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REVIEW

A Review of Immune-Mediated Adverse Events in Melanoma

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ABSTRACT

The use of checkpoint inhibitor-based immunotherapy has transformed the treatment landscape for melanoma as well as many other cancer types. With the ability to potentiate tumor-specific immune responses, these agents can result in durable tumor control. However, this activation of the immune system can lead to a unique constellation of side effects, distinct from other cancer therapies, collectively termed immune-mediated adverse events (irAEs). This review will focus on irAEs and guidelines for management related to the most clinically relevant checkpoint inhibitors, those that target programmed death receptor-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4).

Keywords: Checkpoint inhibitor; CTLA-4; Immune-related adverse events (irAEs); Ipilimumab; Melanoma; Nivolumab; PD-1; Pembrolizumab; Toxicity

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INTRODUCTION

Immune checkpoint proteins, including cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death receptor-1 (PD-1), prevent unopposed immune activation and tissue damage by initiating signaling cascades that inhibit T cell function [1, 2]. Immune checkpoint blocking antibodies bind to immune checkpoint proteins in an effort to overcome tumor-mediated inhibition of T cell function. While multiple checkpoints are being investigated as potential therapeutic targets, the current clinical use of immune checkpoint inhibitors (ICI) has focused on antibodies that block CTLA-4 (ipilimumab, tremelimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab), and its ligand PDL-1 (atezolizumab, avelumab, and durvalumab). These therapies have revolutionized the treatment of many cancers, in particular melanoma, where they have resulted in improved survival and the potential for durable responses [3–5].

While there is a potential for an antitumor effect, this disinhibition of T cell function can lead to a distinct constellation of inflammatory side effects, collectively termed immune-related adverse events (irAEs). Although the exact mechanism of irAEs is not known, translational

Table 1 Presentation, workup, and management of irAE toxicities

Toxicity	Presentation	Workup	Initial management
Dermatologic	Maculopapular or papulopustular rash Pruritis Vitiligo Sweet's syndrome Lichenoid reactions Eczema Bullous disorders DRESS SJS/TEN	Complete skin examination Consider skin biopsy Consider ANA, SS-A, SS-B if autoimmune condition suspected Consider infection and other drug-induced rash	Grade 1: emollients, topical corticosteroids, and/or oral antihistamines Grade 2: hold ICI if no improvement to grade 1 Grade 3–4: hold ICI; treat with systemic 1–2 mg/kg/day steroids; dermatology consultation
GI			
Colitis	Colitis Diarrhea Fever Abdominal pain Rectal bleeding	CBC, CMP, TSH, ESR, CRP CMV serologies Stool culture, *C. difficile*, ova and parasite Consider CT abdomen/pelvis Consider GI consult for endoscopy with biopsy for grade 2 and higher	Grade 2–4: hold ICI until recovery to grade 1 or less; start 1–2 mg/kg/day steroids; consult gastroenterology If no response within 3–5 days, consider single 5 mg/kg dose of infliximab Consider vedolizumab in cases refractory to or a with a contraindication to infliximab
Hepatitis	Asymptomatic elevation of AST/ALT Fulminant hepatitis	CMP Viral studies Consider ANA, anti-smooth muscle antibodies, and ANCA if autoimmune hepatitis suspected Consider CT abdomen/pelvis if liver metastases suspected Consider other drug-induced hepatitis	Grade 2: hold ICI until recovery to grade 1 or less; start systemic steroids if no improvement Grade 3–4: hold ICI; hepatology consult; start 1–2 mg/kg/day steroids For steroid-refractory cases, consider mycophenylate mofetil
Endocrine			
Thyroid	Hypothyroidism Hyperthyroidism Thyroid storm Myxedema	TSH Free T4 AM cortisol to rule out concurrent adrenal insufficiency TSH receptor antibodies if Graves' disease suspected	Hypothyroidism: thyroid hormone replacement Symptomatic thyrotoxicosis: consider endocrinology referral; propranolol can be used to manage symptoms

Table 1 continued

Toxicity	Presentation	Workup	Initial management
Pituitary	Hypophysitis Dysfunction of thyroid, adrenal, or gonadal axis	Serum electolytes TSH Free T4 ACTH Cortisol or cosyntropin stimulation test Testosterone (men) Estradiol (women) FSH LH Consider MRI of sella	Hold ICI until stabilization on hormone replacement Life-long physiologic hormone replacement is usually required Endocrinology consult in cases of confirmed hypophysitis Patient education about stress doses of hydrocortisone; medic alert bracelet
Pneumonitis	Cryptogenic organizing pneumonia Nonspecific interstitial pneumonitis Hypersensitivity pneumonitis Usual interstitial pneumonitis Pulmonary fibrosis	Chest x-ray Chest CT Consider nasal swab and sputum and blood culture	Grade 2–4: hold ICI; start steroids 1–2 mg/kg/day and broad-spectrum antibiotics; pulmonology consult for bronchoscopy Consider infliximab, cyclophosphamide, or mycophenylate mofetil in steroid-refractory cases
Rheumatologic	Seronegative spondyloarthropathy Polyarthritis Large joint reactive arthritis Sicca syndrome Myositis	ANA, RF, anti-CCP, ESR, CRP CK, aldolase if myositis suspected Consider HLA B27 testing Consider imaging of affected joints EMG or muscle biopsy in cases of myositis	Grade 1: NSAIDs; prednisone if no improvement Grade 2–4: hold ICI; treat with systemic steroids; rheumatology consult Consider methotrexate, sulfasalazine, leflunomide, or anti-cytokine therapy in conjunction with rheumatology

