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Review Article

Immune-related adverse events from immune checkpoint inhibitors: Review of risk factors in clinical practice

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have significantly driven the oncology treatment landscape as they immensely shift better clinical outcomes among various type of cancers. Challenges of using this approach are, without doubt, the immune related adverse events (IrAEs). These can have vital impact to affect multiple organs and some cases lead to fatality. Therefore, risk stratification should be cautiously taken into consideration while clinicians are dealing with ICIs. In this article, the risk factors from clinical trials or real-world reports that relevant to onset, level of severity, and particular type of IrAEs were discussed in order to promote IrAEs prompt attention in clinical practice

1. INTRODUCTION

Immune checkpoint inhibitors (ICI) are among the current advancement of cancer therapy that has shifted paradigms to improve patient clinical outcomes in several types of cancer. Ipilimumab was the first agent of ICIs that retrieved United States Food and Drug Administration (USFDA) approval. These targeted at the specific immune cells, specifically T cells lymphocytes, to modulate the inherent immune-sensitive system and upregulate responses.

Normally, T-cells are produced in thymus and are responded to specific antigen. The activation of T-cell proliferation requires 2 signals. With signal one, T-cell activation begins with recognition of particular antigen via antigen-presenting cell (APC). The T-cell receptor (TCR) on both Cluster of differentiation 4 (CD4+) helper T cells and CD8+ cytotoxic T cells binds to the antigen in a structure called the major histocompatibility complex (MHC) on the surface of the APC2. Signal two is then needed as co-stimulant in order to respond to particular threat. At this step, the CD 28 on T-cell surface will bind to CD80 or CD86 at APC to initiate T-cell proliferation. However, soon after the signal 2 initiated, the production of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is also started. CTLA-4 competes with CD28 to mute the activation of T-cells, therefore, lessening immune response, in other word, an inhibitory signal[1,2].

Programmed cell death 1 (PD1) and its ligand are also key regulators of immune system to maintain self-tolerance.

They control T-cell response as a negative regulatory signal. PD1 is a transmembrane protein on activated T-cell and is upregulated in naïve T cells following the APC activation. Unlike the CTLA-4, PD-1 will only bind to its ligand (PD-L1) then deliver inhibitory signal to mitigate T-cell proliferation.

Several cancer cells escape the host immune responses by up-regulating those negative regulatory systems. Consequently, the inhibitory signal is prominent in cancer cells thereby less T cell lymphocytes scavenge the abnormal cells. Hence, targeting drugs at CTLA-4, PD-1 or PD-L1 to block the inhibitory signaling pathway will enhance T-cell function by increasing T-cell activity against tumor cells. There are 3 groups of ICIs that are categorized by mechanisms of action by targeting at 1) cytotoxic T-lymphocyte- associated protein 4 (anti-CTLA4) such as ipilimumab 2) programmed cell death-1 (anti-PD-1) such as nivolumab, pembrolizumab, and 3) programmed cell death ligand 1 (anti-PD-L1) include avelumab, atezolizumab and durvalumab.

