

Research Progress in Target Cancer of Immune Checkpoint Inhibitors

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Abstract. Despite the long-standing emphasis on the role of T lymphocytes in cancer immunosurveillance, initiatives to improve the effectiveness of antitumor immune responses have been stimulated by the recognition that tumors may evade the response of T cells. Current research progress in T-cell immunobiology contributed to overcoming tumor immune escape mechanisms. Because of the inhibition of T-cell regulatory type in cancer patients, immune checkpoint inhibitors have shown significant antitumor activity. In this paper, we systematically review the current research progress on immune checkpoint inhibitors in tumor therapy in recent years to improve the accuracy of immunotherapy.

Keywords: Immunotherapy, Checkpoint inhibitors, Anti-tumor.

1. Introduction

Immune checkpoint inhibitors based on T lymphocyte biology and tumor immunology breakthroughs that have skyrocketed in recent years have reshaped tumor therapy. Early in the study, the involvement of T cells in tumor immunosurveillance was demonstrated in both mouse models and clinical observations, showing the importance of T cell responses for tumor immune control. Subsequently, the recognition that T cell receptor stimulation without co-stimulation cannot induce full T cell activation has advanced the understanding of the nature of the signals that regulate T cells. In addition to the need for co-stimulatory signals induced by cell surface molecules called immune checkpoints (ICPs) and instructive cytokines secreted by antigen-presenting cells (APCs) as 2nd and 3rd signals, as well as "1st signals" provided by antigen stimulation received by the T cell receptor to activate T cells. The identification of ICPs of the co-repressor signaling pathway could better regulate T cell activation [1]. ICPs are involved in different phases of the T cell response, either as stimulators or inhibitors. ICPs of the co-inhibitory pathway act as fail-safes in maintaining immune homeostasis to protect the immune system from abnormal activation, but many cancers suppress anti-tumor T-cell responses by overexpressing consistent ligands bound to ICPs of the co-inhibitory pathway, thus promoting tumor immune escape. Immune checkpoint inhibitors (ICIs) of the co-inhibitory pathway, developed based on the above principles as monoclonal antibodies corresponding to ICPs, effectively block inhibitory signaling between cancer cells and immune cells to avoid cancer immune escape [2].

ICIs have yielded unprecedented clinical benefits in tumor treatment. ICIs currently have several popular targets [3]. Programmed death-1 (PD-1) is expressed in immune cells and programmed death ligand 1 (PD-L1) could be expressed in cancer cells [4]. Inhibitory signals are generated by the binding of PD-1 and PD-L1 in T cells to inhibit immune response and T cell activation [5]. Cytotoxic T lymphocyte protein 4 (CTLA-4) is also expressed in the T cells and other immune cells, and the blockade of it could activate immune response [6]. Starting with the approval of anti-CTLA-4 in advanced melanoma therapy, ICIs rapidly gained FDA approval for cancer therapies, showing unprecedented prolonged patient survival. Currently, based on the efficacy and resistance mechanisms of ICIs, a variety of emerging immunotherapies such as ICIs monotherapy, ICIs in combination, and ICIs in combination with other immune agents are flexibly applied to treat cancer to achieve broader, longer-lasting efficacy and higher safety. This article reviews the research progress of ICIs in targeting cancer to improve the accuracy of immunotherapy.

2. Liver cancer

Liver cancer, which is divided into metastatic and primary liver cancer, ranks seventh-most common incidence and fourth in mortality worldwide and is a global health problem that cannot be ignored [7]. Due to the increasing incidence of liver cancer, it is urgent to find safer and more effective treatment modalities. There are many types of primary liver cancer, including hepatocellular carcinoma (HCC) for approximately 75%, intrahepatic cholangiocarcinoma (ICC) for 10%, and other rare tumors such as hepatoblastoma and fibrous lamellar carcinoma [8, 9]. Common causative factors of liver cancer include fatty liver, hepatitis B virus, hepatitis C virus (HCV), and alcohol-related cirrhosis. The characteristic pathogenesis of multicentric carcinogenesis, intrahepatic metastasis, and multistep carcinogenesis is associated with a high recurrence rate of hepatocellular carcinoma after curative treatment. Patients are usually diagnosed with hepatocellular carcinoma at a late stage, leading to a poor prognosis after local resection, and liver transplantation only caters to a minority of patients, and these treatment modalities have a limited effect on hepatocellular carcinoma. Patients with hepatocellular carcinoma need new treatment options with a higher safety profile and better prognosis. Based on published findings and clinical data, immunotherapy, represented by ICIs, has shown promising clinical results and therapeutic prospects and is being investigated for solid tumors such as primary liver cancer [9]. The specific situation of combined hepatitis cirrhosis and the immunosuppression of the liver tumor microenvironment in HCC patients result in a poorer sensitivity of hepatocellular carcinoma to ICIs than several other tumors [10].

2.1. Blocking PD-1/PD-L1 in liver cancer

A global Phase I clinical trial, CheckMate 040, on the rationale for Nivolumab as a first-line therapy option for patients with advanced HCC and sorafenib-resistant or refractory HCC of different etiologies, demonstrates positive trial results.

