A Review of Cancer Immunotherapy Toxicity

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The immune system has developed a complex series of mechanisms to detect and eradicate cancer cells. These pathways protect against the development of malignancy but can promote the selection of tumor cells, which are equipped to avoid the host’s immune response. The concept of cancer immunoediting, which highlights the dual role of the immune system in protecting against tumor growth while also shaping tumor immunogenicity, describes the process of tumor development using 3 steps: elimination, equilibrium, and escape. During the elimination phase, the host’s innate and adaptive immune systems recognize and respond to tumor-specific antigens. Some tumor cells survive elimination and enter the equilibrium phase, during which the adaptive immune system prevents outright tumor growth but exerts a selective pressure on the remaining malignant clones. Tumor cells escape when they develop resistance to the antitumor immune response. Multiple mechanisms have been described to account for the evolution of this escape, including alteration or loss of antigens, manipulation of cytokine expression, and upregulation of immune checkpoint proteins.

Cancer immunotherapies, which were developed based on studies of the mechanisms of tumor escape, manipulate the immune system to reactivate the antitumor immune response and overcome the pathways leading to escape. Early approaches to cancer immunotherapy targeted cytokines to affect immune cell function. For example, high-dose interleukin 2 (IL-2) and interferon (IFN) α-2b lead to multiple downstream effects and have been used to treat advanced melanoma and renal cell carcinoma (RCC). Therapeutic approaches to manipulate multiple aspects of the immune system have subsequently been investigated, including immune checkpoint inhibitors (ICIs), adoptive cell therapy, oncolytic viruses, and cancer vaccines.

Immunotherapies have transformed the treatment landscape for multiple solid and hematologic malignancies but confer unique toxicity profiles, which vary depending on the type of immunotherapy and are related to the specific mechanism of action. Cytokines, such as high-dose IL-2, lead to multiple downstream effects on T cells and natural killer (NK) cells, which, in turn, cause capillary leakage.
and a sepsis-like syndrome. In severe cases, this can result in multiorgan failure, which has historically limited the clinical utility of cytokine therapy. ICIs, including antibodies against cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1) and its ligand PD-L1, disinhibit T-cell antitumor function, which can lead to a distinct constellation of organ-specific inflammatory side effects, or irAEs. Another approach to immunotherapy is the ex vivo modification of patient T cells to generate specific antitumor reactivity, a process termed adoptive cell therapy. For instance, chimeric antigen receptor (CAR) T cells, which are engineered to recognize a tumor-associated antigen, are used to treat hematologic malignancies and are being investigated in multiple solid tumor types. The most common CAR-T toxicities in hematologic malignancies are cytokine release syndrome (CRS) and ICANS. Because of these toxicity profiles, treatment with cancer immunotherapies requires close monitoring, and toxicity often requires specific management, which can include steroids or immune-modulating agents. As the use of immunotherapy in cancer continues to expand, guidelines addressing the management of ICI and CAR-T toxicity have also been developed.

In this review, we discuss the pathophysiology, presentation, diagnosis, and management of toxicities associated with cancer immunotherapies.

**Checkpoint Inhibitors**

Immune checkpoint proteins, including PD-1 and CTLA-4, initiate signaling pathways that suppress T-cell function. CTLA-4 is expressed on the surface of CD4-positive and CD8-positive lymphocytes and competes with the T-cell-costimulatory receptor CD28 for binding to T-cell–costimulatory factors, which are expressed on the surface of antigen-presenting cells in the early phase of the immune response. CTLA-4 binding reduces IL-2 production and T-cell proliferation. PD-1 is a cell-surface receptor expressed on multiple immune cell types, including T cells, B cells, and NK cells, and binds to the ligand PD-L1 and PD-L2. PD-L1 is expressed on multiple tissue types, including tumor cells, whereas PD-L2 is expressed primarily on hematopoietic cells. PD-L1 expression is stimulated by IFN-γ produced by activated T and NK cells. PD-1 signaling inhibits previously activated T cells in peripheral tissues. CTLA-4 and PD-1 signaling are tightly regulated to permit self-tolerance; however, tumor cells can use these pathways, including checkpoint protein signaling, to evade the immune response and establish a microenvironment that permits tumor growth.