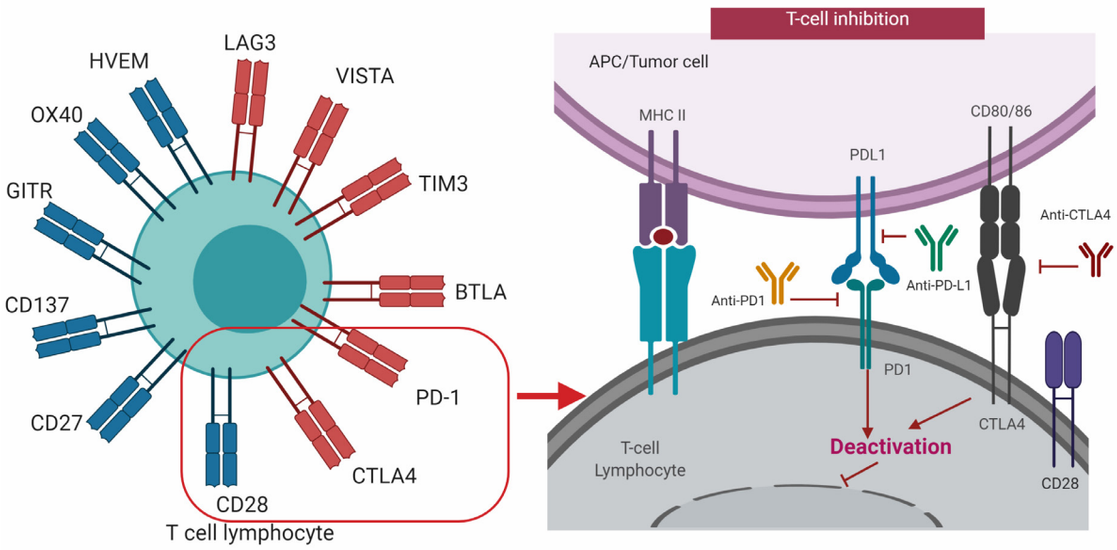

Figure 1. Mechanism of action of immune checkpoint inhibitors
BTLA – B and T lymphocyte attenuator, CD27 - cluster of differentiation 27, CD28 – cluster of differentiation 28, CD137 cluster of differentiation 137, CTLA4- cytotoxic T lymphocyte antigen 4, GITR – glucocorticoid induced tumor necrosis factor receptor, OX40 – O specific antigens of *Proteus Bacilli* serogroups 40 (also known as cluster of differentiation 134, CD134), HVEM – herpes virus entry mediator , PD1 – programmed cell death 1, LAG3 – lymphocyte activation gene 3, TIM3 – T-cell immunoglobulin and mucin-domain containing 3, VISTA – V domain Immunoglobulin G suppressor of T cell activation

Despite the revolutionized approach of treatment, ICIs carry significant concerns on the occurrences of immune related adverse events (IrAEs) which require early recognition and prompt intervention. These involve with multiple organ systems in several types of cancers. Risk factors associated IrAEs remain uncertain. However, understanding and determining predisposing risk factors for the development of IrAEs can provide invaluable help minimizing risk of severe complications[3,4].

2. INCIDENCE OF IrAEs

Michot JM et al. reported that IrAEs usually occur within 3-6 months after the initiation of the ICIs. All IrAE types accounted for up to approximately 90 percent and 70 percent for anti-CTLA4 and anti-PD-1/anti PD-L1, respectively. Most common types are grade 1 and 2 of skin or digestive system. Risk factors of IrAEs development seem to involve with anti-CTLA4 and the combination therapy of ICIs in clinical trials[5]. Peng-Fei Wang

and colleagues conducted a meta-analysis to study the IrAEs in cancer patients receiving the anti-PD-1 or anti-PD-L1 including nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and BMS-936559. The study found that the overall IrAEs incidence of all severity levels was 26.82% (95% CI, 21.73-32.61; I^2, 92.80) and 6.10 % in the severity level 3 and 4 (95% CI, 4.85-7.64; I^2, 52.00). The incidence of IrAEs varied based on the types of cancer and treatment that patients received. IrAEs are often associated with higher dose which more notably in anti-CTLA-4 agent. In contrast, toxicities with anti-PD-1 or anti-PD-L1 antibodies are reported to be dose-independent[6].

Wang DY et al. internationally reported 613 fatal ICIs toxic events from 2009 through January 2018. One hundred and ninety-three of patients who received anti–CTLA-4 were associated with deaths, most events were from colitis (70%), whereas anti–PD-1 or anti-PD-L1–related mortalities were often from pneumonitis (35%), hepatitis (22%), and neurotoxic effects (15%). Combination of anti-PD-1 and anti-CTLA-4 associated deaths were frequently from colitis (37%) and myocarditis (25%). Fatal toxicities typically occurred early after treatment initiation for combined ICIs therapy compared to anti–PD1/anti-PDL-1 monotherapy or ipilimumab monotherapy. The median time to onset of those treatments were at 14.5, 40, and 40 days, respectively. Myocarditis had the highest mortality rate (52 of 131 reported cases), whereas endocrine events and colitis had only 2% to 5% of death reports[7].