Table 1 continued

Toxicity	Presentation	Workup	Initial management
Neurologic	Autoimmune encephalitis Myasthenia gravis Guillain-Barré syndrome Peripheral neuropathy PRES Aseptic meningitis Transverse myelitis	Brain/spine MRI Lumbar puncture B12, folate, TSH, HIV Acetylcholine receptor, antistriated muscle antibodies, and PFTs with NIF if myasthenia gravis suspected Antiganglioside antibody tests and electrodiagnostic testing if GBS suspected	Grade 2–4: hold ICI; systemic steroids; neurology consult Consider intravenous immunoglobulin or plasmapheresis in steroid-refractory cases
Renal	Acute interstitial nephritis Minimal change disease Lupus-like nephritis Thrombotic microangiopathy	BMP Urinalysis Renal ultrasound Consider other drug-induced causes.	Grade 2–4: hold ICI; nephrology consult; consider steroids if there is no other identifiable cause
Ocular	Uveitis Peripheral ulcerative keratitis Choroidal neovascularization Thyroid-associated orbitopathy Idiopathic orbital inflammation	Referral to ophthalmology for full vision examination	All grades: prompt referral to ophthalmology Grade 2: topical corticosteroids Grade 3–4: systematic corticosteroids
Cardiovascular	Myocarditis Pericarditis Cardiac fibrosis Arrhythmias Heart failure	Troponin ECG BNP Echocardiogram Chest x-ray Consider stress test, cardiac MRI, and cardic catheterization	All grades: hold ICI; high-dose steroids (dose and route decided on case-by-case basis); cardiology consult

Table 1 continued

Toxicity	Presentation	Workup	Initial management
Hematologic	Hemolytic anemia Red cell aplasia Neutropenia Thrombocytopenia Myelodysplasia Cryoglobulinemia	CBC with differential Peripheral smear LDH, haptoglobin, reticulocyte count, bilirubin, and free hemoglobin if hemolysis suspected Consider evaluation for viral or bacterial causes Consider bone marrow biopsy in conjunction with hematology	All grades: consider hematology consult; steroids on a case-by-case basis

DRESS drug reaction with esosinophilia and systemic symptoms, *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis, *ANA* antinuclear antibodies, *CBC* complete blood count, *CMP* complete metabolic panel, *TSH* thyroid-stimulating hormone, ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *CMV* cytomegalovirus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ANCA* antineutrophil cytoplasmic antibodies, *ACTH* adrenocorticotropic hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *RF* rheumatoid factor, *anti-CCP* anti-citrullinated protein antibody, *CK* creatine kinase, *EMG* electromyography, *PRES* posterior reversible encephalopathy syndrome, *PFT* pulmonary function testing, *NIF* negative inspiratory force, *GBS* Guillain-Barré syndrome, *ECG* electrocardiogram, *BNP* brain natriuretic peptide

research suggests that irAEs develop through a combination of pathways involving autoreactive T cells, autoantibodies, and cytokines [6, 7]. For instance, T cell infiltration directed at antigens in both normal and tumor tissue has been described [8, 9]. T cell activation leads to production of inflammatory cytokines, including interleukin-17 (IL-17), which has been implicated in colitis [10, 11]. Direct binding of anti-CTLA-4 antibodies to CTLA-4, which is expressed in normal pituitary tissue, leads to complement activation and hypophysitis [12, 13]. Anti-PD-1 therapy may affect humoral immunity, leading to increased levels of pre-existing autoantibodies, including anti-thyroid antibodies [14].

Unlike the adverse effects associated with more traditional forms of therapy, such as cytotoxic or molecularly targeted agents, irAEs can be variable in their onset and often require specific management [15, 16]. Consensus guidelines from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Society for Immunotherapy of Cancer (SITC) provide recommendations for monitoring, diagnosis, and treatment of irAEs [15–18].

Incidence of any-grade irAEs with single-agent ICI varies by agent and by trial. Overall incidence of any-grade irAE in studies including multiple solid tumor types has been reported at $< 75\%$ for anti-CTLA-4 monotherapy with ipilimumab [19] and 66% with anti-PD-1/PD-L1 monotherapy [20]. Combined PD-1 and CTLA-4 blockade leads to a higher incidence of irAEs [21, 22]. This review will focus on the presentation, incidence, and management of irAEs of ipilimumab and PD-1 antibodies, as these are standard-of-care therapies for melanoma (Table 1).

We searched MEDLINE via PubMed (pubmed.gov) in October 2018 to identify all publications and trials reporting on immune checkpoint inhibitor toxicities in melanoma. The search was conducted using the terms melanoma and PD-1 (nivolumab, pembrolizumab) and CTLA-4 (ipilimumab, tremelimumab). Society guidelines (ASCO, ESMO, SITC, and NCCN) were also reviewed; references

from these consensus statements were reviewed for relevant data. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

DERMATOLOGIC TOXICITY

Dermatologic toxicity is the most common irAE reported in patients with melanoma who are treated with either CTLA-4 or PD-1 blockade [4, 23]. All-grade dermatologic toxicity has been reported in 30–40% of patients treated with PD-1/PD-L1 inhibitors [24, 25] and 50% of patients treated with ipilimumab, though the majority of dermatologic irAEs were grade 1 or 2 [24, 26]. A meta-analysis of dermatologic toxicity, which included eight clinical trials of nivolumab and five of pembrolizumab, reported an incidence of all-grade rash of 16.7% and 14.3%, respectively [26]. Of note, vitiligo, which was seen only in patients with melanoma and is associated with tumor response [27], has been reported in 7.5% of patients treated with nivolumab and 8.3% of patients treated with pembrolizumab [26].

The presentation varies and includes maculopapular or papulopustular rash, pruritis, vitiligo, Sweet's syndrome, urticarial dermatitis, lichenoid reactions, eczema, and bullous disorders [28, 29]. The most common skin toxicity seen in anti-PD-1 or anti-CTLA-4 therapy is a rash [28–31]. Severe toxicities including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) are more common with combination ICI [15]. Onset typically occurs within days to weeks [32, 33] but may not appear until after several months of treatment [33].

