

The Current Achievements and Existing Shortage of Immune Checkpoint Inhibitor

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Abstract. Immune checkpoint inhibitor (ICI) is drug used to treat cancer by blocking immune checkpoint molecules and activating the immune system to attack tumor cells. ICI has limitations, including varying patient immune tolerance, immune-related adverse events, and unclear biomarkers. However, it is currently the most widely used, versatile, and highly effective immunotherapy drug. By comparing the efficacy of ICI with other treatment methods and citing examples of its breakthrough role in different cancers, the superiority of ICI is demonstrated. At the same time, it still has great potential and clinical value in the field of immunotherapy, and there is great room for development in both the design of new targets and the new application of known targets. This article discusses the advantages of ICI, particularly when combined with radio chemotherapy and chemotherapy, in cancer treatment. The summary outlines its mechanism of action, current applications, achievements, and limitations in the field further needed to be addressed.

Keywords: Immune checkpoint, immune checkpoint inhibitors (ICI), immune tolerance.

1. Introduction

Immune checkpoints are essential components of the immune system that prevent the excessive strength of an immune response from destroying healthy body cells. The immune system usually can identify and eliminate cancer cells. Cancer cells can send signals to immune checkpoints, activating their immunosuppressive effects and avoiding recognition by the immune system.

The immune system, comprising organs, cells, and immunoactive substances, is vital in preventing foreign invasion and ensuring internal stability. It has three basic functions: immune defense, surveillance, and homeostasis. Defense prevents foreign pathogen invasion, surveillance detects and eliminates abnormal cells, and homeostasis maintains internal stability through tolerance and regulation. Insufficient immune surveillance can lead to cancer development, as it fails to clear cancer cells in a timely manner.

Cancer cells are invasive and can reproduce indefinitely, destroying normal cells. They can also undergo distant metastasis due to their unique structure. The immune system can identify and eliminate cancer cells (Figure. 1), but they often escape through three methods: disguise themselves, create environments conducive to growth, and release cytokines. Overactivation of the immune system can lead to an "immune storm," requiring immune checkpoint molecules to balance the immune system. Tumor cells also use the immune system's regulatory function for immune escape, especially during immune checkpoint molecule interaction.

Cancer treatment methods can have adverse effects on the immune system. Chemotherapy drugs attack cancer cells and kill normal fast-growing cells, causing side effects like nausea and immune suppression. Radiotherapy, which irradiates tumor tissue, has a good therapeutic effect on tumors but can also kill normal cells, leading to impaired immune system function. Patients may also experience gastrointestinal reactions like loss of appetite, vomiting, diarrhea, and nausea after radiation therapy.

Researchers are studying the use of immune cells to achieve effective treatment for certain types of cancer, known as immunotherapy. Immunotherapy is a new milestone in cancer treatment. In solid tumors, most successful cases are achieved through ICI. It primarily antibodies against checkpoint proteins, prevent the "off" signal from binding with partner proteins, enabling T cells or NK cells to kill cancer cells. ICI-related drugs are constantly emerging, categorized into various types based on different targets.

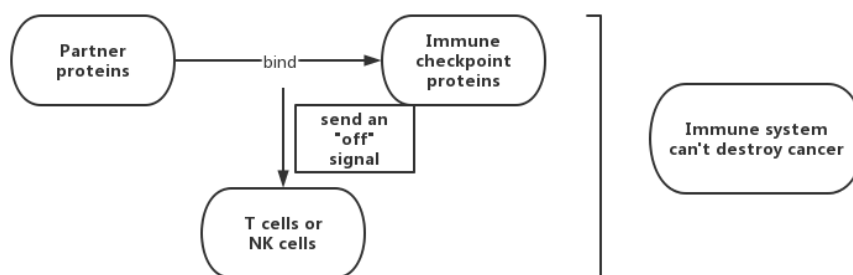


Figure 1. Mechanism of immune checkpoints in cancer

2. Classification of Immune checkpoint

2.1. Current used immune checkpoint

2.1.1 CTLA4

CTLA4, also known as CD152, is an immune checkpoint that downregulates immune responses, and anti-CTLA-4 antibodies have been found to cure or reduce tumor burden.

