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Evaluating the Efficacy of Immune Checkpoint Inhibitors Across Different Cancer Types: Focusing on Lung Cancer, Breast Cancer and Melanoma

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Abstract. Lung cancer, breast cancer, and melanoma are three of the most studied cancers at the moment due to their high incidence and mortality rates. Recently, immune therapies, especially immune checkpoint inhibitors (ICI) drugs, are being studied and developed to cope with these cancers. Clinical trials have shown significant improvements in cancer treatments after using the ICI drugs including PD-1/PD-L1 and CTLA-4 inhibitors. This review covers the efficacy of using different ICI drugs in treating NSCLC, TNBC, and melanoma. The results demonstrated overall improvements in OS, PFS, and ORR rates in patients who received ICI treatments. Besides, some approved combination therapies show even more significant improvement in the therapeutic effects of ICI drugs. However, there are still challenges, such as the toxicity of ICI drugs, left to be solved. This review provides insights for future studies on further development of combined therapies and personalized treatments. The aim is to minimize the adverse effects of ICI and increase the efficacy of the drugs at the same time.

Keywords: Immunotherapy; immune checkpoint inhibitor; tumor microenvironment; programmed cell death protein 1.

1. Introduction

Cancer is considered one of the main causes of mortality nowadays. Besides the existing therapies, including chemotherapy, radiotherapy, and targeted therapy, immunotherapy has become a leading topic and treatment of cancers. As a part of the immune system, the immune checkpoints (ICs) have been focused on as one of the most important aspects of developing immunotherapies. The immune checkpoint inhibitors (ICI) upregulate the function of the immune system in the tumor microenvironments (TME). In the TME, some receptors and ligands on the immune cells, such as cytotoxic T cells, can be activated by tumor cells which inhibits the immune response towards the tumor [1]. The upregulation of the activity of the immune system is achieved by mainly inhibiting either the receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or inhibiting the ligands such as programmed death-ligand 1 (PD-L1) [2].

Besides what ICI has contributed to treating cancers, the efficacy of this treatment varies across different types of cancers. The differences arise from different TME, the toxicity of ICI, and the severity of cancer, leading to different responses of the immune system and thus the ICs [3]. These factors and differences are acting as challenges for ICI as well. Significantly, numerous research has been done on using the ICI to treat lung cancer, breast cancer, and melanoma. Several biomarkers in this research, such as overall responsive rates (ORR) indicate the efficacy of the ICI [4]. Moreover, research has also been done on combined therapies, indicating a combination of ICI and other approved cancer therapies such as chemotherapy and radiotherapy. These combination therapies aim to enhance and improve the efficacy of cancer treatments and lead to differences in ICI treatment efficacy at the same time [5].

Overall, this literature review goes over the mechanisms of some of the basic ICs and ICIs in TME. Three common types of cancers, including lung cancer, breast cancer, and melanoma, are used as

examples to analyze the efficacy of ICI in treating different types of cancers. Their ORR to ICI diverges to an obvious extent. Simultaneously, combination therapies are covered in order to provide a more comprehensive comparison of cancer treatments. Furthermore, future research directions and clinical applications will be presented. With a deeper analysis of these aspects of ICI, improved treatments in immunotherapy in clinical use can be expected in future developments.

2. Mechanism of Action of ICIs

2.1. Immune Checkpoints: PD-1/PD-L1, CTLA-4

PD-1, identified in 1992, is a kind of inhibitory protein receptor commonly seen on the surface of immune cells such as T cells, natural killer (NK) cells, dendritic cells (DC), etc., while PD-L1 is the ligand that is complementary to PD-1, and it can be found on both the tumor cells and the immune cells including T cells, B cells, and DCs. The binding of PD-L1 to PD-1 inhibits the activation of the immune cells, such as cytotoxic T cells. This is achieved by the recruiting of SH2 domain-containing protein tyrosine phosphatase-2 (SHP-2) which dephosphorylates the signaling molecules [6]. As a result, the binding can either be beneficial, since the inhibition of T cell activation prevents autoimmune responses and inflammations, or potentially harmful when immune responses are inhibited when tumor cells are presented. Specifically, PD-L1 expressed on the surface of the tumor cells aims to enable the tumor cells to escape from the anti-tumor responses in the TME. Pembrolizumab and Nivolumab are commonly used as anti-PD-1 or PD-1 ICIs, while Atezolizumab and Durcalumab are anti-PD-L1 or PD-L1 ICIs [2].