Grade 1 dermatologic irAEs are managed with emollients, topical corticosteroids, and/or oral antihistamines [15, 16]. ICI can be continued with grade 2 toxicity but should be held if the irAE does not improve to grade 1 [15, 16]. ICI should be stopped for grade 3 or 4 toxicity, and treatment with systemic corticosteroids should be considered in addition to other supportive care [15, 16]. ICI should be permanently discontinued and patients referred to a specialist in life-threatening cases, especially if there is concern for a rare dermatologic irAE such as SJS/TEN or DRESS [15].

GASTROINTESTINAL TOXICITY

Diarrhea or Colitis

Diarrhea is commonly reported in patients on ICI therapy, though incidence is higher in patients receiving anti-CTLA-4 blockade. A systematic review, which included ten clinical trials of patients with multiple solid tumor types, reported diarrhea in 27–54% and colitis in 8–22% of patients treated with anti-CTLA-4 therapy [34]. The highest incidence of colitis is reported in patients treated with combination CTLA-4/PD-1 blockade, and risk of grade 3 or 4 symptoms is also increased with combination compared with monotherapy. A lower incidence is seen with CTLA-4 monotherapy; colitis with PD-1 blockade alone is rare [15]. A randomized phase III trial of 945 previously untreated patients with advanced melanoma reported any-grade colitis in 2.2% of patients treated with nivolumab, 11.3% of patients treated with ipilimumab, and 12.8% of patients treated with ipilimumab and nivolumab. Grade 3 or 4 colitis was reported in 1% of patients with nivolumab, 7.7% with ipilimumab, and 8.3% with combination ipilimumab-nivolumab [21].

Diarrhea is felt to be due to underlying colonic inflammation or colitis, though in many cases these are reported separately. Patients with overt colitis can present with diarrhea but may also complain of fever, abdominal pain, and rectal bleeding [15]. In patients treated with anti-CTLA-4 monotherapy, the average time to onset of GI irAEs is after the third infusion, although symptoms may occur as early as after the first infusion [19]. Additionally, diarrhea or colitis may recur after discontinuation of therapy and can have a similar presentation to chronic inflammatory bowel disease [35, 36].

The differential diagnosis of diarrhea in patients on ICI includes an irAE, viral, bacterial, or parasitic GI infection or tumor-related symptom. A workup for other causes of

diarrhea, including infection by *C. difficile* or other GI pathogens and metastasis to the GI tract, should be considered [15]. In patients presenting with persistent grade 2 or higher diarrhea/colitis, ICI should be stopped, and 1–2 mg/kg/day of steroids should be started. If there is no response within 3–5 days, infliximab should be considered; a single 5 mg/kg dose is usually sufficient [15, 16].

Case reports have described the use of vedolizumab, an anti-integrin α4β7 antibody with gut-specific effects, for patients with steroid-dependent or -refractory ICI-induced colitis [37, 38]. A series of seven patients with melanoma or non-small-cell lung cancer (NSCLC) who were treated with nivolumab or ipilimumab and developed steroid-dependent or partially refractory colitis reported steroid-free enterocolitis remission in six patients, which occurred at a median of 56 days after starting vedolizumab and which was not associated with any significant adverse events [37]. Similarly, a case report described nivolumab-induced enteritis, which was refractory to steroids and infliximab and responded rapidly to vedolizumab [38]. Patients with refractory colitis and enteritis should be managed in conjunction with a gastroenterologist. Larger, prospective studies will clarify the role of vedolizumab in management of steroid-dependent or -refractory colitis.

Hepatitis

Incidence of hepatitis in patients treated with ipilimumab is dose-dependent, with < 4% incidence of any-grade hepatitis in patients treated with 3 mg/kg [3] and 15% in patients treated with 10 mg/kg [39]. Any-grade hepatitis is reported in 1–6% of patients treated with anti-PD-1 therapy compared with 30% in patients treated with combination therapy [21, 40]. Grade 3–4 elevation in AST/ALT has been reported in 6–9% of patients treated with ipilimumab and nivolumab compared with 1–2% of patients treated with either ipilimumab or nivolumab monotherapy in a phase III trial of previously untreated patients with advanced melanoma [21]. A pooled safety analysis of 576 patients with melanoma treated with nivolumab reported a median time to resolution of hepatic irAEs of 3.3 weeks [41].

Hepatitis most commonly presents with asymptomatic elevation of AST and ALT with or without elevated bilirubin [16, 29], although a more severe presentation with fulminant hepatitis has been reported [40]. Transaminase elevation is most often seen between 6 and 14 weeks following initiation of treatment [40].

Differential diagnosis of patients who develop transaminase elevation while on ICI therapy includes drugs (ICI or other), alcohol, and infection, especially viral hepatitis [16]. In patients with grade 2 toxicity, ICI should be held and LFTs monitored; therapy can be resumed if there is resolution to grade 1. Steroids (methylprednisolone 0.5–1 mg/kg/day or prednisone 1–2 mg/kg/day) should be started if there is no improvement [15, 16]. In cases of grade 3 or 4 toxicity, steroids should be started at 1–2 mg/kg/day. Rare cases are refractory to high-dose steroids, and then mycophenolate mofetil (500–1000 mg twice daily) should be considered. In contrast to the management of steroid-refractory diarrhea and colitis, infliximab is contraindicated because of concerns regarding hepatotoxicity-related to infliximab [15, 16]. Successful use of anti-thymocyte globulin has been reported in a steroid-refractory case, and this may be considered, particularly in cases of acute clinical deterioration [42]. Referral to hepatology and liver biopsy should be considered in steroid or mycophenolate mofetil-resistant cases [15, 16].