Upregulation of the PD-1 pathway by tumor cells can promote the development of T-cell exhaustion, characterized by reduced T-cell effector function and proliferation. ICIs bind to immune checkpoint proteins to overcome this tumor-mediated inhibition of T-cell function. Current clinical use of checkpoint inhibitors has focused on anti–CTLA-4 antibodies (ipilimumab, tremelimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab), and its ligand, PD-L1 (atezolizumab, avelumab, and durvalumab). Checkpoint inhibitors have transformed the treatment algorithms and are approved for the treatment of multiple malignancies, including but not limited to melanoma, RCC, lung cancer (small cell and non–small cell), head and neck squamous cell carcinoma, gastric cancer, ovarian cancer, Hodgkin lymphoma, and tumors with DNA mismatch repair defects. Indications for ICI therapy have also expanded to include adjuvant therapy in addition to advanced disease, and multiple clinical trials for both solid and hematologic malignancies are underway.

Disinhibition of T-cell function by ICIs can lead to a spectrum of inflammatory side effects, or irAEs. Multiple mechanisms have been proposed to account for the development of irAEs, although the exact pathophysiology is not fully understood. Translational research suggests that irAEs may develop through a combination of pathways involving autoreactive T cells, autoantibodies, and cytokines. For example, T-cell infiltration of both normal and tumor tissue has been observed. T-cell activation leads to the production of inflammatory cytokines, which can contribute to the development of irAEs. IL-17 is a cytokine that is upregulated in inflammatory bowel disease, and a study of patients with melanoma treated with neoadjuvant ipilimumab found that baseline serum IL-17 levels were correlated with the development of grade 3 diarrhea or colitis. Studies have examined the role of pituitary CTLA-4 expression in the development of hypophysitis. In a series of 7 patients with ipilimumab-induced hypophysitis, pituitary antibodies were negative at baseline but developed in all 7 patients, predominantly against thyroid-stimulating hormone–secreting cells, although some patients also developed antibodies against follicle-stimulating hormone–secreting or adrenocorticotropic hormone (ACTH)–secreting cells. These antibodies led to defects in the associated hormone axis. CTLA-4 expression was observed in normal pituitary tissue, suggesting that ipilimumab–induced hypophysitis may result from binding of anti–CTLA-4 antibodies to CTLA-4 in the pituitary. An autopsy series of 6 patients treated with CTLA-4 blockade, which included patients with and without hypophysitis, found that CTLA-4 was expressed by pituitary cells in all patients at different levels, with the highest level of CTLA-4 expression noted in a patient with severe hypophysitis, suggesting that the administration of anti–CTLA-4 antibodies to patients with high levels of pituitary CTLA-4 expression may lead to severe hypophysitis. The pathophysiology of thyroid dysfunction associated with PD-1 blockade is incompletely understood.
although a study of patients with advanced non–small cell lung cancer (NSCLC) treated with pembrolizumab found that antithyroid antibodies were present in 80% of patients who developed hypothyroidism compared with 8% of patients who did not, suggesting that anti–PD-1 antibodies may modulate humoral immunity.20 Studies have suggested that irAEs may develop through the targeting of antigens shared by normal and tumor tissue. A prospective study of autoimmune dermatologic toxicity in patients who received anti–PD-1 therapy for NSCLC described 9 T-cell antigens that were shared between tumor tissue and skin, suggesting that T cells targeting cancer cells may also target normal tissues with shared antigens.21 Similarly, a case series of ICI-induced myocarditis found high levels of muscle–specific antigens in tumors from 2 patients who developed myocarditis, suggesting that myocarditis may develop through T-cell targeting of a shared antigen expressed by tumor, skeletal muscle, and heart.22 Studies have evaluated the role of microbial factors in the development of irAEs. For instance, a prospective study of colitis in patients treated with ipilimumab for melanoma found that Bacteroidetes bacteria were enriched in patients resistant to ICI-induced colitis.23 A case report of fatal ICI-induced encephalitis identified Epstein-Barr virus–specific T-cell receptors and Epstein-Barr virus–positive lymphocytes in the cortex and meninges, suggesting a relationship between viral infection and the development of irAEs.24 Future studies will clarify the pathophysiology of irAEs and will identify risk factors and strategies for monitoring and prevention.

