Review

From PD-1 and CTLA-4 immunotherapy for hepatocellular carcinoma, to explore the hope and future challenges of CAR-T in the treatment of intermediate and advanced hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) poses a serious threat to human health. Most patients are diagnosed at an advanced stage with a poor prognosis. Although targeted drugs for tumors have prolonged the overall survival of HCC patients, tumor cells are generally resistant, and only a few patients in the middle and advanced stages benefit. In recent years, immunotherapy has made rapid progress in various malignant tumors. The combination of immunotherapy and targeted drugs has shown significant efficacy, among which immune checkpoint blockade (ICB) has developed the fastest, such as targeting PD-1, PD-L1, and CTLA-4. In addition, CAR-T has made breakthroughs in acute lymphoblastic leukemia and has begun to challenge the treatment of solid tumors, mainly liver cancer. This article will explore the progress of immunotherapy mainly targeting PD-1 and CTLA-4 and the prospects and challenges of CAR-T in the treatment of advanced HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive tumor that is commonly found in patients with chronic liver diseases and liver cirrhosis. According to the statistics by Rebecca L Siegel and other researchers[1] from the American Cancer Society Institute, in 2022, there were 431,383 HCC patients in China, with a majority being male. Among the cancer mortality rates in China, the mortality rate related to liver cancer ranks sixth.

The treatment of HCC mainly relies on surgical resection. However, based on the characteristics of middle and advanced stage HCC, only 15% - 20% of patients can achieve long-term benefits[2]. Interventional therapy causes tumor ischemia and necrosis by embolizing tumor blood vessels, but its applicable scope is narrow. Targeted therapy is the core treatment method for middle and advanced stage HCC. The original first-line treatment strategies include systemic systemic treatments mainly based on sorafenib and oxaliplatin. In recent years, immunotherapy has developed rapidly, and the first-line treatment strategies for liver cancer have been updated, with new combination treatment regimens such as sintilimab combined with bevacizumab being added[3].

The History of Immunotherapy

In the 1950s, Professor Frank Macfarlane Burnet proposed the immunosurveillance theory[4]. Since then, there have been continuous explorations in the immunotherapy of malignant tumors. Studies such as the treatment of bladder cancer with Bacillus Calmette-Guérin (BCG), attempts to use inactivated tumor cells as cancer vaccines, the idea of monoclonal antibodies, cytokine and various cellular immunotherapy studies have demonstrated the possibility and effectiveness of immunotherapy. After the US Food and Drug Administration (FDA) approved sipuleucel-T for the treatment of metastatic castration-resistant prostate cancer in 2010, immunological checkpoint therapy has received much attention.

The Relationship between HCC and Immunotherapy

The progression of HCC often originates from chronic liver inflammation, with viral infections, steatosis, etc. being the inducing factors. Under the inflammatory condition, a variety of immunosuppressive factors are continuously expressed and activated, leading to the immune escape of tumor cells, such as interleukin - 10, transforming growth factor - β, and prostaglandin E2, etc. Immunosuppressive cells such as regulatory T cells, myeloid-derived suppressor cells, and cancer-associated fibroblasts accumulate in the liver, causing T cell exhaustion or dysfunction, resulting in HCC escaping immune surveillance and killing. This indicates that restarting and maintaining the body's immune response is helpful for controlling tumor progression[5]. This article will start from the immunotherapy of liver cancer with programmed cell death protein 1 (PD - 1) and cytotoxic T lymphocyte-associated protein 4 (CTLA - 4), and explore the hope and future challenges of chimeric antigen receptor T cell (CAR - T) in the treatment of middle and advanced stage hepatocellular carcinoma.

PD - 1

The Exploration Path of PD - 1

In 1991, Yasumasa Ishida first discovered PD1, which was a transcript isolated from the cDNA of mouse T cells[6]. In 1994, Hiroyuki Nishimura produced PD1 knockout (KO) mice and found that the B cells and T cells of PD1-deficient mice were abnormally activated[7]. In 1998, Yoshiko Iwai found that many cell lines could bind to the fusion protein of the PD1-immunoglobulin Fc domain, and the tumor cell lines transfected with programmed death-ligand 1 (PD - L1) grew at a lower rate in PD1-KO mice, demonstrating that PD1 blockade could activate the immune system and enhance the cytotoxic activity against tumor cells[8]. In 2004, Medarex developed the humanized anti-PD1 antibody

nivolumab. In 2006 and 2008[9], it entered phase I clinical trials in the United States and Japan respectively. A double-blind randomized trial in 2015 showed that nivolumab had a significant effect as the first-line treatment for melanoma, and it was later approved for use in more than 25 types of tumors.

