

Immune Checkpoint Inhibitors' challenges, mechanisms and management

Sijie Yin *

Department of clinical medicine, Anhui Medical University, Anhui, China

* Corresponding author: 2013010555@stu.ahmu.edu.cn

Abstract. Numerous studies have demonstrated that the ability of protecting malignant cells from immune destruction—particularly from T and B lymphocytes, macrophages, and natural killer cells—is linked to the aetiology of cancer. Malignant cells hold the capacity to activate specific immunological checkpoint pathways that have immunodepressant qualities, which is why immunosuppression is connected to the growth and spread of cancer. Immunotherapy has grown to be a crucial method of therapy for cancer. Immune checkpoint blocking increases anti-tumor immunity by preventing intrinsic down-regulated factors of immunity, like CTLA-4 and PD-1, or PD-L1. Unquestionably, ICIs have advanced the area of cancer immunotherapy. In spite of ICIs' success, various challenges to these drugs, such as resistance and immune side effects, have made treatment difficult. Therefore, more in-depth understanding of the mechanism of ICI treatment and its toxicity is needed. Ultimately, on the basis of these insights, biologists will eventually be able to refine ICIs to achieve longer lasting efficacy and improved security. Here, we review the mechanisms and clinical applications of ICIs, examine the various challenges facing ICIs, including the mechanisms of resistance to treatment and the manifestation of irAEs and explore more sound management measures on this basis.

Keywords: Cancer immunity; immune-related adverse events (irAEs); Immune checkpoint inhibitors.

1. Introduction

A growing corpus of evidence indicates that two characteristics common to all malignancies may have a role in the aetiology of various cancers. One is the ability to change, or reprogram, the metabolism of cells to best promote the growth of neoplastic growth. The latter permits malignant cells to avoid being destroyed by the immune system. Tumor cells use a variety of strategies to avoid immune monitoring and spread. The foundation of cancer immunotherapy is the study of tumor escape mechanisms. It manipulates the immune system to stop cancer escape routes and restart the anti-tumor immune response.

Based on different mechanisms, we can divide them into two groups. One group is to enhance the immune system make it stronger to fight the cancer, such as adoptive T cell therapy (ACT), anti-tumor antibodies, cancer vaccines, stimulatory factors (cytokines). The other group is to Inhibit the suppressive immune environment of the tumor (Activate the immunological cells by inhibiting their inhibition.), the more mature ones such as CTLA-4 inhibitor, PD-1 and PDL-1 inhibitors. Immune checkpoints under investigation include LAG-3 (CD223), TIM-3, B7-H3 (CD276), TIGIT, VISTA. ICIs have left a lasting impression on the field of cancer immunotherapy. This was evident when the US FDA approved ICIs—which now also include antibodies directed targeting PD-1 and PD-L1 in order to treat a variety of cancer types, after the use of anti-CTLA-4 for advanced-stage melanoma was authorized in 2011 [1].

Their course of action is directly related to these results. T cell activation is mostly caused by dual signaling. In the first signal, T cell receptors (TCRS) bind to MHC and deliver antigens. The second signal is composed of co-stimulus and co-inhibition signals [2]. Tumor cells are able to efficiently impede T cell activation and induce T cell death due to immunological checkpoints present on T cells and their receptors. This makes it possible for cancers to evade immune surveillance. ICIs can bind

to the immunological checkpoint and prevent it from interacting with its receptor, allowing immune cells to be identified and eliminated once more.

ICIs, however, are tied to multiple kinds of irAEs. ICI treatment still faces many challenges, such as drug resistance and immunotoxicity. To explore the mechanisms behind these challenges, we can better improve cancer immunotherapy and achieve safer and more effective cancer immunotherapy management.

In this review, we delve into the clinical use of FDA-approved ICIs, as well as the underlying mechanisms of resistance and irAEs associated with these therapeutic interventions. Then we explore approaches to overcome these obstacles in order to increase the number of patients for whom ICI is beneficial.