The incidence of irAEs with single-agent ICI varies by agent, tumor type, and disease setting. The incidence of any-grade irAE in trials including patients with multiple solid tumor types has been reported at 72% with ipilimumab monotherapy,25 and 66% with anti–PD-1/anti–PD-L1 monotherapy.26 The incidence of irAEs is higher with combined PD-1 and CTLA-4 blockade.27,28 A meta-analysis of fatal irAEs in patients treated with PD-1, CTLA-4, or combined blockade reported toxicity-related fatality rates of 0.36% with anti–PD-1, 0.38% with anti–PD-L1, 1.08% with anti–CTLA-4, and 1.23% with combined anti–PD-1/anti–PD-L1 and CTLA-4.29 The type of fatal irAE observed varied by regimen, with death most often resulting from colitis (70%) with anti–CTLA-4 therapy, compared with pneumonitis (35%), hepatitis (22%), or neurotoxicity (15%) with anti–PD-1/anti–PD-L1 therapy. The most frequent causes of therapy–related death in patients treated with combined PD-1/PD-L1 and CTLA-4 blockade were colitis (37%) and myocarditis (25%). Furthermore, fatal toxic events most often occurred early after treatment initiation, with a median time to onset of 14.5 days with combination therapy versus 40 days with either anti–PD-1 or anti–CTLA-4 monotherapy.

IrAEs can be variable in their onset, kinetics, and presentation and often require specific management. Toxicity can affect nearly any organ system, and multiple presentations of rare but severe irAEs have been reported, highlighting the importance of vigilant monitoring and multidisciplinary collaboration. Common irAEs are summarized in Table 1. Consensus guidelines from the American Society of Clinical Oncology, the European Society of Medical Oncology, the National Comprehensive Cancer Network (NCCN), and the Society for Immunotherapy of Cancer provide recommendations for monitoring, diagnosis, and treatment of irAEs.5,9-11

Further studies are needed to define the optimal management of steroid-refractory irAEs. A retrospective series that included 298 patients who received ipilimumab for melanoma found that 35% of patients required steroids for an irAE and 10% of patients required additional systemic immunosuppression,30 highlighting the importance of optimizing treatment algorithms for patients with refractory irAEs. Data to inform the management of refractory irAEs are often drawn from case reports, small series, and expert opinions given a lack of prospective data.31 A recent review of emerging strategies to manage refractory irAEs suggests that biologic therapy for refractory irAEs could be selected based on the pathophysiology of the specific irAE.31 Some authors have proposed a strategy of the standard use of IL-6 receptor blockade with tocilizumab in refractory irAEs. For instance, a retrospective, single–center series, in which tocilizumab was used as second-line therapy for high–grade irAEs, reported the use of tocilizumab in 34 of 87 patients who were treated with nivolumab for multiple solid tumor types.32 The most common irAEs treated with tocilizumab were pneumonitis and serum sickness/systemic inflammatory response syndrome, and clinical improvement was observed in 27 of 34 patients. IL-6 expression has been shown to promote tumor growth and metastasis; therefore, IL-6 blockade may offer the potential for the effective treatment of refractory irAEs and maintenance of immunotherapy efficacy.31

Dermatologic Toxicity
Dermatologic toxicity is the most common irAE reported in patients who received treatment with CTLA-4 or PD-1/PD-L1 blockade.33 All-grade dermatologic toxicity is reported to occur in 30% to 40% of patients treated with PD-1/PD-L1 blockade33 and 50% of patients treated with ipilimumab, although the majority of dermatologic toxicity is grade 1 or 2.33,35 A meta-analysis of dermatologic irAEs associated with the use of nivolumab and pembrolizumab for multiple solid tumor types reported an incidence of all–grade rash of 16.7% and 14.3%, respectively.35 Vitiligo, which has been reported only in patients with melanoma,
### Table 1. Overview of Common Checkpoint Inhibitor Toxicities