ENDOCRINOPATHIES

Endocrinopathies associated with ICI include hypo- or hyperthyroidism, thyroiditis, hypophysitis, primary adrenal insufficiency, and insulin-dependent diabetes mellitus (IDDM) [43]. The most common endocrinopathies reported with ICI are thyroid and pituitary toxicity. Primary adrenal insufficiency and IDDM are rare endocrine irAEs and have been reported in 0.7% and 0.2% of patients, respectively [43]. Endocrinopathies may present with non-specific symptoms, including fatigue,

headache, or weakness and can therefore be challenging to diagnose [44]. The time to onset of endocrine irAEs varies by agent. The median onset of moderate-to-severe endocrine irAEs in melanoma patients treated with ipilimumab occurs at 7–20 weeks [45]. A single-institution retrospective review of patients with melanoma treated with ipilimumab reported a median time to onset of hypophysitis of 4 months; however, timing of onset ranged from 8 to 19 months after initiation of therapy [46]. Hypothyroidism was reported within the first 5 months and up to 3 years after initiation [46]. A pooled analysis of safety events with nivolumab reported a median time of onset of approximately 10 weeks [41]. Unlike other irAEs, which resolve with treatment, endocrinopathies are often permanent and require lifelong hormone replacement [47].

Thyroid Toxicity

Hypothyroidism is more common with ICI therapy than hyperthyroidism [43]. A subset of patients develop an initial hyperthyroid phase, often subclinical, which is later followed by hypothyroidism. A meta-analysis of 38 randomized controlled trials to determine the incidence of endocrine irAEs after ICI treatment reported an overall incidence of hypothyroidism of 6.6%, with lowest incidence (3.8%) in patients treated with ipilimumab and highest incidence (13.2%) with combination therapy [43]. Hyperthyroidism is less common with overall incidence reported at 2.9%; the lowest incidence occurs with PD-L1 inhibitors (0.6%) and the highest incidence with combination therapy (8%) [43]. Thyroid storm has rarely been reported in patients treated with ICI [48]. Median onset of thyroid dysfunction occurs 4 weeks after starting treatment [49].

Thyroid-stimulating hormone (TSH) and free thyroxine (T4) should be checked at baseline and routinely during ICI therapy [15–18]. Patients with hypothyroidism should be treated with thyroid hormone replacement [15]. Thyroiditis should be managed conservatively during the thyrotoxic phase; however, other causes of thyrotoxicosis, including Graves' disease, should be ruled out with laboratory tests and imaging and referral to endocrinology as appropriate [15]. Symptomatic hyperthyroidism may be treated with beta blockers.

Pituitary Toxicity

The highest incidence of hypophysitis occurs with anti-CTLA-4 monotherapy and combination therapy. Incidence increases with increasing doses of ipilimumab (1–4% with ipilimumab 3 mg/kg; 16% with 10 mg/kg) [24, 46, 50, 51]. Hypophysitis is rare with anti-PD-1 monotherapy [43]. Median onset occurs after 8–9 weeks or after the third dose of ipilimumab [52]. Median onset with nivolumab monotherapy occurs at 4.9 months (range 1.4–11 months) [53].

Hypophysitis presents with non-specific symptoms, including fatigue, headache, and weakness, requiring a high degree of clinical suspicion for prompt diagnosis. Symptoms vary depending on the region of the pituitary affected and may result from dysfunction of the thyroid, adrenal, or gonadal axis [53], with adrenocorticotropic hormone (ACTH) and TSH deficiency most commonly described in anti-CTLA-4-associated hypophysitis [54]. Hypogonadotropic hypogonadism has been described, although the incidence is difficult to determine given the effect of severe illness on the gonadal axis. Diabetes insipidus is rare [54].

Baseline testing of serum ACTH and cortisol can be considered, especially in patients with pre-existing endocrine disease [15, 18]. Patients with clinical or laboratory features of hypophysitis should undergo the following testing of thyroid, adrenal, and gonadal axes, preferably in the morning and prior to the administration of steroids: TSH, free T4, ACTH, cortisol or cosyntropin stimulation test, testosterone (men), estradiol (women), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and MRI of the sella [15]. Results consistent with hypophysitis include deficiency of at least one pituitary hormone with MRI abnormality or deficiency of two or more pituitary hormones in the presence of symptoms [15]. MRI findings may include stalk thickening,

pituitary enlargement, and heterogeneous enhancement [15].

Adrenal insufficiency secondary to ICI-induced hypophysitis is usually permanent, requiring lifelong hormone replacement [54]. Recovery of secondary hypothyroidism and hypogonadism has been described with frequency varying from 6 to 64% and 11 to 57%, respectively [54]. A small retrospective study of patients with advanced melanoma and ipilimumab-induced hypophysitis found that treatment with glucocorticoids did not improve the frequency of resolution or time to resolution of hypophysitis [55].

If a diagnosis of hypophysitis is made, endocrinology consultation should be strongly considered [15]. Patients should be treated with replacement of the deficient hormones, including physiologic steroid and thyroid hormone replacement. If adrenal insufficiency and hypothyroidism are both present, steroids should be started prior to thyroid hormone replacement to prevent adrenal crisis [15]. Patients with adrenal insufficiency should receive comprehensive education regarding the potential life-threatening nature of adrenal crisis and be provided with stress doses of hydrocortisone in case of infection, trauma, or illness [15].

PNEUMONITIS

Pneumonitis is the most common pulmonary toxicity of ICI therapy [15] and should be considered in any patient presenting with new respiratory symptoms. Overall, the incidence of pneumonitis is low. The incidence is slightly higher with PD-1 monotherapy compared with CTLA-4 monotherapy and increases with the use of dual checkpoint inhibition [56]. The largest published series of pneumonitis after anti-PD-1 and PD-L1 therapy reported 5% incidence among 915 patients, with 1–2% grade 3–4 pneumonitis [56].