2. Immune checkpoint

Immune system checkpoints are a typical component. Their function is to keep the immune system from reacting inappropriately and destroying the body's wholesome cells. When T cells recognize cancer antigens, immune checkpoint molecules, which are mostly produced on the T cell membrane, attach to the ligands on cancer cells and APCs to regulate T-cell activation [3]. To enhance comprehension of the ICIs' mechanism, let us quickly recapitulate CTLA-4, PD-1, and PD-L1.

CTLA4, often referred to as CD152, is a protein receptor of the B7/CD28 family that suppresses immunological responses and serves as an immune gatekeeper. Tregs express CTLA-4 on their outermost layer, which are crucial in inhibiting immunological responses, in addition to being overexpressed on T cell surface activation. However, CTLA-4 was upregulated only in activated conventional T cells, particularly in cancer. When affixed to antigen-presenting cells' surface via CD80 or CD86, CTLA4 acts as an "off" switch. CD28 is in charge of producing cytokines, such as IL-1. Via the T cell-extrinsic and T cell-intrinsic routes, CTLA-4 suppresses T cell activity. Phosphatase recruitment, ubiquitin ligase activation, and inhibition of transcription factors related to the activity of T cells, including NF- κ B, NFAT, and AP-1, are the inherent outcomes of signaling via the receptor. CTLA-4 can lower the effective quantity of costimulatory signals that T cells receive by extrinsically fighting for ligand binding with CD28.

Another receptor that is important for anti-tumor T-lymphocytes is PD-1 [4]. It attaches itself to PD-L1 and PD-L2 ligands [5]. T-lymphocyte survival, proinflammatory cytokine production, and T-lymphocyte proliferation are all reduced when PD-1 is activated [4]. Tumor cells can employ checkpoint protein signals to evade the immune system, and they can also induce t cell death by upregulating the PD-1 pathway, which results in reduced t cell effector function and proliferation ability.

3. Immune checkpoint inhibitors

3.1. The definition of ICI

Among the most recent classes of medications that successfully overcomes resistance of cancer cells is immune-checkpoint inhibitors, which work by enabling host immune cells to recognize and destroy tumor cells [6].

The humanized or human immunoglobulin (IgG1), with the exception of IgG4 antibodies, such as nivolumab, target different proteins are known as ICI [6]. The companion proteins and checkpoints work together to convey a "off" signal to T or NK cells. This might prevent the immune system from eliminating the malignancy. Immunotherapy medications known as immune checkpoint inhibitors, primarily antibodies directed against these checkpoints, function by preventing the binding of checkpoint proteins for their partner proteins. Consequently, the "off" signal is not sent, enabling T cells or NK cells to destroy malignant cells. Depending on the immune checkpoint to which these inhibitors bind, FDA approved ICI can be divided into three categories: Anti-CTLA4, Anti-PD1,

Anti-PD-L1. Targeting CTLA-4, ipilimumab was the first ICI to be licensed for the management of individuals with metastatic melanoma [7].

Three antibodies against PD-L1—avelumab, durvalumab, and atezolizumab—have been given FDA approval in recent times to treat various cancer types [1]. Anti-PD-1 antibodies have been authorized for the greatest number of cancer types when it comes to ICIs [1]. Phosphorylation occurs in the cytoplasmic immunoreceptors of PD-1 when it interacts with its ligands [1]. PD-1 belongs to the family of costimulatory receptors known as B7/CD28. By attaching to its ligands, programmed death ligands 1 (PD-L1) and 2 (PD-L2), it controls T-cell activation. Like CTLA-4 signaling, PD-1 binding decreases T-cell survival and suppresses the generation of IFN- γ , IL-2, and T-cell proliferation. Concurrent TCR and PD-1 binding results in PD-1-generated signals that lessen T cell activation. A telltale sign of "exhausted" T cells is the expression of PD-1, indicating a decrease in CD4+ T-cell assistance or a high degree of stimulation. T-cell dysfunction characterizes this exhausted condition that arises during cancer and persistent infections, leading to inadequate management of tumors and infections.