In real world practice, some IrAEs from ICIs may be higher than the data reported in the trials. According to study from the Palliative and Supportive Care in Oncology Symposium, IrAEs incidences were reported at 71.4% of patients who received nivolumab versus 25% for pembrolizumab and 3.6% for atezolizumab. These data were pooled from US commercial payer in non-small cell lung cancer database. The analysis of the claimed data showed overall rates with ICI therapy of 4.9% for pneumonitis, 5.9% for hypothyroidism, and 1.9% for hypophysitis at the time of last dose of ICIs treatment. Additionally, reports of IrAEs are still problematic even after drug discontinuation. At 60 days after the last dose, the rates for those IrAEs were 10.9% for pneumonitis, 7.0% for hypothyroidism, and 2.8% for hypophysitis[8]. All of those occurrences were greater than in the major clinical trials of ICIs. Therefore, this study had brought clinicians attention that the IrAEs from ICIs might carry some other risks beyond in clinical trials. Some clinical risk factors that observed in clinical trials and real practice were discussed here.

3. RISK FACTORS OF IMMUNE-RELATED ADVERSE EVENTS

3.1 Patient related factors

3.1.1. Gender

The study that conducted in patients with metastatic melanoma who were treated with anti-PD1 therapy at the Mayo Clinic from 2014 to 2017 described an intriguing result. The author observed the disproportionate number of women who were hospitalized for IrAEs. Those reports included colitis to diabetic ketoacidosis. Result also revealed that, among participants, 60% were men, 12% were premenopausal women, and 27% were postmenopausal women. Baseline characteristics were similar among groups. Premenopausal women had more likelihood to experience IrAEs (67%) than postmenopausal women (60%) and men (46%). Premenopausal women were also more likely than men to experience endocrinopathies (35% vs 10%) such as diabetes and thyroid abnormalities, and cutaneous reactions (25% vs 15%). All cases of diabetic ketoacidosis were observed in premenopausal women. No differences in grade 3 or greater toxicities were observed across groups. Clinical benefit of patients with IrAEs were more likely than those without IrAEs regardless of gender (68% vs 44%)[9]. The author concluded that premenopausal women with metastatic melanoma were more likely to develop IrAEs and discontinue treatment due to toxicity. However, it is important to note that there will be a need of more information to confirm this observation including other types of cancer.

3.1.2. Age

Several clinical controlled trials showed similar results that checkpoint inhibitors immunotherapy appears to have at least equivalent in efficacy and toxicity in those who were 65 years

old or greater and those who were <65 years of age[10]. A meta-analysis of randomized trials compared clinical efficacy and safety of anti–PD1/anti-PDL-1 (nivolumab, pembrolizumab, or atezolizumab) with anti-CTLA4, or chemotherapy or targeted therapy in various types of solid tumors. There was a consistent clinical advantages and adverse events including IrAEs for immunotherapy across all trials. There were no differences on IrAE concerns between those who were <65 and 65 years old or greater. However, there were some unanswerable questions of IrAEs due to the lack of analysis in more vulnerable elderly age particularly patients who were 75 years or older[10,11].

Another study by Herin H et al. aimed to determine the relationship of chronological age associated IrAEs. The study was a retrospective and case-control study using data to perform safety analysis in patients who received nivolimab, ipilimumab, and pembrolizumab. Case group defined as patients who aged 70 years or older while controlled group designated in patients who were < 70 years old. There was statistically significant of IrAEs incidence among the case group versus the controlled group. The result showed that 22 % of case group had developed IrAEs whereas 13 % in controlled group (p-value = 0.05). Moreover, incidence of grade 1-2 of IrAEs was significantly higher in case group than controlled group ($p < 0.05$). Nonetheless, no significant difference was observed between the two groups for grade 3 or 4 of IrAEs[11]. The results from this study might create awareness of prescribing ICIs in elderly patients especially in those who are greater than 70 years old.

