mainly comprehensive treatment and systematic treatment, with poor therapeutic effect and high recurrence rate and metastasis rate. The existence of immunosuppressive microenvironment is an important reason for liver tumor cells to escape from the host immune system, and also an important basis for the occurrence and development of liver cancer. With the recent transformation of the target of tumor therapy from tumor cells to tumor cell immune microenvironment, immunotherapy has emerged quietly. It is a new strategy for the treatment of hepatocellular carcinoma to improve the immune attack on tumor cells by changing the immunosuppressive environment of hepatocellular carcinoma cells. Immune checkpoint is the main mechanism by which liver cancer cells escape the host immune system. PD-1/PDL-1 and CTLA-4 are targeted immunocheckpoint inhibitors, which have shown good therapeutic effects and application prospects in the clinical treatment of HCC. This article reviews the latest advances in immunocheckpoint inhibitors in the immunotherapy of hepatocellular carcinoma.

Keywords

Liver Cancer, Immunotherapy, Immunosuppressive Microenvironment, Immune Checkpoint Inhibitor, PD-1/PDL-1, CTLA-4

1. Introduction

China is a large country with hepatitis B, and half of the world's liver cancer also occurs in China [1]. Because of the concealment of its pathogenesis, liver cancer is mostly found in the late stage. The current treatments for liver cancer include

radical surgical resection, liver transplantation, radiofrequency ablation, TACE, radiotherapy and chemotherapy, and molecular targeted therapy, but the treatment effect is not satisfactory [2]. Due to the early diagnosis concept and the continuous development of systemic treatment, the prognosis of liver cancer has been greatly improved compared with 10 years ago. The 5-year survival rate of radical resection of liver cancer reached 70% [3], but the recurrence rate and metastasis rate of liver cancer still have not improved significantly. The clarification of the tumor immune microenvironment and the mechanism of immunosuppression point make the rise of immunotherapy in the field of cancer treatment, and at the same time give a new treatment strategy for liver cancer.

The normal adaptive immunity and innate immune system of the human body can recognize and attack liver cancer cells at any time. Immune cells or tumor cells in the liver cancer microenvironment have high expression of inhibitory co-stimulatory molecules, that is, immune checkpoints, leading to the inactivation of anti-tumor T lymphocytes. An immunosuppressive microenvironment is formed [4], which leads to immune escape of tumor cells and further tumor progression and metastasis. The mechanism of immunotherapy is activation of specific T lymphocytes, activation and enhancement of anti-tumor immune response in patients, targeted attack and clearance of tumor cells. It mainly includes adoptive immunotherapy, tumor vaccine and checkpoint suppression, among which some checkpoint inhibitors have shown good clinical efficacy, and some checkpoint inhibitors have been approved for clinical treatment in the United States and Europe. Here, the author mainly reviews the latest development of immunological checkpoint inhibitors in immunotherapy.

Among the current clinically significant results are programmed death protein-1 (PD-1)/programmed death protein ligand-1 (PDL-1) and cytotoxic T lymphocyte-associated antigen (CTLA-4) inhibitors.

2. PD-1/PDL-1

PD-1 (programmed death 1) is a kind of important immunosuppressive molecules, which is a membrane protein of 268 amino acid residues. Also known as CD279, it induces immune suppression and promotes the immune response of tumor cells to escape cytotoxic T cells. PD-1 is mainly expressed on T cells, B cells and natural killer cells. The ligands for PD-1 include PDL-1 and PDL-2. PDL-1 is also known as B7-H1 or CD274, and PDL-2 is also known as B7-H2 or CD273, and their regulation is different. Natural killer cells (NK) or activated T cells induce PDL-1 expression in activated hematopoietic cells and endothelial cells by secreting interferon (IFN)-γ. PDL-2 is more likely to be induced by interleukin (IL)-4 than IFN-γ, which is expressed on the surface of activated dendritic cells (DCs) and macrophages.

PD-1/PDL-1 signaling pathway plays an important role in tumor immune escape. PD-1 functions in the effector phase of T cell activation. It inhibits T cell immune activity and promotes tumor growth by binding PDL-1. Therefore,

blocking the binding of PD-1 and PDL-1 can reactivate the immune activity of T cells and enhance the killing effect of the patient's immune system on tumor cells.

