Proceedings of the 3rd International Conference on Environmental Geoscience and Earth Ecology
DOI: 10.54254/2753-8818/94/2025.22375

The Challenges Faced by Immune Checkpoint Inhibitors and Strategies to Enhance Their Efficacy

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Abstract: Cancer has remained to be a huge global threat in 21 centuries. The immune checkpoint inhibitors (ICIs) mark a huge breakthrough in cancer immunotherapy by reactivating T-cell-mediated anti-tumor responses through blockade of inhibitory pathways like CTLA-4 and PD1/PDL1. Despite their clinical success, ICIs face some limitations. One of them is varying response rate. Some patients never respond to ICIs (primary resistance) and some others show resistance after initial response to ICIs (acquired resistance). Moreover, the incidence of immune-related adverse events (irAEs) that result from aberrant immune system activation increases with the use of ICIs which further complicates treatment and limits the use of ICIs. To overcome these limitations, biomarkers that predict the efficacy of ICIs like PDL1 expression, microsatellite instability (MSI-H), and mismatch repair deficiency (DMMR) have emerged, though sometimes not accurate. Furthermore, combination therapy that integrates different ICI agents and pair ICI with traditional cancer therapy is becoming increasingly used to overcome the resistance in mono ICI therapy. Emerging studies highlight the pivotal role of gut microbiome in modulating the response of ICIs. The gut microbiome intervention like fecal microbiota transplantation (FMT) has been proposed to increase the efficacy of ICIs. Optimizing the broader application of ICIs requires elucidating ICIs resistance mechanism to minimize the occurrence of resistance, enhancing biomarkers accuracy, and mitigating irAEs.

Keywords: immune checkpoint inhibitors, immune-related adverse events, predictive biomarker, gut microbiome, immunotherapy

1. Introduction

In the 21st century, cancer-generally defines as the malignant growth and proliferation of cells-have imposed a huge threat to global health. According to data from GLOBOCAN, there are around 10 million cancer-associated death and 20 million new cancer case in 2022 with annual incidence rates projected to continue rising in the coming decades [1]. Thus, the development of effective new cancer treatment could be critical. The human immune system has played a pivotal role in controlling and eliminating cancer cells through immune surveillance, a process where both innate and adaptive immunity identify cancer cells that escape cell's intrinsic tumor suppression mechanism and try to eliminate them before they become malignant tumor [2]. Thus, cancer immunotherapy, leveraging the immune system natural protective mechanism, has been proposed as a promising new treatment in addition to traditional cancer therapy (e.g. surgery, chemotherapy, radiation). However, cancer cells develop various ways to evade the destruction and detection of

DOI: 10.54254/2753-8818/94/2025.22375

immune system, collectively known as cancer immune evasion mechanisms. The mechanism generally falls into two categories: tumor cell intrinsic factors and extrinsic factors associated with the tumor microenvironment (TME). One major intrinsic immune evasion mechanism involves the expression of high-level immune checkpoint molecules [3]. Immune checkpoints molecules can broadly be defined as proteins that are involved in various coinhibitory signaling pathways which are crucial for maintaining immune self-tolerance. One common immune checkpoint molecule is CTLA-4.It suppresses the interaction between CD28 on T cells and B7 ligands on antigen-presenting cells which activating T cells. And thus, inhibiting T cells proliferation. The others are PD1/PDL1. The interaction between PD1 on T cells and PDL1 on other cells or tumor cells effectively inhibit T cells' effector function [4]. By activating these immune checkpoint pathways, the tumor cells inhibit the activity of T cells which are the major leukocyte in anti-tumor immune response.

To overcome these limitations, immune checkpoint inhibitors (ICIs)are become increasingly used cancer immunotherapy. ICIs function by blocking those checkpoint molecules and thus its inhibition pathways. By blocking these "brakes" for T-cell activation, common ICI such as ipilimumab (monoclonal antibody that block CTLA-4) and pembrolizumab(anti-PD1) restore T-cell anti-tumor activity. Clinical applications of ICIs have shown promising outcomes, particularly in case of metastatic melanoma, renal cell carcinoma, and ovarian cancer [5]. Despite the success, the ICIs face significant limitations. Most studies about ICIs point out they tend to have different response rates among patients. Less than half of patients achieve substantial clinical responses to a single ICI drug and many patients show resistance to ICIs [3,6]. Additionally, the use of ICIs increases the incidence of immune-related adverse events (irAEs). One major challenge that hinders the broader application of ICIs immunotherapy is to overcome ICIs resistance while trying to mitigate the irAEs. Several methods have been proposed to address this issue, include the use of combination therapy to overcome the resistance of ICIs, using predictive biomarkers to predict ICIs efficacy before the start of immunotherapy and modulation of gut microbiome to increase the efficacy of ICIs. This review discusses the current understanding of the resistance of ICIs, mechanisms for irAEs, and how to optimize the outcome for the ICI immunotherapy.

