Checkpoint Inhibitors: Limitations and Potential Strategies

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Abstract. Immune checkpoint inhibitors (ICIs), as monoclonal antibodies, function when combining with three major types of immune checkpoints which include cytotoxic T lymphocyte antigen 4 (CTLA4), programmed death 1 (PD-1) and PD1 ligand (PD-L1). In the progress, ICIs prevent these checkpoints from releasing anti-autoimmune signaling, which results in an antitumor immune response, thus in certain cases producing prolonged and profound benefits. Till now, ICI therapy has revolutionized the treatment of various malignancies. For instance, hepatoma, lymphoma, melanoma and so on, with the most severe effects observed in metastatic melanoma, a kind of cancer, which seldom responds to traditional treatments and has a historically low average survival time of under a year [1]. However, the toxicity of ICI and the resistance patients have to it restrict the number of patients achieving effective responses. This review systematically summarizes the limitations and the current potential strategies for a safe and effective anticancer immune response following ICI therapy.

Keywords: Immune Checkpoint Inhibitors, Toxicities, Resistance.

1. Introduction

Recently, despite the significant improvements in radiotherapy, chemotherapy and surgery, cancer still ranks the first among various diseases in the aspect of the rate of morbidity and mortality. This means the discovery of successful therapies is still full of difficulties and traditional methods are under great urgency to be improved. Fortunately, immunotherapy, which is one of the novel methods of treating malignant tumors, has achieved great progress in the past ten years. Immune checkpoint inhibitors (ICIs) are typical of this promising therapy.

Tumor cells are known to elude the host immunological response by exploiting the checkpoint molecules to suppress T-cell function. Thus, ICIs work through a variety of mechanisms that fight against the immunosuppression and help to bring immune attack towards cancer back, meaning to reactivate T-cell function. As monoclonal antibodies, ICIs currently are designed to target cytotoxic T lymphocyte antigen 4 (CTLA4), programmed death 1 (PD-1) and PD1 ligand (PD-L1). Among them, an antibody against CTLA4, also named ipilimumab, was the first ICI drug to be recognized to treat metastatic melanoma, which is a skin tumor owing to the uncontrollable proliferation and mutation of melanocytes in the basal layer of the skin [2]. The second category of ICIs is the antibodies which can competitively obstacle the inhibitory receptor PD-1 on T cells, which thwarts active T cell responses by interacting with its ligands PD-L1 and PD-L2. To date, anti-PD-1 antibodies like nivolumab and pembrolizumab are FDA authorized. The two types of drugs above were both first applied to treat melanomas in their advanced stage but later were authorized for other malignancies' treatment as well. The last group of ICIs is anti-PD-L1, which have three main representatives as atezolizumab, durvalumab, and avelumab. Different from anti-CTLA4 and anti-PD-1, anti-PD-L1 was primarily approved for the treatment of non-small cell lung cancer (NSCLC), Merkel cell carcinoma, urothelial carcinoma. These drugs are accepted as both monotherapy and combined therapy for a variety of cancer types.

However, the immunostimulation of ICIs lacks site specification, which results in toxicities acting on normal tissues or organs, thus side effects can occur as clinical applications with checkpoint inhibition grows. Additionally, the problem exists that many patients and cancers respond poorly or even do not respond to ICI therapy and patients who have been diagnosed to be cured by ICIs experience dramatic tumor regression after a few months. This review summarizes the limitations of

ICIs which have been discovered till now and provides potential strategies to overcome some of the limitations.

2. Immune-related adverse events (irAEs) of ICIs

Many toxicities are originated from the non-specific immunostimualtion of ICIs which resemble autoimmune diseases and have been predefined in clinical trials as immune-related adverse events (irAEs). IrAEs are indirectly caused by checkpoint inhibitors, due to their non-specific immunostimulation, ultimately resulting in an immune-based assault on healthy tissues,