The Relationship between HCC and PD - 1

In the past decade, the efficacy of PD - 1 inhibitors in the treatment of HCC has been promising. PD - 1 is a transmembrane protein that can regulate the body's immune system's response to self and tumor cells. Normally, the body's T cells express PD - 1, and normal cells express an appropriate amount of PD - L1 to maintain the balance of immune tolerance[10]. However, HCC tumor cells will overexpress PD - L1, leading to immune escape. PD - 1 inhibitors can block the interaction between the two, restoring the activity of T cells and the ability of the body's immune system to kill tumor cells. PD - 1 has both positive effects of regulating harmful immune responses to maintain immune tolerance and negative effects of interfering with protective immune responses and causing the expansion of tumor cells within the body's immune system[11].

Immune checkpoints are divided into two categories: promoting and inhibitory. In the initial stage of T cell activation, CTLA - 4 binds to the B7 molecule on the surface of dendritic cells (DCs), leading to T cell apoptosis and failure of activation[12]. In the effector stage, PD - 1 binds to the PD - L1 molecule on the surface of tumor and surrounding cells, leading to T cell apoptosis. Monoclonal antibody drugs targeting CTLA - 4 and PD - 1/PD - L1 can block the inhibitory checkpoints and promote the anti-tumor immune effect[10]. However, the lack of effective predictive biomarkers will lead to the delay of HCC detection and the ineffectiveness of immunotherapy.

The Advantages of PD - 1 in the Treatment of Middle and Advanced Stage HCC

For patients with middle and advanced stage HCC, PD - 1/PD - L1 immunotherapy has a promising future. The phase III HIMALAYA trial in 2018 evaluated the efficacy of durvalumab + a single priming dose of tremelimumab in patients who refused sorafenib and other treatments[13, 14]. It showed that durvalumab monotherapy as a first-line treatment had good tolerability and its effect was not inferior to that of sorafenib. The ChecMeta040 experiment in 2023 found that the use of anti-PD - 1 blocking immunotherapy alone increased the objective response rate (ORR) to 15% - 20% in HCC patients pre-treated with sorafenib, which was three times that of sorafenib alone[15]. However, due to the high heterogeneity of HCC, the ORR is still low. And the study suggests that biomarkers such as overexpression of PD - L1 and tumor mutation burden are related to the treatment responsiveness, so it is urgent to establish predictive biomarkers.

Most liver cancers in Asian countries are associated with hepatitis B or hepatitis C virus infections, and these patients have a stronger response to immunotherapy. The RATIONALE 301 study in 2023 showed that compared with sorafenib, tislelizumab achieved non-inferiority in overall survival (OS)[16]. The median OS in the tislelizumab group was 15.9 months, and that in the sorafenib group was 14.1 months, with a 15% reduction in the risk of death and an extension of median OS (mOS) by 1.8 months. Moreover, as the treatment time prolongs, the trend of survival benefit increases, and it also has advantages in tumor remission and the duration of continuous remission. The KEY NOTE - 394 study verified the clinical benefit of pembrolizumab in the second-line treatment of liver cancer patients in Asia (mainly in China)[17]. The median OS was 14.6 months,

reducing the risk of death by 21%, and the two-year survival rate was significantly increased. It is the first and only phase III clinical trial in which a PD - 1 inhibitor monotherapy has achieved positive results in advanced liver cancer.

In 2020, the study led by Professor Qin Shukui showed that the PD - 1 inhibitor camrelizumab combined with apatinib ("Shuangai" combination) had a significant effect in the treatment of resectable hepatocellular carcinoma patients with medium/high recurrence risk[18]. The major pathological response rate was 46.2%, and the pathological complete response rate was 5.8%. In the same year, the CARES - 310 study for the first-line treatment of unresectable liver cancer showed that the median progression-free survival of the "Shuangai" combination was significantly improved, and the median overall survival reached 22.1 months, becoming the treatment plan with the longest OS data in the current phase III clinical research of the first-line treatment of advanced liver cancer, which has changed the situation of liver cancer treatment[19].

CTLA - 4

The History of CTLA - 4

In 1987, Pierre Golstein isolated CTLA - 4 from activated CD8 + T cells and stated that it had the same chromosomal region and a high degree of sequence similarity with CD28[20]. Professors Peter linsley and Jeffrey Ledbetter constructed a soluble CTLA - 4 protein and found that its binding affinity to B7 was 20 times that of the soluble CD28, establishing that CTLA - 4 was the second receptor of B7[21].