2. The Resistance to Immune Checkpoint Inhibitors

Resistance to ICIs can be divided into primary resistance and acquired resistance. The mechanism for each resistance can generally be due to intrinsic factors and TME-associated extrinsic factors [3]. The intrinsic factor commonly refers to characteristics within the tumor cells themselves and TME-associated extrinsic factors are factors that outside the tumor cell and in TME (tumor microenvironment) that influence the efficacy of immunotherapy.

Primary resistance means the patient never responds to ICIs. The immunotherapy failed to elicit proper respond at the start [6]. Several mechanisms for primary resistance have been proposed. The three main mechanisms are lack of immunogenicity, defects in antigen presentation machinery and immunosuppressive TME. The lack of immunogenicity is specific to the tumor type and case. The tumor that expresses less neo-antigens for T cell recognition generally shows less satisfactory response toward ICI treatment. Because if there is no T cells activity against tumor cells at the beginning, reactivating them won't be as effective. The lack of T cells infiltration at tumor site will have similar effect. One well known example of this kind of tumor is pancreatic ductal adenocarcinomas (PDACs). It expresses a median of 38 neo-antigen per tumor and that is far less than a more frequently mutated melanoma cancer which typically shows good respond to ICIs [7,8]. The defects in antigen presentation machinery refer to the case when MHC1 on tumor cells is loss or downregulated. Thus, the presentation of tumors associated antigen to cytotoxic T cells is inhibited which leads to the evasion of cancer [3]. Indeed, loss or downregulation of MHC1 due to

DOI: 10.54254/2753-8818/94/2025.22375

impaired B2M expression is often observed in ICI-resistant lung cancer [9]. The prevalence of immunosuppressive cells such as tumor-associated macrophages (TAMs), T regs and myeloid-derived suppressor cells (MDSCs) is also a main reason for ICI primary resistance. The existence of immune suppressive molecules produced by these cells such as IDO (indoleamine 2,3-dioxygenase) can inhibit the proliferation and clonal expansion of T cells [10].

Acquired resistance refers to the case when patients show resistance to ICI after a period of response. The previously responding tumor developing escaping mechanism for immune system due to the selection pressure under ICI treatment [11]. The acquired resistance is very common for ICI treatment. In a study with a median follow-up of 21 months, around 40% of patients with advanced melanoma discontinue their treatment of Pembrolizumab (anti-PD1) due to disease progression [12]. There are a variety of reasons for acquired resistance. An important one is the loss of tumor antigen expression (immunoediting). The constant interaction between tumor cells and immune system leads to new cancer cells that lack of expression of neoantigen and become insensitive to ICI treatment. The study of non-small-cell lung cancer shows that relapsing patients show loss of expression of tumor associated neoantigen [13]. Please note that these mechanisms are not exclusive to one type of resistance. Some mechanisms that cause primary resistance in some patients may lead to acquired resistance overtime in others and some factors that cause acquired resistance in some patients may present at the beginning for primary resistance patients.

3. The Toxicity of Immune Checkpoint Inhibitors and Immune-Related Adverse Events

The irAEs are common during the ICI treatment and the severity of irAEs range from mild to lethal. The irAEs can affect almost every part of the body. The most common affected organs are skin, colon, liver, lungs, kidneys, and heart [14]. The incidence and severity of irAEs are dependent on the type of ICI agent used. Generally, the anti-PD1 and anti-PDL1 trigger less mild and extreme irAEs compared to anti-CTLA4 in melanoma patients. The type of irAEs also vary with different ICI agents [15]. The specific toxicity of ICI may be more prevalent in specific cancer types. As an example, during anti-PD1 treatment, melanoma patients experience lower incidence of pneumonitis than NSCLC patients but experience higher incidence of gastrointestinal and skin irAEs [16].