Similarly, CTLA-4 is another type of commonly seen protein receptor acting as an immune checkpoint molecule expressed on T cells. It downregulates the immune responses as PD-1 and PD-L1. Cluster of Differentiation 28 (CD28) has to be mentioned when talking about the mechanism of CTLA-4 since they are homologous receptors and are structurally similar to each other [7]. They share a similar ligand called B7. Bindings of B7-1 or B7-2 on the CD28 or CTLA-4 can either regulate T cell activities [8]. However, CD28:B7 binding increases T cell activities, while CTLA-4:B7 binding has inhibitory effects on T cells [7]. In addition, CTLA-4 is more competitive in binding to B7 compared to CD28 [7]. As a result, when a similar amount of CTLA-4 and CD28, and a limited number of B7 are presented in the environment, an inhibitory effect on T cells is more easily and possible to be triggered to have an immunosuppressive effect.

2.2. ICIs in TME

In the TME, tumor cells with antigens presented on their surfaces can be easily recognized and eliminated by the immune cells such as cytotoxic T cells. However, some tumor cells without presented antigens cannot be recognized and can escape the immune responses which enables them to continue to survive at the cancer site or even undergo metastasis. Therefore ICI drugs are used to cope with these situations by blocking the immunosuppressive mechanisms carried out by the tumor cells in the TME. As mentioned in the previous section, there are two main pathways of immune checkpoints in TME: the PD-1/PD-L1 pathway and the CTLA-4 pathway. Corresponding ICI drugs to these pathways bind to either the receptors or the ligands to occupy the binding sites. Therefore, the inhibitory effects of the T cells cannot be activated. As more T cells are activated due to the intake of ICIs, they can recognize and carry out their functions against the tumor cells.

3. ICIs in Lung Cancer

3.1. Approved ICIs for Lung Cancer

Lung cancer is the most common cancer in the world in terms of incidence and mortality rates. As a result, it is chosen as one of the research objects. Researchers have done many studies on non-small cell lung cancer (NSCLC) as a usual lung cancer, and anti-PD-1/PD-L1 antibodies are being used in clinics, while the CTLA-4 inhibitor, ipilimumab (anti-CTLA4), is approved by FDA to treat lung cancers at the moment [9]. In clinical practice, ICIs acting as PD-1 inhibitors include nivolumab and pembrolizumab, while PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab. These drugs block either the PD-1/PD-L1 or the CTLA-4 inhibitory pathways by binding to the binding sites of the receptors or the ligands, which then upregulate the activity of T cells in the TME. The ICI drugs mentioned above are all approved by the FDA for treating solid tumors [10,11]. This section will use NSCLC as an example to discuss the efficacy of ICIs treating NSCLC

3.2. Clinical Efficacy and Response Rates

Some PD-1/PD-L1 inhibitors commonly used to treat NSCLC include nivolumab, pembrolizumab (anti-PD-1), and atezolizumab. According to the research conducted by Benjamin Herzberg, Meghan J. Campo, and Justin F. Gainor [4], these patients who received PD-1/PD-L1 inhibitors immunotherapy had a significant improvement in OS.

Take Nivolumab trials as an example, to be more specific, according to several key clinical trials, it demonstrated significant efficacy in treating patients with previously treated NSCLCs. For patients who had been diagnosed with squamous NSCLC, the OS improved from 6.0 months (docetaxel) to 9.2 months. For patients who had been diagnosed with nonsquamous NSCLC under similar conditions, the OS improved from 9.4 months (docetaxel) to 12.2 months [4]. Clinical trials of pembrolizumab and the PD-L1 inhibitor atezolizumab showed the same trends.

