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Progress in Research and Application of Novel Tumor ICIs

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Abstract: ICIs have become a significant therapy in the course of tumors treating, which is particularly effective in relieving T-cell inhibition, activating the ATIR of the immune system. The ICIs represented by PD1 have been widely used in clinics. In this paper, the principle, biological characteristics and clinical application of ICIs in the treatment of cancer are comprehensively discussed. By preventing ICs from attaching to their ligand, which eliminate the immune function inhibition brought on by ICs, thus reactivating immune cells to play anti-tumor role. Currently, a number of ICIs have achieved remarkable results in clinical applications for anti-tumor. For example, inhibitors targeting CTLA-4, PD-1 and PD-L1 have been effectively employed in the therapeutic management of a number of malignant tumors, including non-small cell lung cancer and melanoma. However, the current application of ICIs against tumors is not mature enough. This paper focuses on the existing drawbacks of ICIs (such as their drug toxicity and drug resistance) as well as the in-depth exploration of the application prospects of ICIs. For example, in order to improve the responsiveness to immunotherapy, the clinical use of special antibodies can simultaneously target two different antigens. By acting on two synergistic or complementary signaling pathways, it can effectively enhance the anti-tumor immunity of ICIs and reduce the drug resistance of ICIs. It also provides ideas for the further improvement of ICI therapy.

Keywords: ICIs, tumor microenvironment, immunotherapy.

1. Introduction

Studies on ICIs are mainly based on their relationship with tumor cells. The immune system of the body can specifically eliminate alien cells, and tumor cells can attract immunosuppressive cells to control the production of tumor markers. Induces T cell apoptosis or functional failure [1], and produces immunosuppressive molecules, inducing the manifestation ofinhibitory ICs, thus forming a highly immunosuppressive tumor microenvironment (TME), and ultimately evading immune surveillance [2]. At present, besides the comparatively developed cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed death-1/PD-L1 (PD-1/PD-L1) some new molecular targets of IC are gradually being identified. Like TIGIT, TIM-3, etc [3]. Furthermore, the combination of ICIs and other therapies can effectively solve the drawbacks of drug toxicity and drug resistance of ICIs alone. The mechanism of drug toxicity of ICIs mainly includes activating effector T cells to kill tumor cells by blocking negative co-stimulation signaling pathway and may cause T cells to attack normal tissues. The release of interleukin interferon induces inflammatory cascade reaction to inflammatory storm, thus activating the immune system and leading to irAEs [4]. irAEs can involve various organ

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systems throughout the body. In addition, ICIS-related toxicity also includes possible off-target reactions. Due to the mutation load of tumor cells, the increase of DNA dMMR and genomic MSI can lead to the increase of tumor neoantigens. When the mutation load is low, the production of effective neoantigens decreases, leading to primary drug resistance. Deletion of tumor antigens, mutations in antigen-processing associated transporters (TAP) such as β2 microglobulin (β2-mg), or structural changes in the major histocompatibility complex (MHC) molecule itself can cause immune escape. In addition, the up-regulated expression of multiple genes in drug-resistant tumor tissues, changes in tumor cell signaling pathways, and mutations or deletion of IFN-γ pathway-related proteins will all lead to ICIs resistance [5], providing new treatment options and hopes for tumor patients [6]. In terms of the efficacy and safety of ICIs, relevant studies have found that adding some immune drugs, such as H1 antihistamines with lower cost, on the basis of ICIs combined with radiotherapy/chemotherapy can improve the efficacy for special tumors and lower the frequency of negative patient reactions.

By focusing on the research and application progress of ICIs treatment at home and abroad in recent years, this paper can effectively and accurately grasp the current development trend of ICIs, and also provide guidance for exploring the future research direction of ICIs (such as optimizing its biomarkers, pharmacodynamic characteristics, screening out beneficial groups, and improving personalized combined diagnosis and treatment protocols [7], etc.).

2. Basic principles of ICIs

2.1. Classification of ICIs

ICIs are classified according to the IC molecules they target and fall into two broad categories: inhibitors, represented by PD1, and activators (still in clinical research). Currently in clinical use, for example, the CTLA-4 gene encodes the transmembrane protein receptor known as CD52, or CTLA-4 antibody, which has a high degree of homology with CD28 (a co-stimulatory molecular receptor on T cell surfaces). It attaches itself to CD86 and CD80 ligands , respectively. Its ability to regulate TREGs and CD4+FoxP3- and CD8+T cells is essential to its immunoregulatory activity. The primary mechanism by which CTLA-4 suppresses T cells is by competing with CD28 (CTLA-4 has a higher affinity for B7 than CD28), bind B7 or recruit phosphatase to its intracellular domain to interfere with and decrease the TCR and CD28 signals.