Patients may develop cough, chest pain, wheezing, shortness of breath, new oxygen requirement, or fatigue; the severity and acuity of onset vary [15]. Additionally, patients can be asymptomatic with the diagnosis made incidentally on imaging studies [56]. In rare cases, hypoxia may progress rapidly and lead to respiratory failure [17]. A retrospective review of patients with multiple tumor types treated with either anti-PD-1/PD-L1 monotherapy or combination with anti-CTLA-4 therapy reported a median onset at 2.8 months, though there was a high degree of variability (9 days to 19.2 months). Onset occurred earlier in patients treated with combination therapy (median 2.7 months) versus anti-PD-1/PD-L1 monotherapy (4.6 months) [56]. A smaller series described earlier onset in patients with NSCLC compared with patients with melanoma (2.1 versus 5.2 months) [57]. Imaging findings vary and include cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis (HP), or usual interstitial pneumonitis (UIP)/pulmonary fibrosis (PF) [15]. Clinical and radiographic features may overlap with pneumonia, lymphangitic spread of tumor, and diffuse alveolar hemorrhage. Given these overlapping features and the potential for rapid development of respiratory failure, a high index of suspicion should be maintained in patients on ICI therapy who develop respiratory symptoms.

Baseline pulmonary function tests (PFTs) should be considered in patients who are at high risk of developing pulmonary toxicity [18]. Because it can be difficult to distinguish between pneumonitis and infection, guidelines recommend concurrent broad-spectrum antibiotics and immunosuppression while workup is underway [15, 16]. In patients with grade 2 pneumonitis, ICI should be held; pulmonology should be consulted for bronchoscopy with bronchoalveolar lavage (BAL), and methylprednisolone 1 mg/kg/day should be started. Re-challenge can be considered if symptoms and imaging improve. For grade 3–4 pneumonitis, initiation of 2 mg/kg/day methylprednisolone is recommended. Additionally, hospitalization may be needed along with a pulmonology consult for bronchoscopy [15, 16]. Limited data exist regarding the management of steroid-refractory pneumonitis, but reports of additional immunosuppression with infliximab, cyclophosphamide, or

mycophenolate mofetil suggest these may be of benefit [15, 16].

RARE IRAES

Sarcoid

Pulmonary and extra-pulmonary sarcoid have been reported in patients treated with both anti-PD-1/PD-L1 and anti-CTLA-4 therapy [58, 59]. Sarcoidosis should be considered when chest imaging shows mediastinal or hilar lymphadenopathy or reticulonodular opacities [15]. Extrapulmonary sarcoid may involve the heart, kidneys, central nervous system, or eyes. The diagnosis is confirmed by the histologic presence of non-caseating granulomas [15]. Alternate diagnoses, including infection and progression of malignancy, should be excluded.

Guidelines for management of sarcoid are extrapolated from guidelines for management of sarcoid in the general population. Corticosteroids should be considered for patients with grade 2 or higher sarcoid, worsening radiographic changes, worsening lung function or pulmonary symptoms, involvement of extrapulmonary organs, or hypercalcemia [15].

Rheumatologic Toxicity

A high index of suspicion for rheumatologic irAEs should be maintained given the prevalence of musculoskeletal complaints in the general oncology population and given the diverse spectrum of rheumatologic irAEs. Arthralgia has been reported in approximately 15% of patients treated with ICI; however, the incidence of inflammatory arthritis and other rheumatologic irAEs is not well characterized [60, 61].

Patients may present with arthritis, including seronegative spondyloarthropathy, polyarthritis affecting the small joints of the hands, which clinically resembles rheumatoid arthritis, or large joint reactive arthritis, which may occur in combination with conjunctivitis and urethritis [15]. Other rheumatologic irAEs include sicca syndrome, myositis, which resembles polymyositis, giant cell arteritis, polymyalgia rheumatica, systemic lupus erythematosus, and sarcoidosis [60–64]. A small case series of patients with multiple tumor types treated with nivolumab or ipilimumab monotherapy or combination therapy reported a time to onset of rheumatologic irAE ranging from 2 to 13 months after initiation of treatment [64]. Symptoms may persist beyond cessation of treatment [60].

Grade 1 toxicity is managed with NSAIDs, followed by prednisone if no improvement. ICI should be held and rheumatology consulted for grade 2 or higher rheumatologic toxicity, as erosion and irreversible joint damage can occur within weeks [15]. Grade 2 and higher toxicity are often managed with prednisone. If symptoms do not improve on steroids, additional immunosuppression, including methotrexate, sulfasalazine, leflunomide, or anti-cytokine therapy, may be needed [15]. In selected cases, ICI can be resumed in consultation with rheumatology if symptoms improve to grade 1 [17].

Neurologic Toxicity

Neurologic irAEs encompass a heterogeneous set of complications. A systematic review of neurologic adverse events associated with ICI therapy, which included 59 clinical trials involving 9208 patients and 23 case reports describing 26 cases, reported a broad spectrum of toxicities with potential for involvement of any aspect of the central or peripheral nervous system [65]. Incidence was 12% with combination therapy, 6.1% with anti-PD-1 therapy, and 3.8% with anti-CTLA-4 therapy [65]. Diagnoses may include autoimmune encephalitis, myasthenia gravis, Guillain-Barré syndrome (GBS), peripheral neuropathy, posterior reversible encephalopathy syndrome (PRES), aseptic meningitis, and transverse myelitis [66]. Median onset is 6 weeks after starting treatment [65]. Most neurologic toxicity is low grade, with higher incidence of grade 3–4 toxicity after anti-CTLA-4 treatment (0.7%) compared with anti-PD-1 treatment (0.4%) [65].

The differential diagnosis for patients with neurologic symptoms includes infection, CNS

metastasis or leptomeningeal spread, paraneoplastic syndromes, vitamin B12 deficiency, and diabetic neuropathy. For grade 2 and higher neurologic symptoms, ICI should be held and steroids started while diagnostic evaluation, including lumbar puncture, brain MRI, and neurology consultation, is performed. If symptoms worsen or fail to improve with steroids, treatment with intravenous immunoglobulin [67] or plasmapheresis [68] can be considered; however, data are limited, and recommendations are drawn from case reports [69].

