Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Immune Checkpoint Inhibitors: Challenges and Potential Strategies

Tianyu Ge
Tangshan No.2 High School, Tangshan, China
LDONA35414@my.sunywcc.edu

Abstract. With the rapid development of science and technology, the treatment of cancer is also constantly being upgraded, but the number of cancer patients continues to grow, this has led to an increasing emphasis on such diseases. Therefore, immune checkpoint inhibitors have become the focus of our research today. In tumor cell proliferation, immune checkpoints develop as one of the ways to assist tumor cells in immune escape, so the use of immune checkpoint inhibitors can activate T cells, reduce T cell function exhaustion and inability, and achieve the purpose of killing tumor cells. In recent years, the results of PD-1, PD-L1 and CTLA-4 inhibitors have also been widely used in the treatment of patients, new treatments based on these inhibitors are also emerging. Despite the success of the ICIs in some ways, however, the researchers still found a number of factors that hindered its continued development, for example, research gaps with overall low response efficiency, therefore, new treatments need to be better improved and designed. Consequently, the research topic of this paper is the problems encountered by immune checkpoint inhibitors in this field and their solutions.

Keywords: Immune checkpoint inhibitors; immunotherapy; immune-related adverse events; inflammatory toxicity; combination therapy.

1. Introduction

Cancer is one of the deadliest diseases in the modern world. According to the World Health Organization (WHO) , by the end of 2022, the number of cancer patients in 185 countries and regions all over the world is about 20 million cases of cancer [1]. The WHO released a report saying, by 2050, there will be about 35 million cases of cancer [1]. The last decade has witnessed tremendous advances in the treatment of cancer through immunotherapy. Through a large number of research findings, one of the most promising ways to achieve anti-cancer immunity is to block the immune checkpoint pathway. Immune checkpoint therapy is a type of treatment that uses immune checkpoint molecules to modulate the response of the immune system. The side effects of treatments such as chemotherapy and radiotherapy become more pronounced, researchers have taken a deeper look at the field of immunotherapy, in 2011, this treatment was introduced as an alternative with fewer side effects and more effective results [2]. Checkpoint inhibitors currently approved by the United States Food and Drug Administration mainly include CTLA-4 inhibitor (Ipilimumab), PD-1 inhibitors (Nivolumab, Pembrolizumab and Cemiplimab),and PD-L1 inhibitors (Atezolimumab, Durvalumab and Avelumab) [2]. Although checkpoint inhibitors have the advantages of wide anti-tumor effects, long-lasting efficacy, low adverse reaction rate, and significant effect of combination therapy, however, it still has shortcomings such as low overall effective rate, limited applicable population, high treatment cost, and unique adverse reactions [3]. This review summarizes current challenges to immune checkpoint inhibitors and provides potential strategies to overcome the limitations.

2. Immune Related Adverse Events (iraes) of Checkpoint Inhibitors

In all regimens for the treatment of advanced malignancies, immune checkpoint inhibitors have become the primary choice. However, there are some drawbacks to this treatment. It is noted in the report of the United States Academy of Dermatology, among all immune-related adverse events caused by nonspecific immune activation, one of the most commen is the effects on the skin and its related sites [4]. A different inflammatory response is one of the many cortical immune-related

adverse events, one of the more common subtypes includes paules, pruritus and psoriasis [4]. Such events usually occur in the early times, macular eruption within the first 6weeks after the initial immune checkpoint inhibitor dose. The presentation of rashes varies greatly depending on the severity of the rash [4]. Among them, PD-1/PD-L1 inhibitors can cause globular pemphigus rash, vitiligo-like skin pigmentation/depigmentation, and psoriatic rash (Fig.1) [4].

With the continuous development of irAEs, side effects range from mild rashes to severe colitis to even life-threatening myocarditis [5]. According to relevant reports, new autoimmune diseases are induced after checkpoint therapy, such as type I diabetes, diabetes associated with ICIs is rare in patients, it is present only in less than 1% of post-treatment patients, these disease occur mainly in the skin and gastrointestinal tract, such as diarrhea, colitis, hepatitis, cholecystitis, cholangitis and pancreatitis [6-8]. Besides, patients may also experience symptoms of fatigue, this symptom may not only occur during the treatment process, it will also occur after the treatment is completed [8]. Other manifestations of ICI-related toxicity include fatigue, such as neurotoxicity and anemia [8]. ICI therapy works differently in every patient, this mainly depends on the patient's own genetic background and family genetic history [9].