The side effects or the toxicities can be generally divided into six aspects: systemic adverse events, dermatologic adverse events, hormonal adverse events, gastrointestinal adverse events, respiratory adverse events and other uncommon adverse events. Among them, systemic adverse events include fatigue which can be caused by hypothyroidism or hypophysis and infusion reactions manifesting as fever, wheeze and so on. Dermatologic adverse events, meaning skin toxicities, affects 40-50% of patients who were receiving anti-CTLA4 therapy and 30-40% of patients undergoing anti-PD-1 therapy [3]. Skin toxicity following anti-CTLA4 tends to be more severe and occur earlier, which is also dose-dependent, reflecting in a morbilliform eruption and pruritus, compared to anti-PD-1 monotherapy, which is associated more commonly with side effects like Lichenoid reactions, eczema and so on [4]. Hormonal adverse events can be divided into three parts: thyroid dysfunction, hypophysis and the rare ones. Patients receiving anti-PD-1 treatment alone tend to experience the first type while the second one is more related to anti-CTLA4 treatment. Gastrointestinal adverse events contain mainly hepatitis and colitis. The latter one causes the most severe side effects in people who receive anti-CTLA4 therapy, manifesting as diarrhea and a series of symptoms following. Although severe colitis is uncommon seen in patients undergoing anti-PD-1 therapy, it is a frequent reason for the discontinuation of patients receiving anti-CTLA4 treatment [5]. In this case, early diagnosis and medical intervention of colitis are essential, even it means stopping ICI therapy. Respiratory adverse events is uncommon but has high mortality once happening in ICI therapy. Correlative symptoms are pneumonitis, sarcoidosis, rheumatologic. Other uncommon adverse effects often take place in neurologic, renal and ocular hematologic ways. In summary, due to their vast diversity, these autoimmune toxicities have the potential to impact nearly every organ system.

However, their frequency of occurrence is different. More specifically, dermatitis and thyroiditis are two typical irAEs in ICIs. Myositis, hypophysis, adrenalitis, colitis, and hepatitis are less frequently occurring but perhaps more serious irAEs. The threatening consequences in the central nervous system and the heart are less frequent still [6]. Anti-CTLA4 monotherapy (ipilimumab) is more likely linked to hormonal and gastrointestinal events and much lower possibilities of respiratory toxicities when compared to anti-PD-1 or anti-PD-L1 treatment. Even though combination treatments have quite diverse modes of action, in certain circumstances ICIs have produced unexpected and unacceptably high toxicity rates when used in combination with other therapeutic types.

Whereas researches regarding cancer immunotherapy are quite productive, irAEs' mechanistic understanding related to ICIs is in poor situation. A study in 2017 found that toxicities triggered by the blockade of CTLA4 were in relation to early T cell repertoire diversification [7]. Additionally, gastrointestinal microbiota, genetics factors, the microenvironment and specific patients' immunological issues that contribute to the worsening of irAEs when receiving ICI regimen are suggested affecting the toxicity and response to the treatment in recent years.

3. Resistance of checkpoint inhibitors

Next issue is correlated with patients' resistance to ICIs. Although ICIs have witnessed considerable clinical success, response can vary and be unanticipated in cancer types that are hard to treat or are just emerging. The highest response rates are often related to higher tumor mutational burden (TMB), like lung, bladder and melanoma, compared with those malignancies with a relatively

lower TMB, like pancreas and prostate cancer [8]. Moreover, no matter what therapy patients receive to fight against tumors, their response can be variable according to individual differences. Some may respond positively while others might not, or even grow resistant to the therapy. Generally, the latter ones can often be classified into two subgroups based on ICI resistance: one subgroup with intrinsic resistance never has responses to regimen, and the other one with acquired resistance who starts with responses to regimen but ultimately develops disease progression.

The general mechanisms of ICI resistance include three types: tumor-intrinsic resistance, tumor-extrinsic resistance and others including patient-related considerations. Among them, tumor-intrinsic resistance consists three main causes [9]. First of all, low TMB inherently present in cancer cells cause absence of tumor antigens, resulting in decreased susceptibility or entire resistance to ICIs. Also, upon exposure to ICI therapy, the tumor may adjust due to gene variations associated with the presentation or processing of neoantigens, which means ICI resistance occurs. Thirdly, epigenetic modifications lead to production of altered cytokine and mutuations in multiple oncogenic signaling pathways, such as CDK4/6, MAPK, IFN-γ pathways, have participated in resistance to ICIs.