The results of the trial showed that rash, eye sweep, and diarrhea accounted for 23%, 21%, and 13% respectively of the adverse events that occurred, and were usually mild. Dose escalation and expansion phases had objective remission rates (ORR) of 15% and 20%, with a 1-year overall survival (OS) rate of 62%. The CheckMate 040 trial demonstrated the anticancer potential and manageable safety profile of Nivolumab in advanced HCC, facilitating FDA approval of Nivolumab.

Pembrolizumab is also a monoclonal antibody targeting PD-1. The Phase II trial KEYNOTE-224 in advanced HCC demonstrated good antitumor activity of Pembrolizumab. After that, KEYNOTE-240, the subsequent Phase III trial, also provided a solid rationale for Pembrolizumab treatment.

2.2. Blocking CTLA-4 in liver cancer

Tremelimumab was the first ICIs to be evaluated as a CTLA-4 target in a study of HCC. tremelimumab's antitumor and antiviral effects were demonstrated in a small phase II trial [11]. Tremelimumab treating HCC demonstrated safety with the adverse events being pruritic rash with an incidence of 65%, diarrhea with an incidence of 30%, and a temporary significant increase in serum transaminases after the first dose, but no other liver dysfunction.

3. Kidney cancer

Kidney cancer is common cancer worldwide, with an incidence of 2.7% of cancer diseases and a generally higher incidence in developed countries. The predominant type of kidney cancer is renal cell carcinoma (RCC) with a global incidence of approximately 0.4 million cases and nearly 180,000 deaths [7]. In clinical studies, the cancer cells in 33% of RCC patients spread to the lungs, liver, and bones at the time of initial diagnosis [12]. Surgical resection can treat limited RCC, but the prognosis after surgery for metastatic RCC is poor and conventional chemotherapy is ineffective. 70% of patients with RCC have an OS rate of 5 years, but the survival rate for patients with advanced RCC plummets to 8% because only salvage systemic therapy can be administered at 8% [13]. RCC is a heterogeneous group of tumors and the 2016 World Health Organization classification shows 16 histological subtypes,

and the most common one is clear cell RCC (ccRCC). ccRCC is characterized by hypoxic stress, deterioration of the tumor microenvironment, and increased angiogenesis, and is thought to be immune-mediated because of the cases in which spontaneous remission has occurred, with a specific response to immunotherapy [14]. The systemic treatment options for advanced ccRCC have undergone several rounds of innovation in the last decades. The former research on early cytokine therapies and targeted therapy with vascular endothelial growth factor (VEGF) have found good therapeutic results, and ICIs are currently listed as clinical options for RCC patients [15]. The combination of ICIs with anti-VEGF therapy has a higher objective remission rate ORR and longer survival than ICIs monotherapy.

3.1. Blocking PD-1 in kidney cancer

A phase I clinical trial (NCT00730639) demonstrated a cumulative response rate of 27% by nivolumab in 33 patients with ccRCC. In a subsequent phase II clinical trial (NCT01354431), Nivolumab demonstrated antitumor effects against RCC in three cohorts at doses of 0.3, 2, and 10 mg, with no serious side effects, observed [16]. Building on previous studies, the phase III CheckMate 025 trial (NCT01668784) was conducted in ccRCC patients who had received anti-VEGF therapy and were randomized to two dosing arms, Nivolumab and everolimus. The results showed that Nivolumab had a better objective remission rate ORR and 5-year survival than everolimus, which supports the subsequent monotherapy study of Nivolumab for ccRCC [17]. In addition to Nivolumab, PD-1 blocking ICIs such as Pembrolizumab, Atezolizumab, and Spartalizumab have also shown good therapeutic and survival benefits for ccRCC patients [18, 19].

3.2. Blocking CTLA-4 in kidney cancer

A phase II trial (NCT00057889) evaluated the safety and efficacy of Ipilimumab for the therapy of metastatic ccRCC in 61 patients with ccRCC. Under randomly assigned monotherapy with different doses of Ipilimumab, partial responses to treatment were shown from 6 patients. Though a high response rate was not observed, this is the first time that a response to ICIs has been observed in patients who had previously received IL-2 therapy without effect.