The second is to either eliminate CD28 and CD86 through endocytosis or decrease their expression in APC. Ipilimumab (FDA-approved melanoma commercial name Yervoy in 2011), one of the first approved ICIs, is also used to treat rectal, kidney and NSCLC. Programmed Death-1 antibody, cloned from apoptotic mouse T cell hybridoma 2B4.11 with two ligands, this significant immunological transmembrane protein is expressed on the surface of T cells, PD-L1 and PD-L2 (another name for CD274/B7-H1 and CD273/B7-DC). In TME, tumor cells can express PD-L1/PD-L2. The intracellular domain becomes tyrosine phosphorylated when PD-L1 and PD-L1 are combined. The phosphorylation of the TCR signaling pathway is reduced by lowering the activation signal downstream of the TCR pathway, enlisting the tyrosine phosphatase SHP-2, and inhibiting T cell activation and cytokine production. Currently marketed are nivolumab, pembrolizumab, etc., and PD-L1 antibodies, such as atezolizumab, which relieve immunosuppression by preventing PD-1 from attaching to its ligand PD-L1. It has been successfully used in the clinical treatment of a variety of malignant tumors. Other ICs have been discovered in recent years such as antibodies to LAG-3 ,TIM-3 antibody, CD47 antibody is a more developed IC that has been explored after PD-1/PD-L1 and CTLA-4 [1].

Other ICIs such as TIGIT (ITIM domain protein and T cell immunoglobulin) antibody, T cells and NK cells share the inhibitory receptor TIGIT, and antibody drugs targeting TIGIT are under clinical

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study. VISTA antibody, it belongs to the Immunoglobulin family, and its antibody drugs are also in the clinical research stage. These ICIs block immunosuppressive signals through different mechanisms and strengthen the immune system's capacity to combat cancer. With the deepening of research, more ICs and corresponding inhibitors are being discovered and studied.

2.2. Basic Structure of ICIs

The basic structure of ICIs usually refers to their chemical and molecular structure as drugs, which allows them to specifically target and block IC proteins. ICIs are monoclonal antibody structures: most ICIs are humanized or fully human monoclonal antibodies, which consist of two main parts: a variable region (Fab segment) responsible for identifying and attaching to a particular antigen; And a constant region (the Fc segment) that is engaged in ADCC and other effector activities. The antigen-binding sites of ICIs are located in the Fab segment containing CDRs, which precisely match the epitopes of the target antigen for highly specific binding. The Fc segment of ICIs can mediate different effector functions, such as ADCC, CDC, and regulation of immune cell activity. To reduce immunogenicity (i.e. to reduce the likelihood that the body will produce an immunological reaction to a medicinal antibody), ICIs are typically designed with adult-derived or fully human antibodies, meaning that they contain a human antibody framework region with only the complementary determinant region derived from the original murine-derived antibody. For example, ICIs that target the PD-1/PD-L1 axis include pembrolizumab (Keytruda) and nivolumab (Opdivo), are humanized IgG4 monoclonal antibodies targeting PD-1. atezolizumab (Tecentriq) is an anti-PD-L1 humanized IgG1 monoclonal antibody. ICIs of CTLA-4: ICIs against CTLA-4, such as ipilimumab (Yervoy), are humanized IgG1 monoclonal antibodies against CTLA-4. In addition to monoclonal antibodies, some new ICIs may include bispecific antibodies, fusion proteins, or other molecular forms that are designed to block or activate immune signals in different ways. These structural features allow ICIs to effectively bind to IC proteins, thereby regulating the immune system's response to tumors. The specific structure of each ICIs may vary, but their common goal is to block immunosuppressive signals and strengthen the immune system's capacity to combat cancer.