| TOXICITY | BASELINE MONITORING | PRESENTATION | DIAGNOSIS | MANAGEMENT |
|----------|---------------------|--------------|-----------|------------|
| Dermatologic | Complete skin and mucous membrane examination Obtain history of immune-related skin disorders | Maculopapular/papulopustular rash | Complete skin examination with attention to lesion type and percentage of BSA affected | Grade 1: emollients, topical corticosteroids, and/or oral histamines |
| | | Dermal hypersensitivity reaction Dermatomyositis Sweet syndrome Pyoderma gangrenosum Bullous disorders DRESS SISTEN Vitiligo (melanoma only) | Consider skin biopsy | Grade 2: high-potency topical corticosteroids and/or oral corticosteroids |
| | | | | Grade 3-4: hold ICI; treat with systemic 1-2 mg/kg/d steroids; dermatology consultation |
| GI | | | | |
| Colitis | Diarrhea | Determine baseline bowel habits | | Grade ≥2: hold ICI until recovery to grade ≤1; evaluate for infection; start 1-2 mg/kg/d steroids; gastroenterology consult |
| | | | | If no response within 3-5 d, consider adding infliximab |
| | Fever | | Infectious workup: stool culture and ova and parasite, *Clostridium difficile*, CMV serologies | In refractory cases or cases with a contraindication to infliximab, vedolizumab can be used; earlier initiation of biologic therapy may lead to improved outcomes |
| | Cramping | Infected | | |
| | Urgency | CT abdomen/pelvis | | |
| | Abdominal pain | Consider GI consultation for EGD/colonoscopy with biopsy | | |
| | | | | |
| Hepatitis | CMP at baseline and every 2-3 wk during ICI | Incidental elevation of AST/ALT Fulminant hepatitis | CMP Viral studies ANA, antismooth-muscle antibodies, and ANCA if autoimmune hepatitis suspected CT abdomen/pelvis to evaluate for liver metastases Review medication list for other causes of drug-induced hepatitis | Grade 1: continue ICI with increased frequency of LFT monitoring |
| | | | | Grade 2: hold ICI until recovery to grade ≤1; start systemic steroids if no improvement |
| | | | | Grade 3-4: hold ICI; hepatology consult; start 1-2 mg/kg/d steroids |
| | | | | For steroid-refractory cases, consider mycophenolate mofetil; infliximab is contraindicated because of concerns about hepatotoxicity |
| Endocrine | Thyroid | TSH, free T4 at baseline and every 4-6 wk on ICI | Hypothyroidism | Asymptomatic hypothyroidism: thyroid hormone replacement if TSH >10 mIU/L |
| | | | Hyperthyroidism | Symptomatic hypothyroidism: thyroid hormone replacement |
| | | | Myxedema | Hyperthyroidism: if symptomatic, consider endocrine consultation and propranolol for symptom control |
| | | | | TSH receptor antibodies if Graves disease is suspected |
was observed in 7.5% of patients treated with nivolumab and 8.3% of patients treated with pembrolizumab. The development of vitiligo has been associated with improved outcomes in patients with advanced melanoma treated with ICI. A meta-analysis of 137 studies that included patients with advanced melanoma who received multiple different types of immunotherapy, including 28 studies using ICI, found that the development of vitiligo was associated with improved progression-free and overall survival. A prospective study that included 67 patients who received pembrolizumab for melanoma found that an objective response to ICI was associated with an increased incidence of vitiligo. Dermatitis has also been associated with improved outcomes. For instance, a retrospective case-control study that included 20 patients with multiple tumor types who were treated with PD-1/PD-L1 blockade and developed biopsy-proven dermatitis found that patients who developed dermatitis had improved progression-free and overall survival compared with patients who did not develop dermatitis.

The presentation is diverse and includes maculopapular or papulopustular rash, dermal hypersensitivity reaction, dermatomyositis, Sweet syndrome, pyoderma gangrenosum, acute generalized exanthematous pustulosis, acniform rash, photosensitivity reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), bullous disorders, psoriasis, vitiligo, and regression of melanocytic nevi. The most commonly reported cutaneous toxicities are maculopapular rash, pruritis, and vitiligo. Severe toxicities, such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or DRESS, are more common with a combination ICI. Cutaneous toxicity is often the earliest irAE to develop, with onset at a median of 5 weeks with anti–PD-1, 3 to 4 weeks with anti–CTLA-4, and 2 weeks with combination ipilimumab-nivolumab. Dermatologic toxicity resulting from combination PD-1/CTLA-4 blockade tends to be more severe with earlier onset.

Grade 1 dermatologic irAEs are managed with emollients, topical corticosteroids, and/or oral antihistamines. An ICI can be continued with grade 2 toxicity but should be withheld if there is no improvement to grade 1. ICIs should be stopped and systemic corticosteroids considered with grade 3 or 4 toxicity. In life-threatening cases, especially if there is concern for SJS/TEN or DRESS, ICI should be permanently discontinued, and patients should be referred to a dermatologist.

