

Immune-related Adverse Events: Overview and Management Strategies for the Use of Immune Checkpoint Inhibitors

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Recent studies on T cell immunology have been instrumental in developing therapies to overcome cancer immune escape, and immune checkpoint inhibitors have emerged as one of the most promising therapeutic tools in advanced cancer patients. Immune checkpoint inhibitors (ICPIs) are monoclonal antibodies that modulate the effects of immune checkpoints. These include cytotoxic T lymphocyte antigen 4 and programmed cell death protein 1, which are co-inhibitory signals responsible for immune suppression. Despite their clinical benefits, ICPIs behave as general immune activators, exerting to several toxic effects called immune-related adverse events attributed to organ-specific inflammation. Here, we review ICPI toxicities, highlighting the importance of their early identification and proper management. (*J Rheum Dis* 2019;26:221-234)

Key Words. Immune checkpoint inhibitors, Immune-related adverse events, Adrenal cortex hormones, Programmed cell death protein 1, CTLA-4 antigen

INTRODUCTION

Concept of cancer immunotherapy

Cancer immunotherapy is a cancer therapeutic paradigm that has been rapidly changing in recent years, especially for metastatic disease treatment. Immunotherapy encompasses the development and use of new compounds to harness the patient's own immune system to fight cancer. The immune system's main function is not to fight cancer because cancer is a "recent" event. However, the concept of cancer immunotherapy starts from the following premise. Cancer arises from our own cells; the cells are not "foreign" like an infection. However, cancers arise because of gene mutations that may result in the expression of abnormal proteins on cancer cells. The abnormal cancer cell proteins could be recognized by the immune system. In such a case, does the immune system "recognize" cancer and destroy cancer cells?

The immune system exerts a strong selective pressure

during cancer progression, leading to immune tumor editing. Cancer cells often co-opt for immune suppressive and tolerance mechanisms to avoid immune destruction. The emergence of cancer immunotherapy is supported by accumulating knowledge about immunology in the carcinogenic process, which is to be summarized as follows. During the early phase of carcinogenesis, genetic and genomic alterations or aberrations drive the advent of tumor-associated antigens (TAAs) or determinants, which are normally recognized and removed by the host immune system. However, the accumulation of TAAs and immune-escaped cancer cells leads to immune evasion or disruption. Thus, cancer cells can evade immunosurveillance and progress through mechanisms like (1) loss of major histocompatibility complex or co-stimulatory molecules (including transforming growth factor and interleukin-10), (2) ineffective presentation of tumor antigens, (3) release of immunosuppressive factors, (4) T cell exhaustions (anergy), and (5) recruitment of immune sup-

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pressive cells (myeloid derived suppressor cells, tumor associated macrophage, neutrophil, regulatory T cell). In this review, we particularly focus on T cell checkpoint dysregulation and the suppression of antitumor immune response [1,2].

Definition of immune checkpoint inhibitors (ICPIs)

We already know that cancer cells can hijack immune checkpoints that act as “brakes” to escape immune detection. We hypothesize that we can make drugs, ICPIs, to “release the brake” and remove inhibitory T-cell activation signals that empower tumor-reactive T cells to overcome regulatory mechanisms and mount an effective antitumor response [3,4]. The immune checkpoint blockade suppresses T cell-negative co-stimulation to unleash antitumor T cell responses that recognize TAAs [5].

Importantly, the development of immune checkpoint blockade therapies was predicated by basic research that identified key regulatory mechanisms in T-cell activation. However, much remains to be elucidated, and further insight would be essential to rationally develop immunotherapeutic approaches. To summarize, immune checkpoints represent immunological brakes that block activating effects. They are crucial for self-tolerance, which prevents the immune system from attacking cells indiscriminately.

For the present, two molecules—cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand (PD-L1)—are active targets for therapeutic interventions to augment immunologic reaction against malignant cells. CTLA-4 (CD152) is expressed on the surface of CD4+ and CD8+ lymphocytes. It transmits an inhibitory signal to T cells by competing with co-stimulatory receptor CD28 for its B7 ligands, CD80 (B7-1) and CD86 (B7-2), which are present on antigen-presenting cells [6]. CTLA-4 binds CD80 and CD86 with greater affinity and avidity than CD28, enabling it to outcompete CD28 for its ligands. Blocking CTLA-4 using therapeutic CTLA-4 monoclonal antibodies like ipilimumab and tremelimumab releases CD28, which binds to B7 ligands to produce a stimulatory signal.

Another target, PD-1 (CD279), is a cell surface protein on T cells, B cells, and natural killer cells. Interacting with its ligands, PD-1 promotes programmed cell death of antigen-specific T-cells in lymph nodes. It also inhibits apoptosis in Treg cells. PD-L1 and PD-L2 promotes T cell exhaustion, which prevents cytotoxicity in cancer cells [5]. Its ligand, PD-L1 is expressed in a variety of cells in-

cluding cancer cells. High expression of PD-L1 is correlated with poor prognosis in several type of cancers. The PD-1:PD-L1 interaction results in T cell suppression (anergy, exhaustion, and death). Overexpression of PD-L1 by cancer cells activates the PD-1 pathway, which subsequently blocks the immune response by down-regulating T cell effector functions [7]. Therapeutic antibodies against PD-1, pembrolizumab and nivolumab, and those against PD-L1, durvalumab, avelumab, and atezolizumab, all block immune checkpoints from binding to their ligands. This releases the brakes and unleashes T cells. These antibodies—called ICPIs—have recently reshaped the therapeutic landscape in a variety of cancers including malignant melanoma, non-small cell lung cancer, colorectal cancer, and urothelial cancers [2]. Moreover, different conventional cancer treatment modalities—chemotherapy, radiotherapy, and anti-angiogenic therapy—are being tested in combination with ICPIs to achieve synergistic effects and overcome ICPI-related resistance.