3.2. The meaning of ICI

In the realm of immune-oncology, the discovery of ICIs represents a major turning point. Since the first approval of ipilimumab in 2011, six more ICIs have arrived (Table 1,2), including three anti-PD-1 antibodies and three anti-PD-L1 antibodies [7].

Table 1. FDA -approved therapies

Mechanism	Therapies	Molecular properties	Disease indicator (approval year)	Selected clinical trials	Pathological type
Anti-CTLA4	Ipilimumab	Human IgG1k monoclonal antibody	① Melanoma(2011) ② Renalcellcarcinoma (2018) ③ Cancer of the liver (2020)	\	\
Anti-PD-L1	Atezolizumab	A humanized anti-PD-L1 mAb	① Urothelial cancer (2016) ② NSCLC(2016) ③ Breast cancer that is triple-negative (2018) ④ Lung cancer with small cells (2019)	POPLAR	NSCLC
	Avelumab	A fully human IgG1 anti-PD-L1 mAb	① Krebs cell cancer(2017) ② Cancer of the urothelial cells (2017) ③ Kidney cell cancer (2019)	JAVELIN Lung 100	NSCLC
	Durvalumab	An IgG1 κ anti-PD-L1 mAb	① Cancer of the urothelial cells (2017) ② NSCLC (2018) ③ SCLC(2020)	PACIFIC	PACIFIC
Anti-CTLA-4 + anti-PD-1	Ipilimumab and nivolumab	\	① Metastatic RCC ② Metastatic colorectal Cancer ③ HCC	\	\

Table 2. FDA -approved therapies

Mechanism	Therapies	Molecular properties	Disease indication (year of approval)	Selected clinical trials	Pathological type
Anti -PD1	Nivolumab	An IgG4 mAb against PD-1	① Skin cancer (2014)	CheckMate057	NS-NSCLC
			② Hereditary lymphoma (2016)	CheckMate017	Squamous NSCLC
	③ Acute urothelial cancer (2017)	④ SCLC(2018)			
Cemiplimab	A human IgG4 anti-PD-1 mAb	Squamous cell cancer of the uterus (2018)	EMPOWER-Lung1	NSCLC with PD-L1 > 50%	
	Pembrolizumab1	A humanized IgG4 antibody against PD-1	① Melanoma (2014) ② Lung cancer (non-small cell) (2015) ③ Lymphoma Hodgkin 2017 ④ Cancer MSI-H (2017) ⑤ Stomach cancer (2017) ⑥ Cervix cancer (2018) ⑦ Cancer of Merkel cell (2018) ⑧ Renal cancer (2019)	KEYNOTE-001	KEYNOTE-001

4. ICI's challenges

For many individuals, ICIs have significantly enhanced cancer treatment. Through the immune system's activation to eliminate tumour cells, these humanised monoclonal antibodies targeting different immunological checkpoints including ligands and receptors efficiently cure a variety of cancers. Although many tumours now have far better prognoses because to these treatments, one consequence that has emerged in clinical practise is immune-related end organ damage [4].

4.1. Dermatologic Toxicity

The most frequent irAE associated with those receiving treatment with ICI is dermatologic toxicity. The three most often cutaneous toxicities reported are vitiligo, pruritis, and maculopapular rash. When using an ICI combination, severe toxicities like DRESS or TEN, sometimes referred to as Stevens-Johnson disorder or toxic epidermal necrolysis are more prevalent. The most common irAE to appear is cutaneous toxicity. It usually shows up after 5 weeks for anti-PD-1, 2-4 weeks for anti-CTLA-4, and 2 weeks for ipilimumab + nivolumab. Forty-one Combining PD-1/CTLA-4 blocking frequently causes earlier onset, more severe dermatologic damage [5].

It might be challenging to evaluate the range of illness since dermatologic responses frequently include non-specific and ambiguous symptomatology. Grading is based on the nature of the response. The following categories apply to non-severe rashes: grade 1 symptoms that do not impair quality of life; grade 2 symptoms that impair quality of life and necessitate the start of treatments; grade 3 symptoms that result from treatment failure for grade 2 toxicity; and grade 4 symptoms that are unmanageable or unbearable [4].