### Gastrointestinal Toxicity

**Diarrhea or colitis**

Diarrhea is a common complication of ICI therapy, with a higher incidence in patients treated with CTLA-4 antibodies. A systematic review of 10 clinical trials reported diarrhea in 27% to 54% and colitis in 8% to 22% of patients treated with anti–CTLA-4 therapy. The highest incidence of colitis occurs in patients treated with combined CTLA-4/PD-1 blockade, and the risk of grade 3 and 4 colitis is also increased.
with combination therapy compared with monotherapy. A randomized phase 3 trial of 945 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 and 4 colitis was described in 1% of patients treated with nivolumab, 7.7% of patients treated with ipilimumab, and 8.3% of patients treated with combination ipilimumab-nivolumab.

In patients treated with anti–CTLA-4 monotherapy, the average onset of gastrointestinal irAEs occurs after the third infusion, although symptoms may occur as early as after the first infusion. Diarrhea or colitis may recur after discontinuation of therapy, and patients may have a presentation similar to that of chronic inflammatory bowel disease.

In patients presenting with persistent grade 2 or higher diarrhea/colitis, ICI should be stopped and systemic corticosteroids started. If there is no response within 3 to 5 days, infliximab should be considered; a single 5-mg/kg dose is usually sufficient. In a retrospective series that included 75 patients who had immune-related enterocolitis, infliximab use was associated with a shorter time to symptom resolution and shorter duration of steroid use, and there was no decrease in overall survival. In another retrospective series, which included 117 patients treated with ICI who developed diarrhea, a steroid duration >30 days was associated with higher rates of infection compared with a shorter duration of steroid use with or without infliximab. In a retrospective series of the endoscopic and histologic features of ICI-induced colitis, patients with ulcerations on colonoscopy were more likely to have steroid-refractory colitis. Vedolizumab, an anti-integrin α4β7 antibody with gut-specific effects, has been investigated for patients with steroid-dependent or refractory ICI-induced colitis. For instance, a retrospective series of 28 patients who were treated with vedolizumab for immune-related enterocolitis that was refractory to steroids and/or infliximab described sustained clinical remission in 24 of 28 patients after a median of 3 doses of vedolizumab.

Retrospective studies have examined outcomes in patients who received earlier treatment with biologic agents. A series that included 1479 patients treated with ICI, of whom 179 developed immune-related enterocolitis, found that patients who received infliximab or vedolizumab ≤10 days after colitis onset had improved clinical outcomes, including decreased hospitalization, a shorter duration of steroid treatment and reduced rates of steroid failure, and shorter symptom duration. Prospective studies are needed clarify the optimal timing of infliximab and vedolizumab. The available retrospective data suggest that earlier initiation of biologic therapy may lead to a reduction in steroid use and improved colitis-related outcomes with similar oncologic outcomes.

Fecal microbiota transplantation (FMT) has been evaluated in a case report of 2 patients with colitis refractory to steroids, infliximab, and vedolizumab. Both patients developed complete resolution of symptoms after FMT, although one patient required a second FMT because of recurrent abdominal pain and persistent ulcers on colonoscopy. A prospective study including 26 patients with metastatic melanoma treated with ipilimumab found an association between gut microbiota composition and both response to treatment and the development of colitis.

**Hepatitis**

The estimated incidence of hepatotoxicity based on pooled clinical study data is 3% to 9% in patients treated with ipilimumab and 1% to 2% in those treated with anti–PD-1/anti–PD-L1 antibodies. The incidence of ipilimumab-induced hepatitis is dose-dependent, with <4% incidence of any-grade hepatitis in patients treated with 3 mg/kg and 15% in patients treated with 10 mg/kg. Hepatitis occurs more commonly in patients treated with combination therapy versus monotherapy. Different dosing regimens of ipilimumab-nivolumab have been investigated with variable toxicity profiles observed given the dose-dependence of ipilimumab-induced hepatitis. For example, CHECKMATE 016 (Nivolumab [BMS-936558; MDX-1106] in Combination With Sunitinib, Pazopanib, or Ipilimumab in Subjects With Metastatic Renal Cell Carcinoma [RCC]) evaluated the safety and efficacy of different regimens of ipilimumab-nivolumab, including nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 1 mg/kg (N3I1), nivolumab at a dose of 1 mg/kg and ipilimumab at a dose of 3 mg/kg (N1I3), and nivolumab at a dose of 3 mg/kg and ipilimumab at a dose of 3 mg/kg (N3I3), for metastatic RCC (mRCC). In the N1I3 arm, 21% of patients developed grade 3 and 4 elevation in aspartate and alanine aminotransferase (AST/ALT) levels compared with a 4% incidence of grade 3 AST/ALT elevation in the N3I1 arm. In a pooled retrospective safety review, which included 448 patients treated with N1I3 followed by maintenance nivolumab for advanced melanoma, hepatic irAEs were the most frequently observed grade ≥3 toxicity, with 17% incidence.