Definition of immune-related adverse events (irAEs)

In contrast to conventional chemotherapy and targeted therapies, ICPIs can cause inflammatory side effects by promoting the activity of the immune system and causing a unique constellation of inflammatory toxicities that are known as irAEs. irAEs may warrant the cessation of therapy or the administration of immunosuppressive agents. irAEs most commonly involve the gastrointestinal (GI) tract, endocrine glands, skin, and liver. Less often, the central nervous system and cardiovascular, pulmonary, musculoskeletal, and hematologic systems are also involved. The incidence of irAEs of any grade is reported to range from 15% to 90% in single agent trials. The rate of severe irAEs requiring medical treatment and withdrawal of immunotherapy is approximate 0.5%~13%. They are sometimes fatal unless appropriately managed [8].

Here, we review the current literature on appropriate steps for patient evaluation with an eye toward the prompt diagnosis of irAEs. We also describe strategies for optimizing patient outcome with suitable treatments.

MAIN SUBJECTS

Assessment and general management principles for irAEs

1) Timing of irAE occurrence

The major pathophysiology of irAE is the non-specific

enhancement of the immune response driven by T-cell activation and subsequent inflammation in normal tissues. Knowing when suspected irAEs began manifestation is sometimes helpful in therapy. Most ipilimumab-related irAEs occur during the induction period, (1) cutaneous manifestation is the earliest to appear at 2~3 weeks after the first dose of ipilimumab, (2) GI toxicities like enterocolitis and hepatitis present approximately 5~10 and 12~16 weeks after the second and the third dose, respectively, (3) endocrinopathy appears from week 9 onwards after the fourth dose, (4) immune-mediated pneumonitis is documented 8~14 weeks after treatment initiation, and (5) nephritis appears much later after 14~42 weeks on immunotherapy [9].

However, similar temporal associations with the appearance of irAEs has not been described for PD-1/PDL-1 antagonists. Pembrolizumab has a median onset of moderate to severe toxicity around nine weeks compared to six weeks with ipilimumab. In a pooled analysis of patients treated with nivolumab, 54% of whom had been treated with ipilimumab, the median onset of skin irAEs was 5 weeks, gastrointestinal at 7.3 weeks, hepatic at 7.7 weeks, pulmonary at 8.9 weeks, endocrine at 10.4 weeks, and renal irAEs at 15.1 weeks [9]. Some patients exposed to ICPIs develop late-onset irAEs that may occur after treatment has been completed.

2) Patient selection and baseline assessment

Patients should be assessed for susceptibility to irAE development before treatment. Initial assessment consists of the patient/family history, general physical condition, underlying autoimmune diseases, baseline laboratory tests and radiological exams (mostly computed tomography [CT] scans of the chest, abdomen/pelvis and often brain magnetic resonance imaging [MRI]). Patients with a history of autoimmune disease or who are being actively treated for it are at risk for worsening the underlying autoimmune disease while on immunotherapy.

The standard system to describe toxicity in clinical trials is to assess and grade according to the Common Terminology Criteria for Adverse Events (CTCAE), and these may also be applied at the bedside. The severity of adverse events is graded on a scale from grade 1 to 5 (1=mild, 2=moderate, 3=severe, 4=life threatening, and 5=mortality related to toxicity). While the CTCAE provides a useful framework, they may underestimate some irAEs like pituitary dysfunction.

3) Clinical landscape of irAEs

Grade 3/4 toxicities occur in 5%~22% of patients undergoing ipilimumab therapy [10-12]. The most common irAE are dermatological (rash, pruritus) or GI (diarrhea, enterocolitis) toxicity. It is noteworthy that ipilimumab toxicity is dose-dependent, with toxicity frequency increasing at a 10 mg/kg dose (e.g., adjuvant setting in melanoma).

In contrast, anti-PD-1 therapies are generally less toxic compared to anti-CTLA4 therapy, with grade 3/4 events reported in approximately 5%~11% of patients treated with nivolumab and 8%~14% of patients treated with pembrolizumab [13-16]. Nivolumab-related irAEs are not dose-dependent; grade 3/4 pembrolizumab toxicities are somewhat higher at a dose of 10 mg/kg every 2 weeks than 2 mg/kg (U.S. Food and Drug Administration [FDA]-approved dose) or 10 mg/kg every 3 weeks [14]. The most common irAEs seen in anti-PD-1 therapy involve rash, pruritus, diarrhea, nausea, loss of appetite and arthralgia [16,17].

Certain irAEs are more common according to cancer types. Pneumonitis is more prevalent in lung cancer patients in whom pre-existing pulmonary inflammation (possibly from tobacco, previous lung damage or carcinogen exposure) can be implicated. The exclusive development of vitiligo is noteworthy in melanoma patients. Melanoma patients also have higher rates of colitis due in part to greater experience with ipilimumab. Hematologic toxicity is more commonly attributed to ICPIs in malignant lymphoma studies, which may represent a reporting bias though. Discovering and validating predictive biomarkers for other irAEs is an area of ongoing research. We might unearth novel irAEs as ICPIs become more widely used in other malignancies. Briefly, anti-PD-L1 antibodies do not seem to cause as many high-grade irAEs compared to anti-CTLA4 antibodies, but this is not conclusive due to the small number of studies.

