

# Side Effects and Research Progress of Immune Checkpoint Inhibitors

Yichen Li\*

School of Health Science and Engineering, University of Shanghai for Science and Technology  
Shanghai, 200093, China

\* Corresponding author: 2135053412@st.usst.edu.cn

**Abstract.** Immune checkpoint inhibitor (ICI) is a new type of tumor treatment drug, also known as immunotherapy drug. They target "checkpoint" molecules in the body's immune system that prevent immune cells from attacking cancer cells. They target "checkpoint" molecules in the body's immune system that prevent immune cells from attacking cancer cells. The use of immune checkpoint inhibitors can help control or treat certain types of cancer by promoting the restoration of inactivated immune cells and enhancing the immune system's ability to attack. -This article focuses on skin reactions, immune pneumonitis, and adverse reactions in the thyroid and digestive tract. Through the analysis of recent relevant research, this question summarizes several different side effects, their causes and treatments. Although there are many treatments to deal with the side effects of this drug, it is important to note that the side effects of this drug are not always well understood. There are many treatments to deal with the related side effects, these side effects are still a barrier to the current use of ICIs. Future development directions should focus more on the development of ICIs. directions should focus more on the development of new targets, optimization of drug pharmacokinetics, and alleviation of side effects caused by ICIs.

**Keywords:** ICIs; skin-related adverse effects; checkpoint inhibitor pneumonia; thyroid-related adverse effects; gastrointestinal-related adverse effects.

## 1. Introduction

Cancer remains one of the leading causes of human death worldwide, and due to the limitations of conventional treatments and the potential of immunotherapy, attention is gradually focusing on the research and application of immune checkpoint inhibitors. It has been nearly a century since the immune system was first observed to reject human cancers, and adaptive immunity can be harnessed to treat cancer, as demonstrated by immune checkpoint inhibitors. Immune checkpoint inhibitors have not only shown significant efficacy in approved cancers such as non-small cell lung cancer and melanoma, but have also shown potential in other cancers such as triple negative breast cancer [1].

Maculopapular rash is a prevalent immune-related adverse reaction affecting the skin. It affects 15% and 25% of patients treated with anti-PD-1 monotherapy and after anti-CTLA-4 and anti-PD-1/PD-L1 combination therapy, respectively [2]. The symptoms usually appear a few weeks after treatment and its severity is dependent on the dosage of the medication, worsening as the treatment cycle progresses. If a sufficient dosage of tumour therapy is to be maintained, it is crucial to detect and manage pemphigus promptly. Pemphigus is commonly marked by extensive duration and gradual recovery, with remission frequently attained within 3 to 10 weeks. Thus, whenever an irregular, persistent and recurring maculopapular rash is encountered, skin biopsy should be contemplated to validate the diagnosis [3]. The mechanism of action of immune checkpoint inhibitors is to increase the ability of the body's immune system to attack tumour cells by inhibiting the action of immune checkpoint molecules. These checkpoint molecules include CTLA-4, PD-1 and PD-L1. The most important immune checkpoints are the inhibitory T cell regulator cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Antibodies that block these checkpoints, such as ipilimumab (anti-CTLA-4), pembrolizumab and nivolumab (anti-PD-1), and atezolizumab and durvalumab (anti-PD-L1), have shown significant efficacy in cancer patients.

However, with the widespread use of immune checkpoint inhibitors, an increasing number of clinical practices and studies have found that immune checkpoint inhibitor therapy can not only lead to immune-related side effects, such as immune-reactive dermatitis and immune-mediated pneumonitis, but can also trigger the development of autoimmune diseases, such as thyroid abnormalities, diabetes mellitus and rheumatoid arthritis.

## **2. Adverse Skin Reactions**

Adverse skin reactions are a frequent consequence of tumor immunotherapy, with immune-related cutaneous adverse reactions being the most common type. This occurs a few weeks after treatment, as per clinical data [2]. Immune-related skin reactions were detected in 90% and 70% of patients treated with CTLA-4 and PD-1/PD-L1 inhibitors, respectively. Moreover, the possibility of immune-associated cutaneous adverse reactions was almost 100% among patients who were treated with combination therapy [3]. These medicines work by improving T cell's capacity for recognition and elimination of cancerous cells. However, while ICIs improve the anti-tumour activity of T cells, they may also inappropriately heighten the immune response in the body's own healthy tissues, causing immune-mediated adverse reactions which can affect several organs and systems.