4. Colorectal cancer

Colorectal cancer (CRC), which used to be slow to be diagnosed, is now the fourth deadliest cancer worldwide [7]. During the 38 years from 1975 to 2013, the incidence of CRC increased at a rate of 10-15 cases per 100,000 among 20-49 years old adults in the United States [20], threatening the health of developing countries with a 20% increase in morbidity and mortality [21]. Adverse factors for CRC include aging, excessive alcohol consumption, weight gain, and smoking. Current research showed that cancer stem cells are the origin of most CRCs that are influenced by genetic factors and genetic mutations, with abnormal colonic crypts at the bottom evolving into polyps that eventually develop into CRCs within about 10-15 years. Mismatch repair (MMR) genes are essential in DNA repair pathways, including MLH-1, MSH-6, MSH-2, and PMS-2, and alterations in microsatellite size may cause loss of gene product function, resulting in MMR defects (dMMR), which is known as microsatellite instability (MSI). MSI may cause increased CRC risk, as evidenced by increased tumor mutation burden and an increased number of tumor-infiltrating lymphocytes (TILs). CRC with MSI phenomenon can be divided into MSI-high (MSI-H) and MSI-low (MSI-L) according to the different phenotypes of MSI. With the refinement of the understanding of CRC pathophysiology, treatment options for localized and advanced CRC have gradually become abundant, including endoscopic and surgical resection, systemic therapy, extensive surgery for localized and metastatic CRC, local ablative therapy, and targeted and immunotherapy [22]. About 25-50% of CRC patients at early diagnosis develop metastatic colorectal cancer (mCRC) with poor prognosis, with only 18.5% of CRC patients in the US having a five-year survival rate, compared to 27.7% in Europe. In the clinical management of patients with advanced CRC, ICIs have demonstrated significant efficacy, but acquired resistance

emerges after a brief onset of effect. Combination therapy can ensure a more significant and durable clinical response to ICIs in CRC patients compared to monotherapy [23].

4.1. Blocking PD-1 in colorectal cancer

A 2015 phase II trial demonstrated a 40% objective remission rate and 5.0 months of OS with pembrolizumab in mCRC patients with dMMR/MSI-H [24]. 2017 Keynote-177 clinical trial compared chemotherapy and pembrolizumab showed that pembrolizumab improved the survival and life quality of mCRC patients with dMMR / MSI-H, demonstrating its remarkable clinical effectiveness as a first-line treatment. Based on this, FDA approved pembrolizumab in 2020 for the therapy of mCRC patients with dMMR / MSI-H. A 2017 clinical trial of nivolumab in adult patients with mCRC with dMMR / MSI-H, checkmate 142, demonstrated 31.1% effectiveness and 69% over 12 weeks of disease control. This positive study result was evidence of the approval of nivolumab by the US FDA.

4.2. Blocking CTLA-4 in colorectal cancer

Studies have shown that ipilimumab combined with nivolumab had an ORR of 55% for mCRC patients with dMMR/MSI-H, progression-free survival of 71%, and disease control of 69% greater than 12 months, demonstrating higher response rates and a more manageable safety profile, prompting the FDA to approve this drug combination with 2018.

5. Prostate cancer

Prostate cancer (PCa) ranks second in cancer incidence and fifth in cancer deaths among men, with nearly 375,000 patient deaths and 1.4 million new cases, making prostate cancer a pressing global health issue [7]. Current studies know little about the etiology of Pca, with aging, familial inheritance, and genetic mutations as possible risk factors for PCa. As PCa is commonly detected late, patients with PCa are classified as limited Pca or advanced PCa. Treatment options for PCa include surgical resection, chemotherapy, radiation therapy, and cryotherapy. A good treatment modality for limited Pca is surgical resection, but advanced Pca-dependent androgen deprivation therapy (ADT) is accompanied by severe side effects, resulting in generally very low patient survival [25]. Resistance develops after a short period of efficient initial treatment, and there is a high probability that PCa will develop into metastatic debulking-resistant prostate cancer (mCRPC), an androgen-insensitive disease with no curative treatment, after 18-24 months. ICIs have achieved significant efficacy in a variety of cancers, but have been less well studied in Pca, and arguably unsuccessful.

5.1. Blocking PD-1 in prostate cancer

High PD-1 expression in CD8 T cells isolated from PCa patients provides an important basis for immunotherapy with PD-1 blockade. There are several speculations on the mechanism of PCa, one is related to the phenotype of prostate infiltrating lymphocytes and another is PD-L1 expression which is associated with increased response to anti-PD-1 monotherapy. Data from current clinical trials showed that the blockade of PD-1 to treat ICIs in PCa is much less effective than in clinical trials of monotherapy, such as in kidney and lung cancer.

5.2. Blocking CTLA-4 in prostate cancer

Only two of the 14 patients with advanced mCRPC in the first trial of anti-CTLA-4 antibodies for PCa demonstrated a decrease in prostate-specific antigen (PSA) $\leq 50\%$. Subsequently, a clinical study expanded the number of mCRPC patients to 71 to test the difference in efficacy of Ipilimumab and radiotherapy combined with Ipilimumab [26]. 16% of patients in the highest dose group had a decrease in PSA of $\leq 50\%$, six had no progression, and one sustained a response.

6. Conclusions

ICIs have demonstrated unprecedented clinical significance in antitumor therapy, and CTLA-4, PD-1, and its ligand PD-L1 are among the popular research targets. Immune checkpoint inhibitors have shown good curative effects, and are thus recommended as first-line medications in many guidelines for liver cancer, kidney cancer, colorectal cancer, and prostate cancer. However, immune-related adverse reactions (irAEs) including the skin, respiratory, digestive, endocrine, nervous system, urinary system, and so on may occur after the treatment of ICIs. Therefore, it is crucial to standardize immunotherapy and develop strategies to address negative effects. Of course, an in-depth investigation into the mechanism of action of ICI and the inflammatory response of tumors is more crucial than just being validated by several clinical studies to make a breakthrough.

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