4.2. Diarrhea or colitis

One of the most frequent side effects of ICI therapy is diarrhoea, which is more likely in individuals receiving CTLA-4 antibody treatment [5].

In a large retrospective analysis, Abu-Sbeih et al. evaluated the incidence of GI-irAEs and their relationship to treatment results for individuals with advanced melanoma receiving ICIs. Of the 346 patients, 173 suffered from colitis, 44 with grade 3 or 4 diarrhoea, and 79 from either diarrhoea or colitis [8].

ICI-mediated colitis may manifest at any point in time, including the start of treatment, the weaning off of steroids, or the end of treatment. The whole duration from 0 to 6.3 months was the start of CIC. Previous investigations have indicated that the start of CIC may change depending on the kind of ICI. In contrast to colitis brought on by PD-1/PD-L1 inhibitors, colitis brought on by CTLA-4 inhibitors appeared to occur later [9].

4.3. Hepatitis

Elevations in alanine and aspartate transaminase are the major manifestation of hepatic ae treated with immune checkpoint inhibitors. However, more severe autoimmune sudden liver failure and elevated bilirubin levels due to hepatitis can also happen. Based on information from combined clinical trials, the estimated incidence of hepatotoxicity is 1% to 2% for patients undergoing anti-PD-1/anti-PD-L1 monoclonal immunotherapy and 3% to 9% for those treated with ipilimumab [1].

4.4. Thyroid toxicity

With ICI treatment, compared to hyperthyroidism, hypothyroidism is more prevalent. 6.6% of people are hypothyroid overall, with ipilimumab-treated patients reporting the lowest rate and combination therapy-treated patients reporting the highest rate [5].

4.5. Pneumonitis

Up to 19% of patients receiving ICI treatment may experience pulmonary problems, which have a 1-2 percent fatality risk. Pneumonitis is the most frequent pulmonary complication and the most frequent cause of irAE-related mortality [4].

Pneumonitis is an uncommon but highly lethal adverse effect of ICI therapy. The incidence is low in the monotherapy group, but can be as high as 10 percent with combination therapy.

When dual checkpoint inhibition is used, the prevalence of lung infections rises and is marginally greater with PD-1 isolation compared to CTLA-4 monotherapy.

4.6. Uncommon Immune-Related Side Effects

4.6.1. Neurologic toxicity

Myasthenia gravis and non-infectious encephalitis are the most severe ICI-specific neurologic effects, with reported death rates of up to 20% and 19%, respectively [4]. Aseptic meningitis was more common while using CTLA-4 treatment as opposed to PD-1 therapy, and the incidence of myasthenia gravis was higher with PD-1 therapy. Surprisingly, myasthenia gravis often coexists with myocarditis, and up to 30% of patients with myasthenia gravis also have myocarditis. Some have elevated CPK without a formal diagnosis of myocarditis, which suggests that the true incidence may be higher.

4.6.2. Renal toxicity

Hematuria, pyuria, increasing hypertension, or rising serum creatinine levels are frequent signs of ICI-associated renal impairment, with most cases exhibiting symptom onset during the first two to three months [4].

4.6.3. Cardiovascular toxicity

Two instances of fulminant myocarditis following ICI therapy were described by Johnson et al. in 2016 [10]. Variations exist in the clinical appearance of myocarditis linked with ICI. Remarkably, about half of the patients show no signs of systolic dysfunction [11]. Conversely, ventricular arrhythmias, conduction problems, and abrupt demise are examples of frequent cardiac arrhythmias. Other cardiovascular irAEs, such as pericarditis and vasculitis, can also result from ICIs [10].

4.6.4. Hematologic toxicity

Despite hematologic irAEs are uncommon, a variety of symptoms have been reported, such as hemolytic anaemia, hemophagocytic lymphohistocytosis, red cell aplasia, neutropenia, myelodysplasia, and haemophilia A.