### **2.1. Maculopapular Rash**

Maculopapular rash is a prevalent immune-related adverse reaction affecting the skin. It affects 15% and 25% of patients treated with anti-PD-1 monotherapy and after anti-CTLA-4 and anti-PD-1/PD-L1 combination therapy, respectively [4]. The symptoms usually appear a few weeks after treatment and its severity is dependent on the dosage of the medication, worsening as the treatment cycle progresses. If a sufficient dosage of tumour therapy is to be maintained, it is crucial to detect and manage pemphigus promptly. Pemphigus is commonly marked by extensive duration and gradual recovery, with remission frequently attained within 3 to 10 weeks. Thus, whenever an irregular, persistent and recurring maculopapular rash is encountered, skin biopsy should be contemplated to validate the diagnosis [5].

### **2.2. Itching (Pruritus)**

Pruritus affects between 14% and 47% of patients treated with CPI and is severe in 1% to 3% of cases. Not all patients who experience pruritus will develop a rash, and if a rash does occur, it is typically found on the trunk and extremities, with rare occurrences on the head and neck [6]. Both the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) guidelines classify pruritus into three grades and suggest proper management when patients undergo tumor immunotherapy. In both guidelines, appropriate cleansing and use of moisturizers are recommended to mitigate itching. Blocking of omalizumab by immunoglobulin E (IgE) has been demonstrated to reduce the itching associated with immune checkpoint inhibitors [7].

Furthermore, immune-related cutaneous adverse reactions consist of erythrodermatitis, psoriasis-like lesions, vitiligo, and various rare conditions. Therefore, while the majority of immune-related adverse skin reactions are not fatal, they can significantly affect the well-being of patients undergoing immunotherapy. As a result, healthcare practitioners must promptly recognize and manage diverse immune-related skin reactions for effective tumour immunotherapy and a better quality of life.

## **3. Checkpoint Inhibitor Pneumonitis (CIP)**

According to relevant research, approximately 3-6% of patients treated with ICI will develop CIP with higher incidence rates observed in non-small cell lung cancer patients compared to other patients. Moreover, studies have demonstrated that the incidence rate of CIP is impacted by the specific type of drug used by patients, with anti-PD-1 having a higher incidence rate than anti-PD-L1 and anti-CTLA-4 [8]. Several studies have demonstrated a clear link between the incidence of chemotherapy-induced peripheral neuropathy (CIP) and the use of combination therapy, as well as immuno-targeted

or radiotherapy or a combination of two immune agents [9]. The severity of CIP is classified into grades 1-5, with slight differences between the standards of ESMO and NCCN [10]. Treatment protocols are developed based on these grades, and corresponding recommendations are provided for each grade. The pathogenesis of CIP is not completely understood, but it might entail immune dysregulation [11]. Induction of immune-related adverse reactions could increase T-cell activity aimed at antigens shared by cancerous and non-cancerous tissues [12]. This phenomenon might be linked to the onset and progression of CIP. Significant enrichment of CD8+T or CD4+T lymphocytes has been observed in the lung or bronchoalveolar lavage fluid of patients with CIP, as demonstrated by previous research [12]. During immunotherapy, lung homeostasis is altered, leading to activation of the immune response in areas with lymphocyte accumulation, such as around tumour lesions, radiotherapy fields, lung infections, cryoablation of lung metastases, and chemotherapy-induced pneumonitis. These alterations may further impact immune homeostasis, resulting in inflammatory responses, further activation of the immune system, and ultimately the induction of CIP [13]. Technical term abbreviations have been explained on first use. The language used is objective, value-neutral, formal and precise, adhering to conventional and grammatical correctness principles. The adverse effects of immune pneumonitis could considerably affect the patient's well-being, and patients, especially those with non-small cell lung cancer, ought to promptly notify their healthcare provider if they manifest respiratory symptoms, including coughing, dyspnoea, and chest pain, during immune checkpoint inhibitors therapy. The clinician shall evaluate the intensity of symptoms and may recommend additional examinations, such as a chest CT scan or pulmonary function tests, to confirm the existence of immune-related pneumonitis. In the event of an adverse event of this kind, the usage of immune checkpoint inhibitors should be reduced or halted, while other drugs may be required to manage the inflammatory reaction.

#### **4. Thyroid-related Adverse Reactions**

Comprise various conditions, such as hypothyroidism, hyperthyroidism, thyroiditis, and thyroid crises, among others. These effects could become irreversible yet challenging to identify during early-stage developments. As such, healthcare professionals should identify immune-related thyrotoxicity during clinical treatment and provide timely, appropriate treatment to patients.

The prevalence of hypothyroidism is estimated to be about 6.6%, making it the most common thyroid-related adverse effect [1]. Anti-PD-1/anti-PD-L1 drugs have a higher likelihood of causing hypothyroidism compared to anti-CTLA-4, but patients generally tolerate this side effect quite well [14]. Nevertheless, studies have demonstrated a connection between the amount of anti-CTLA-4 administered and the occurrence of hypothyroidism, with an elevated prevalence of hypothyroidism and thyroiditis being linked to higher doses [15].