2.3. Biological Characteristics of ICIs

The biological characteristics of ICIs are mainly concerned with how they affect the immune system, especially the function of T cells. ICIs works by blocking IC molecules. These checkpoint molecules are the immune system's natural "brake" system, used to prevent excessive immune responses and autoimmune diseases. Tumor cells can use these checkpoint molecules to avoid being monitored by the immune system. In addition, ICIs disrupt immunosuppressive signals, which improves T cell detection and assault of tumor cells. For example, PD-1/PD-L1 blocking can restore the effector function of T cells, allowing them to kill tumor cells more effectively. Certain ICIs may also help boost immune memory, which is the immune system's ability to remember and respond quickly to the same threat it encounters again. However, at the same time, the application of ICIs also has side effects, because ICIs increase the immune system's activity, they sometimes lead to auto-immune-like adverse events, affecting the skin, intestine, liver, endocrine system and other organs, resulting in related adverse reactions.

The effect of ICIs can be influenced by, for example, TME, such as the quantity of tumor-infiltrating T cells and the degree of PD-L1 expression, and other immunomodulatory molecules. At the same time, tumor cells may resist ICIs treatment by up-regulating PD-L1 expression, which is an immune escape mechanism. Tregs and memory T cells are among the immune cells that are impacted by ICIs, and natural killer (NK) cells, which can enhance the immune system's ability to monitor tumors, help recognize and eliminate tumor cells, affect immune tolerance mechanisms, or enhance

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their ability to fight tumors by promoting T cell proliferation and survival. It also affects the migration of immune cells from the blood to the TME. These biological features illustrate how ICIs can treat cancer by regulating the complex network of the immune system. However, numerous factors, including as a person's genetic background, affect the effects and side effects of various treatments, the biology of the tumor, and the timing and duration of treatment.

3. Tumor Treatment by ICIs and its Mechanism of Action

ICIs function by preventing an IC from attaching to its ligand. For instance, PD-1/PD-L1 inhibitors can prevent PD-1 from attaching to its ligand, PD-L1, release the activation and proliferation inhibition of T cells, make tumor-specific T cells in an activated state, and restore the killing function of T cells. Tumor cells can inhibit the activation, proliferation and cytokine production of tumor-specific T cells by elevated PD-L1 expression, mediating tumor immune escape. ICIs enhances T cell activity by blocking this pathway, thus exerting anti-tumor effects. There are many immunosuppressive factors in TME, such as TGF-β and GDF-15, which may suppress the activation of T cells. ICIs can reduce the impact of these factors and improve TME, thereby enhancing the immune response. By decreasing T cell proliferation and effector molecule production, including granzyme B, GDF-15 impairs T cell killing ability [8]. ICIs may restore the killing ability of T cells by inhibiting GDF-15 function. By lowering CD80/CD86 levels on the surface of antigen-presenting cells via trans-endocytosis, CTLA-4 prevents T cell activation. CTLA-4 inhibitors such as ipilimumab block this mechanism and enhance T cell activity.

By stimulating the body's immune system, ICIs have an anti-tumor effect [9]. They can stimulate the body's immunological response and increase the activity of immune cells, thus playing an anti-tumor role. ICIs, while boosting anti-cancer immunity, may also damage B cells, which are immune cells in the immune system that produce antibodies to fight off common infections. These mechanisms work together to enable ICIs to effectively strengthen the immune system's reaction to cancers and prevent their growth and spread. However, the effects of ICIs are not applicable to all patients and may be linked to negative immune-related events, which highlights the complexity and individual variability of ICIs treatment.

4. ICIs-related Drugs and Their Use

4.1. Currently Listed ICIs

PD-1 and PD-L1 /CTLA-4, oncolytic virus OV combined immunotherapy, CD3L1 antibodies, CD73 inhibitors, VPS18/VP35, LAG-3 inhibitors, VISTA inhibitors, CAR T cell therapy, etc.

4.2. ICIs Drug Use

ICIs can kill tumor cells by activating the anti-tumor immune function of the patient's own T lymphocytes, and has been widely used in clinic. They have demonstrated promising outcomes in anti-tumor therapy and mostly target CTLA-4, PD-1, or its ligand, PD-L1. Ten PD-1 inhibitors, five PD-L1 inhibitors, one CTLA-4 inhibitor, and one PD-1/CTLA-4 bispecific antibody are among the 17 ICIs that China has authorized. As of January 2023, there are a total of 8 drugs for PD-1 inhibitors, 2 drugs for PD-L1 inhibitors, and 1 drug for dual antibodies listed in China. Most of the ICIs drugs obtained the qualification of medical insurance negotiation, but the medical insurance negotiation mainly focused on the four drugs of carrellizumab, sindillizumab, Tirellizumab and triplizumab, and no breakthrough was made in other ICIs. In actual clinical practice, there are cases of off-label use of ICIs. According to a survey, 77.9% of doctors have written off-label drug prescriptions, the main reasons for off-label drug use include that the indication has been approved abroad, there is a high