2.1.2 PD-1 / PD-L1

PD-1, a B7/CD28 receptor, regulates T cell activation by binding to PD-L1 and PD-L2 ligands, inhibiting T cell proliferation and some cytokines production, thereby controlling infection and tumors.

2.1.3 LAG-3

LAG-3 is a gene that activates lymphocytes, interacting with MHC class II. It downregulates T cytokine production, expands CD4 and CD8 T cells, and promotes Treg phenotype, controlling tumors.

2.1.4 The Application of current immune checkpoint

The FDA has approved multiple ICIs, including ipilimumab and pembrolizumab, for marketing, and PD-1 and 3 PD-L1 monoclonal antibodies for treating 11 cancers (Table. 1).

2.2. Potential immune checkpoint could be used

2.2.1 VISTA

VISTA, a negative checkpoint regulator, is primarily expressed on hematopoietic cells and is found at high levels in murine cancer models on myeloid cells infiltrating tumors.

2.2.2 TIGIT

TIGIT, a lymphocyte-specific inhibitory receptor, has been identified as a potential cancer immunotherapy target due to its interaction with CD155.

2.3. Comparing: advantage and shortage

2.3.1 Outcome comparing with current treatment

2.3.1.1 Curative effect

More kind of cancer had better therapy than before.

Ipilimumab, the first CTLA-4 monoclonal antibody approved in 2011, is used for treating advanced melanoma in solid tumors like renal cell carcinoma, NSCLC, and colorectal cancer, benefiting about 10%-20% of tumor patients. AstraZeneca's tremelimumab and Innovent Biologics' IBI-310 are in phase III clinical studies. Among them, a phase III clinical study of tremelimumab (clinical trial number: NCT03298451) showed that tremelimumab combined with durvalumab showed significant improvement in overall survival (OS).

Table 1. List of all FDA-approved ICIs with their current indications [1]

Therapy	Immune check point	First approved	Indication
ipilimumab	CTLA-4	2011	Melanoma (SKCM), colorectal cancer (CRA), renal cancer, non-small cell lung cancer (NSCLC).
pembrolizumab	PD-1	2014	Skin cancer, NSCLC, small cell lung cancer (SCLC), renal cell cancer (RCC), Hodgkin's lymphoma, head and neck cancer (HNSC), bladder cancer (BLCA), colorectal cancer (CRA), hepatocellular carcinoma (HCC), esophageal cancer (EC), stomach cancer (SC), triple negative breast cancer (TNBC).
nivolumab	PD-1	2014	Skin cancer, NSCLC, SCLC, RCC, Hodgkin's lymphoma, HNSC, BLCA, CRA, HCC, EC, SC.
atezolizumab	PD-L1	2016	Skin cancer, NSCLC, SCLC, BLCA, HCC, TNBC.
durvalumab	PD-L1	2017	NSCLC, SCLC, BLCA.
avelumab	PD-L1	2017	Skin cancer, HCC, BLCA.
cemiplimab	PD-1	2018	Skin cancer, NSCLC.
tremelimumab	CTLA-4	2022	HCC.
dostarlimab-gxly	PD-1	2021	Endometrial cancer.
relatlimab	LAG-3	2022	Metastatic melanoma.

The PD-1/PD-L1 monoclonal antibody targets tumors by blocking PD-1's binding to PD-L1 protein, reactivating T cell immune responses, and has shown good safety and anti-tumor efficacy since 2012. Phase III trials have shown significant benefits for malignant tumors. In the phase III trial CheckMate-066 for advanced melanomas, nivolumab showed a significantly higher 1-year survival rate compared to dacarbazine. Phase III trials for non-small cell lung cancer demonstrated significant clinical benefits compared to docetaxel, with PD-1/PD-L1 antibody drugs showing long-lasting and powerful efficacy in some tumor patients. 10 PD-1 monoclonal antibodies and 3 PD-L1 monoclonal antibodies have been approved for 11 cancers currently.