4. ICIs in Breast Cancer

4.1. Approved ICIs for Breast Cancer

Ipilimumab, an anti-CTLA4, was the first ICI that gained the FDA approval. It functions by blocking the binding between CTLA-4 and the B7 molecules. Therefore, the B7 molecules are free to bind with CD 28, which hence decreases the immunosuppressive responses of the T cells in the TME [12]. Besides, tremelimumab is another CTLA-4 inhibitor used for breast cancers, and it shares the same mechanism of reducing immunosuppressive effects of T cells as ipilimumab [12]. Similar to ICIs treating lung cancers, nivolumab, and pembrolizumab are widely used in breast cancer as PD-1/PD-L1 inhibitors as well [12].

4.2. A Clinical Efficacy and Response Rates

In order to carry out more accurate comparisons with treatment of the other cancers, this section will focus on analyzing the efficacy of pembrolizumab, nivolumab, and atezolizumab.

According to several key clinical trials from the research conducted by Nicola Gaynor, John Crown, and Denis M. Collins, different ICI drugs showed varying results in OS, progression-free survival (PFS), objective response rate (ORR), and relapse-free survival (RFS) under respective treatment conditions in treating triple-negative breast cancer (TNBC) [13]. Without comparison groups, the median OS of the pembrolizumab treatments are 10.2 (metastatic) and 9 (advanced) months, and the PFS is 1.9 (metastatic) and 2 months (advanced) [13]. When TNBC is treated with nivolumab, the ORR is 20%, while the ORR of using atezolizumab, 24%, is the highest among the three ICI drugs discussed in this section [13]. Another research has demonstrated data and information about TNBC as well [14]. However, the overall ORR of pembrolizumab treatment is higher than that of atezolizumab [14].

5. ICIs in Melanoma

5.1. Approved ICIs for Melanoma

FDA-approved ICI drugs used to treat melanoma include ipilimumab, pembrolizumab, and nivolumab [3]. It is important to point out that ipilimumab, used to treat metastatic melanoma, was one of the first FDA-approved ICI drugs in 2011, followed by pembrolizumab and nivolumab, etc. [11]. This is a milestone for the entire use of immunotherapy in treating cancer [11].

5.2. Clinical Efficacy and Response Rates

According to the same study [13], the efficacy of pembrolizumab, nivolumab, and ipilimumab vary in treating melanoma under different conditions.

When pembrolizumab is used to treat metastatic melanoma as the main treatment, patients have a median OS of 32.7 months compared to patients treated with ipilimumab with an OS of 15.9 months. Similarly, these patients have a median PFS of 8.4 months compared to those who were treated with ipilimumab with 3.4 months of PFS. The ORR is 33.3% for those patients, which is higher than the 11.9% ORR of the comparison group [13]. According to the trial where pembrolizumab is used as adjuvant therapy, the RFS is 75.4% which is higher compared to the comparison group which takes placebo with RFS of 61.0% [13].

Similar trends are illustrated when nivolumab is used as either the main or adjuvant therapy to treat melanoma, while the differences between the experimental groups and comparison groups (ipilimumab) are smaller than those of pembrolizumab. Even though ipilimumab is used as comparison groups in these trials, and the trials shows less efficacy compared to pembrolizumab and nivolumab, it still has relatively high OS, PFS, and ORR [13], indicating it being effective in treating melanoma.

6. Combination Therapies

6.1. Chemotherapy

FDA approved combination of chemotherapy and ICI drugs include but not limited to pemetrexed and platinum chemotherapy with pembrolizumab as the immunotherapy, carboplatin and nabpaclitaxel chemotherapy with atezolizumab as the immunotherapy to treat NSCLC; nabpacilitaxel chemotherapy and atezolizumab as the immunotherapy to treat breast triple negative cancer, etc. [15].