4) Management strategy for irAEs

It is imperative for oncology personnel to be well-versed in the heterogeneous presentations of irAEs and to do comprehensive assessment for patients. Patient and caregiver education about the significance of early detection and prompt reporting is important for timely recognition and management. Education should include the discussion of key points about irAEs, criteria for early intervention, and confirmation of the patient's ability to verbalize symptoms. It should emphasize that symptoms

may be intermittent and can even occur weeks to months after completion of the treatment. Consultation with other specialties is also advisable. General guidelines for the management of irAEs using ipilimumab are described in the FDA Risk Evaluation and Management Strategies [18]. A similar approach is expected to apply to PD-1 inhibitors. Recently, Clinical Practice Guidelines were developed in accordance with the European Society for Medical Oncology (ESMO) standard operating procedures for Clinical Practice Guidelines development [19,20].

As a rule, the management of severe irAEs requires immediate interruption of the drug and initiation of corticosteroids. For patients with grade 2 toxicities, ICPIs should be withheld and not resumed until toxicity is grade 1 or lower. If symptoms do not resolve within a week, corticosteroids (prednisone 0.5 mg/kg/day or equivalent) must be initiated. On the other hand, for patients experiencing grade 3/4 irAEs, the drug should be permanently discontinued and high doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) should be started. When the symptoms subside to grade 1 or lower, steroids should be gradually tapered off over a month. However, in intractable cases, administration of infliximab (for GI toxicity) or mycophenolate (for hepatotoxicity) should be considered [21]. Following is sum-

mary of several general rules that are widely accepted irrespective of the affected organs, and a general irAE management guideline is summarized in Table 1.

- For grade 2 irAEs: ICPI should be interrupted and resumed when symptoms or laboratory values decrease to grade 1 or lower. Glucocorticoids (prednisone 0.5~1 mg/kg/day or equivalent) should be considered if symptoms persist for more than 1 week.

- For grade 3/4 irAEs: High doses of glucocorticoids (prednisone 1~2 mg/kg/day or equivalent) should be started. The glucocorticoids should be tapered off gradually when symptoms subside to grade 1 or lower. Patients on 20 mg or equivalent prednisone doses for at least 4 weeks should also consider prophylactic management against *Pneumocystis jirovecii*.

- If symptoms continue for more than 3 days on intravenous (IV) glucocorticoids, alternative immunosuppressive agents should be considered (infliximab 5 mg/kg; mycophenolate mofetil for hepatitis). Infliximab 5 mg/kg should be repeated after 2 weeks for persistent symptoms.

- For grade 4 irAEs: ICPIs should be discontinued permanently (except in endocrinopathies when controlled by proper hormone replacement). Therapy can be resumed in selected patients with grade 3 toxicities (see below organ-specific toxicities section).

Table 1. General management guideline of immune-related adverse events

Severity CTCAE grade	Type of patient care	Use of steroid	Use of additional immunosuppressive agents	Continuation of next cycle immunotherapy	Other medication
1	Outpatient	Generally, not necessary	Not recommended	Continue	Not recommended
2	Outpatient	Topical steroids or oral steroids: Prednisone 0.5~1 mg/kg/d	Not recommended	Suspend temporarily: outside skin or endocrine disorders, where immunotherapy can be maintained	Not recommended
3~4	Consider hospitalization according to the specific case	IV or oral steroids; prednisone or methylprednisolone 1~2 mg/kg/d for 48~72 hours, then reduce to 1 mg/kg/d; course of generally 2~4 weeks; steroids must be reduced gradually over a period of at least 1 month	Considered administration of infliximab (5 mg/Kg) and eventually repeat after 14 days; Consider mycophenolate mofetil (500 mg every 12 h)	Skipping a dose of immunotherapy or discontinuing the immunotherapy can be considered, depending on the benefit/risk ratio of each given situation; If grade 4 toxicity occurs, discontinue permanently	If a dose equivalent to 20 mg of prednisone is administered for over 4 weeks, consider prophylaxis for pneumocystis infections with trimethoprim/sulfamethoxazole (80+40 mg/d or 160/800 mg TIW)

CTCAE: common terminology criteria for adverse events, TIW: 3 times a week.

ICPIs should also be stopped permanently in the following circumstances:

- Grade 2 reactions lasting for 6 weeks or more. However, anti-PD-1/PD-L1 therapies can be continued in endocrinopathies when controlled by proper hormone replacement.
- Inability to reduce glucocorticoid dose to 7.5 mg prednisone or daily equivalent for patients treated with anti-CTLA-4 antibodies and less than 10 mg/day within 12 weeks for anti-PD-1 therapy.
- Grade 2~4 ocular toxicities not improving to grade 1 within 2 weeks after treatment with topical immunosuppression or requiring systemic treatment.

The mechanisms of action of commonly used immunomodulatory medications are summarized as follows, and communication with other specialists is highly recommended to combine expertise on non-steroid immunosuppression strategies.

(1) Steroids have various effects on T cells, B cells and macrophages, which include inhibition of cytokine or interleukin production, inhibition of neutrophil apoptosis, and reduced macrophage function.

(2) Infliximab is a monoclonal antibody that prevents tumor necrosis factor alpha (TNF- α) from binding to its receptors.

(3) Mycophenylate mofetil (MMF) suppresses inosine monophosphate dehydrogenase, an enzyme involved in nucleotide production, particularly in activated lymphocytes.

(4) Tacrolimus and cyclosporine are calcineurin inhibitors that limit transcription of interleukin-2, which is involved in T cell proliferation.

The association between irAEs and the efficacy of ICPIs is still controversial, and a recent retrospective analysis reported similar overall survival in patients who received immunosuppression. Combination immunotherapy has only been approved for metastatic melanoma. The onset of G3/4 toxicities for either monotherapy with nivolumab or combination immunotherapy differs, since irAEs may develop earlier in combination therapy and may start over a prolonged period of time.