Relatlimab is a LAG-3 monoclonal antibody. In phase II clinical trials, relatlimab alone has limited antitumor efficacy, whereas its combination with multiple ICIs can improve antitumor efficacy. The combination of relatlimab and nivolumab for melanoma prolongs progression-free survival (PFS) twice as much as nivolumab alone (10.1 versus 4.6 months).

Antibody drugs Sym023, INCAGN2390 and LY3321367 targeting TIM-3 are being conducted as monotherapies in clinical trials for advanced solid tumors and lymphomas (NCT03489343, NCT03652077, NCT04443751). LY3321367 monotherapy showed good safety in phase I clinical trials, but limited antitumor activity [2].

2.3.1.2 Progress of other cancer

The clinical use of ICI has led to breakthroughs in the treatment of many cancers. Not only is it reflected in the efficiency of clearing cancer cells, but it is also reflected in the overall therapeutic effect on patients' condition when combined with other treatment methods, which is far superior to before.

Ipilimumab is effective in treating melanoma, with a 5-year survival rate of 18.2%, a median relapse-free survival period of 27.6 months, and a median overall survival period of 15.7 months. However, the median 5-year OS of the PD-1 inhibitors pembrolizumab increased to 32.7 months and nivolumab increased to 34.8 months, respectively, indicating a higher efficacy [3].

PD-1/PD-L1 inhibitors are crucial in lung cancer immunotherapy, with clinical trials confirming their safety and efficacy for 5 years in advanced NSCLC patients. The three main drugs used in the third phase of the signed trial were nivolumab, pembrolizumab, and atezolizumab. Nivolumab's 5-

year OS increased from 8.1 to 11.1 months compared to chemotherapy, while pembrolizumab's ranged from 11.8 to 26.3 months. Significant PFS and OS benefits were observed in NSCLC patients.

Due to the increasing internal drug resistance in cancer and the weakened efficacy of the currently used ICI drugs, the development and use of a new generation of ICI are urgent. The next generation ICI therapy has played some role in Philadelphia negative classic myeloproliferative tumors (MPN) [4].

2.4. The current shortage

The clinical use of ICI has significantly improved cancer treatment efficiency and overall therapeutic effect when combined with other treatments, resulting in a more superior overall treatment for patients compared to previous methods.

2.4.1 Immune tolerance

ICI therapy has improved cancer prognosis, but only a few patients have sustained responses. For instance, 60-70% of melanoma patients with the highest ICI response rate have no objective response to PD-1 treatment, and 20-30% of those who responded show ultimate tumor recurrence and progression.

The study of why patients fail to respond to ICI therapy is a complex issue, with resistance mechanisms categorized as primary and acquired. Primary resistance occurs when no initial response to checkpoint treatment is observed, while acquired resistance occurs when patients initially respond to ICI but later become refractory.

Primary resistance often occurs due to three conditions. As an example, this will explain the mechanism of action of primary resistance in HCC.

Tumor neoantigens are abnormal peptides produced by tumor cells due to genomic mutations, as they lack defects in neoantigen production and antigen presentation. Tumor-specific antigens, such as neoantigens, are more immunogenic than tumor-associated antigens and do not induce autoimmunity [5]. Tumors with higher tumor mutation burden (TMB) produce more nonsynonymous mutations, leading to more neoantigens and increased immune system activation for tumor recognition. Dendritic cells in tumor-metastasis necrosis (TME) can exhibit immature phenotypes, causing dysfunction in tumor antigen presentation and T cell activation. The major histocompatibility complex (MHC) is crucial for the presentation of human antigens. It enables antigen-presenting cells to trigger specific immune responses by presenting antigen peptides. Studies indicate that HLA-I deficiency in HCC is frequently linked to immunosuppression and resistance to immunotherapy, while high HLA-I expression is strongly associated with improved HCC prognosis [6].

Studies show that Wnt/ β -catenin signaling activation in HCC mice enhances immune escape and resistance to PD-1 therapy by inhibiting CCL5 expression, reducing CD103⁺ dendritic cells, and antigen-specific CD8⁺ T cells, which are implicated in cancer development and immunotherapy resistance. In the study of soluble cytokines in mediated immunotherapy resistance, TGF- β in urothelial carcinoma can inhibit anti-tumor immunity by limiting T cell infiltration, and promote tumor cell proliferation and invasion [7].