Studies indicate that Hyperthyroidism is the second most frequent type after hypothyroidism [14]. It has been observed that patients are more susceptible to developing hyperthyroidism with anti-PD-1 therapy than with anti-PD-L1 therapy. However, there was no significant difference observed between the incidence of hyperthyroidism associated with the use of either anti-PD-L1 or anti-CTLA-4 [15].

The frequent use of ICIs necessitates increased attention to resulting thyroid-related adverse effects. Physicians in oncology and endocrinology should foster interdepartmental cooperation for the timely identification of related conditions and provision of treatment to patients.

As per the current research, ICIs-related thyroid toxicity may have an association with immune thyroiditis. The article outlines the potential pathogenesis of several thyroid-related adverse reactions.

1) Both hypothyroidism and hyperthyroidism in patients undergoing ICIs treatment result from destructive thyroiditis caused by cytotoxic T cells attacking the thyroid gland. The thyroiditis is mainly a T-lymphocyte-mediated process, where CD8+ and CD4- CD8- T lymphocytes are prominent in the thyroid gland [16].

2) Research has discovered that cytokines, including the chemokine receptor CXCR3 and its ligand (IFN- $\gamma$ -inducible chemokine ligand), could be linked to related thyrotoxicity [17]. Studies have validated that after IFN- $\gamma$  stimulation, CXCL10 secretion is increased by thyroid epithelial cells, inducing chemotaxis of type 1 T helper lymphocytes, and further secretion of IFN- $\gamma$  commences, ultimately triggering and sustaining the autoimmune process. It has been discovered that anti-PD 1 treatment increases the expression of human leukocyte antigen (HLA-DR) on natural killer cells and inflammatory mediators CD14+CD16+ monocytes [18]. This finding facilitates further research on the pathogenesis of associated thyrotoxicity.

3) The association between relevant thyrotoxicity and gene polymorphisms and inter-gene interactions has been recently demonstrated [19]. Variations in specific genes can elevate or reduce the chance of experiencing thyrotoxicity, and interactions among different genes can also play a role in influencing this risk. Although immune checkpoint inhibitors can commonly cause thyroid-related adverse effects, their therapeutic advantages in treating malignancies outweigh the risks involved. Patients must remain vigilant of their medical conditions during immunotherapy and receive proper treatment under the supervision of their healthcare provider.

## **5. Digestive Tract Adverse Reactions**

Immunotherapy-induced gastrointestinal toxicity (GIT) is categorised into upper and lower gastrointestinal sections. Upper gastrointestinal effects, such as nausea and vomiting, have a 36% occurrence rate in patients, while lower gastrointestinal events, including diarrhea, colitis, or inflammation of the small intestine, occur between 30% to 50% of the time. In rare instances, intestinal obstruction and gastritis were observed. Studies have demonstrated a higher likelihood of gastrointestinal (GI) adverse events associated with anti-CTLA-4 treatments compared to anti-PD-1 and anti-PD-L1 treatments. Such adverse events may arise at any point during treatment, and even after treatment concludes [20]. GI-related reactions to treatment have a profound effect on patients' quality of life and can be fatal in severe cases. Hence, when patients undergo immunotherapy, healthcare professionals and patients themselves should carefully monitor for gastrointestinal adverse effects. If adverse events transpire, reducing or ceasing the use of immune checkpoint inhibitors ought to be promptly considered. Correct treatment options should be administered for GI adverse effects to effectively safeguard the patient's safety and maintain their quality of life.

## **6. Conclusion**

Immune checkpoint inhibitors, a pioneering method for tumour treatment, have attained outstanding results in clinical practice. Nonetheless, despite their immune system-enhancing effects, they may trigger a range of side effects. This review provides an overview of the prevalent side effects of immune checkpoint inhibitors and offers relevant recommendations. Firstly, skin reactions rank among the most frequent side effects of these inhibitors. Maculopapular rash, rash, and pruritus are frequent skin reactions, often mild or moderate in intensity and treatable by topical medications like hormonal drugs. Immune checkpoint inhibitors can also cause endocrine disruption and immune-related adverse reactions, such as abnormal thyroid function and immune pneumonitis. Early detection and intervention can help alleviate the impact of these side effects. Secondly, immune checkpoint inhibitors commonly cause gastrointestinal reactions as side effects. Gastrointestinal symptoms such as diarrhea, nausea, and vomiting may cause gastroenteritis. Healthcare professionals should seek treatment to minimize the impact of these side effects. Future research could concentrate on developing safer immune checkpoint inhibitors with lower side effects risk. Research is not limited to seeking more selective targets, such as inhibiting particular immunosuppressive molecules overexpressed on the surface of tumour cells, or modulating specific signalling pathways to enhance immune cells' ability to attack tumour cells. It also involves the optimisation of pharmacokinetics, including the route of administration and the individual dosage adjustment.