There are many potential underlying mechanisms that lead to irAEs. One important cause for irAEs during ICI treatment could be the reactivated T cells may not only targeted the tumor cell but also attack healthy tissue that expresses similar nonspecific tumor associated antigen. In a study of 73 NSCLC patients receiving anti–PD1 therapy, researchers identify nine T-cell antigens that are present in both NSCLC tissue and skin. These shared antigens are shown to elicit both cd4+ and cd8+ cell response in vitro [17]. One probable cause of irAEs exacerbation is called epitope spreading. This occur when dying tumor cell releases self-antigen into pre-inflammatory environment (due to aberrant activation of autoreactive T-cells in ICI treatment) that exacerbates inflammation and irAEs [3]. Also, since the natural self-tolerance mechanism is disrupted, ICI treatment may exacerbate the pre-existing autoimmune disease or lead to new autoimmunity disease especially in patients who are predisposed to them [18]. It's important to note that the exact pathophysiology of irAEs has yet to be elucidated.

Interestingly, the onset of irAEs seems to positively correlate to efficacy of ICIs. The onset of irAEs has been proposed as a potential clinical biomarker to predict response for anti-PD1 and anti-PDL1 treatment. Patients who receive anti-PD1 and anti-PDL1 treatment and experience some extent of irAEs generally show improvements in progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) compared to those who don’t. However, this association is less consistence in patients receiving anti-CTLA-4 treatment [19]. The exact mechanism underlying this association is still being investigated and more study should be done to confirm this association is universal for various cancer types and patients.

DOI: 10.54254/2753-8818/94/2025.22375

4. Predictive Biomarkers Identified for the Efficacy of Immune Checkpoint Inhibitors

ICIs have been used to treat various cancers including melanoma and NSCLC. However, the patients' responses varied significantly. While the "responders" typically show delayed tumor progression and satisfactory objective response rate (ORR), the "non-responders" show unfavorable ORR and resistance to ICI. ICI treatment is expensive and may induce irAEs. So, several biomarkers have been proposed to predict the efficacy of ICI treatment aiming to provide each patient with their personalized cancer treatment and exclude "non-responders" from ICI treatment. The first one is the expression of PDL1. PDL1 is expressed by several immune cells and tumor cells which bind to PD1 on T cells and inhibit their anti-tumor activity. PDL1 expression is detected by immunohistochemistry (IHC) and is the first FDA approved and primary biomarker for ICI response [20]. Previously found the expression of PDL1 can be stimulated by inflammatory cytokines. Thus, the high expression of PDL1 typically means there is stronger immune response and inflammation in TME [21]. High expression of PDL1 also indicates there are a lot of activated T cells that inhibit by PD1-PDL1 interaction in TME. By removing that interaction through anti-PD1/PDL1 agent, these T cells' anti-tumor activity can be restored. In the KEYNOTE-048 study of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC), PDL1 expression level is positively correlated with ICI treatment effect. PDL1 positive patients typically show significant overall survival improvements toward pembrolizumab treatment compared to PDL1 negative patients [22].

Other established ICI biomarkers are microsatellite instability (MSI) and mismatch repair deficiency (DMMR). The DMMR system is crucial for repairing the error during DNA replication. DMMR often leads to accumulation of errors and mutations in short, repetitive DNA sequences called microsatellites, resulting in MSI [21]. MSI-H (microsatellite instability-high) and DMMR are most prevalent in colorectal cancer (CRC) and endometrial carcinoma [20]. The MSI/DMMR status is typically diagnosed by IHC and next-generation sequencing (NGS). Tumor with high microsatellite instability typically produce more neoantigens which makes it easier to recognize by immune cells which correspond to higher immune cells (including B cells, CD4+ T cells, and CD8+ T cells) infiltration in TME. Similarly, the increase in immune cell infiltration results in more active and inflammatory TME and better response to ICI treatment [14]. Interestingly, although the exact mechanism is unclear, MSI-H seems to correlate with increasing expression of PDL1 on tumor cells which make them more sensitive to ICI treatment [23]. Generally speaking, the MSI-H/DMMR patients show better response to ICI treatment. This association is observed in various cancer types, including colorectal cancer, gastric cancer and endometrial cancer [14]. However, despite their clinical value, these biomarkers are not perfect. Sometimes false positive or negative results may arise during detection of these biomarkers. People who are positive or negative to these biomarkers may not respond to ICI as expected. This limitation underscores the importance of identifying additional complementary biomarkers to enhance predictive accuracy. Comprehensive genomic profiling, which aims to measure and assess different biomarkers simultaneously to give a better prediction of ICI efficacy, has become increasingly popular.