The inhibitory immune microenvironment is part of the immune escape mentioned earlier and is one of the causes of primary resistance. Studies on HCC patients reveal a depleted immune microenvironment, limited immune infiltration, and a high number of immunosuppressive cells, leading to immune resistance and a small percentage of immunoactive individuals. This also proves that targeting suppressor cells in the immune microenvironment is also one of the important research directions to improve ICI drug resistance.

Acquired resistance is the initial response to ICI therapy, followed by disease progression or recurrence. No breakthrough has been made in preventing or reversing ICI acquired drug resistance, and studying its mechanism is challenging due to lack of unified diagnostic criteria, difficulty in obtaining good clinical samples, and extensive DNA/RNA sequencing.

Acquired drug resistance occurs when tumor cells and the immune system interact, leading to clonal selection and retention of low immunogenicity or neoantigen expression cells, resulting in ICI

resistance. There can also be immune cell depletion and up-regulation of immune checkpoints, which refers to the dysfunction of immune cells during cancer development and immunotherapy.

In 2018, only 12.5% of patients met eligibility criteria for ICI treatment, highlighting the need for a deeper understanding of primary drug resistance factors to increase its benefits.

2.4.2 Immune related adverse events (irAEs)

The relationship between irAEs and anti-tumor immune response is complex and may vary based on the irAE organ. Low-grade irAEs have a positive correlation with ICI response. A recent study investigates the relationship between inflammatory bowel disease (irAE) and tumor microenvironment, aiming to understand the therapeutic objectives of irAE management. The study emphasized the clinical and molecular connection between irAE and anti-tumor immunity, and the potential role of irAE treatment in enhancing the anti-tumor immune response. Interventions may reduce the anti-tumor effect of ICI treatment, suggesting a better understanding of irAEs could improve treatment efficacy.

2.4.3 Biomarkers

The tumor mutation burden (TMB) is a biomarker that reflects cancer mutations, which are processed into new antigens and presented to T cells by the MHC protein. Cancer uses checkpoints to inhibit T cell reactivity, and immune checkpoint inhibitors (ICIs) alter treatment by reactivating T cells. Higher TMB leads to more new antigens, increased T cell recognition, and better ICI results in clinical practice. However, TMB is an imperfect reaction biomarker, necessitating a composite predictor that includes MHC and T cell receptors.

Immunotherapy has significantly improved colon cancer treatment, especially for patients with high microsatellite instability (MSI-H). FDA approved ICI pembrolizumab in 2020 for metastatic MSI-H patients, but further research is needed to identify predictive biomarkers for stratifying patients. This study on colon cancer can confirm that biomarkers indeed play an important role in immunotherapy, especially in the clinical pharmacological responses targeting different patients. For different types of ICI, cancers, and individual patients, there are many undiscovered biomarkers. Exploring more biomarkers is a direction that requires more experimentation and research for the treatment of patients and the development of ICI drugs [8].

2.5. Therapeutic strategy of ICI

2.5.1 Combination with radiochemotherapy

The survival improvement of glioblastoma patients with simple RT therapy is minimal, as RT not only promotes immune activation but also induces immune suppression. Different doses of radiation have different effects on anti-tumor immune response. Existing studies suggest that RT at doses exceeding 10 Gy per dose can effectively enhance anti-tumor immune response and provide relevant targets for immunotherapy, but low doses of radiation can induce immunosuppressive TME. Research has found that the optimal timing for RT combined with inhibitors at different immune checkpoints varies. In the report evaluating the ideal timing of radiotherapy and anti PD-1 treatment, it was found that synchronous therapy is superior to sequential therapy under the same dose of radiation. However, in the treatment of radiotherapy and anti CTLA-4, it was found that the combination therapy was most effective 7 days before a single dose of 20 Gy radiation, rather than synchronous therapy or medication administered after radiotherapy; In the same model, the treatment effect of anti OX40 drugs one day after radiotherapy is the best. Whether this conclusion is effective in the treatment of GBM requires further verification, but according to current preclinical and clinical data, RT combined with immune checkpoint inhibitors has a positive anti-tumor effect on GBM.