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level of evidence-based medicine evidence, no standard treatment, patient requirements and patients can pay [10]. At the same time, ICIs therapy may cause unfavorable effects associated to the immune system, such as AKI, which occurs in 0.8% to 29% of patients and can occur weeks or months after initial treatment or even after withdrawal. When using ICI for treatment, clinicians should fully recognize the risk factors of related adverse reactions caused by ICI, and do a good job in baseline check before treatment and evaluation during medication. In addition, for the elderly and patients with poor physical fitness (ECOG PS $\geq$ 2), the elderly and frail patients can benefit from immunotherapy without increasing adverse reactions, but more evidence-based medical evidence is still needed overall.

5. Drawbacks of Current ICIs

5.1. Drug Toxicity of ICIs

The toxicity of ICIs, also known as irAEs, is a side effect of particular concern with the use of these drugs. The incidence of widespread irAEs caused by ICIs ranges from 65% to 76% for all grades of irAEs and from 3% to 5% for irAEs above grade 3, although most of the toxicity is mild and reversible. However, there was still 0.3%~1.3% severe lethal toxicity [11]. Its toxicity can vary in frequency and severity and impact nearly every organ. Organ-specific irAEs include skin, lower digestive tract, lung, pituitaritis, thyroid, liver, heart, nerve, eye, rheumatic, renal, and hematological irAEs. Severe lethal toxicity is a significant cause of unexpected death in cancer patients. In addition, the combined use of ADC and ICIs may increase the risk of specific toxicities, such as ILD/ pneumonia.

A number of guidelines on irAEs management have been published, with management points including the individual decision to reintroduce ICIs after discontinuing ICIs for irAEs. Permanent ICI discontinuance is recommended in those who have experienced severe adverse reaction to the eyes, liver, pancreas, and lungs [12]. New autoimmune disease symptoms, such as joint pain, myalgia, and dyspnea, appear. The mechanisms of ICIS-related toxicity are not fully understood and can occur at any stage of immunotherapy, even after discontinuation. Most toxicities occurred within 30 weeks of first use. For grade 3-4 toxicity, where there is no improvement after 48-72 hours of adequate glucocorticoid administration, the possibility of steroid resistance should be considered and other immunosuppressive therapy should be initiated as soon as possible with multidisciplinary consultation [11].

5.2. Resistance to ICIs

When it comes to cancer treatment, resistance to ICIs is a significant problem that may be broadly classified into two types: acquired resistance and primary resistance. Primary resistance is when a patient does not respond to ICIs at all and the disease progresses rapidly or eventually. Primary drug resistance may be related to the characteristics of tumor cells themselves, such as tumor mutation load, DNA dMMR, and genomic MSI, It may enhance the effectiveness of immunotherapy by increasing tumor-associated neoantigens. When the tumor's mutation burden and the dMMR/MSI ratio are low, less effective neoantigens are produced, which could result in main medication resistance. Acquired resistance refers to patients who have an initial response to treatment for a period of time and then eventually develop disease progression. Acquired drug resistance may be related to a variety of mechanisms, including changes in tumor cell signaling pathways, deficiency and presentation of tumor antigens, aggregation of immunosuppressive cells, and metabolic changes in TME [5].

T cell activation is largely responsible for the various mechanisms of resistance to ICIs, which include decreased cytotoxicity of T cells, defective T cell migration and/or infiltration, and inadequate antigen identification by T cells. Resistance mechanisms can be classified into resistance mechanisms

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associated with T cell effector activities, T cell motility and/or infiltration, and antigen recognition. There are many factors affecting immunotherapy resistance, and one of the main causes of immunotherapy resistance is thought to be the metabolic reprogramming of immune cells in TME. As a new research field, immune metabolism provides a new perspective for us to understand immunotherapy resistance [13].

Research has demonstrated that dMMR is a biomarker that may be used to forecast how well ICIs will work. In addition, ICI resistance is linked to risk factors such as EGFR/ALK/ROS1 mutations and getting ICI therapy as a second-line treatment [14]. To increase ICI's efficacy and expand our knowledge of the processes underlying cancer treatment resistance. Finding novel, efficient, and bearable combination treatments is essential. Cutting-edge treatments that reactivate T cell responses after resistance is established are also being investigated [15].

