Examining the Application of Immune Checkpoint Inhibitors in Cancer Immunotherapeutic: A Systematic Review

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Abstract. To define the clinical utilizations, effectiveness, and challenges of immune checkpoint inhibitors (ICIs) in cancer treatments. A systematic review of the literatures regarding the efficacy of ICI therapy in the management of advanced melanoma, non-small cell lung cancer (NSCLC), and hepatocellular carcinoma (HCC) was performed. The effectiveness and safety profile of anti-PD-1 (Nivolumab, Pembrolizumab, and Cemiplimab /PD-L1 (Atezolizumab, Durvalumab, and Avelumab), anti-CTLA-4 (Ipilimumab) drugs were measured and evaluated in several clinical trials via treatment-related indicators (response rate, survival rate, progression-free survival, overall survival, median overall survival, and treatment-related adverse events). Considering the increasing use of ICI therapy in days to come due to its great potential, this review can be valuable in assisting professional students or even oncologists to have a general overview of the role of ICIs in cancer immunotherapeutic, particularly targets the advanced melanoma, NSCLC, and HCC.

Keywords: Immune checkpoint inhibitors, cancer treatment, melanoma, non-small cell lung cancer, hepatocellular carcinoma.

1. Introduction

Immune Checkpoint Inhibitors (ICIs) are a form of cancer therapy that involves blocking checkpoint proteins from binding with their partner proteins, which are often highly expressed on the surface of cancer cells. These checkpoint proteins consist of molecules that either activate or inhibit the immune response, such as CD28 and PD1. When the immune system attacks pathogens, these immune checkpoint proteins play a crucial role in protecting the normal cells from being attacked by regulating the immune response. However, some tumor cells can avoid the immune system's oversight by binding immune checkpoints with antigens and implementing interference to reduce immune response. Currently, cytotoxic T lymphocyte antigen (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) have become the focus of research on dealing with tumor immune escape, among which CTLA-4 and PD-1 have been deeply studied as immune checkpoint receptors. Moreover, the blockers of these checkpoints have been vigorously developed recently, corresponding to the characteristics and function of immune checkpoint proteins. The existing ICI drugs include three main types which are corresponding to three types of immune checkpoints. As for CTLA-4 inhibitors, Ipilimumab is the focus. Ipilimumab (Yervoy) works in treating a series of cancers such as melanoma and advanced renal cell carcinoma by inhibiting the function of CTLA-4. Additionally, researchers found that the immune response rates and survival rates in several kinds of cancer types would be enhanced with the combination usage of CTLA-4 and PD-1 blockers [1]. In 2020, the US Food and Drug Administration (FDA) authorized the combination of Yervoy (Ipilimumab) and Opdivo (Nivolumab) as a first-line treatment for non-small cell lung cancer (NSCLC) and unresectable malignant pleural mesothelioma (MPM) [2]. Nivolumab, Pembrolizumab and Cemiplimab are the main inhibitors for PD-1, while there also have three types of PD-L1 blockers (Atezolizumab, Avelumab, and Durvalumab) were also approved by FDA and used in NSCLC, melanoma, and such solid tumors.

This article systematically reviews ICI therapy in various cancers and adverse events through analyzing a certain number of field-related literatures and recent clinical trials. Given the anticipated heterogeneity in study designs and outcomes, a narrative synthesis of other studies' findings was generated.

2. Applications of ICI Therapy Across Various Cancers

ICIs have transformed the way that cancer is treated by playing a part in activating the immune system through the binding of monoclonal antibodies to inhibitory checkpoint molecules that are expressed on the cell membrane of antigen-presenting cells or T cells. To date, the FDA has granted approval for seven ICIs as mentioned above. This diverse array of ICIs has made them available for treatment across more than 13 common cancer types. Whereas chemotherapy and radiotherapy continue to be the standard of care and the cornerstone of treatment for the majority of cancer types, ICIs are now used in front-line therapies for multiple solid tumors, covering but not restricted to advanced melanoma, NSCLC, and primary liver cancer specifically hepatocellular carcinoma (HCC) type.