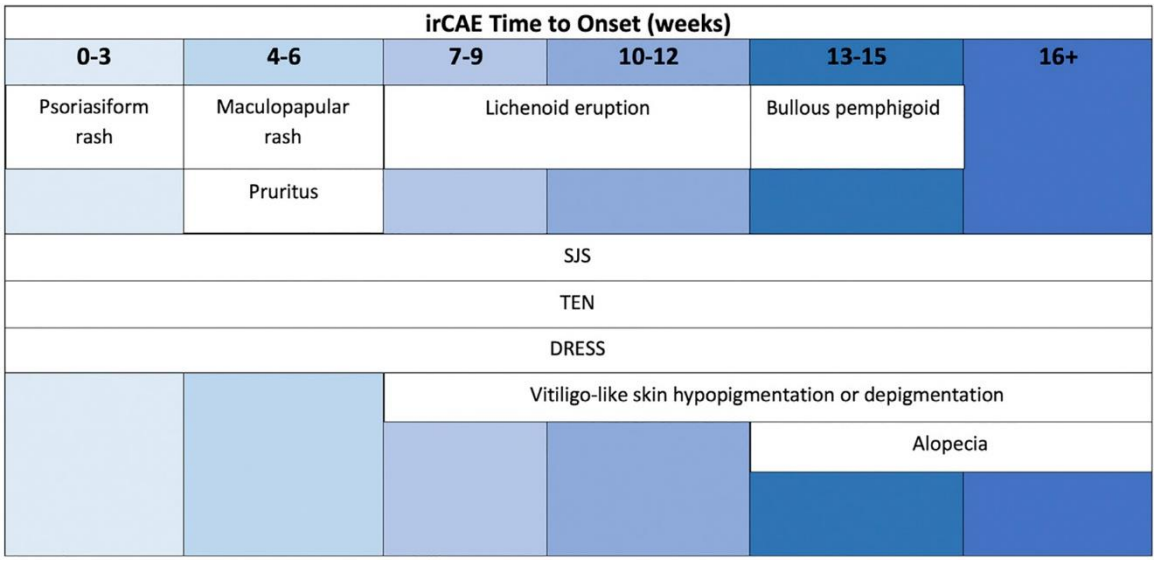

Figure 1. Time to onset of immune-related cutaneous adverse events [4]

3. Resistance of Checkpoint Inhibitors

While ICI therapy has improved the prognosis of patients with multiple cancer types, however, only a small percentage of patients treated with ICIs showed sustained responses [5]. Among all tumor types, melanoma patients have the highest objective response rate to ICI therapy, however, 60-70% of melanoma patients do not respond objectively to anti-PD-1 therapy, among the remaining 30-40% of patients with such tumors who have an objective response to ICI therapy, there are also a large number of patients who show tumor recurrence and related lesions after treatment, resistance can even develop [5]. After an initial response to PD-1/PD-L1 blockade, most patients develop acquired resistance [7].

Resistance mechanisms can be classified in a variety of ways, it is generally divided into primary and acquired [5]. Both primary and acquired mechanisms are involved in a heterogeneous to immune checkpoint blockade [7]. However, in clinical definition, there has never been a uniform definition. Until 2020, the United States National Institutes of Health published a definition of resistance to PD-1/PD-L1 inhibitors after ICI treatment was discontinued. Definition, in different cases, it can be divided into primary resistance, secondary resistance, and progression after discontinuation of treatment [9]. After ICI treatment is discontinued, the definition of resistance includes resistance that is not related to toxicity. Patients who will develop primary drug resistance, usually there is no benefit in the ICI treatment, later, the follow-up treatment was not completed due to various reasons. A panel

of experts said, it does not matter when the recurrence is, any patient who relapses after an initial objective response can be considered acquired resistance [10].

4. Toxicity

In the development of all checkpoint inhibitor therapies, inflammatory toxicity was an important factor hindering its development during this decade [11]. The toxicity induced by ICIs is actually autoimmune, it is called irAE [6]. These irAEs can interfere with any organ in the human body in any way that is unpredictable to humans, it can cause inflammation and toxicity in endocrine and other organs [6]. Chief among these is hypothyroidism, it is reflected in about 10-20% of the patients, temporary thyroxication usually begins with a temporary onset of thyroidism, generally, it will persist after the end of the treatment process. These toxicities affect the human body differently, otherwise, it can lead to a delay or termination of treatment, in severe cases, it will endanger the life safety of patients. These toxicities also provide avenues for in-depth study of human immunomodulatory mechanisms [11].

Using different ICI therapies, can lead to a different distribution of irAEs in the human body and its effects on the human body. For the most part, CTLA-4 blockade is more toxic during treatment than PD-1 blockade, especially in intestinal inflammation and pituitary gland inflammation. But in thyroiditis, are often more closely associated with PD-1 blockade. On the side, combination immunotherapy is much more toxic than treatment with CTLA-4/PD-1 alone, usually, the risk of toxicity with ICI therapy is stacked. Histopathological considerations, CTLA-4 blockade was similar to the toxicity induced by PD-1/PD-L1inhibitors, there is no significant difference [11]. Clinically speaking, it may be that the organ of onset and the severity of the disease determine the treatment of irAEs, are not the CTLA-4, PD-1, and PD-L1 inhibitors used in the treatment [11].