Further research into strategies to prevent side effects of immune checkpoint inhibitors is needed, including early immune detection and intervention, and individualized dose adjustment based on analysis of the genome, immunomics, and other relevant factors. This will help reduce the incidence and severity of side effects, ultimately improving immune therapy. While ICIs offer new options for cancer treatment, it is important to also consider the potential for corresponding side effects. ICIs have brought new options for cancer treatment, but they also come with corresponding side effects, which researchers and medical professionals should weigh in order to help patients recover better.

## References

- [1] Jiang Pei, Yao Weirong, Shen Qinglin. Current status and challenges in the treatment of immune checkpoint inhibitors in triple-negative breast cancer. *Chinese Journal of Cancer Prevention and Control*, 2023, 30 (17): 1062 - 1068.
- [2] Wang LL, Patel G, Chiesa-Fuxench ZC, et al. Timing of onset of adverse cutaneous reactions associated with programmed cell death protein 1 inhibitor therapy. *JAMA Dermatol*, 2018, 154 (9): 1057 - 1061.
- [3] Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*, 2017, 5 (1):95.
- [4] Tattersall IW, Leventhal JS. cutaneous toxicities of immune checkpoint inhibitors: the role of the dermatologist. *yale J Biol Med*, 2020, 93 (1): 123 - 132.
- [5] Cheng Haixing, Zhang Daojun, Hao Fei. Skin adverse reactions associated with immune checkpoint inhibitors. *Chinese Journal of Dermatology and Venereology*, 2023, 37 (6): 727 - 731.
- [6] Phillips GS, Freites-Martinez A, Wu J, et al. Clinical characterization of immunotherapy-related pruritus among patients seen in 2 oncology dermatology clinics. *JAMA Dermatol*, 2019, 155 (2): 249 - 251.
- [7] M D B, S G P, N A G, et al. IgE blockade with omalizumab reduces pruritus related to immune checkpoint inhibitors and anti-HER2 therapies. *Annals of oncology: official journal of the European Society for Medical Oncology*, 2021, 32 (6).
- [8] Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated with Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol*. 2017, 35 (7): 709.
- [9] Huang YF, Fan HY, Lin, et al. Risk of immune-related pneumonitis for PD1/PD-L1 inhibitors: systematic review and network meta-analysis. *Cancer Med*, 2019, 8 (5): 2664.
- [10] Wang WX, Wang Q, Xu CW, et al. Chinese expert consensus on the multidisciplinary management of pneumonitis associated with immune checkpoint inhibitor. *Thorac Cancer*, 2022, 13 (23): 3420.
- [11] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*, 2018, 378 (2): 158 - 168.
- [12] Shibata Y, Murakami S, Kato T. Overview of checkpoint inhibitor pneumonitis: incidence and associated risk factors. *Expert Opin Drug Saf*, 2021. 20 (5): 537 - 547.
- [13] Pozzessere C, Bouchaab H, Jumeau R, et al. Relationship between pneumonitis induced by immune checkpoint inhibitors and the underlying parenchymal status: a retrospective study. *ERJ Open Res*, 2020, 6 (1): 165.
- [14] Li Hong-Min, Zhao Yong-Cai, GUO Peng, et al. Progress of immune checkpoint inhibitor-associated thyrotoxicity. *Modern Oncology Medicine*, 2023, 31 (8):1568 - 1572.
- [15] Ascierto PA, Vecchio MD, Robert C, et al. ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomized, double-blind, multicentre, phase 3 trial. *Lancet Oncol*, 2017, 18 (5): 611 - 622.
- [16] Barroso SR, Barry WT, Garrido AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and Meta-analysis. *JAMA Oncol*, 2018, 4 (2): 173 - 182.
- [17] Antonelhi A, Ferrari SM, Fallahi P. Current and future immunotherapies for thyroid cancer. *Expert Rev Anticancer Ther*, 2018, 18 (2): 149 - 159.
- [18] Kotwal A, Gustafson MP, Bornschlegl S, et al. Immune checkpoint inhibitor-induced thyroiditis is associated with increased intrathyroidal T lymphocyte subpopulations. *Thyroid*, 2020, 30 (10): 1440 - 1450.
- [19] Zhang Y, Garofano F, Wu XL, et al. Integrative analysis of key candidate genes and signaling pathways in autoimmune thyroid dysfunction related to anti-CTLA-4 therapy by bioinformatics. *Invest New Drugs*, 2020, 38 (6): 1717 - 1729.
- [20] Dong MY, Peng WY. Immune checkpoint inhibitor-associated gastrointestinal toxicity. *Chinese Journal of Clinical Physicians*, 2023, 51 (10): 1140 - 1144.