4.7. Tumor Metabolism

A hostile TME produced by tumour cells has a variety of effects on T cells' metabolic fitness. Different immunological and metabolic checkpoints present challenges for T cells: Depletion of glucose and amino acids, increased acidity and lactate, and immunological checkpoint upregulation affect T cell metabolism to inhibit glycolysis, which lowers T cell activation and proliferation.

4.8. Systemic Adverse Effect

Exhaustion and infusion responses are examples of systemic adverse effects of ICI treatment. The most common immunological side event found in trials using ipilimumab and anti-PD-1 was fatigue.

4.9. Hypophysitis

Hypophysitis was uncommon before ipilimumab was developed. Fatigue, headaches, and weakness are common nonspecific symptoms of hypophysitis; fewer common symptoms include disorientation, sleeplessness, cold intolerance.

4.10. Resistance to immune checkpoint inhibitors

While many cancer types have seen better patient outcomes as a result of ICI therapy, not all patients who get ICI treatment see a long-lasting response [1]. Extensive research has been conducted to determine the reasons behind the majority of patients' failure to respond to or maintain their response to ICIs. There are two types of resistance to tumor immunotherapy: acquired and primary [5].

Primary resistance: Evidence of disease progression following at least six weeks (two cycles) but no more than six months of ICI therapy is referred to as primary resistance.

Acquired resistance: When Inhibitors of PD-1/PD-L1 exhibit a robust and successful reaction at the beginning of treatment, nevertheless, after a period of therapy, the inhibitors' therapeutic effectiveness is significantly diminished or, in some cases, ineffective, this is known as acquired drug resistance [2].

4.11. OTHERS

4.11.1. Clarifying the Advantage of Natural Immunity vs. Artificial Immunity

Treatments that synthetically link T cells to cancer cells—which they may not typically act in accordance with the appropriate binding of a T cell receptor to a certain MHC complex—cause synthetic immune responses. A customised strategy could be needed to optimise the advantages of employing synthetic immunity. In light of the aforementioned, treatments combining synthetic and natural immunological modalities may be very synergistic.

4.11.2. Applying artificial intelligence for cancer immunotherapy

While immunotherapy represents a significant advancement while addressing cancer, it may often be

difficult to determine whether a given patient will benefit from the therapy. Nonetheless, the development of AI raises the likelihood that cancer immunotherapy will be effective. As evidence of the growing breadth of AI's applicability in immunotherapy, current AI-based techniques have demonstrated promising results in the production of vaccines targeting the MHC-II immunopeptidome and the MHC-II epitope prediction based on amino acid sequence strength.

5. Mechanisms of challenges

The mechanisms of interaction between tumors and immune cells are complex and variable. Some mechanisms apply to almost all immune adverse events, and others are context-specific.

5.1. The general mechanism

5.1.1. TME

Often characterized like low pH, low oxygen, and a variety of metabolic alterations, including increased glycolysis and aberrant metabolism of fatty and amino acids, the TME is the environment in which tumors thrive. More TAMs, TADCs, Treg and M2-like macrophages, increased CD8+Tmem cells, decreased Teff cells, and a variety of harmful compounds, including glutamine, canine urine, and lactic acid were among the immune cells in the microenvironment that changed as a result of these changes, along with a decrease in inhibitory cells.

5.1.2. Genetic factor

It has been suggested that genetic factors underlying germ cells may also influence the occurrence of immune adverse events.

5.1.3. Gut microbiota modulation

The microbial community's dysbiosis typically results in the disruption of the intestinal barrier, which makes it easier for bacteria and metabolites to leak in. This promotes the growth of tumors by causing lipid metabolism disorders, chronic inflammation, and impaired myeloid cell function in clearing mutant, senescent, and malfunctioning cells [12].

Additionally, by producing different metabolites that might enter the human circulation, the gut microbiota can potentially affect protection against tumors. The impact of SCFAs on macrophage and DC function stimulation of proinflammatory TH1 and TH17 cells, as well as anti-inflammatory Treg cells and IgA production by plasma cells in TdLN and TME is a notable example [12].