6. ICIs Modified Regimen for Treatment

6.1. Combination treatment strategy

Combination therapy is becoming a key strategy to break through the bottleneck of cancer treatment. For example, in response to the immunosuppression caused by SPP1hi-TAMs through the adenosine signaling pathway, the research team explored the possibility of adenosine A2A receptor (A2AR) inhibitors in combination with ICIs, and preliminary results confirmed its potential application [16].

6.2. Bispecific Antibodies

The development of ICIs based on novel ICs and bispecial antibodies targeting multiple ICs for cancer therapy is a major research focus at present. Bispecific antibodies can simultaneously target two different antigens, act on two synergistic or complementary signaling pathways, and effectively enhance the anti-tumor immunity of ICIs and reduce the drug resistance of ICIs. A variety of bispecic antibodies targeting different ICs have been developed, such as anti-PD-1/TIM-3, anti-PD-L1/TIGIT, and anti-PD-1/CTLA-4, and numerous clinical trials are assessing their effectiveness and safety [1].

6.3. Improvement of Drug Resistance Mechanism

There are various mechanisms of drug resistance, such as reduced T cell cytotoxicity, poor T cell motility and/or infiltration, and insufficient antigen identification by T cells, the majority of which are connected to the T cell activation process. Therefore, modified regiments targeting these resistance mechanisms are being investigated to enhance ICI treatment's clinical results.

6.4. Combination Immunotherapy

Immunocombination therapy is the primary clinical response strategy, including double immunotherapy combination, immune-chemotherapy combination, immune-radiotherapy combination, immune-targeting combination, immune-anti-angiogenesis combination and so on. For instance, the combination of nebuliumab and ipilimumab is safe and well tolerated by patients, and it offers a greater therapeutic benefit for the first-line therapy of advanced non-small cell lung cancer.

6.5. LAG-3 Blocking Therapy

LAG-3 is another ICs whose blocking can enhance the proliferation and cytokine secretion of TILs and enhance anti-tumor immunity. The blocking of LAG-3 has shown an impact on preclinical cancer therapy models that inhibits the growth of tumors. LAG-3 molecules are crucial for preserving immune system homeostasis, encouraging tumor immune escape, and adversely regulating T cells.

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As one of the new targets, LAG-3 has great potential in tumor immunotherapy [17]. Studies of patients with melanoma, It has been discovered that LAG-3 is expressed on Treg cells in peripheral blood and tumor tissues in colorectal and non-small cell lung cancer. Treg cells that express LAG-3 generate high quantities of the immunomodulatory cytokines IL-10 and TGF-β and prevent TIL activation [18]. Like PD-1, LAG-3 plays a role in the immunological escape mechanism of malignancies. Currently, the main suppression methods developed for the immunotherapy of LAG-3 are monoclonal antibody or dual antibody that targets LAG-3 and the LAG-3-IG fusion protein.

6.6. New Generation ICIs Therapy Combination

6.6.1. ICIs+ Chemotherapy

Chemotherapy is thought to be immunosuppressive to rapidly proliferating cells, and recent studies have found that chemotherapy drugs can have a variety of immunomodulatory effects on cells under appropriate dosage, so they can work together with ICIs therapy. Chemical drugs can increase the immunological response using a number of methods, such as anthracyclines, camptothecin derivatives, cyclophosphamide lamps can promote the immunogenic death of tumor cells; Some chemotherapeutic drugs, such as camptothecin derivatives, can enhance T cell X's capacity to identify tumor cells and enhance its killing effect by directly increasing antigen expression [19,20]. Similar to how viral infections do, anthracyclines can similarly trigger an immune response, directly stimulating T cell activation; Paclitaxel, gemcitabine and other drugs can promote the invasion of ICIs, and then enhance the synergistic action of immune cells in the tumor site.

6.6.2. ICIs+ Radiation Therapy

Radiation therapy serves as the foundation for the combination of ICIs and radiation therapy because of its capacity to stimulate immunological responses and activate immune cells.