3.1.3. History of autoimmune diseases

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death receptor-1 (PD-1) share vital role in maintaining immunologic homeostasis. There is a major concern that blockade of these receptors could lead to exacerbations of underlying autoimmune conditions or immune-related toxicity. Additionally, data from animal models have found the flares of autoimmune conditions led to fatal consequences during anti-CTLA-4 therapy despite immunosuppressant[12]. Not surprisingly, many ICIs clinical trials extrapolated the animal models result to exclude patients who had history of autoimmune diseases especially with those who require immune suppression. Conclusions regarding treatment with ICIs in large numbers of such patients with autoimmune diseases is unknown.

Retrospective studies analyzed the outcomes from pre-existing autoimmune diseases with advanced melanoma patients who were treated with ipilimumab, pembrolizumab or nivolumab. With ipilimumab, the most extensive data were from retrospective case series of 30 patients. The most common autoimmune diseases included rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Exacerbation of underlying autoimmune conditions occurred in 8 of 30 patients (27 %) while 23 cases (34 %) developed a new IrAE reported in case series. All patients were successfully managed with corticosteroids without the cease of anti-CTLA4[13]. For anti PD-1/anti-PD-L1, patients also had pre-existing autoimmune disorder, 20 patients (38%) had a flare of the autoimmune disorder requiring immunosuppression. However, the majority of flare events were mild and manageable. There were 2 patients required discontinuation of anti PD-1/anti-PD-L1[14].

It is important to note that this could be challenging for clinicians to distinguish whether patients manifest the pre-existing autoimmune exacerbation or occurrences of IrAEs. These 2 conditions may appear at the same organs and share same clinical presentations. To confirm the diagnosis, biopsy of affected organs may be necessary. However, overall management of those 2 issues generally partake same approach which are the use of immunosuppressant such as corticosteroids. Thus, the confirmed result with invasive procedure may not be practical and provide sufficient benefit for overall management.

3.1.4. Kidney function

Currently, there are no recommendations for dose adjustment in renal impairment patients when using anti PD-1/anti PD-L1 and CTLA4 inhibitors. Dosage regimen is mainly calculated by patient's actual weight. However, based on recent retrospective evaluation of risk factors to IrAEs, study revealed that patients with impaired kidney function especially with stages 3 or greater is correlated with a higher risk of IrAEs (odds ratio; OR: 10.66; 95%CI 2.41 to 47.12)[15]. Proposed

mechanism of this circumstance may be partially explained by the increased inflammatory process in patients with poor kidney function. However, several confounding factors could not be ignored such as underlying diseases, cancer staging, and dosing of ICI. The authors hinted that monitoring the occurrences of IrAEs in patients with poor kidney function is vital. Future studies evaluating the requirement to determine whether renal-adjusted doses are appropriate are warranted.

4. TREATMENTS OR DISEASES RELATED IrAEs

4.1. Anti-CTLA-4 and anti-PD-1/PD-L1 Combination

Currently, the combination of ipilimumab and nivolumab has been established in many oncology guidelines to enhance clinical benefits as compared with single agent. In contrast to efficacy, approximately 40% of patients with advanced melanoma who received combination approach in clinical trials discontinued treatment because of adverse events (AEs). With combination therapy, IrAEs commonly appear earlier and last longer than single ICI. The likelihood of IrAEs is increased compared with CTLA-4 or PD-1/PD-L1 blockade alone[3,5]. To reiterate, death is also occurred in combination of PD-1/CTLA-4 which were frequently from colitis (7%) and myocarditis (25%). Median time to life threatening toxicities typically occurred for combination therapy, anti–PD-1, and ipilimumab monotherapy at 14.5, 40, and 40 days, respectively[7].

Recent data estimates hepatotoxicity about 13% from combined therapy with median time to onset at 2.1 months. Overall incidence of ALT elevations from baseline (with or without hepatotoxicity) could be higher to 17.6%[16]. In addition, recent meta-analysis of the pooled randomized controlled trials in advanced cancer patients who treated with nivolumab and ipilumumab have resulted in several interesting findings. The result showed that many reported IrAEs were higher in combination group including pneumonitis, diarrhea associated colitis, and hypophysitis with pooled OR of 4.45, 6.11, and 12.67 respectively when compared with nivolumab monotherapy[17]. However, those IrAEs seemed to be manageable with appropriate corticosteroid and/or immunosuppressant. Interestingly, no new toxicity profiles have been observed with the combination of these agents.