5. Combination Therapy

ICIs have revolutionized the cancer therapy, but their efficacy is somehow limited to a subset of patients. Only around 20-40% of patients respond to single ICI agents (anti-PD1, anti-PDL1, anti-CTLA-4) [21]. To prevent tumor evasion and increase efficacy of ICI therapy, several combinational therapies have been proposed.

One approach involves pairing two distinct ICI, such as combining anti-CTLA-4 agents with anti-PD1/PDL1 inhibitors. This strategy aims to solve the issue that T cells reactivated by one ICI

DOI: 10.54254/2753-8818/94/2025.22375

agent may still be inhibited by other checkpoint molecules and their pathways. Different checkpoint molecules play a different role in T cells' regulation. As an example, CTLA-4 primarily influences the early stages of T cells' activation including clonal expansion and trafficking while PD1 mainly operates in peripheral tissues and regulates the downstream effector function of T cells [3]. So, using anti-PD1/PDL1 with CTLA-4 can have a synergetic effect that not only T cells' infiltration to the TME will increase, but also T cells' effector function within TME. Thus, this practice will lead to more long-lasting and robust anti-tumor response. In the study of 945 stage III or IV metastatic melanoma patients, the therapy that combines nivolumab(anti-PD1) and ipilimumab(anti-CTLA-4) significantly increases the median progression-free survival of patients compared to the group that only use single ICI agent especially for patients with PDL1–negative tumors [15]. This combination therapy has been approved by FDA in 2020 to treat various cancers including advanced melanomas and NSCLC [21]. However, it is important to note using more than one ICI agent at the same time may increase the incidence of irAEs due to the broader activation of T cells. The same study above indicates that the combination therapy group experience around 4-fold increases in grade 3 or 4 treatment related adverse events compared to groups that only use nivolumab and around 2-fold increases compared to group only use ipilimumab [15]. So balancing side effects and benefit of combination therapy is crucial.

Another common practice is to combine ICIs with conventional cancer therapies like chemotherapy. These traditional therapies aim to modify the TME which makes it more favorable for T cells and thus inducing potential synergistic effects. Chemotherapy can enhance the antitumor immune response through various ways such as eliminating or inhibiting the infiltration of immunosuppressive cells (MDSC, T regs, and tumor associated macrophages) in TME and induce death of immunogenic cells which cause release of tumor associated antigens [24]. Since different chemotherapy agents will affect TME differently, choosing the right one in combination with ICIs is important. In the study of small sample NSCLC patients, combining nivolumab with standard chemotherapy delay the tumor growth compared to group only receiving chemotherapy. The same synergy effect of ICI agent and chemotherapy is observed in head and neck squamous cell carcinoma mouse models. In both studies, combination therapy is generally well-tolerated, without significant increase in immune-related adverse events and increased incidence of certain toxicities that were mostly mild [3,24].

6. Gut Microbiome Modulation

The human microbiome refers to the diverse community of microorganisms, including bacteria, fungi, and viruses that inhabit various parts of the human body. These microorganisms are especially abundant in the gastrointestinal tract [21]. The gut microbiome (GM) is increasingly recognized to influence tumor biology through multiple mechanisms. Recent evidence further suggests GM is also associated with the efficacy of ICIs. The exact mechanism is unclear. One prevailing hypothesis is that higher microbial density in the gut might enhance the secretion of various cytokines such as IL-2, interferon-gamma, as well as antigen presentation [25, 26]. These factors collectively modulate T cells activity, thereby potentially enhancing the efficacy of ICI. One crucial application of characterizing a patient's GM is predicting his responses to ICI treatment. In addition to the general trend that higher baseline gut microbiome diversity is often associated with favorable clinical outcomes receiving ICI, specific bacterial taxa show associations with either positive or negative responses to ICI. For instance, in multiple studies, the abundance of certain species like Akkermansia muciniphila, Bifidobacterium pseudocatenulatum, and various members from the Lachnospiraceae and Ruminococcaceae families often have consistently been correlated with better ICI responses. Conversely, an enrichment of immunosuppressive bacteria like Eggerthellaceae, Veillonellaceae, and Gammaproteobacteria has been associated with reduced

DOI: 10.54254/2753-8818/94/2025.22375

response and resistance to ICI therapy [27]. However, there remains variability and limited reproducibility across studies regarding precise GM signatures, suggesting GM profiling should be used in combining with other ICI biomarkers to provide a more accurate prediction of ICI efficacy.