The Duvalizumab and radiation group had a significantly higher 1-year overall survival rate and progression-free survival rate (66.3% and 17.2 months) than the placebo group (55.6% and 5.6 months) in the clinical study of patients with incurable non-small cell lung cancer, and the time of tumor metastasis was delayed [21]. This significantly reflects the advantages of ICIs combined with radiotherapy. Radiation therapy can also enhance immunity using a range of methods: Apart from eliminating tumor cells directly by rupturing the double strand of DNA, radiation therapy can also activate immune cells and promote the killing of tumor; It can also make tumor cells release antigen, enhance immune cell infiltration and tumor identification. By enhancing the secretion of IFN-γ by T cells, the killing ability of immune cells can be improved, and at the same time, the up-regulation of tumor cells MHC-I can be promoted, the recognition of antigen can be increased, and the immunity can be further enhanced. Radiotherapy can also show a "distal effect", that is a reduction and regression of tumors far from the site of irradiation. This is related to the release of associated antigens, DAMP and other "in situ vaccine" effects in tumor cells at the site of irradiation, and the production of nitric oxide molecules by irradiation. Increased tumor immunogenicity after radiation therapy promotes systemic T cell response, mediates systemic anti-tumor response, and thus exerts efficacy on non-irradiated sites.

6.6.3. ICIs+ Tumor Vaccine

Tumor vaccines deliver tumor antigen or nucleic acid substances encoding antigen to the tumor site, thereby stimulating a powerful immune response of the body to achieve the purpose of killing tumor efficiently. Adequate infiltration of immune cells is a prerequisite for the efficacy of ICIs. However, many tumors are "cold tumors" and lack sufficient TILs, resulting in poor efficacy of ICIs treatment.

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One of the prominent effects of tumor vaccines is to increase the infiltration and activation of T cells. Therefore, the combination of tumor vaccine and ICIs therapy is conducive to fully activating the immune system and enhancing the killing effect on tumors. An oncolytic virus vaccination called T-VEV is used to treat melanoma that is incurable or recurring. Patients in the combination treatment group had a higher objective response rate in the Phase II clinical trial of ipilimumab-assisted melanoma treatment, the combination treatment not only reduced the tumor at the administration site, but also played a systemic role, and 52% of patients had a reduction in visceral lesions [22]. According to the aforementioned research, a possible anti-tumor method is the combination of ICIs therapy with tumor vaccination.

6.6.4. ICIs+ Other Therapies

Other therapies include thermotherapy, antiangiogenic therapy, cytokine therapy, adoptive cell therapy, and the combination of two ICIs. Compared with traditional therapy, this new type of therapy can more effectively activate T cell activity, stimulate the increase of CD4+(CD8+)T cell number, or make the immune conditions that target the tumor site more suitable for the drug to work,and significantly improve the anti-tumor effect.

7. Conclusion

This article reviews the use of ICIs in tumor therapy in recent years, especially the recent utilization of PD-1 or PD-L1 antibody therapy (which has become the most promising new therapy among tumor therapy), and analyzes the key relationship between ICIs and tumor therapy. ICIs drugs can block IC molecules on tumor cells. Turn on the immune system and get rid of the cancerous cells. Combined with the existing clinical studies and the currently approved ICIs drugs for clinical tumor therapy, this paper reveals the reasons why ICIs drugs change the existing tumor therapy pattern. The advantages and disadvantages of the current ICIs application are deeply explored, and the existing disadvantages are analyzed. Through the analysis of this paper, it is found that the main advantages of ICIs are to increase the long-term survival rate of severe cases, small adverse reactions, long-lasting clinical benefits. In addition, ICIs is non-specific to the removal of T cell immunosuppression, so it can lead to a wide range of immune cell activation. ICIs also has the potential to be used in combination with other therapies to attack tumor cells from different angles, significantly increasing the likelihood of a cure. However, there are still problems of drug resistance and drug toxicity in the treatment of tumors with ICIs drugs. Since the mechanism of immunomolecule-induced drug resistance of ICIs depends on signaling pathways and related factors, defects in the antigen presenting mechanism and IFN-γ signaling pathway will lead to resistance to ICIs drugs. ICIs may also lead to a series of irAEs, toxicity can occur in any tissue and any organ, common manifestations include fatigue, itching, rash and diarrhea, and severe irAEs can be life-threatening. Several irAEs management guides have been published.

Addressing the above side effects is the trend of future clinical research on ICIs drugs, addressing the existing drawbacks while looking forward to possible technological advances and its potential for patient management, including reducing the occurrence of irAEs, studying new ICs and combination therapy of ICIs, and developing broader prospects for the treatment of ICIs against cancer.

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