4.2. Immune checkpoint blocking agents plus targeted therapy

4.2.1. Vascular endothelial growth factor (VEGF) inhibitors

In addition to antiangiogenic property, VEGF blocking agents have been reported to modulate immune effects such as promoting T-cell trafficking, reducing myeloid derived suppressor cells (MDSCs), T-regulatory cells, and suppressive cytokines at the tumor microenvironment. As a result, the immune response in combination therapy with VEGF inhibitors cannot be ignored[18]. The preliminary clinical data on the safety of the combination of pembrolizumab and pazopanib (the VEGF-tyrosine kinase inhibitor) in advance renal cell carcinoma (RCC) causing significant hepatotoxicity[19]. However, another study from Nadal R et al reported contrary result. There were no differences of IrAEs in these combination therapy both in renal cell carcinoma and colorectal cancer patients[20, 21]. The question on clinical impact of combination therapy with subsequent VEGFR-inhibitor therapy remains inadequately described.

4.2.2. Sequential Anti-PD-1/PD-L1 and osimertinib

Most recent report of severe IrAEs in concurrent of PD-1 or PD-L1 inhibitor with osimertinib in non-small cell lung cancer patients has been described in the study from Schoenfeld AJ et al. Authors have found severe IrAEs occurred in 15% of the 41 patients who received a PD-1 or PD-L1 inhibitor (pembrolizumab, nivolumab, atezolizumab, or durvalumab) followed by the third-generation EGFR–tyrosine kinase inhibitor (TKI), osimertinib. Interestingly, none of the 29 individuals who were given osimertinib prior to PD-1 or PD-L1 inhibitor had developed IrAEs. All patients with IrAEs required corticosteroids and most of patients required hospitalization. The reported grade 3 or 4 IrAEs included pneumonitis, colitis, and hepatitis. The median time to events was 20 days after osimertinib. These IrAEs seem to only associate with osimertinib and none in first or second generation of EGFR TKIs. The proposed mechanism is still not elucidated but may involve with osimertinib enhancing T cell activity by increasing interferon (IFN) gamma induced MHC presentation[22]. Nonetheless, the

correlation of the third-generation EGFR-TKI treatment sequence after PD-1 or PD-L1 inhibitor and IrAEs requires more investigation.

4.2.3 BRAF inhibitors

An immunological response is partially explained the efficacy of RAF/MAPK inhibition through various mechanisms, including enhanced CD8 cell recruitment, reducing T-regulatory cell activity, increased expression of major histocompatibility complex (MHC) class I. Therefore, the immunological impact of using these combinations with ICIs should be monitored. However, several clinical trials reported no differences of IrAEs in melanoma patients where this combination of ICI and BRAF inhibitors is commonly practiced[23].

4.3. Immune checkpoint inhibitors combined with radiotherapy

Recently, Dwight HO and colleagues retrospectively review to examine the effects of the IrAEs on overall survival (OS) and safety of patients with lung cancer who were treated with nivolumab. Twenty-four patients (26.7%) reported pneumonitis (n = 8), thyroid dysfunction (n = 6) and rash / pruritus (n = 5). Others IrAEs include colitis, new onset diabetes, and autoimmune hepatitis. None of these patients resulted in a statistically significant in overall survival compared with others who had no IrAEs (median OS 5.8 vs 8.1 months, p-value = 0.11). The study also reported that exposure to thoracic radiation (TR) was not associated with pneumonitis occurrences[24].

Ionizing radiation possess immunogenic death in the tumor microenvironment which can turn into more antigenic effects specifically increasing numbers of antigen presentation by tumor cells, increased cytokine release, recruitment of T cells to the tumor microenvironment, and impaired dendritic cell function[25]. These consequences lead to clinical presentation potentially as pneumonitis. Pneumonitis is broadly defined as inflammation of the lung parenchyma and has been described in up to 10% of patients receiving anti-PD-1/PD-L1 therapy either alone or in

combination and appears to occur more in patients with lung cancer in clinical trials. Interestingly, this adverse event was not well-described in treatment of anti-CTLA-4 alone. The incidence of pneumonitis may be higher in some studies where anti-PD-1/PD-L1 are combined with other agents, such as chemotherapy and targeted therapies[24,26]. The risk factors for radiation pneumonitis concurrently with ICIs have been reported. The timing and schedule of RT sessions, dose intensity at the thoracic, pre-existing lung conditions, and circulating cytokines are included. However, controversial observations also described in several studies