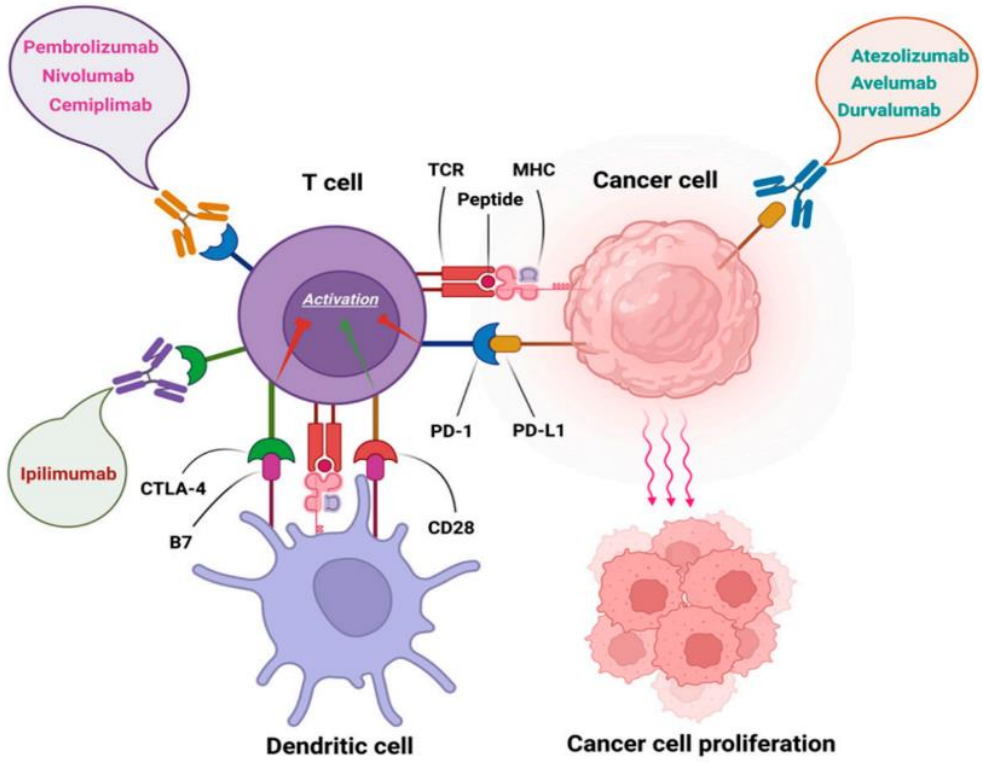


Figure 1. Various types of ICIs approved by the FDA. PD-1 inhibitors Pembrolizumab, Nivolumab, and Cemiplimab, CTLA-4 inhibitors Ipilimumab, and PD-L1 inhibitors Atezolizumab, Avelumab, and Durvalumab [2].

2.1. Advanced Melanoma

Melanoma, also known as malignant melanoma, is one of the most dangerous skin cancers caused by the formation of malignancy in melanocytes. It can spread to other areas in the body quickly and has exhibited an increasing incidence in the past years. Most patients with early-stage melanoma can be cured by removing the tumor surgically while this therapeutic method is unsuitable for the patients suffering from stage III, stage IV or advanced melanoma. In other words, there lacks options to treat advanced melanoma which has spread far from where the cancer started and cannot be easily removed with surgery. Compared to other traditional therapies, ICI therapy stands out for its efficacy in durably controlling cancer. As for advanced melanoma and many other malignancies, ICIs targeting CTLA-4 and PD-1 checkpoints have shown positive results in managing such cancers [3].

Ipilimumab, an inhibitor blocking the CTLA-4 checkpoint, was used to treat advanced melanoma patients and successfully improved the overall survival rate. To illustrate more, Hodi et al. (2010) point out that Ipilimumab has shown great promise for overall survival improvement in melanoma patients. In a phase 3 clinical study, Ipilimumab and gp100 peptide vaccine were used for advanced melanoma treatment and to make a comparison. The results indicate that Ipilimumab indeed

contributes to the overall survival in metastatic melanoma patients no matter whether the gp100 peptide vaccine were injected or not. Notably, the survival time for the Ipilimumab-plus-gp100 group was 21.0 months, the Ipilimumab-alone group was 27.8 months, and the gp100-alone group was 17.2 months after these patients were traced for 55 months. At the meantime, Ipilimumab showed a substantially improved median overall survival in both Ipilimumab arms compared to the vaccine alone --10.1 months in the Ipilimumab-gp100 combined group and 10.0 months in the Ipilimumab-alone group vs. 6,4 months in gp100 group only [4].