PD-1/PDL-1 antibody, also known as PD-1/PDL-1 inhibitor, whose mechanism is as follows: T cells recognize the antigen MHC on the surface of tumor cells, MHC stimulates T cell activation, and activates T cells to synthesize cytokinins. T cells that are activated for a long time produce PD-1, and cytokinins induce tumors. The cells produce PDL-1, and PD-1 on the surface of T cells binds to PDL-1 on the surface of tumor cells, thereby inhibiting T cell proliferation and differentiation, leading to decreased T cell function and even apoptosis [5], which ultimately causes tumor cells to escape the immune system. The attack, the tumor cells survive, forming a microenvironment of tumor immunity, in which the tumor cells survive and progress. In the presence of PD-1 inhibitors or PDL-1 inhibitors, PD-1 and PDL-1 cannot bind to produce inhibitory effects on T cells. Continuous activation of T cells destroys the immunosuppressive microenvironment for the survival of tumor cells and produces a strong immune effect on tumor cells, thereby killing them (Figure 1).

2.1. PD-1 Inhibitors

Currently, PD-1 inhibitors mainly include Nivolumab [6] [7] and Pembrolizumab [8], which are used for the treatment of non-small cell lung cancer, malignant melanoma, gastric cancer, liver cancer, colorectal cancer and other tumors [9]. Hepatocarcinoma has a high degree of immunosuppression in the microenvironment. Among them, Nivolumab has a significant effect on liver cancer. It was approved by the US Food and Drug Administration (FDA) as a second-line
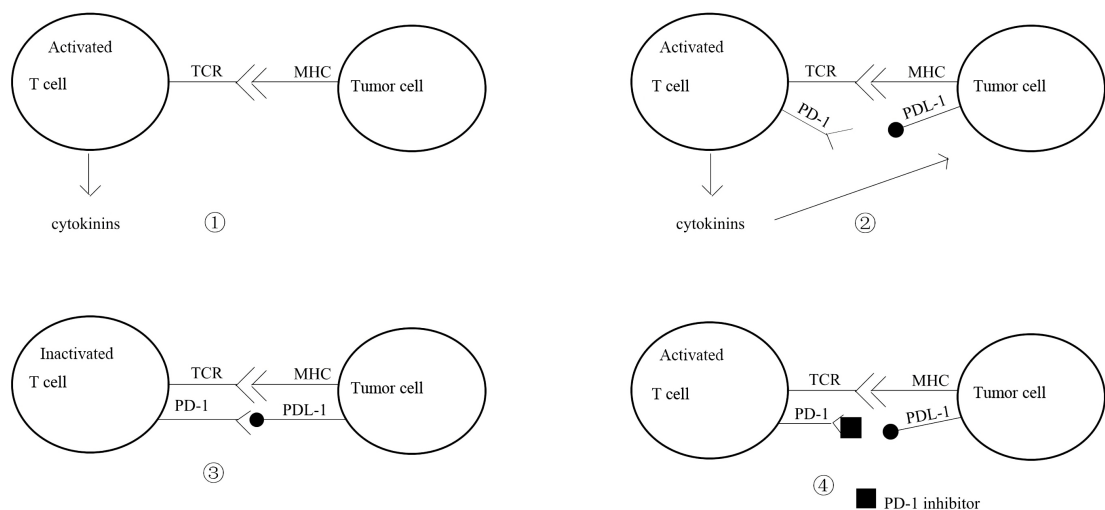

Figure 1. (1) T cells identify tumor cell surface antigen MHC, thus becoming activated T cells. Activated T cells produce cytokinin; (2) Activated T cells produce PD-1, at the same time, cytokinin induces tumor cells to produce PDL-1; (3) The combination of PD-1 and PDL-1 inhibits the activation of T cells, thus tumor cells survive. (4) When PD-1 inhibitors combined with PD-1, PD-1 and PDL-1 could not be combined to inhibit T cells, T cells continued to activate and kill tumor cells.