Organ-specific adverse events and management

1) Cutaneous toxicity

Cutaneous toxicity is the most common and the earliest developing irAE, and it shows myriad clinical manifestations, including maculopapular, follicular, pustular, vesicular and acneiform eruptions. These were earlier categorized by Curry et al. [22] into 4 groups, according to

their histomorphology: (1) inflammatory, (2) immunobullous, (3) alterations of epidermal keratinocytes and (4) alterations of epidermal melanocytes. Approximately half of patients treated with ipilimumab will experience rash or pruritus, and rashes are often mild in severity and present after the first or second dose [23]. Skin biopsy usually reveals perivascular lymphocytic infiltrates extending deep into the dermis [24]. Rare cases of Steven-Johnson syndrome have also been reported [10,25]. Combination immunotherapy was associated with a higher rate of severe skin toxicity (2.9%) [26].

Regarding the maculopapular rash, the most frequent cutaneous toxicity, CTCAE classification proposes:

- Grade 1: macules/papules covering less than 10% the body surface area (BSA) with or without symptoms (e.g., pruritus, burning, tightness);
- Grade 2: macules/papules covering 10%~30% BSA with or without symptoms (like pruritus, burning, tightness); limiting instrumental activities of daily living (ADL);
- Grade 3: macules/papules covering more than 30% BSA with or without associated symptoms; limiting self-care ADL;
- Grade 4: papulopustular rash associated with life-threatening superinfection; Stevens-Johnson syndrome, toxic epidermal necrolysis, and bullous dermatitis covering more than 30% of BSA and requiring intensive care unit (ICU) admission.

Dermatological toxicity is also observed with anti-PD1 therapy (30%~40%) [27]. Interestingly, skin toxicity mainly develops in patients with melanoma. For example, vitiligo was reported in approximately 10% of patients [13,26], but it was not described in lung or renal cell carcinoma studies [28,29]. Notably, vitiligo was also shown to be predictive of a durable response [30]. Treatment management for skin toxicity can be summarized as follows.

- Grade 1/2 toxicity: ICPIs should be continued for at least 1 week. Treatment with topical emollients, antihistamines in the case of pruritus or topical mild strength corticosteroid creams should be started. ICPI should be re-initiated when at or below G1.
- Grade 3 toxicity: ICPI should be interrupted and treatment with topical emollients, antihistamines, and high strength corticosteroid creams should be start immediately.
- Grade 4 toxicity: ICPI should be discontinued permanently, the patient should be hospitalized and dermatological consultation for skin biopsy should be scheduled.

IV corticosteroids (1~2 mg/kg [methyl]prednisone) should be started, and steroids should be tapered off over 1 month after resolution of AE to grade 1 [11,25].

GI toxicity: diarrhea and enterocolitis

Diarrhea is a common clinical manifestation in ICPI treatment. Diarrhea is clinically different from enterocolitis, which involves abdominal pain and radiological and laboratory signs of colonic inflammation. Diarrhea most commonly arise within 6 weeks on ipilimumab or nivolumab and as late as 6 months on pembrolizumab [25,31]. Both conditions should be excluded from enterocolitis caused by *Clostridium difficile* and other pathogens.

In a phase III ipilimumab trial for melanoma, diarrhea of any grade was reported in 30% of patients. Grade 3/4 toxicity, defined as 7 or more stools above baseline, fever, ileus or peritoneal signs, was observed in 10% and was dose-dependent (10% at a 10 mg/kg dose vs. 1% at a 3 mg/kg dose) [10]. Meanwhile, enterocolitis appears to be less common, with an incidence of approximately 5% [10]. Endoscopic findings revealed mucosal edema with biopsies demonstrating neutrophilic, lymphocytic or mixed neutrophilic-lymphocytic infiltrates [32]. CT scan findings associated with ICPI-induced colitis included mesenteric engorgement and bowel wall thickening [33]. Diarrhea or colitis was less frequent with PD-1 blockers compared to CTLA-4 blockers, and G3/4 toxicity was seen in about 1% to 2% of cases [13,16,34]. Interestingly, patients who developed significant diarrhea and enterocolitis during CTLA-4 blockade were subsequently been treated with PD-1 antibodies without experiencing complications [35].

Management starts with maintaining oral hydration. In patients with mild diarrhea, administration of ICPIs should be continued without starting corticosteroids. Low residual diet and anti-motility agents like loperamide can help. Colonoscopy is reserved for patients with G2 or higher diarrhea or in cases where diagnosis is unclear. If G3/4 enterocolitis develops, ipilimumab should be permanently discontinued and high dose IV corticosteroids should be started [23,36]. If symptoms do not resolve in 3 days, treatment with 5 mg/kg anti-TNF antibody infliximab once every two weeks is recommended [37]. In infliximab-refractory cases, mycophenolate mofetil can be used. In rare cases, enterocolitis can result in perforation and require colostomy. Treatment management can be summarized as follows.

- Grade 1 toxicity, defined as fewer than 4 liquid stools per day over baseline; ICPI can be continued. High fiber/lactose diet should be avoided. Treatment with anti-diarrheal medication, like loperamide, should be prescribed.

- Grade 2 toxicity, defined as 4 to 6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes, ICPI should be interrupted and the patient should start with corticosteroids depending on the severity and other symptoms (either budesonide or oral corticosteroids 1 mg/kg). If the patient shows no improvement within 3 to 5 days, colonoscopy should be done and, in the case of colitis, infliximab 5 mg/kg should be administered.

- Grade 3/4 toxicity, defined as 7 or more liquid stools per day, is life-threatening. It requires hospitalization and isolation until the infection is treated. ICPI should be permanently discontinued and (methyl)prednisone 2 mg/kg IV should be initiated. Patients who respond to IV corticosteroids within 3 to 5 days should be switched to the oral formula, which should be tapered off over 8 to 12 weeks. Patients who do not respond to corticosteroids within 3 to 5 days should be transitioned to infliximab, unless it is contraindicated.