CTLA - 4 exists on regulatory T cells and activated T cells. It is an inhibitory co-receptor and plays an important role in regulating the function of CD4 + T cells. In HCC, CTLA - 4 inhibits T cell proliferation, promotes the production of inhibitory factors interleukin - 10 and indoleamine 2,3-dioxygenase, and induces the activity of regulatory T cells (Tregs). The core of the immune system's ability to distinguish between self and non-self is the binding of the T cell receptor to antigen recognition. The immune checkpoint pathway regulates T cell activation to maintain peripheral tolerance, and the CTLA - 4 and PD - 1 immune checkpoint pathways are the core. This pathway can be exploited by tumors to induce an immunosuppressive state.

The "Link" between CTLA - 4 and PD - 1

CTLA - 4 is considered the "leader" of immune checkpoint inhibitors. In the late stage of the immune response, the PD - 1 pathway mainly regulates the previously activated T cells in the peripheral tissues. CLTA - 4 prevents potentially autoreactive T cells at the initial stage of Naïve T cell activation, creating conditions for the PD - 1 pathway[22]. The inhibition of the immune checkpoint pathway has led to the approval of new drugs such as ipilimumab (anti-CTLA - 4), pembrolizumab (anti-PD -1), and nivolumab (anti-PD - 1). These inhibitors can restore the anti-tumor immune response. Blocking both the CTLA - 4 and PD - 1 pathways simultaneously has a higher efficacy than blocking them alone or sequentially, and the side effects may be lower, providing evidence for the combined effect of immune checkpoints[23].

CAR - T

CAR - T and PD - 1

In recent years, chimeric antigen receptor-specific T cells (CAR - T) have become a new tool for treating some cancers. CAR - T therapy is an ex vivo gene therapy that reprograms the immune system to attack cancer cells[24]. CAR-modified T cells have an HLA-independent recognition mechanism and can recognize and kill tumor cells expressing the corresponding antigen[25].. It has a significant therapeutic effect in acute B lymphoblastic leukemia, but its therapeutic effect in solid tumors still needs to be explored

The selection of antigens for CAR design is challengeable. The surface antigens of solid tumor cells are often also expressed on non-cancer cells, and tumors upregulate inhibitory ligands after immune attack[26]. For example, the interaction between PD - 1 and PD - L1 limits the therapeutic effect of CAR - T cells[27]. The study by Guodi Liu and others shows that PD - 1 silencing can enhance the anti-tumor effect of mesothelin (MSLN)-targeted CAR - T cells on several types of cancers[25]. PD - 1/PD - LI may affect the efficacy of CAR - T cells from two aspects: the high expression of PD - L1 on tumor cells or CAR - T cells[28].

The Source and Evolution of CAR - T

In 1986, Professor Steven A. Rosenberg discovered tumor-infiltrating lymphocytes in the tumor tissues of melanoma patients[29]. He isolated and expanded the T cells, reinfused them, and injected a large dose of interleukin - 2 (IL - 2) to enhance their killing ability, with an effective rate of up to 40%[29]. This became the basis of adoptive cellular immunotherapy. Later, Zelig Eshhar proposed to actively equip T cells with receptors that recognize tumor-specific antigens, and the first generation of CAR - T was born[30]. However, due to the lack of co-stimulatory signals, it led to the premature aging of T cells.

In 2010, Professor Carl H. June and his team from the University of Pennsylvania developed the second-generation CAR - T, which targeted the CD19 antigen and used 4 - 1BB as the co-stimulatory domain. In 2012, Emily Whitehead became the first child leukemia patient cured by CAR - T therapy. The Novartis CTL - 019 therapy she participated in was later approved for marketing by the FDA. The third-generation CAR - T cells use lentivirus as the transfection vector, and the intracellular fragment can contain two co-stimulatory domains. However, the curative effect is not necessarily better than that of the second generation, and the second generation is still the mainstream[27].

The fourth-generation CAR - T, that is, precision CAR - T cells, aims to solve the problem of toxicity. It controls the survival time by adding a suicide gene or a controllable suicide gene, or adds a photoswitch to make it active under specific blue light. The fifth-generation CAR - T technology aims to achieve large-scale production, reduce costs, and expand the scope of application. It uses a "third-party" system to endow the ability to recognize multiple antigens and uses gene editing technology to eliminate the graft-versus-host disease reaction. However, there are still technical barriers and safety challenges, and the domestic research is still in the initial stage.