For patients with advanced melanoma who had not previously received therapy, two PD-1 inhibitors that were more effective than Ipilimumab were used: Nivolumab and Pembrolizumab. A comparative study between Pembrolizumab and Ipilimumab demonstrated greater duration of overall survival (OS) and progression-free survival (PFS) in the Pembrolizumab group than that of Ipilimumab treatment group. In the study between Pembrolizumab and Ipilimumab at appropriate doses by Robert et al. (2015), Pembrolizumab was administered at a dose of 10 mg/kg body weight every two or three weeks, whereas Ipilimumab was given at a dose of 3 mg/kg every three weeks. The findings present that Pembrolizumab showed higher PFS after 6 months, with 47.3% and 46.4% respectively vs. 26.5% in the Ipilimumab group, and a higher rate of OS after 12 months, with approximately 70% vs. 58% when using Ipilimumab. Furthermore, Nivolumab was approved for treating unresectable melanoma in Japan in 2014, symbolizing the first clinical use of anti-PD-1 drug [5].

Moreover, due to the complementarity of Ipilimumab and nivolumab in regulating the immune response, the therapy combining these two drugs shows remarkable efficacy in the treatment of advanced melanoma. An evidential phase 1 trial was conducted, whose analysis has revealed impressive outcomes of the combined use of ipilimumab and nivolumab in treating patients with melanoma, especially bringing about a high objective response rate with deeper responses such as higher tumor regression rate [6]. Nevertheless, it is essential to note that the combination therapy did show a higher occurrence of side effects when compared with monotherapy.

2.2. Non-Small Cell Lung Cancer (NSCLC)

One of the major causes of cancer-related death is lung cancer, with only a 17.7% five-year survival rate among patients. The two primary pathological forms of lung cancer are small cell lung cancer (SCLC) and NSCLC, while the latter accounts for the majority and can be further divided into more subgroups, including sarcomatoid neoplasms, squamous cell carcinoma frequently happens in man and adenocarcinoma large cell carcinoma commonly happens in women. Compared to common therapies such as surgical resection and chemotherapy, ICI therapy shows greater effectiveness and higher safety when applied to NSCLC treatment [5].

The first breakthrough in the utilization of ICIs in the treatment of NSCLC was PD-1 inhibitor Nivolumab. Two phase III trials CheckMate 057 and CheckMate 017 were conducted to evaluate the effectiveness of Nivolumab and docetaxel (a chemotherapy drug) on non-squamous NSCLC (NS-NSCLC) and squamous NSCLC respectively. In phase 3 study on NS-NSCLC patients, either a dose of 3 mg/kg of body weight of Nivolumab every two weeks or a dose of 75 mg/m2 of body-surface area of docetaxel every three weeks were assigned to two groups of patients (n1 = 292; n2 = 290). The results show that the Nivolumab group had significantly higher median OS, overall survival rate (in 12 and 18 months), and response rates than another control group. Treatment-related side events were also reduced in the Nivolumab group in the meantime [7]. Echoing this finding, a similar study implemented among squamous-cell NSCLC patients indicates a more remarkable efficacy and safety profile of Nivolumab than docetaxel. In the ICI drug group (n = 131), the median OS was 9.2 months, compared to 6.0 months in the docetaxel group (n = 129). Similarly, the one-year overall survival rate, response rate, and median PFS with Nivolumab were higher than that with docetaxel, while the risk of death and grade 3 or 4 adverse events with the former group was much lower than with docetaxel group [8]. The comparable results are presented in Table 1 below. Shortly after, Pembrolizumab and Cemiplimab also received FDA approval.

Table 1. Comparison of indicators showing the effectiveness of Nivolumab and Docetaxel in CheckMate 057 and CheckMate 017 trials [7, 8].

	NS-NSCLC (CheckMate 057)		Squamous NSCLC (CheckMate 017)	
Drug	Nivolumab (n=292)	Docetaxel (n=290)	Nivolumab (n=292)	Docetaxel (n=290)
Dose	3mg/kg	75mg/m^2	3mg/kg	75mg/m^2
Frequency	Every 2 weeks		Every 3 weeks	
Median OS (months)	12.2	9.4	9.2	6.0
One-year OS rate	51%	39%	42%	24%
Grade 3 or 4 adverse events	10%	54%	7%	55%

2.3. Hepatocellular Carcinoma (HCC)

Alongside intrahepatic cholangiocarcinoma, HCC is one of the most prevalent types of primary liver cancer. It is becoming the fourth greatest cause of cancer-related death globally and is more common in people with cirrhosis and chronic liver disease. Due to the complex prevalence situation of liver cancer patients, ICI therapy may not show great results in HCC treatment as it is in the treatment of advanced melanoma and NSCLC, however, such therapy still displays huge promise in the treatment of HCC. Apart from the seven approved ICIs, Tremelimumab, another type of CTLA-4 monoclonal antibody (mAb), also plays an important role in the application in HCC.