5.2. The Specific mechanisms

5.2.1. Colitis

The fundamental cause of colitis linked to ICIs is yet unknown. However, a number of studies have indicated that the factors that have been proposed to cause the development of an autoimmune-type presentation, proinflammatory condition, and Teff cell hyperactivation are accompanied with lymphocyte infiltration and a rise in memory T cells in circulation [9]. The kind and relative quantity of the intestinal microbes may have an impact on how CIC develops [9]. We know that *prausnitzii* plays a role in maintaining the gut mucosa's integrity, so the enrichment of this bacterium is closely related to the occurrence of colitis.

5.2.2. Cardiovascular toxicity

It is unknown what the molecular causes of myocarditis linked with ICI are. Nonetheless, there is no question that the environment has an impact on the autoimmune myocarditis disease aetiology. A commensal bacteroides species has been shown to stimulate Gut-derived Th17 cells and facilitate the progression from fatal cardiomyopathy to myocarditis. Mice's CD4+ cells provided confirmation of this mechanism [10].

Some scholars also believe that cytokines can play a role in inducing myocardial dysfunction in the

later stage of the course of viral myocarditis [13,14].

5.2.3. Thyroid toxicity

The majority of ICI-treated patients exhibit hypothyroidism or destructive thyroiditis, which is assumed to be brought on by inflammatory cells infiltrating the thyroid gland.

According to a mouse research, mice given pd-1 antibody were shown to suffer severe thyroiditis. This implies that after receiving an injection of anti-CD4 antibodies, CD4 T cells contribute significantly to the development and elimination of thyroiditis. Furthermore, it has been discovered that CD4 T lymphocytes with thyroiditis directly harm thyrocytes by focusing on thyroglobulin and MHC molecules that are produced by thyrocytes.

5.2.4. Hypophysis, pneumonitis, hepatitis

ICI primes antigen-specific T cells to attack tumors by interfering with immunological tolerance, a defense mechanism. Nevertheless, it may also result in irAE and autoimmune diseases directed against self-organs.

5.2.5. Hematologic toxicity

According to the general notion, immunological activation generated by ICI results in the peripheral tolerance decline to the patient's own cells as well as tumor-specific T-cell responses. In other words, Hepatocyte damage and T-cell-mediated hepatitis mortality result from immunological activation against hepatocytes.

5.2.6. Dermatologic Toxicity

The pathogenesis is not yet clear, but research has demonstrated that PD-1 axis down-regulates Th1/Th17 signaling pathway. Thus, PD-1 blockade promotes Th17 lymphocyte-mediated secondary overexpression of proinflammatory cytokines.

5.2.7. Resistance

① low tumor mutational burden: Increased tumor mutational burdens are highly correlated with the responsiveness to CTLA-4 and anti-PD-1 therapy in a variety of cancer contexts. As a result, tumor types that show a low load of tumor mutations are frequently linked to ICI resistance. Primary resistance to ICIs is mostly caused by low mutational load [1]. ② The activation mechanism of T cells: The anticancer ICIs' impacts depend on the activation mechanism of T cells. To directly combat cancer cells, T cells must travel into the TME and penetrate it. These chemokines are produced by surrounding immune cells and cancer cells, and ICI resistance is brought on by interference with the chemokine synthesis process. Consequently, IFN- γ signaling, linked to these chemokines, prevents T cell infiltration into the TME [3]. ③ Immunosuppressive cells: The mechanisms of ICI resistance facilitated by diverse immune-stifling cells, including Treg cells, TAMs, and CAFs, have mostly been documented in murine models [3]. ④ Tumor-intrinsic mechanisms of resistance: Intrinsic characteristics of cancer cells, such as their mutational landscape and the way in which interferon signaling pathways work, are essential for eliciting an immune response when immune checkpoint blockage is in place. Similarly, abnormalities in any of these crucial tumor features may lead to resistance to ICI [15]. ⑤ Insufficient tumor antigenicity: Tumor neoantigens have been shown in several studies to be viable targets for antitumor immunity, and there is a relationship between the responsiveness to immune checkpoint blockage and the mutational load of various malignancies [15]. Tumor-extrinsic factors are related to TME: TME primarily functions by inhibiting immunosuppression and generating pro-inflammatory factors.