CAR - T and HCC Treatment

CD133 is a transmembrane glycoprotein that is highly expressed in more than half of various solid tumors and is highly correlated with the late tumor stage of HCC[31]. It is a marker of cancer stem cells and endothelial progenitor cells and is involved in tumor metastasis and recurrence, making it an effective target for

immunotherapy in advanced CD133-positive HCC patients. Multiple trials of autologous chimeric antigen receptor-modified T cells directed against CD133 (CAR - T - 133) have shown that repeated cell infusions can provide a longer disease stabilization period for patients whose tumors shrink after the first infusion, and can eliminate HCC cells expressing CD133, demonstrating its feasibility and effectiveness[32].

Glypican3 (GPC3) is one of the common targets for CAR - T treatment in middle and advanced stage HCC[33]. It is expressed in about 75% of middle and advanced stage HCC patients and is not expressed in normal hepatocytes. Studies have shown that GPC3-CAR - T has a good effect in inhibiting the tumor growth of xenografts derived from hepatocellular carcinoma patients[34]. Another method of constructing CAR - T cells is to express chemokine receptors on their surface to respond to tumor-derived chemokines[35].

One of the obstacles to CAR - T treatment is toxicity, including cytokine release syndrome, off-target effects, and on-target off-tumor effects[36]. Currently, strategies such as "turning off the switch" or suicide genes have been developed to reduce toxicity. With the progress of clinical trials, CAR - T therapy is expected to become one of the effective treatment measures for middle and advanced stage HCC[37].

FUTURE CHALLENGES OF IMMUNOTHERAPY

The Advantages of Immunotherapy in HCC Research

The treatment of middle and advanced stage HCC is a multidisciplinary comprehensive treatment. Immunotherapy has obvious advantages: it can improve the survival rate, activate the immune system to recognize and attack liver cancer cells; inhibit tumor growth and spread; has relatively mild side effects and little impact on the quality of life; can be individualized; and can synergize with other treatment methods[38].

Although immunotherapy has developed rapidly, it is still not mature and requires a large amount of data to verify its reliability. The ORR of single-agent immune checkpoint inhibitors (ICIs) in patients with middle and advanced stage HCC is 15 - 20%, and most patients do not have significant OS benefits. About 30% of patients are generally resistant to ICIs. Immunotherapy combinations such as the combination of anti-PD - 1/PD - L1 antibodies and bevacizumab may have a synergistic effect and may have better efficacy in the treatment of middle and advanced stage HCC[39].

The Challenges Faced by Immunotherapy in HCC Research

HCC immunotherapy is full of hope but also poses great challenges. The immune nature of the liver is unique. It is both an immune activation organ and an immune tolerance organ. The anti-tumor potential of immune cells is strong, but some cells may affect the anti-cancer immune response[40].

One of the greatest challenges of immunotherapy is to control immune-related adverse events (IRAEs). Studies have shown that 43% of patients receiving PD - 1 immunotherapy have experienced IRAEs, and the common occurrence sites are the skin, musculoskeletal system, and endocrine system. High risks are related to factors such as age, body mass index, gender, medication, and smoking[41]. Having certain diseases and long-term use of certain drugs will also increase the risk. A large meta-analysis reported that the incidence of IRAEs of CTLA4 inhibitors is 83%, that of PD - 1 inhibitors is 72%, and that of PD - L1 inhibitors is 60%. The occurrence mechanism is related to the impact of

immune checkpoint inhibitors on the immune system[42].

Although CAR - T cell therapy has been successful in the treatment of hematological malignancies, it faces difficulties in the treatment of solid tumors such as HCC. The tumor microenvironment is complex, including immunosuppressive factors, hypoxic environment, and immune escape mechanisms, etc., which limit the activity and anti-tumor effect of CAR - T cells. The physiological characteristics of the liver make it face the risks of damaging normal hepatocytes and toxic reactions. There are few suitable targeted antigens, which limits its application. There are various treatment approaches available, which also restricts the application of CAR - T cell therapy. In addition, the treatment cost is also an important factor considered by patients.

Although CAR - T cell therapy still has a long way to go in the treatment of middle and advanced stage HCC, researchers are constantly making efforts to improve it, and there may be more breakthroughs in the future and play a greater role in the treatment of solid tumors.

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