5. Potential Strategies

Immune checkpoint inhibitor therapy has brought cancer immunotherapy to a new stage, however, there are drawbacks to this type of treatment, it does not benefit all the patients. In the midst of this, one of the main problems is the avoidance immune response of the tumor microenvironment (TME), thus was born the ability to be immunosuppressed. Furthermore, one of the main factors limiting the efficacy of ICI therapy is tumor-associated hypoxia. There is also a causal relationship between these two factors, due to the presence of macrophages associated with the immunosuppressive capacity of the tumor microenvironment, as a result, the lack of oxygen in the tumor is more severe, finally, the therapeutic effect of ICI therapy is not obvious [12]. These reasons have driven the creation of combination therapies, so far, many drugs have been discovered that may help in enhancing the efficacy of ICI therapy, this also includes non-anticacer drugs. New treatments have followed, such as metering therapy, epigenetic therapy, and radiation therapy [12]. Metering therapy replaces traditional chemotherapy, compared to chemotherapy, there are significant improvements in the immune response and reduced resistance to treatment. Some drugs that were previously used for chemotherapy treatment , such as paclitaxel, etoposide, and methotrexate, it is now widely used in metered chemotherapy for various types of cancer [12].

As indicated in some studies, the microscopic effects after radiation therapy are slightly different from those of prior immunotherapy. Radiation therapy is achieved by activation of latent substances in the tumor, the TAM is polarized to the M2 phenotype, immunosuppressive TME is then enhanced. In addition to these drugs that are applied to the treatment, there are also drugs that are not applied to treatment but are used for research, some of them are used in clinical trials, has played an important role [12].

6. Conclusion

The advent of immune checkpoint inhibitors offers new hope for curing cancer, it provides an effective tool for researchers in the field of cancer, the efficacy of ICI therapy has also evolved over the past decade. In this review, through the collection of various literature, in terms of immune-related adverse events, drug resistance, toxicity, and potential srategies, this paper summarizes the challenges that immune checkpoint inhibitors still need to experience and the results that can be achieved in the future. CTLA-4, PD-1, and PD-L1 inhibitors are the most widely used and most obvious therapeutic inhibitors of all inhibitors. It is not harmless, new diseases may also develop after treatment ends. Some patients may receive such treatments, however, some patients are not physically suitable for this treatment. Among patients who treated with immunotherapy, only a few cases can be cured. At present, immunotherapy used in treatment still has problems such as low effective rate and small scope of applicable population, therefore, immunotherapy is not yet complete, there is no one dominant treatment yet. The researchers are still working to break through these obstacles.

References

[1] World Health Organization (WHO). Global cancer burden growing, amidst mounting need for services. February 1, 2024. Retrieved from: https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services.

[2] Shiravand, Y., Khodadadi, F., Kashani, SMA. et al. Immune Checkpoint Inhibitors in Cancer Therapy. Current Oncology 29, 3044-3060 (2022).

[3] Marin-Acevedo, JA., Kimbrough, EO., Lou, YY. Next Generation of Immune Checkpoint Inhibitors and Beyond. Journal Hematology Oncology 14, 45 (2021).

[4] Amaris, N. Geisler., Gregory, S. Phillips., Dulce, M. Barrios. et al. Immune Checkpoint Inhibitor–related Dermatologic Adverse Events. Journal of the American Academy of Dermatology 83 (5), 1255-1268 (2020).

[5] Sreya, Bagchi., Robert, Yuan., Edgar, G. Engleman. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. Annual Review of Pathology: Mechanisms of Disease 16, 223-249 (2021).

[6] Wright, J.J., Powers, A.C., Johnson, D.B. Endocrine Toxicities of Immune Checkpoint Inhibitors. Nat Rev Endocrinol 17, 389-399 (2021).

[7] Luisa, Barrueto,. Francheska, Caminero,. Lindsay, Cash. et al. Resistance to Checkpoint Inhibition in Cancer Immunotherapy. Translational Oncology 13 (3), 100738 (2020).

[8] Brahmer, JR., Abu-Sbeih, H., Ascierto, PA. et al. Society for Immunotherapy of Cancer (SITC) Clinical Practice Guideline on Immune Checkpoint Inhibitor-related Adverse Events. Journal for Immunotherapy of Cancer 9, 34172516 (2021).

[9] Antonio Passaro et al., Managing Resistance to Immune Checkpoint Inhibitors in Lung Cancer: Treatment and Novel Strategies. Journal of Clinical Oncology 40, 598-610 (2022).

[10] Kluger, HM., Tawbi, HA., Ascierto, ML. et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. Journal for Immunotherapy Cancer 8. 32238470 (2020).

[11] S. Jennifer, Wang., Stephanie, K. Dougan., Michael, Dougan. Immune mechanisms of toxicity from checkpoint inhibitors. Trends in Cancer 9, 543-553 (2023).

[12] Varayathu, Hrishi., Sarathy, Vinu., Thomas, Beulah, Elsa. et al. Combination Strategies to Augment Immune Check Point Inhibitors Efficacy - Implications for Translational Research. Frontiers in Oncology 11, (2021).