Given these insights, modulation of GM to promote beneficial microbial populations and suppress detrimental bacteria has been proposed as a promising strategy to enhance ICI efficacy. One critical approach involves minimizing the usage of antibiotics during ICI treatment. There is extensive evidence that indicates the use of antibiotics will lead to significant reduction of diversity of gut microbiomes and negatively impact ICI outcomes. In the study of NSCLC patients, patients who received antibiotics show underrepresentation of beneficial bacteria such as Ruminococcaceae and abundance of Hungatella which is generally associated with poorer ICI response in their feces. This suggests that antibiotics might deplete "good" bacteria linked to better ICI outcomes and promote the growth of "bad" bacteria. Similarly, the use of other drugs that affect gut microbiome such as proton pump inhibitors may also impair ICI effectiveness [27,28]. Another way is through fecal microbiota transplantation (FMT) which refers to transfer of fecal material, containing a community of microorganisms, from a healthy donor to a recipient. Preclinical mouse study has shown that FMT from mice responding favorably to ICI treatment can effectively restore responsiveness in germ-free or antibiotic-treated mice [27]. Moreover, clinical evidence from advanced melanoma patients indicates FMT can overcome their resistance to anti-PD1 agent [29]. Similarly, dietary intervention such as increasing dietary fiber intake, supplementation with certain beneficial bacteria (e.g., Bifidobacterium) might have potential synergistic effects when combined with ICIs, further highlighting the significant role dietary modification could play in optimizing cancer immunotherapy outcomes.

7. Conclusion

ICIs have revolutionized cancer immunotherapy. Different ICI agents are being used to treat various malignancies. However, the response to ICIs varies significantly between patients. The effective implementation and broad application of ICIs face some challenges. The first major challenge is resistance to ICI agents which can be categorized as primary and acquired resistance. Primary resistance which patients never respond to ICI mainly arise from tumor intrinsic factors such as lack of immunogenicity, defect in antigen presentation pathway and extrinsic immunosuppressive conditions within the tumor microenvironment. Acquired resistance that develops over initial response to ICI is often due to immunoediting that is induced by selective pressure. Notably, the mechanism for each resistance is not mutually exclusive and may overlap, underscoring the complexity in designing personalized cancer treatment. Concurrently, irAEs represent another critical concern during ICI therapy, with their varying organ-specificity and severity. The type of irAEs emerging during treatment is influenced by both the type of ICIs used and tumor. Interestingly, there is clinical evidence shows that the presence and irAEs may positively correlate with better respond to ICI treatment. Although promising, such correlation needs to be confirmed in more patients and cancer types.

In order to overcome the limitations and resistance that arise with monotherapy that use only single ICIs agent, combination therapy approaches have become increasingly used to enhance the overall efficacy of ICI treatment. There are different ICI combinations such as concurrent usage anti-CTLA-4 and anti-PD1/PDL1 agents, and combine ICI with traditional cancer therapies. Clinical evidence has shown superior clinical outcomes including improved progression-free survival and overall survival rates, although sometimes at the expense of increased incidence of irAEs. This suggests that effective and broad application of combination therapy mandates a nuanced balance between enhancing efficacy and mitigating the associated toxicity risks. Reliable biomarkers aiming for reducing unnecessary exposure to expensive and potentially toxic therapies

DOI: 10.54254/2753-8818/94/2025.22375

are very important for personalized ICI treatment. Currently, PDL1 expression, microsatellite instability high (MSI-H), and mismatch repair deficiency (DMMR) status are clinically established markers associated with improved responses. However, they are not always accurate and false-positive or false-negative outcomes persist. Furthermore, emerging research highlights the pivotal role of the gut microbiome as a determinant of ICI treatment responsiveness. Enhancing microbiome diversity and growth of beneficial bacteria through dietary intervention, avoiding using drug that disrupt microbiomes like antibiotic and proton pump inhibitors, and fecal microbiota transplantation are some novel ways to overcome the ICI resistance and increase the efficacy of ICI therapy.

In conclusion, a deeper understanding ICIs resistance mechanism, develop biomarkers that can more accurately predict ICIs responsiveness, mitigating the irAEs during combination therapy and develop more targeted microbiome interventions are very important to better utilize ICIs, enhance their therapeutic efficacy, and improve clinical outcome.

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