GI toxicity: hepatotoxicity

Hepatotoxicity has been observed with both anti-CTLA-4 and anti-PD-1 inhibitors. It occurs within 8~12 weeks after treatment initiation and generally manifests as elevation of levels of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Elevation of total bilirubin level is a rare consequence of prolonged periods of elevated liver enzyme levels [11]. The phase III melanoma trial of ipilimumab reported grade 2 hepatotoxicity in 2.5% in patients and the incidence of grade 3 to 5 events reached 2% [10]. In the large phase I trial of anti-PD-1 blockers, grade 1/2 liver dysfunction was noted in approximately 5% of patients, and grade 3~5 events were rare (1%) [16]. The incidence of hepatotoxicity is higher with the combination of ipilimumab and nivolumab, with grade 3/4 events up to 20% [26]. Liver biopsy may be considered to assist differential diagnosis. Lobular hepatitis indistinguishable from autoimmune hepatitis is commonly reported, and most cases are panlobular but inflammation may be confined to zone 3. Additional sinusoidal histiocytosis and central vein endothelitis may help identify ipilimumab-associated inflammation [26].

In the clinic, liver enzymes should be monitored regu-

larly prior to each dose of ICPIs. Management of hepatotoxicity starts by ruling out other liver injury etiologies, including concomitant medications, alcohol consumption, and combined viral hepatitis. Radiological studies should be performed to exclude metastatic disease. In the case of immune-related hepatitis, CT scan can show surface nodularity, intrahepatic biliary dilatation, varices, and ascites.

Treatment with systemic corticosteroids should not be delayed [25]. As immune-related hepatitis may persist, a minimum of a three-week treatment with subsequent tapering of the dose is required. For grade 2 hepatotoxicity, defined as AST or ALT values 2.5 to 5 times the upper limit of normal (ULN) and total bilirubin values between 1.5 to 3 ULN, treatment with ICPIs should be withheld. Steroid therapy should continue until toxicity resolves to grade 0 or 1. For grade 3/4 immune-related hepatitis (AST/ALT values above 5 times the ULN or total bilirubin level above 3 times ULN) the drug should be permanently discontinued and liver biopsy could be considered. Hospitalization is required if liver enzyme levels are above 8 times ULN. In rare cases of corticosteroid refractory hepatitis, mycophenolate mofetil (500 mg every 12 hours) should be given [11,25]. Infliximab should not be administered, since it carries a risk of hepatotoxicity.

- Grade 2 hepatitis: ICPI should be withheld and AST/ALT levels should be closely monitored (1~2 times/week). If there is no improvement in a week, treatment with (methyl)prednisone (0.5~1 mg/kg) should be started. This should be tapered off over several weeks under close monitoring of AST/ALT and bilirubin levels.

- Grade 3 hepatitis: ICPI should be discontinued and treatment with (methyl)prednisone 1~2 mg/kg should be immediately started. If there is no improvement in 2 to 3 days, MMF (1,000 mg 3x daily) should be added. Immunosuppression should be tapered off over 4 to 6 weeks under close monitoring of AST/ALT and bilirubin levels.

- Grade 4 hepatitis: ICPI should be permanently discontinued, hospitalization and initiation of (methyl)prednisone 2 mg/kg IV is needed. MMF should be added if no improvement is observed within 2 to 3 days. A hepatology specialist should be consulted if no improvement is seen under double immunosuppression. Other immunosuppressive drugs to consider are anti-thymocyte globulin and tacrolimus. Sometimes the patient should be referred to experienced centers. Treatment should be tapered off over 6 weeks under close liver function

monitoring.

Endocrinopathies

Immunotherapy has been causatively associated with several endocrinopathies, including hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism. The median onset of endocrinopathy is about 7 weeks for ipilimumab and 10 weeks for nivolumab [11,38], and clinically significant endocrinopathies typically occur in less than 5% of patients on ipilimumab. For anti-PD-1 therapies, grade 3/4 events are rarer (approximately 1%) [39,40].

1) Hypophysitis

Hypophysitis, an inflammation of the anterior lobe of the pituitary gland, has been associated with ICPIs in patients with various malignancies. Large differences (0%~25%) in the incidence of ipilimumab-induced hypophysitis have been reported in different trials [41]. In the phase III trial of ipilimumab, severe hypophysitis was reported in 1.8% of patients [10]. On the other hand, tremelimumab has been much less frequently shown to be related to hypophysitis (0.5%~4%) [42]. Similarly, hypophysitis is a rare event with anti-PD-1 antibodies [34,43]. The median time to onset is approximately 2 to 4 months after treatment initiation, but delayed presentations can occur [44,45].

The pathophysiology of anti-CTLA4-induced hypophysitis remains unclear. In a mouse model, researchers noted low-level ectopic CTLA4 RNA and protein expression on thyrotropin and prolactin secreting cells of the pituitary gland [32]. Anti-CTLA4 treatment could lead to mononuclear cell infiltration in the pituitary gland, anti-pituitary antibodies and activation of the complement cascade in these animals, causing inflammation of the gland like what was observed in full-blown hypophysitis patients [46].

Hypophysitis presents with non-specific symptoms like headache, fatigue, and visual disturbances. A swollen or enlarged pituitary gland may be visible in brain MRIs [47]. Diagnosis is based on low pituitary hormone levels (adrenocorticotropic hormone [ACTH], follicle stimulating hormone, thyroid-stimulating hormone [TSH], luteinizing hormone and growth hormone), and differential diagnosis includes primary hypothyroidism (low thyroxine, high TSH) and primary adrenal insufficiency (low cortisol).