Overall, the combined therapy of chemotherapy and ICI drugs have clinical benefits of increasing patients' rates of OS. For example, patients with NSCLC in trial using pemetrexed+platinum as the chemotherapy and pembrolizumab as the immunotherapy has an OS of 69.2% in a 12 months period compared to 49.4% of the comparison group. Similar trials are demonstrated in other NSCLC and TNBC trials [15]. As a result, it can be concluded that the combination of chemotherapy with ICI drugs can maximize the efficacy of both therapies.

6.2. Targeted Therapy

In the same study, it is illustrated that ICI drugs can be combined with targeted therapies, such as vemurafenib and cobimetinib targeted therapy combined with the use of atezolizumab to treat patients with BRAF V600(+) advanced melanoma [15]. In this trial, the PFS of the combined therapy is increased from 10.6 months to 15.1 months compared to the comparison group. Therefore, combined therapies of ICI drugs and targeted therapies is beneficial in treating melanoma, while there is limited data in the efficacy in NSCLC and breast cancers.

7. Comparison of Efficacy

7.1. Differences in Efficacy and Response Rates

The efficacy of ICI drugs varies among different cancers. In the NSCLC trials, ICIs has shown improvements in OS. On the contrary, the efficacy of ICIs treating breast cancer, or TNBC, is more variable using different drugs under different conditions. For melanoma, perbrolizumab is the most commonly used ICI drug, and shows relatively high efficacy in clinical trials.

The efficay of ICI drugs can be further improved by combination therapies. The data shows an improvement in OS when NSCLC and TNBC are treated by ICI drugs combining with chemotherapy. When combined with targeted therapy, ICI increases the PFS of patients with melanoma.

7.2. Toxicity and Adverse Effects

Even though most of the clinical trials show positive results in using ICI drugs and combination therapies to treat different cancer types, there is still a larger proportion of patients in the sample responded or had an obvious beneficial effect on the cancer after receiving the treatments.

Besides the unresponsiveness, ICI drugs used in immunotherapy are leading to toxicity and adverse effects as well. A key concept of immune-related adverse events (irAEs) is used to describe these adverse effects. Common irAEs include skin toxicity, endocrine toxicity, gastrointestinal toxicities, etc. [16]. According to a study, using nivolumab to treat melanoma leads to skin toxicity in 18.2% of patients, and using a combination of ipilimumab and nivolumab leads to endocrine toxicity up to 40.2% of the patients, even though this combination has the highest OS at the same time [16]. In addition, patients received pembrolizumab has both skin and endocrine toxicities in 16% which is much higher than those who received ipilimumab at 4%, despite the higher OS [16].

In regard to ICI drugs treating NSCLC, pembrolizumab leads to endocrine toxicity in 20.7% of patients compared to traditional chemotherapies in 3.3% of patients. Moreover, using pembrolizumab even leads to colitis while none of the patients receiving chemotherapies have this problem according to the trial [16]. Furthermore, nivolumab leads to higher rates of irAEs, such as skin, gastrointestinal, hepatic, endocrine, and pulmonary toxicities, in treating melanoma compared to NSCLC [16].

8. Conclusion

This review analyzed the efficacy of ICI drugs, such as nivolumab, perbrolizumab, atezolizumab, etc. in treatments of different cancer types including NSCLC, TNBC, and melanoma. While the results of efficacy vary with different drugs used, tumor types, and different research conditions such as TME, there is an overall improvement in treatment of cancers on a small-scale of the sample. For combination therapies, the improvement of the ICI treatments is more remarkable.

These results emphasize the significance of further research and development on ICI therapies. For instance, since the efficacy of ICI treatments is only seen in a small proportion of patients, while the rest have no obvious changes, future research can focus more on personalized approaches, which improves the precision of ICI drugs. Referring to the toxicity and adverse effects caused by ICI drugs, researchers should focus on the combination of ICI with targeted therapies to minimize the effects of the adverse effects of ICIs on healthy cells and tissues. Additionally, measures that are able to deal with these adverse effects should be discussed as well.

Due to limited data and resources, this review only analyzed three common cancer types, and limited number of ICI drugs. Besides, most of the research and data in this review only allows comparison of the efficacy of different drugs in treating the same type of cancer, instead of comparing the efficacy of the same drug in treating different cancer types.

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