treatment for advanced liver cancer in 2017. In some studies, Nivolumab was used to treat patients with advanced liver cancer, with a disease control rate of 81.8% and an objective remission rate of 63.6%. This study included a total of 11 patients, with the lack of large sample trials, but it also suggested that Nivolumab may have a good benefit in the treatment of advanced liver cancer [10]. In a trial using Nivolumab (Checkmate-040) [11], 48 patients were enrolled in stage I, with a low dose of Nivolumab (less than 3 mg/kg) with an objective response rate of 15% and an overall survival of 15 months; Phase II included 214 patients, treated with Nivolumab (3 mg/kg) until the disease progressed, 2 of them achieved complete remission, 33 achieved partial remission, and the duration of complete remission and partial remission was 14 to 17 months and 8 In the month, all patients enrolled in this stage had an overall survival of 82.5% and 70.8% at 6 and 9 months, an objective response rate of 16%, and a disease control rate of 68%. Phase III of the study (CheckMate-459) compared the efficacy of sorafenibmonotherapy in patients with liver cancer and liver cancer patients who received Nivolumab after treatment with sorafenib, which showed a significant increase in survival and survival.

Pembrolizumab is another PD-1 inhibitor. It has been reported that patients with liver cancer have been treated with Pembrolizumab for 8 months after failure of sorafenib treatment, showing good tolerance and no significant adverse reactions [12]. A phase II trial (KEYNOTE-224) [13] in the United States for the use of Pembrolizumabmonotherapy in patients with liver cancer showed nearly the same data and efficacy as Nivolumab. In addition, there are many trials in the world about Pembrolizumabmonotherapy and combination therapy, and it is believed that the results will definitely bring new dawn to the treatment of liver cancer.

2.2. PDL-1 Inhibitor

Currently commonly used PDL-1 inhibitors are Avelumab, Durvalumab and Atezolizumab. At the 2017 American Society of Clinical Oncology meeting, a trial of Durvalumab was published [14]: Objective remission rate after 40 patients with advanced hepatocellular carcinoma who failed to receive Duvalumab (10 mg/kg) after treatment with sorafenib At 10%, the overall survival is 13.2 months. In the treatment of advanced liver cancer, Durvalumab showed better efficacy. Expect more clinical trials and data to better use PDL-1 inhibitors.

3. CTLA-4

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), also known as CD152, is a leukocyte differentiation antigen and a transmembrane receptor on T cells. CTLA-4 is a key inhibitory receptor that affects T cell function, and is mainly expressed on the surface of activated CD4+ T cells, CD8+ T cells and Treg cells. CTLA-4 is involved in the negative regulation of T cell activation, inactivating T cells, and thus tumor cells survive and progress.

The mechanism of action of CTLA-4 antibody is as follows: T cells require two signaling pathways to be simultaneously activated, and antigen presenting cells provide B7 and MHC ligands, which bind to CD28 and TCR on the surface of T cells, respectively, and T cells are activated, thereby killing tumors cell. When T cells are over-activated, T cells express CTLA-4 protein themselves, CTLA-4 competes with CD28 for binding to B7, and CTLA-4 binds to B7, which blocks CD28-B7 signaling pathway, thereby inactivating T cells. The cells survive. Tumor cells use this negative regulation feature to induce T cells to express a large amount of CTLA-4, compete with CD28, and reduce T cell activity, so that tumor cells escape the immune system attack. CTLA-4 antibody can bind to CTLA-4 expressed by T cells, so that CD28 can re-engage with B7, the signal pathway is restarted, T cells can be reactivated, the immunosuppressive microenvironment is broken, and the body's immunity to tumor cells is improved.

The CTLA-4 antibodies currently approved for the treatment of tumors on the market are mainly Tremelimumab and Ipilimumab. Tremelimumab is a human IgG2 monoclonal antibody that blocks CTLA-4. A small sample of viral-related liver cancer patients showed clinical trials using Tremelimumabmonotherapy with a partial response rate of 17.6%, a disease control rate of 76.4%, and a tumor progression time of 6.48 months. The study also found a significant reduction in hepatitis viral load in patients treated with Tremelimumab [15]. This suggests that Tremelimumab may have better antiviral and antitumor effects and requires a larger sample of clinical trials to further confirm its efficacy and safety. Compared with monotherapy, studies have shown that combination therapy, such as radiofrequency ablation or TACE, may benefit more [16]. Clinical trials of Nivolumab + Ipilimumab in combination with liver cancer are also underway.