6. Management

6.1. General management measures

6.1.1. Grading standard

IrAE affects several bodily systems and organs, and its precise categorisation changes depending on which target organs are affected. Patients with grade 1-2 adverse effects are often asymptomatic or minor, and they do not necessitate hospitalization. Hospitalisation was necessary for grade 3 adverse events, and patients experienced severe symptoms or persistent symptom worsening. Adverse occurrences of grade four need admission to an intensive care unit in order to avert life-threatening symptoms or indications.

6.1.2. Strategy

Elucidation of the mechanism of all adverse events must be of the utmost importance. Secondly, considering that immunotherapy has been booming worldwide, we must establish a perfect international system to strictly regulate the use of drugs. Finally, this is a complex procedure, and clinical multidisciplinary must be encouraged.

6.1.3. Cytokines

This may facilitate the continuation of antitumor immunity and the resume of cancer immunotherapies by encouraging a quicker resolution of irAEs.

Corticosteroids are hormones capable of broadly inhibiting a variety of inflammatory processes, whereas cytokines are more targeted. This gives us clinical investigators a major caveat about the need for appropriate selection of immune adverse events on a case-by-case basis. One study showed that other mice had attenuated responses to antibodies compared with mice not treated with TNF antagonists, and at the same time, tumor rejection was also greatly increased.

6.1.4. Predictive biomarkers in ICIs therapy

Despite the strong anti-tumor efficaciousness of ICI treatment, certain individuals fail to respond as intended to this therapeutic intervention. As a result, the discovery and development of predictive biomarkers for ICI's response has received increased attention [16].

We mentioned earlier that the tumor mutational burden is important for the response to ICI therapy. TMB, or total amount of DNA mutations found in cancer cells, has been employed as a biomarker recently. The better the therapy, the greater the number.

T cell clonal proliferation of CD4+ and CD8+ occurred long before the onset of grade 2 immunotoxicity in patients who had an immune adverse event. This suggests that changes in cellular diversity are also related to the occurrence of immunotoxin events and have the potential to be used as predictors.

Furthermore, the development of immune-related toxicity has been linked to the proliferation of eosinophils during ipilimumab therapy.

It has been shown that ipilimumab-induced hypophysitis and pituitary CTLA-4 expression are strongly correlated. This correlation has been validated at the nucleic acid and macromolecular levels. In conclusion, pituitary antibodies or abnormal CTLA-4 expression in the pituitary may indicate pituitary toxicity associated with ipilimumab.

Early in the development of the disease, some changes in indicators give us great hints, for example, increased serum levels of thyroid autoantibodies are closely related to ICI thyroid toxicity.

Cytokines as Signposts to irAE Propensity. It may be possible to use circulating cytokines as biomarkers to identify those who are susceptible to irAEs.

6.2. Specific management measures

6.2.1. Dermatologic Toxicity

Topical corticosteroids, oral antihistamines, and/or emollients are used to treat grade 1 dermatologic irAEs. If grade 2 toxicity does not improve, an ICI should be stopped; otherwise, it should be maintained. When using systemic corticosteroids with grade 3 or 4 toxicity, ICIs should be discontinued [5].

6.2.2. Diarrhea or colitis

An assessment of FMT was conducted on two colitis patients who were resistant to vedolizumab, infliximab, and steroids. Following FMT, both patients experienced full symptom resolution. Retrospective research and expert opinion serve as the foundation for the current management guidelines, which consistently advocate systemic corticosteroids as the first-line treatment [9]. The basic foundation for specialist management is the severity level. Pretreatment exams include testing for infectious aetiology, blood, hepatitis serology, and tuberculosis [9]. Colitis is an early and timely detection and intervention can greatly improve the prognosis of the disease, so the timely diagnosis and identification of clinicians is extremely important. It needs to be distinguished primarily from a gastrointestinal infection, and pathogen testing should be performed in patients who present with diarrhea to aid in the diagnosis. The presence of faecal calprotectin may help determine if the cause is inflammatory.