Components in immunosuppressive tumor microenvironment (TME) contribute to tumor-extrinsic resistance in both primary and acquired ways by decreasing pro-inflammatory mediators or increasing anti-inflammatory meidators. Particularly, the response to ICIs might be impacted by the tumor immunophenotype and three of them have been identified: immune-desert tumors, immune-excluded tumors and inflamed tumors. Among them, the immune-desert tumors as well as the immune-excluded ones are associated with low ICI effectiveness, whereas inflamed tumors are involved in response to ICI-based immunotherapy. [10].

Patient-specific factors linked to response to ICIs are more complex than former two types. For instance, the intesitinal microbiota significantly influences how the immune response is modulated. In other words, dysbiosis of them may probably influence the ICI resistance by activating dendritic cells, upregulating levels of MHC-II and increasing the number of effector T cells. Apart from that, gender appears to be another factor to consider. According to certain studies, male patients have a better response to ICIs than woman do because of the longer OS and PFS in the male group [11].

4. Potential strategies

Nowadays, the toxicities, the intricacy of tumor response and the mechanisms behind resistance in ICI therapy remain to be the major challenges. Fortunately, recent studies have found three key factors that can contribute to successful future therapeutics. They are enhancing T cell homing, minimizing T cell fatigue and interfering with the mononuclear phagocytic system in tumor microenvironment [12].

The first mechanism used for improvement is regulating T cell homing. T cell entrance into particular sites of tissues is normally organized by the complicated crosstalk made up of many cell types and soluble molecules. It is on the endothelial cells that the expression of pertinent adhesion molecules will be reduced when the growth of a tumor alters the normal tissue architecture, which can severely compromise T cell homing [13]. Currently, T cell homing deficiencies can be rescued by numerous therapeutic strategies using the method of diminishing the inhibitory factors or boosting the ability of T cells to migrate. For example, some combination treatments that target PD1, PDL1, or PDL2 as well as VEGF or VEGF receptor are authorized for use in clinical settings.

Another method of preventing T cell exhaustion is aimed at reversing transcriptional programs which can enhance T cell antitumor activity and restrict its function through the method of targeting specific components of fatigue like cytokines or immunosuppressive metabolites that are outside the cells.

The third direction is to inhibit the way that MPS functions. Mononuclear phagocytes participate in critical oncogenic processes, such as the immunosuppression and the angiogenic switch, in a protumor genic manner. The most significant components of MPS biology are preventing mononuclear phagocytes from being attracted to and engaging with expanding tumor areas or

preventing MPS from functioning as a support system for the TME. In the system, monocyte-derived dendritic cells are specialized to present antigens which will trigger antitumor immune responses.

5. Conclusions

ICI therapy has revolutionized the field of cancer immunotherapy and brought many obvious benefits to clinical patients. It is necessary to acknowledge that though widely used, even the most prominent ICI agents have their toxicities and patients' variable responses to them. Other challenges still exist as well. For example, the absence of pre-clinical animal models imitating the auto-immune toxicities observed in patient cases presents a significant obstacle to understanding ICI therapy and causes. A critical issue in this study is the creation of preclinical tumor mouse models utilizing autoimmunity-prone mice. But this is not the most emergent problem. Numerous studies show that there are certain signs of immuno-oncology (IO) drug development saturation, including a dearth of novel modes of action demonstrated in clinical settings, a stalemate in the approval process, and space saturation for just a few tumor indications and targets.

Fortunately, multiple studies have found the directions of improving ICI therapy. It may be possible to get around the checkpoint inhibitor bottlenecks that have previously encountered by finding cancer-specific weak spots that are vulnerable to immunomodulatory medicines and use improved checkpoint inhibitors combined with these novel medications. Furthermore, combinatorial targeting therapy will achieve the best therapeutic effect when the tumor cell is diagnosed to mutate and the TME components that prevent immune attack have been altered. Ultimately, all these prospective improvements can be concluded to the two objectives: to expand the patient population eligible for ICIs as well as to assist in the development and discovery of novel medicines soon.

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