In grade 1 hypophysitis, defined as asymptomatic or

mild symptoms, only clinical or diagnostic observation is recommended. In any grade 2 or higher hypophysitis which limits self-care ADL (headache, fatigue, sepsis, severe ataxia), ICPI should be interrupted and high-dose corticosteroids should be started (prednisone 1 mg/kg daily). Permanent discontinuation of the drug is recommended for grade 3/4 toxicities. Endocrinology consultation and long-term supplementation of affected hormones due to secondary hypothyroidism and hypoadrenalism is necessary [25]. Long-term supplementation of affected hormones is often required, including secondary hypothyroidism requiring levothyroxine replacement or secondary hypoadrenalism requiring replacement hydrocortisone. In most cases, the immune checkpoint inhibition can be continued. Long-term HRT is required in most patients.

2) Thyroid gland dysfunction

Both hyper- and hypothyroidism have been reported, but hypothyroid disorders are more common than hyperthyroidism [25]. Still, little is known about the pathogenesis of thyroid disorders following ICPIs. It is thought to be mediated by T cells rather than B cell autoimmunity. Hypothyroidism is more common with anti-PD-1 therapies than with ipilimumab 3 mg/kg, but a higher incidence can be seen at high doses (10 mg/kg) [26, 34,43,48].

Hypothyroidism is usually subclinical; hormone replacement therapy with levothyroxine can be initiated and ICPI treatment can be continued without interruption. If concurrent hypophysitis is suspected (low TSH, low T4), treatment should not be solely based on TSH measurement. Instead, free thyroxine and T3 levels should also be considered [39]. On the other hand, hyperthyroidism is less common and might be a result of transient thyroiditis preceding hypothyroidism or TSH-receptor antibodies and Grave's disease [38]. Persistent hyperthyroidism should be treated as primary hyperthyroidism.

According to the ESMO guidelines, substitution with thyroid hormone should be considered in the case of fatigue or other complaints that could be attributed to hypothyroidism even with subclinical hypothyroidism. In symptomatic patients, especially in the case of hyperthyroidism, treatment with beta-blockers should be started (propranolol or atenolol). Rarely, carbimazole or steroids are used. In those cases, treatment with ICPIs should be interrupted until symptom recovery. Hormone

replacement therapy is usually long-lasting [19].

3) Adrenal insufficiency

Primary adrenal insufficiency was reported in 1.5%~2% of patients [39]. It should be distinguished from hypophysitis based on measurement of ACTH levels. Acute adrenal insufficiency (adrenal crisis) constitutes an emergency manifesting as dehydration, hypotension, hyperkalemia, and hyponatremia. Patients suspected to have adrenal crisis should be immediately hospitalized with prompt initiation of IV corticosteroids [11]. Endocrinology consultation is also warranted.

4) Type I diabetes mellitus

Type I diabetes mellitus (DM) can occur with both anti-CTLA-4 and anti-PD-1 blockade at a rate of less than approximately 1% [39]. Incidence is doubled with the use of combined ipilimumab and nivolumab [26]. Insulin treatment is recommended. Finally, cases of low testosterone have been reported in patients treated with ipilimumab [45].

5) General guideline of endocrinopathies

Below is the summary of management principles for endocrinopathy according to ESMO guidelines [19];

- In symptomatic hyperthyroidism of grade 1/2, ICPI should be interrupted and beta-blocker therapy (propranolol or atenolol/metoprolol) should be started. ICPI should be restarted when asymptomatic.
- In the case of hypothyroidism (rarely higher than grade 2), HRT should be started depending on the severity (50~100 μ g/day). The dose should be increased until TSH level is normal. In the case of thyroid gland inflammation, treatment with 1 mg/kg prednisone should be started orally. This should be tapered based on recovery from clinical symptoms. Interruption of ICPI treatment should be considered when symptomatic.
- In the case of hypophysitis (rarely higher than grade 2), when headache, diplopia or other neurological symptoms are present, treatment with (methyl)prednisone 1 mg/kg should be started orally and taper over 2 to 4 weeks. Start HRT depending on the affected hormonal axis (levothyroxine, hydrocortisol, testosterone).
- In patients with type I diabetes mellitus grade 3/4 (ketoacidosis [sub]coma), hospitalization is needed to start treatment of newly onset type I DM. The role of corticosteroids in preventing complete loss of insulin producing cells is unknown and not recommended.

Immune-mediated pneumonitis

Pneumonitis is an uncommon toxicity of ICPIs, but the implicated mechanisms are still undetermined. The hypothesis is that dysregulated effector T cells are accumulated in the pulmonary interstitial, leading to an increased inflammatory response [49]. It can occur with both anti-CTLA-4 and anti-PD-1 treatment. Ipilimumab-induced pneumonitis has been reported in up to 5% of patients in monotherapy [13,34]. A combination of nivolumab and ipilimumab results in pneumonitis at a higher incidence (5% to 10%, with 2% G3/4) [26]. Pneumonitis can occur in 2% to 5% of patients with nivolumab, and more commonly in patients with renal cell and lung cancer than in patients with melanoma [34,50,51].