Due to GBM's invasive infiltration and unclear boundary with surrounding normal brain tissue, it is difficult for surgery to completely remove it. Moreover, radiation resistance and drug resistance exist in radiotherapy and chemotherapy, so human GBM remains one of the worst prognosis tumors. RT can activate anti-tumor immune responses while killing tumor cells, and produce synergistic anti-

tumor effects with immune checkpoint inhibitors, achieving good therapeutic effects in preclinical experiments of GBM [9].

2.5.2 Combination with chemotherapy

Recently, there have been reports that ICI, anti-angiogenesis, and chemotherapy are new adjuvant treatment methods for locally advanced cancer.

ICI and anti-angiogenic agents exhibit some activity in patients with advanced gastric cancer. The Phase II trial results show that combining neoadjuvant anti-PD1, anti-angiogenic agent, and chemotherapy improves treatment efficacy in T4a/bN+M0 gastric cancer patients [10].

A phase III trial found that ICI outperformed placebo in treating advanced gastric cancer, prolonging overall survival and reducing the risk of death compared to chemotherapy alone. In theory, due to the integrity of the immune system, sufficient new antigens, and low tumor clonality, neoadjuvant devices are the best choice for immunotherapy. The investigation of new adjuvant therapies based on ICI has successfully treated resectable NSCLC. The suitability of this treatment has not been thoroughly investigated.

Tumor angiogenesis is crucial for tumor progression, and anti-angiogenic agents, like ICIs, target tumor microenvironment components and promote CD8+T lymphocyte infiltration and activation. The anti VEGFR2 antibodies and inhibitors have been approved for second and third-line treatment of advanced gastric cancer, demonstrating improved ICI efficacy.

2.5.3 Combination with another ICI

In 2015, a drug consisting of a combination of two different target ICI drugs was first launched. Ipilimumab and nivolumab are CTLA-4 and PD-1, respectively, which is the first time that the efficacy of one plus one greater than two in combination with two or more target ICIs has been recognized. The successful attempt in 2015 allowed for further development of research on the combination of multiple ICIs. Nowadays, when combined with other treatment methods, composite ICI products are often used.

2.5.4 Design new target of cancer

The design of new generation ICI drugs did not focus on the discovery of new targets, as there are still many areas worth paying attention to, such as Immune tolerance, irAEs, biomarkers, etc. The research on targets of next-generation ICI drugs mainly focuses on IGIT and VISTA mentioned earlier, and these new targets are gradually entering the clinical trial stage. It has shown good performance in tumor immune resistance, with a lower probability and degree of resistance compared to placebo.

2.5.5 AI associated design

Researchers have developed a WSI analyzer using artificial intelligence to identify three immune phenotypes: inflammation, immune rejection, and immune desert, which are associated with tumor response to immune checkpoint inhibitors (ICI) and survival rates in advanced NSCLC patients. The AI-driven spatial TIL analyzer was able to predict clinical outcomes of ICI in advanced NSCLC patients, and patients who had previously received monotherapy for ICI were associated with higher tumor response rate (TRR) and longer progression-free survival (PFS) in patients with IP inflammation. This is the first study in advanced NSCLC to study automatic TIL analysis driven by AI [11].

3. Summary

The emergence of ICI is a new hope for cancer patients, as it has greatly improved their survival time and quality of life. When used alone, the toxicity and side effects are much lower than those of chemotherapy and radiotherapy. When combined with other types of ICI, it can work together to stimulate the body's own tumor immune response ability at multiple sites. Its clinical efficacy is undoubtedly the most significant and widely used among current immunotherapy regimens. At the

same time, its combination with radiotherapy and chemotherapy, as well as the design of the new generation of ICI, has broad prospects and more directions, requiring more clinical trials and new ideas. At the same time, with the development of internal drug resistance in tumors, existing ICI drugs have also emerged that can be optimized, such as drug delivery methods and coordinated use between different targets. This review discusses the current development of ICI drugs and their potential future role in cancer treatment, highlighting their advantages when combined with radio chemotherapy, chemotherapy, and various types of ICI, and their significant impact on cancer patient care.

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