Renal Toxicity

Renal irAEs are rare, with incidence of 2% with ICI monotherapy and 5% with combination ipilimumab/nivolumab [70, 71]. However, more recent studies suggest that the incidence of renal irAEs was under-reported in earlier studies and that true incidence may be closer to 13–29% [70]. Patients may present with hematuria, worsening hypertension, electrolyte imbalance, altered urine output, or rising creatinine [70].

Acute interstitial nephritis (AIN) is the most commonly reported pathology [70]. Other pathologies, including minimal change disease, lupus-like nephritis, and thrombotic microangiopathy, have also been described with ipilimumab therapy [70]. Renal toxicity occurs earlier with ipilimumab (2–3 months) compared with anti-PD-1 therapy (3–10 months) [70].

Distinguishing between immune-related and other causes of kidney injury is challenging given the prevalence of kidney injury due to dehydration, sepsis, and other medications in the oncology population. Workup includes inquiry about new medications and assessment of volume status; urinalysis and renal ultrasound can be performed. ICI should be held for cases of grade 2 and higher nephrotoxicity, and steroids should be considered if there is no other identifiable cause [15].

Ocular Toxicity

Ophthalmologic toxicity occurs in < 1% of patients treated with ICI [72] and includes uveitis, peripheral ulcerative keratitis, Vogt-Koyanagi-Harada syndrome, choroidal neovascularization, melanoma-associated retinopathy, thyroid-associated orbitopathy, and idiopathic orbital inflammation [72]. Median onset occurs at 2 months [72]. Few case reports describing the ocular toxicity of ICI have been published [72].

Ocular toxicity is often seen in combination with other irAEs, particularly colitis; therefore, full review of systems should be performed. Prompt ophthalmologic referral is necessary in all cases of visual complaints to distinguish between different grades and pathologies of ocular toxicity. Grade 2 toxicity can be treated with topical corticosteroids, while grade 3–4 toxicities often require systemic corticosteroids [15].

Cardiac Toxicity

The true incidence of cardiac irAEs is unknown but is estimated to be < 1% [8]. The incidence is likely under-reported given the lack of systematic monitoring in clinical trials and difficulty in accurately diagnosing cardiac toxicity, particularly myocarditis [15, 73]. In an analysis using a pharmacovigilance database for patients receiving nivolumab with or without ipilimumab, a total of 18 cases of drug-related severe myocarditis were reported among 20,594 patients (0.09%). A higher incidence was seen in patients treated with combination ipilimumab/nivolumab (0.27%) compared with nivolumab alone (0.06%) [8].

Cardiac irAEs include myocarditis, pericarditis, cardiac fibrosis, arrhythmias, and new onset heart failure [8, 15, 74–77]. There may be a link between development of rhabdomyolysis, myositis, vasculitis, and cardiac toxicity; therefore, patients who develop these toxicities should be monitored closely for cardiac symptoms [15].

ASCO and SITC guidelines recommend baseline electrocardiography and troponin in all patients; the ideal optimal monitoring frequency for troponin during therapy has not been defined [15, 17]. Patients who develop symptoms concerning for cardiac irAE should

undergo workup including electrocardiogram, troponin, brain natriuretic peptide (BNP), echocardiogram, and chest x-ray [15–18]. Myocarditis can be rapidly fatal; therefore, early cardiology consultation and admission to the hospital in cases of suspected myocarditis are recommended. Patients with confirmed myocarditis should be treated with high-dose corticosteroids, and ICI therapy should be stopped. The timing of corticosteroid initiation is made on an individual basis, as there are no data available to establish a threshold (for example, cutoff troponin) for starting corticosteroids in cases of suspected myocarditis [15].

Hematologic Toxicity

Hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, myelodysplasia, cryoglobulinemia, and hemophilia A have been reported following ICI therapy [25, 40, 78–83].

The differential diagnosis for progressive cytopenias includes cancer progression or bone marrow involvement, GI bleeding, and drug effect. Guidelines recommend treatment with corticosteroids on a case-by-case basis in conjunction with hematology consultation [15].

STEROID-REFRACTORY IRAES

Management of steroid-refractory irAEs is based on case reports and single-center series [84]. Interleukin-6 (IL-6) receptor blockade with tocilizumab is used to treat immune-related toxicity from other therapies, including cytokine release syndrome (CRS) associated with chimeric antigen receptor (CAR) T therapy. A retrospective series of 87 patients with various solid tumor types (82% lung cancer) who were treated with nivolumab reported use of tocilizumab for treatment of irAEs in 34 patients [84]. In this single-center study, high-grade irAEs in patients who were already receiving corticosteroids were treated with tocilizumab, and clinical improvement was observed in 27 of 34 patients. The most common irAEs treated with tocilizumab were pneumonitis and serum sickness/systemic inflammatory response syndrome (SIRS). Similarly, a series of three patients with metastatic melanoma who were treated with tocilizumab for severe arthritis due to ICI described significant clinical improvement in all three patients [85]. Intestinal perforation is a rare complication of IL-6 inhibition [86]; therefore, guidelines recommend avoiding tocilizumab use in patients with colitis or GI metastases [17]. Randomized studies are needed to clarify the relative safety and efficacy of tocilizumab and other immunomodulators in the treatment of steroid-refractory irAEs.