6.2.3. Hepatitis

Patients can get supportive care while receiving ICI treatment for grade 1 toxicity. Patients with grade 2 toxicity or greater should either stop receiving ICI treatment or put it on hold. Furthermore, prednisone or an equivalent should be begun for grade 2 toxicities, high-dose prednisone or an equivalent is indicated for grade 3–4 toxicity [4].

6.2.4. Thyroid toxicity

Individuals who have both hyper- and hypothyroidism grade 1 toxicities are nonetheless able to get ICI treatment. In patients with hyperthyroidism of grade 2 or above, beta-blockers, such as propranolol, should be started as a treatment instead of continuing ICI medication. Systemic steroids are also necessary for hyperthyroidism in grades 3 or 4 [4].

6.2.5. Pneumonitis

Patients with grade 2 severity or above should get empiric antibiotics along with a potential bronchoscopy and bronchoalveolar lavage. Additionally, prednisone or an equivalent is needed for individuals whose severity is grade 2 or above. If symptoms do not improve after two days, individuals with grades 3-5 may eventually require non-ICI immunomodulators such as infliximab or mycophenolate mofetil; nonetheless, over 80% of patients get well with steroids [4].

6.2.6. Renal toxicity

In situations with grade ≥ 2 nephrotoxicity, ICI should be delayed; in the absence of any other apparent reason, steroids may be used [5].

6.2.7. Cardiovascular toxicity

The difficulty in interpreting elevated blood troponin concentrations in patients with no symptoms emphasises the necessity for enhanced predictive biomarkers. The best ways to monitor individuals at high risk for ICI-associated myocarditis require prospective, multi-institutional collaborations [10]. Patients with potential cardiac problems, regardless of the irAE grade, should contact a cardiologist for possible catheterization or advanced testing, high-dose steroids of prednisone or equivalent, and temporary to permanent cessation of ICI treatment [4].

6.3. Modulating the gut microbiota increases the effectiveness of cancer immunotherapy

Various tactics can be employed as therapies to increase the effectiveness of tumour immunotherapy and can control the gut flora. When paired with immunotherapy, a monoclonal antibody and a microbiome rich in living bacteria may significantly enhance the prognosis of cancer patients. Furthermore, a great deal of clinical experience has demonstrated that faecal transplantation in conjunction with ICI can increase ICI's effectiveness, while the precise mechanism is unknown.

7. Future prospects

7.1. New strategies to prevent and overcome resistance

7.1.1. Combined treatments

In order to overcome resistance and increase the therapeutic utility of immunotherapy, combination treatments using ICIs are usually necessary. Given that few patients respond to ICI treatment and that many will relapse, it is imperative that critical advances be made in combination therapy [16]. In a study of squamous cell carcinoma, pembrolizumab combined with carboplatin and taxane chemotherapy was much better than chemotherapy alone. Although radiotherapy is an important means to treat tumors, more and more studies have shown that when ICI and radiation are administered together, T cell activation in TME can be enhanced, thereby greatly improving the therapeutic effect.

7.1.2. VEGF

VEGF can improve TME by increasing cytotoxicity and decreasing inhibitory cells, which may be closely connected to its ability to promote the activation of immunosuppressive cells. Therefore, many clinical scholars have begun to study from the direction of VEGF, and a large number of researchers are optimistic about the development prospects of this direction.

8. Summary

Immunosuppressive checkpoint therapy is an important part of cancer immunotherapy, which has changed the treatment prospect of many tumors. However, there are many challenges in the process of ICI treatment, such as irAEs and drug resistance. The increasing number of people receiving ICIs worldwide reminds us that we must actively face these challenges and deeply explore their mechanism of action, so as to optimize the use of ICIs to benefit more people. At the same time, there are many new development prospects, such as the application of AI technology, the predictive role of biomarkers for prognosis, and the development of drugs targeting inhibitory molecules in the tumor microenvironment, which will become our exploration fields.

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