The most acute form is acute interstitial pneumonitis/diffuse alveolar damage syndrome, which is sometimes life-threatening [52]. Organizing inflammation and sarcoidosis-like granulomatosis has been described [53-55]. Rarely, pneumonitis worsens despite immunosuppression, and may be fatal due to superimposed infection or progressive disease. Patients presenting with symptoms of upper respiratory infection like coughing or shortness of breath should be evaluated using appropriate imaging. However, radiological findings of pneumonitis are not pathognomonic, and may demonstrate ground glass opacities, a cryptogenic organizing pneumonia-like appearance and interstitial pneumonia pattern, and characteristics of hypersensitivity pneumonitis. Although lung biopsy or bronchoscopy is not usually required for decision, it may assist in discriminating acute infection, or lepidic or lymphangitic spread of lung cancer, from a variety of inflammatory changes described above. The treatment strategy is summarized according to the ESMO guidelines [19];

- Grade 1 pneumonitis: defined as radiographic change only and non-symptomatic, delay ICPI treatment, consider steroids (e.g., prednisone 1 mg/kg/day orally [PO] or methylprednisolone 1 mg/kg/day IV). To follow-up, reassessment should be done after 3 weeks. If it worsens, patients should be treated as grade 2 or 3/4.
- Grade 2 pneumonitis: defined as mild-to-moderate symptoms (dyspnea, cough, shortness of breath) limiting instrumental ADL, ICPI treatment should be delayed and hospitalization considered. Symptoms should be monitored daily. Steroids are recommended (prednisone 1~2 mg/kg/day PO or methylprednisolone 1~2 mg/kg/day IV). Empiric antibiotics (if suspicious for concurrent infection) should be considered. To follow-up, manage-

ment should be reassessed every 1 to 3 days. If improvement is observed, steroids is tapered and treatment continued if symptoms resolve completely. If it worsens, the condition should be treated as grade 3/4.

- Grade 3/4 pneumonitis: defined as severe symptoms limiting self-care ADL, ICPI is discontinued permanently and hospitalization is needed, even in ICU if necessary, and high-dose (methyl)prednisone 2~4 mg/kg IV should be immediately started. Infliximab should be added, and MMF or cyclophosphamide should be added in the case of deterioration under steroids. The drugs should be tapered over a period of 4 to 6 weeks. Prophylactic antibiotics should be added for opportunistic infections. Bronchoscopy with biopsy should be considered. Management should be reassessed daily.

Renal toxicity

The prevalence of renal insufficiency was reported to be low (0%~4%) but it has been reported from both anti-CTLA-4 and anti-PD-1 blockers [38]. The highest incidence reported was in the phase II trial with nivolumab in non-small-cell lung cancer [56]. The histopathological findings of CTLA-4-induced nephrotoxicity include acute granulomatous interstitial nephritis and lupus membranous nephropathy [57,58]. In the case of nephritis, first rule out other causes of renal failure. Interrupt or permanently discontinue ICPI depending on the severity of the renal insufficiency. Stop other nephrotoxic drugs. Start (methyl)prednisone 1~2 mg/kg. Consider renal biopsy to confirm diagnosis.

- Grade 1 toxicity: defined as creatinine above 1~1.5x baseline; proteinuria 1+, less than 1.0 g/24 h: monitor renal function, promote hydration and cessation of nephrotoxic drugs.
- Grade 2 toxicity: defined as creatinine above 1.5~3.0x baseline; proteinuria 2+, 1.0~3.4 g/24 h: exclude non-immune causes, commence prednisolone 0.5~1 mg/kg. If it worsens, manage as per grade 3 and discontinue ICPI.
- Grade 3/4: defined as creatinine above 3.0x baseline; proteinuria at or above 3.5 g/24 h: initiate prednisolone 1~2 mg/kg or IV equivalent. Consider renal biopsy. Discontinue ICPI.

Neurological toxicity

Neurological AEs were reported to be as rare as 1% [43,56]. However, recent analysis involving 9,208 patients demonstrated a somewhat higher incidence: 3.8%

in patients receiving anti-CTLA4, 6.1% in patients receiving anti-PD-1 agents and 12% in patients with anti-CTLA4 in combination with anti-PD-1 drugs [48]. Symptoms are varied; polyneuropathy, facial nerve palsy, demyelination, myasthenia gravis, Guillain-Barre syndrome, posterior reversible leukoencephalopathy, transverse myelitis, enteric neuropathy, encephalitis and aseptic meningitis [59,60]. Depending on the clinical presentations, a work-up including nerve conduction studies and lumbar puncture may assist in diagnosis. Early consultation with a neurologist is warranted.

In the case of mild neurological AEs, ICPI should be withheld and work-up should be performed to define the nature of the neurotoxicity. In the case of deterioration or severe neurological symptoms, the patient should be admitted and started on (methyl)prednisone 1~2 mg/kg orally or IV. In the case of Guillain-Barre or myasthenia-like symptoms, adding plasmapheresis or IV immunoglobulin should be considered.

Rheumatological or musculoskeletal toxicity

Rheumatologic or musculoskeletal irAEs observed in patients treated with ICPIs have been mainly focused on arthralgia and myalgia, with a prevalence ranging from 1% to 43% and from 2% to 20%, respectively [61]. It is more common with an anti-PD-1 agent. However, the prevalence may have been underestimated because only high-grade irAEs were reported in some trials [32]. A pattern associated with inflammatory rheumatological conditions (morning stiffness, synovitis, proximal weakness) may be elicited. In addition, arthritis, seropositive rheumatoid arthritis (RA), (poly)myositis, sicca symptoms, Sjögren's syndrome, and less commonly (temporal) vasculitis, cryoglobulinemic vasculitis and lupus nephritis are also reported [25,56,61,62]. Time to onset of rheumatic manifestations varies from weeks to months after ICPI initiation. Belkhir et al. [63] suggested there be a contrast between irAEs occurring after blockade with CTLA-4 (colitis, endocrine disorders, skin rashes) and PD-1/PD-L1 (non-specific arthritis, sicca syndrome, RA, polymyalgia rheumatica, and other connective tissue diseases).