4. Combination of PD-1 Inhibitor and CTLA-4 Inhibitor

Clinical trials of PD-1 inhibitors combined with CTLA-4 inhibitors for advanced liver cancer are in progress. A trial of advanced melanoma showed that the combination of Nivolumab + Ipilimumab has a higher objective response rate and higher progression-free survival than monotherapy, indicating that the combination therapy may have a more complete therapeutic effect [17].

5. Immunological Checkpoint Inhibitors Combined with Traditional Treatment Methods

Immunological examination inhibitors are combined with existing traditional treatment methods, including radiofrequency ablation, transcatheter arterial chemoembolization, surgical resection, radiation therapy, and molecular targeted therapy. By combining the immunosuppressive microenvironment that destroys tumor cell survival, inducing local inflammation and releasing new antigens to activate the immune system and improve the efficacy of immunotherapy, there may be better and faster results. Studies have used CTLA-4 antibody

as a follow-up adjuvant therapy in patients with advanced liver cancer after TACE or radiofrequency ablation, prolonging patient survival [18]. This combination also increases the number of CD 3+ and CD 8+ cells in untreated lesions. These findings demonstrate that immunological checkpoint inhibitors can be combined with hepatic artery embolization chemotherapy or as an adjuvant therapy after surgical resection or radiofrequency ablation. A clinical trial of a combination of rivastatinib and Pembrolizumab in the treatment of liver cancer showed a higher rate of tumor remission [19]. In 2017, the American Society of Clinical Oncology (ASCO) reported that this combination therapy has a 50% - 70% response rate and a lasting drug effect in the treatment of solid tumors [20]. Therefore, traditional topical therapy combined with immunosuppressive agents such as PD-1, PDL-1 and CTLA-4 may be superior to traditional treatment, which requires a large number of clinical trials to further verify.

6. Conclusion

Liver cancer is a highly immunosuppressive disease. Traditional treatment methods have a high recurrence rate and cannot achieve satisfactory benefits. The emergence of immunotherapy has brought a new perspective to the treatment of liver cancer. In response to the immunosuppressive microenvironment of liver cancer, immunological checkpoint inhibitors reactivate the patient's own immune activity, destroy the immunosuppressive microenvironment, improve the patient's anti-tumor ability, and even completely eliminate tumor cells. PD-1/PDL-1 inhibitors and CTLA-4 inhibitors have achieved good results in most clinical trials. Patients have longer survival and reduced treatment-related adverse reactions, but immunotherapy for liver cancer still needs a multicenter, large sample clinical trial to confirm its effectiveness and safety. The immune mechanism needs to be further clarified. Immunological checkpoint inhibitors also require our further exploration and development, and drug-related adverse reactions also require clinical trials to validate and evaluate. The safety and efficacy of immunological checkpoint inhibitors in combination with other therapies need to be further explored. At present, the treatment of liver cancer is still based on traditional treatment. The combination of immunological checkpoint inhibitors and traditional treatment may completely cure liver cancer, which in turn will change the treatment of liver cancer. Immunotherapy has shown unparalleled therapeutic prospects and is expected to cure liver cancer in the future, thus becoming the first-line treatment for liver cancer treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation Note List

HCC	hepatocarcinoma
PD-1	programmed death-1
PDL-1	programmed cell death 1 ligand 1
PDL-2	programmed cell death 1 ligand 2
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
TACE	transcatheter arterial chemoembolization
CD279	cluster of differentiation 279
CD274	cluster of differentiation 274
CD273	cluster of differentiation 273
CD152	cluster of differentiation 152
CD28	cluster of differentiation 28
B7	costimulatory molecule B7
B7-H1	B7 homolog 1
B7-H2	B7 homolog 2
DC	dendritic cells
MHC	major histocompatibility complex