ROLE OF DOSE REDUCTION

Studies have compared the efficacy and tolerability of lower doses of ICI therapy to minimize irAEs while maintaining response rates. For example, the phase IIIb/IV Checkmate 511 study randomized 360 patients with melanoma to receive either nivolumab 1 mg/kg and ipilimumab 3 mg/kg or nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, followed by nivolumab 480 mg every 4 weeks [87]. Grade 3 or higher treatment-related adverse events occurred in 34% of patients treated with nivolumab 3 mg/kg and ipilimumab 1 mg/kg compared with 48% of patients treated with nivolumab 1 mg/kg and ipilimumab 3 mg/kg. Efficacy end points were descriptive, and objective response rate (ORR) and progression free survival (PFS) were similar between the two groups. The phase 1b KEYNOTE-029 study treated 153 patients with melanoma with pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, followed by pembrolizumab 2 mg/kg every 3 weeks [88]. Grade 3 or higher treatment-related adverse events occurred in 45% of patients. ORR was 61%, suggesting that standard-dose pembrolizumab in combination with reduced-dose ipilimumab exhibits anti-tumor activity and a tolerable safety profile. Future data will clarify duration of response and long-term survival. Currently, there are no data regarding the role of dose reduction in patients who previously experienced irAEs. Until additional evidence is available on the outcomes of dose reduction or decreased dose frequency, ASCO guidelines recommend interruption of

ICI therapy or permanent discontinuation instead of dose reduction [17].

BIOMARKERS TO PREDICT IRAE

To facilitate prevention and early detection of severe irAEs, studies have examined the predictive value of various serum biomarkers; however, data on the monitoring of biomarkers to prevent irAEs are limited. A study of 35 patients with locally and regionally advanced melanoma who received ipilimumab before and after surgery assessed serum cytokines at baseline, during, and after therapy and found that baseline levels of IL-17 were significantly associated with development of grade 3 diarrhea/colitis [11]. Decreased levels of IL-10, which correlated with development of an irAE including ischemic papillopathy and optic neuritis, have been described in a patient who was treated for bladder cancer with anti-CLTA-4 therapy [89]. A study of 98 patients with melanoma who were treated with anti-PD-1 monotherapy or combination therapy prospectively analyzed serum samples for 65 cytokines to predict development of irAE [90]. Eleven cytokines were significantly upregulated in patients who developed severe irAE at both baseline and early treatment (week 1–6) compared with patients who did not develop severe irAE. These studies suggest that monitoring of serum cytokine levels may be used to determine risk of irAE; however, the optimal nature and frequency of testing has not been defined. Larger, multi-institution prospective studies will clarify the clinical utility of patients' cytokine signatures and will assist with clinical decision-making based on risk stratification.

ICI USE IN SPECIAL POPULATIONS

Autoimmune Disease

Data on safety of ICI therapy in patients with preexisting autoimmune disease are limited, as these patients were excluded from trials leading to FDA approval given concern for exacerbation of autoimmunity. In a series of 30 patients with advanced melanoma and autoimmune disease who were treated with ipilimumab, 27% of patients developed an exacerbation of autoimmune disease, most of which were manageable with low-dose corticosteroids. Conventional grade 3–5 irAEs were reported in 33% of patients, and there was one fatality from colitis in a patient with skin-limited psoriasis; however, 50% of patients had no major toxicity or flare [91]. A series of 119 patients with advanced melanoma and autoimmune disease and/or previous irAE with ipilimumab who were treated with anti-PD-1 therapy reported flare requiring immunosuppression in 38% of patients; 85% of flares were mild, but 10% of flares led to permanent discontinuation of therapy. Response rate was 33%, suggesting that ICI therapy can lead to clinical benefit even in the presence of autoimmune disease requiring immunosuppression [92]. A systematic review including 123 patients with multiple autoimmune comorbidities and tumor types treated with anti-PD-1 or anti-CTLA-4 monotherapy or combination therapy reported exacerbation of autoimmunity in 41%, de novo irAEs in 25%, and both exacerbation of autoimmunity and de novo irAE in 9%. There were fewer adverse events in patients who were receiving immunosuppression at the time of ICI initiation, although the data are insufficient to determine whether there is a role for maintenance immunosuppression to reduce the risk of adverse events [93]. Long-term prospective studies are needed to clarify the optimal approach to ICI therapy in patients with autoimmune disease. The available evidence suggests that flares of autoimmunity and irAEs often occur in this population and can be managed successfully with steroids, although severe and fatal events can occur. Therefore, initiation and monitoring of ICI therapy in patients with autoimmune disease require multi-disciplinary collaboration.

Re-Challenge After High-Grade irAEs

Guidelines recommend permanent discontinuation of ICI therapy after grade 4 irAEs, except for endocrine toxicity, which can be managed

with hormone replacement [15–17]. Permanent discontinuation after grade 3 toxicity in cases with high risk of morbidity and mortality, including following pulmonary, hepatic, pancreatic, ophthalmologic, and neurologic irAEs, is also recommended. Studies have addressed the safety and efficacy of re-challenge in patients who develop clinically significant irAEs with ICI therapy.

A multicenter, retrospective analysis, which included 80 patients with melanoma who had stopped combination therapy for an irAE and who were re-challenged with anti-PD-1 monotherapy, described recurrence of the same irAE in 18% of patients and development of a de novo irAE in 21% of patients [94]. Forty (50%) patients developed any grade irAE; of these, 26 were grade 1–2, and 14 were grade 3–5. Thirty percent of patients discontinued anti-PD-1 therapy for irAE. There was one grade 5 recurrence in a patient who had a grade 2 rash with combination therapy and developed SJS/TEN with anti-PD-1 re-challenge and died despite high-dose steroids, intravenous immunoglobulin (IVIg), and infliximab. Colitis was less likely to recur than other irAEs (6% versus 28%); hypophysitis was also unlikely to recur. Other toxicities, including hepatitis, pneumonitis, nephritis, and pancreatitis, appeared to have higher risk of recurrence, although the sample size was small. The authors suggested two mechanisms to account for the high rate of irAE observed with anti-PD-1 re-challenge: (1) immune priming by combination ICI therapy may increase risk of toxicity with re-challenge and (2) delayed presentation of combination therapy toxicity may occur.

Reviews have also examined the safety of re-challenge with anti-PD-1 therapy in patients who developed toxicity with anti-CTLA-4 monotherapy. In a retrospective series of 67 patients with melanoma who developed significant irAEs with ipilimumab (76% grade 3, 10% grade 4) and were re-challenged with anti-PD-1 monotherapy, 2 patients had recurrence of irAE, and 23 developed de novo irAEs [92]. Eight patients discontinued therapy because of irAEs, and there were no treatment-related deaths.