ICPI treatment may aggravate pre-existing autoimmune rheumatic disease (ARD) in 40%~50% of cases. The most frequent is psoriasis exacerbation, but exacerbation or aggravation of other disease-RA, scleroderma, chronic cutaneous lupus or systemic lupus erythematosus, vasculitis, Sjögren's syndrome, ankylosing spondylitis, my-

ositis, sarcoidosis-have all been reported [64,65]. Moreover, rheumatologic patients seem to have a higher proportion of flares compared with patients affected by non-rheumatologic autoimmune diseases.

For treatment, non-steroidal anti-inflammatory drugs should be started under ICPI continuation for mild symptom of arthralgia. Sometimes, rheumatic irAEs spontaneously disappear. In the case of no improvement, low-dose steroids (10~20 mg prednisone) can be considered. For severe or fatal cases, multidisciplinary expertise of oncologists and rheumatologists is crucial for successful management. Treatment with 1 mg/kg prednisone should be started. Infliximab or another anti-TNF- α inhibitor drug is sometimes required for arthritis improvement. There seem no differences in adverse events between patients with active disease and those with inactive disease, whereas patients receiving immunosuppressive therapy at initiation of ICPI seem to have fewer irAEs than those not receiving treatment [65].

Cardiac toxicity

The incidence of cardiac AEs is less than 1%, but a wide range of toxicities including myocarditis, pericarditis, arrhythmias, cardiomyopathy, and impaired ventricular function have been reported after treatment with ipilimumab, pembrolizumab and nivolumab [25,31,48,59]. However, the incidence of cardiac toxicity is higher with the combination of ipilimumab and nivolumab (0.27%) compared with nivolumab alone (0.06%). Early consultation with a cardiologist is recommended. According to the recent ESMO guidelines, when myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1~2 mg/kg). In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus).

Ocular toxicity

Ocular irAEs are rare (less than 1%) treated with ICPIs. The clinical presentation can be one of two types: ocular inflammation, like peripheral ulcerative keratitis, uveitis and Vogt-Koyanagi-Harada syndrome, orbital inflammation, including thyroid-associated orbitopathy and idiopathic orbital inflammation (scleritis, myositis, neuritis, dacryoadenitis); or retinal and choroidal disease (choroidal neovascularization and melanoma-associated retinopathy) [25,31,48,59].

The treatment of these rare toxicities depends on their severity, with topical corticosteroids in the case of epis-

cleritis and anterior uveitis, and systemic corticosteroids in the case of severe ocular inflammation and orbital inflammation. Intra-vitreous anti-vascular endothelial growth factor is indicated for choroidal neovascularization.

Hematological toxicity

Fatigue is the most commonly reported AE in many of the ICPI trials, although rarely at a high grade. It is crucial to rule out secondary causes like hypothyroidism and hypoadrenalism. If other causes are excluded, short-term application of prednisolone (10~20 mg) may be helpful in managing intolerable cases.

Red cell disorders—hemolytic anemia, red cell aplasia and acquired hemophilia A—are all reportedly related to ipilimumab [66,67]. Mortality from probable drug-induced neutropenia was reported in one patient on nivolumab [10]. Grade 3 myelodysplasia was also reported in one case with Hodgkin's lymphoma on nivolumab. Pembrolizumab has only been associated with low grade anemia and neutropenia [5]. ICPI-associated sarcoidosis has been reported with ipilimumab at both 3 mg/kg and 10 mg/kg. Visceral and even neurosarcoid findings have been noted [68,69]. If new lymphadenopathy is documented in an otherwise well and responding patient, a tissue diagnosis should be obtained to avoid unnecessary antineoplastic treatment. Treatment with steroids (prednisolone 1~2 mg/kg) may be required, as in the case of symptomatic neuro-sarcoidosis. In an asymptomatic patient, observation may be appropriate [70].

CONCLUSION

Although immune-checkpoint inhibitors have improved survival for a range of cancer types, they are commonly associated with various types of irAEs. Some irAEs are severe and sometimes fatal. However, they are usually reversible if recognized early and promptly and properly managed. Management algorithms for irAEs have been developed and provide a framework within which individual clinicians may exercise their discretion. Thoughtful management of short and medium-term irAEs is important in optimizing quality of life and long-term outcomes.

Prospective management strategy trials are lacking in this field and are required to advance knowledge. Therefore, where possible, histological or serological confirmation would be helpful to enlighten the nature of

the autoimmune process, since this may differ. For example, hyperthyroidism may be mediated by thyroiditis or Grave's disease, and this can impact the management. One challenge lies in deciding when to instigate next-line immunosuppression after steroids. Given the potential for fatal perforation in those with colitis, we advocate the use of infliximab sooner rather than later. These need to incorporate prolonged durations of follow-up to identify possible late complications.

Lastly, the field must establish true contraindications to use second-line ICPI when the first has been complicated by severe irAEs, or whether patients experiencing grade 3 or 4 toxicity were included in the re-treated cohorts. While most clinical trials of ICPIs after first-line treatment excluded patients who had a prior grade 3/4 toxicity and mandated a minimum 4-week rest between different agents, the practice outside of trials differs under the discretion of the physicians. Moreover, the best way is an informed discussion with the patient regarding the risk versus benefit of rechallenge with an ICPI in the context of prior severe irAEs, especially when balanced with the chance of death from metastatic disease. Patients may also be prepared to accept greater toxicity than that predicted by their physicians for a relatively small perceived benefit.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

H.C.J. conception and design of study, acquisition of data, analysis and/or interpretation of data, drafting the manuscript, revising the manuscript critically for important intellectual content. S.E.O. acquisition of data, drafting the manuscript, revising the manuscript critically for important intellectual content. J.H.K. drafting the manuscript, revising the manuscript critically for important intellectual content.

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