4.4. Tumor burden

Sakata Y et al. reported a significant difference in tumor burden among lung cancer patients with severe IrAEs and those without severe IrAEs. The odds ratio of severe IrAEs and high tumor burden was 8.62 (95% CI = 1.96–37.9, p = 0.004) where they defined the size of lung tumor greater than 90 millimeters as high burden. The author additionally analyzed the prediction of this correlation and reported sensitivity and specificity at > 85.2%, and 60% respectively[26]. The authors also reported the better response of efficacy in patients who develop IrAEs. The underneath pathophysiology has not been well-explained. However, it might associate with the high tumor burden patients carry loads of neoantigen which will subsequently activate strong T cells activation especially during ICI therapy. Therefore, the use of ICI in this population may need extra care for IrAEs monitoring.

5. OTHER CONCURRENT MEDICATIONS

5.1. Proton pumps inhibitors

Recent studies have shown the gut microbiome modulates the efficacy of anti-PD1/PD-L1 by increasing the activity of CD8+ T-cells. Proton pump inhibitors (PPIs) have been known to affect the gut microbiome that might cause the change of defensive mechanism in gastrointestinal tract so that colitis may occur during the ICIs treatment. PPIs have long standing to be known as one of the risk factors of *Clostidium difficile* infection. Therefore, colitis should be in the monitoring plan after ICI initiation. Additionally, PPIs trigger host immune response by haptenization or having direct interaction with immune receptors and/or major histocompatibility complex (MHC) proteins[27].

This may interfere the activation of T cell during the concurrent treatment of ICIs and PPIs

Additional IrAEs relevant to PPIs are emerged. Recently, Shirali et al reported 6 cases with biopsy-proven acute tubular nephritis (ATN) during treatment with nivolumab or pembrolizumab in lung cancer patients. Five out of 6 cases in their report using PPIs concomitantly. Of these patients, kidney function returned to baseline in 4 cases after PPI discontinuation[28]. The author proposed that the blockade of PD-1 signaling modulate peripheral immune tolerance of PPI that had been used previously in those patients. However, based on the nature observational studies, it is not known whether ICIs therapy actually the only isolated cause of adverse events against PPI users. The author concluded that the result may only indicate the importance of reviewing concomitant medications known during the treatment with PD-1 blockade**.**

6. PROMISING DIRECTION OF IRAES PREDICTION

Several biomarkers are able to forecast clinical response with checkpoint inhibitors including the expression of programmed death ligand-1 (PD-L1), microsatellite instability (MSI), and tumor mutational burden (TMB). However, there are currently scant predictors to the onset or the severity of IrAEs. Not surprisingly, exploration of reliable biomarkers to determine patients at high risk for severe IrAEs are in pipeline of research such as auto-antibodies, T-cell epitope and auto-reactive T-cells, and microbiome diversity on immune tolerance[29]. In addition, the increased level of certain cytokine is also attractive to have more investigation. For example, IL-17, a pro-inflammatory cytokine, has been predominantly exerted in significant autoimmune diseases such as inflammatory bowel disease and multiple sclerosis. This cytokine plays vital role for T-cell activation pathway; therefore, may be a marker for therapy directing T-cell function[30]. Until then, carefully individualized treatment with ICIs and patient characteristic are still the main consideration of IrAEs management approach

7.CONCLUSION

Immune checkpoint inhibitors have significantly shifted cancer treatment landscape and improved overall survival and diseases progression among several types of cancers. Despite this success, these medications carry significant challenges particularly immune related adverse reactions that presented in multiple organs. Identification of potential risk factors such as type of ICIs, other combinations therapy and patient's underlying diseases may help clinicians' prompt recognition and adequate planning to offer best supportive care and prevent severe reactions

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