These studies suggest that re-challenge with anti-PD-1 therapy can be considered following clinically significant irAEs with anti-PD-1, anti-CTLA-4, or combination therapy; however, caution should be used as fatal events have been reported. One limitation of these retrospective studies is the subjectivity of the decision to re-challenge following irAE. Decision to re-challenge with anti-PD-1 therapy should be made on a case-by-case basis with consideration of prior irAE, organ affected, clinical scenario and severity, and alternative treatment options.

Patients with History of Solid Organ Transplant

Pre-clinical studies have shown that the PD-1 and CTLA-4 pathways are involved in the maintenance of immune tolerance to transplanted organs [95–98]. Therefore, patients with a history of solid organ transplant were excluded from clinical trials leading to FDA approval of anti-PD-1 and anti-CTLA-4 agents given the concern about precipitating rejection [99]. It is important to clarify the safety and use of ICI therapy in this patient population given the increased incidence of malignancy in transplant recipients who are receiving chronic immunosuppression and given the increasing use of ICI therapy to treat advanced cancers.

Data to support the use of ICI in organ transplant recipients are limited to case series. A review of 12 case reports of organ transplant recipients, including 9 kidney, 2 liver, and 1 heart transplant, who were treated with anti-PD-1, anti-CTLA-4, or both sequentially for multiple tumor types (7/12 melanoma) reported graft rejection in 4/9 kidney transplant patients, none of whom could be salvaged with immunosuppression. Increased risk of rejection was seen in patients treated with anti-PD-1 agents. None of the patients treated with anti-CTLA-4 monotherapy developed rejection; however, 4/8 patients treated with anti-PD-1 monotherapy and 2/3 patients treated with ipilimumab followed by anti-PD-1 agents developed rejection. Of the 12 patients included in the series, 8 had a response or stabilization with ICI therapy [99]. The observed increase in risk with anti-PD-1 therapy supports the observation in mouse studies that the PD-1 pathway

plays a more dominant role in allograft tolerance [98]; however, larger studies are needed to clarify the relative risk of graft rejection with anti-PD-1 and anti-CTLA-4 therapy.

Factors that may contribute to risk of graft rejection include choice of ICI therapy, time since organ transplant, tumor type, strength of immunosuppressive regimen required to maintain graft tolerance, and immunogenicity of the transplanted organ [99]. The risks of ICI therapy, including the possibility of graft failure, should be discussed with patients and their transplant physicians prior to treatment. Given the challenges of ICI therapy in this population, optimal management involves multi-disciplinary collaboration with transplant specialists.

HIV+ Patients

Pre-clinical studies have shown that during chronic HIV infection, CD8+ T cells express high levels of PD-1, which leads to decreased cytokine production and reduced activity against HIV-infected cells, a phenomenon called immune exhaustion [100]. In mice and non-human primates, blockade of PD-1 can lead to improvement in immune exhaustion [100]. A phase I study of a PD-L1 antibody described improvement in HIV-specific immunity in a subset of patients [101], suggesting that checkpoint inhibitors may have activity in the treatment of chronic HIV infection.

Patients with HIV are at increased risk of multiple types of malignancy, and several current clinical trials are evaluating the safety and efficacy of checkpoint inhibitors in HIV+ patients. For example, a multi-center phase I trial including 30 HIV+ patients with multiple solid tumor types or non-Hodgkin lymphoma (NHL) and CD4 count $\geq$ 100 cells/μl and antiretroviral therapy (ART) for at least 4 weeks who were treated with pembrolizumab reported grade 3 adverse events in 20% of patients. One patient developed fatal Kaposi's sarcoma-associated herpesvirus-associated multicentric Castleman disease (KSHV-MCD) [102]. A multi-center phase II study including 20 HIV+ patients with multiple solid tumor types treated with durvalumab reported grade 1–2 adverse events in 40% of patients, no high-grade adverse events, and no viral reactivation [103].

A systematic review, which identified 73 patients with HIV who were treated with anti-PD-1, anti-CTLA-4, or combination therapy for various solid tumor types reported grade 3 or higher irAEs in 6 of 70 patients with reported adverse events. The majority of these adverse events occurred in patients who had received ipilimumab, including one patient who was treated with ipilimumab monotherapy and three patients who were treated with combination ipilimumab/nivolumab. There were no reports of immune reactivation inflammatory syndrome (IRIS). Of the 28 patients with undetectable HIV viral load before treatment, HIV became detectable in the blood of 2 of 28 patients; however, 5 of 6 patients with a detectable viral load had a decrease in viral load with ICI therapy [104]. A retrospective series of ten patients with HIV and metastatic melanoma or Merkel cell carcinoma who were treated with anti-PD-1, anti-CTLA-4, or combination therapy described irAEs in 50% of patients, with two of these graded as severe. There were no treatment-related deaths, and there was no significant increase in HIV viral load in the seven patients whose viral loads were monitored [105]. The results of these studies suggest that HIV+ patients can be safely treated with ICI therapy; ongoing prospective studies will clarify risk factors for severe adverse events in this patient population.

CONCLUSIONS

ICI therapy has transformed the treatment landscape for multiple malignancies. Anti-PD-1 therapies are approved for treatment of melanoma, renal cell carcinoma, non-small cell lung cancer, and head and neck squamous cell carcinoma. Furthermore, indications for ICI therapy have expanded to include adjuvant therapy in addition to treatment of advanced malignancies. The evolving application of ICI therapy highlights the importance of recognition and management of immune-related toxicity. Future studies will identify risk factors and biomarkers for toxicity and will clarify the safety and efficacy of ICI therapy in patient populations that have

been excluded from clinical trials. Multi-disciplinary collaboration is essential to optimize the management of irAEs and to guide decision-making in challenging situations.

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