In 2013, Tremelimumab was used to conduct a phase II study with 21 HCC patients resulted from hepatitis C virus (HCV) and showed great safety profile, anti-tumor and antiviral abilities, with the results of 17.6% overall response rate (ORR), 76.4% disease control rate, 6.48 months average time to progression (TTP) and the significantly lower viral load of HCV in the patients. In the meantime, the density of cytotoxic T lymphocyte (CTL) was found to increase in punctured tumor tissue, indicating the great potential of Tremelimumab's combination with local therapy [9].

Anti-PD-1 drug Nivolumab showed great effectiveness in phase I clinical research of patients with HCC named CheckMate 040 (n = 262), with the findings demonstrating 20% of ORR and 62% of one-year OS. Nonetheless, adverse events such as 25% of grade 3 or 4 treatment-related side effects, and 6% of immune-related adverse events (irAEs) hurting skin and other organs occurred among a great number of patients (n = 48) while the results showed that the safety of Nivolumab was still manageable.

3. Findings on the Challenges Facing ICI Therapy

ICIs have radically altered the way cancer is treated by directing the immune system to specifically target and destroy cancer cells. However, there are several challenges associated with ICI therapy, including toxicity and the development of resistance.

3.1. ICI Toxicity

ICI toxicity refers to the side effects or adverse events that can occur as a result of the immune system becoming overly active or mistakenly attacking healthy tissues in addition to cancer cells. These toxicities are often referred to as irAEs, which can affect various organs and systems in the body. These irAEs can be mild, moderate, or severe and may include skin rashes, colitis, pneumonitis, hepatitis, and more. Long-term monitoring and management of irAEs can be challenging.

In some cases, ICIs can trigger autoimmune disorders, where the immune system attacks healthy tissues and organs. These autoimmune reactions can persist long-term and require ongoing management. Meanwhile, ICIs have been associated with cardiovascular complications, including myocarditis, and pulmonary complications, such as pneumonitis, these events can have long-term effects on a patient's heart and lung health or even other organs [10, 11]. Although less common, ICIs can lead to neurological adverse events like neuropathies or encephalitis, which may result in long-

term neurological deficits [12]. ICI therapy can disrupt the endocrine system, leading to long-term hormonal imbalances, such as thyroid dysfunction or adrenal insufficiency.

3.2. Resistance to ICIs

Resistance to ICIs is a significant challenge. Resistance refers to the phenomenon where a patient who initially responds to ICI treatment experiences a relapse or a lack of sustained response over time. Primary resistance and acquired resistance are two common types. Some patients do not respond to ICIs at the beginning, known as primary resistance. The underlying reasons for primary resistance are not yet fully understood but may be related to the tumor's microenvironment and its ability to evade immune recognition. However, even when patients initially respond to ICI therapy, they can develop acquired resistance over time, which is similar to the principle of the development of resistance to antibiotics. This can be due to three main mechanisms that might be causing the suppression of the T-cell activation process, including factors inhibiting antigen recognition, T-cell migration/infiltration, and effector function of T cells [13]. As shown in Figure 2, the process of T-cell activation is divided into seven steps, with resistance mechanisms related to antigen recognition inhibiting steps 1 to 3 and 6, T-cell migration and/or infiltration resistance mechanisms inhibiting steps 4 and 5, the inhibition of effector function of T-cells happened in step 7.

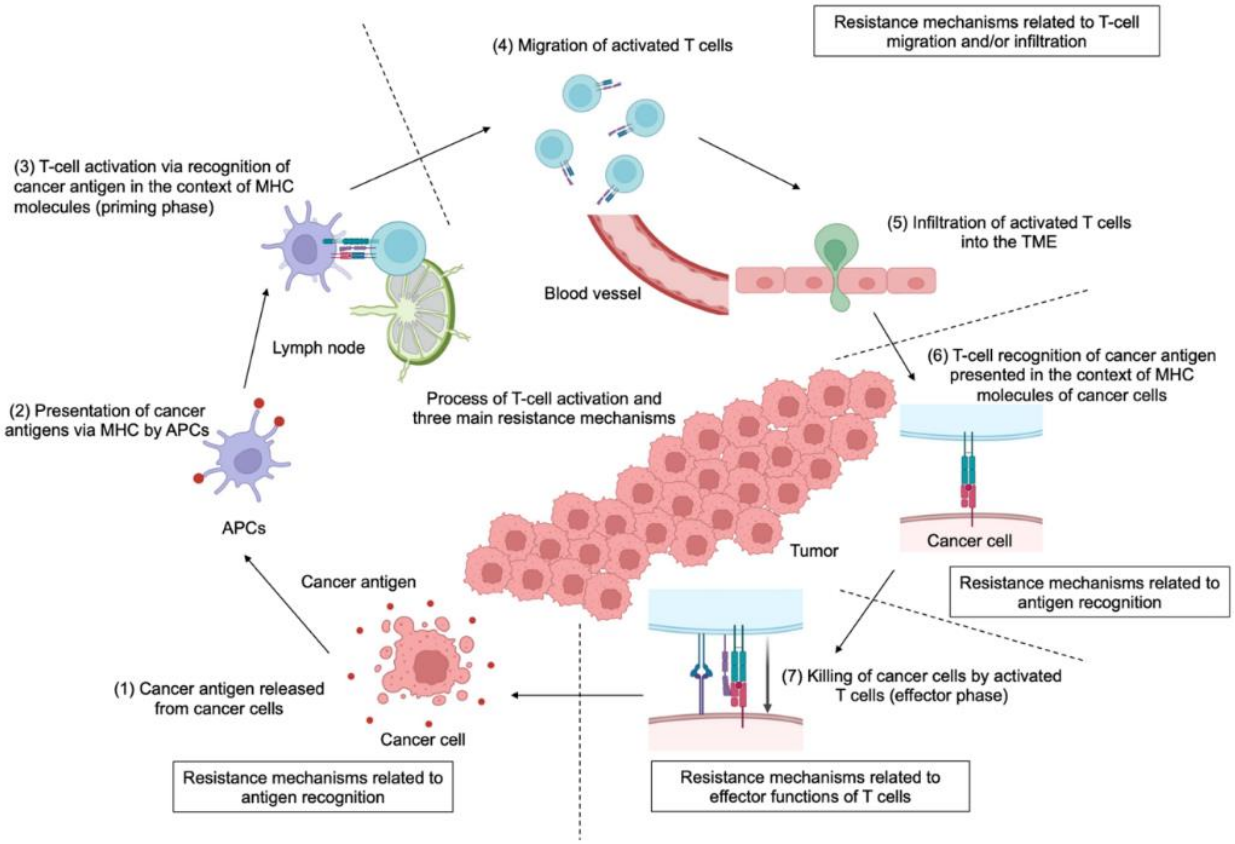


Figure 2. Process of T-cell activation and three main mechanisms that inhibit the process and lead to resistance to ICIs. The process that how T-cells play a role in killing the cancer cells is illustrated, while mechanisms of resistance are divided into possible factors that may inhibit the steps in T-cell activation [13].

4. Limitations and Future prospects

First and foremost, the limitations of the literatures included in this paper embody the prevalence situations of patients and their response to the ICIs in most trials differed from each other. Objectively, it is hard or even impossible to successfully control such variables. The limitation of this paper is mainly generated because the results from the literatures are summarized qualitatively with few

quantitative ICI treatment-related indicators, while no meta-analysis was carried out due to the diversity of the included papers.

The potential of ICI development in the next 5-10 years and ways that the effectiveness of ICI therapy can be improved involves the ways to improve the safety profile, lower adverse events, reduce resistance to ICIs, design and develop more effective inhibitors. While ICI therapy has shown remarkable efficacy in treating various cancers, it is not without its challenges. Managing long-term adverse events and addressing resistance are active areas of research to improve the safety and effectiveness of immunotherapy for cancer patients.

5. Conclusion

The application of ICIs represents a groundbreaking advancement in cancer therapy. The potential to revolutionize cancer treatment has been demonstrated by the success of CTLA-4 and PD-1/PD-L1 inhibitors in treating various cancers, including but not limited to melanoma, NSCLC, and HCC. Results of treatment have shown considerable improvement in PFS, OS, and other indicators for treated patients, bringing renewed hope to patients suffering from advanced malignancies. However, while ICIs represent a monumental advancement, challenges persist, including a series of toxicities triggered by irAEs, and resistance to ICIs. Therefore, there is a great need to build up vigilant management and monitoring systems during ICIs treating process. Meanwhile, the importance of developing broader combination strategies with other therapeutic modalities such as chemotherapy and radiotherapy. Research into innate immune cells offers promise for enhancing anti-tumor effects and expanding the utility of immunotherapy. As we look ahead, ongoing investigation and innovation in the field of immune checkpoint inhibitors hold the potential to further transform cancer care, providing hope for countless patients worldwide.

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