Patients most often present with asymptomatic elevations of AST and ALT with or without hyperbilirubinemia. Transaminase elevation is observed between 6 and 14 weeks after the initiation of treatment. Although most cases resolve with treatment discontinuation, multiple reports of acute liver failure secondary to nivolumab, pembrolizumab, and ipilimumab have been published. A series of 16 patients who developed grade ≥3 hepatitis during ICI therapy identified different histologic patterns of liver injury in patients treated who received anti–CTLA-4 compared with anti–PD-1/anti–PD-L1 therapies.
The differential diagnosis for transaminase elevation during ICI therapy includes drugs (ICI or other), alcohol, and infection, especially viral hepatitis.\textsuperscript{5} In cases of grade 2 toxicity, ICI should be held and liver function tests monitored; therapy can be resumed when there is resolution to grade 1, and corticosteroids should be started if there is no improvement.\textsuperscript{5,9} Rare cases are refractory to high-dose steroids, and then mycophenolate mofetil should be considered. Infliximab is contraindicated according to some guidelines given concerns about hepatotoxicity.\textsuperscript{5,9,10} However, a case report describing the use of infliximab in a case of life-threatening hepatitis refractory to high-dose steroids and mycophenolate mofetil in a patient who received ipilimumab-nivolumab for metastatic melanoma has been published.\textsuperscript{56} The patient received 2 cycles of infliximab at a dose of 5 mg/kg 2 weeks apart with a partial response achieved; there were no identifiable hepatic AEs resulting from infliximab. Additional studies are needed to clarify the safety of infliximab for this indication. The successful use of antithymocyte globulin has been reported for a case of steroid-refractory hepatitis and can be considered in cases of acute clinical deterioration.\textsuperscript{57}

**Endocrinopathies**

Endocrinopathies associated with ICI include hypothyroidism or hyperthyroidism, thyroiditis, hypophysitis, primary adrenal insufficiency, and insulin-dependent diabetes mellitus.\textsuperscript{58} The pattern of endocrinopathy varies by agent, with the highest incidence after combination therapy. A meta-analysis including 38 randomized clinical trials compared the incidence of endocrinopathies resulting from different regimens and found that the incidence of hypophysitis was highest in patients who received ipilimumab and that the incidence of thyroid dysfunction was more common with anti–PD-1 monotherapy than with anti–CTLA-4 monotherapy.\textsuperscript{59} Other endocrinopathies, including primary adrenal insufficiency and insulin-dependent diabetes mellitus, are rare and were reported in 0.7% and 0.2% of patients, respectively.\textsuperscript{58} A similar meta-analysis including 101 clinical trials of patients with multiple solid tumor types reported a pooled 5.6% incidence of hypophysitis in patients treated with ipilimumab.\textsuperscript{59} The incidence of hypophysitis with tremelimumab, the other CTLA-4 therapy investigated, was lower (1.8%). The difference in the incidence of hypophysitis with ipilimumab versus tremelimumab is hypothesized to be because of their different immunologic subclasses. Because ipilimumab is an immunoglobulin G1 antibody, it can activate the classical complement cascade, leading to a type II hypersensitivity reaction. Tremelimumab, conversely, is an immunoglobulin G2 anti–CTLA-4 antibody and thus carries a lower likelihood of complement cascade activation.\textsuperscript{59}

The time to onset of endocrine irAEs varies by agent and endocrinopathy. The median onset of moderate to severe endocrine irAEs in patients with melanoma who are treated with ipilimumab occurs at 7 to 20 weeks.\textsuperscript{60} A single-institution retrospective review including 256 patients with melanoma who received ipilimumab reported a median time to onset of hypophysitis of 4 months; however, the timing was variable, ranging from 8 to 19 months after initiation of therapy.\textsuperscript{61} The timing of hypothyroidism was also variable, with presentation occurring within the first 5 months and up to 3 years after the initiation of therapy.\textsuperscript{61} A pooled analysis of safety events in patients with melanoma who received nivolumab reported a median time to onset of approximately 10 weeks.\textsuperscript{62}

A high degree of vigilance is required to diagnose ICI-induced endocrinopathies, as presentation may be nonspecific, including nausea, fatigue, headache, or weakness.\textsuperscript{11} Guidelines recommend checking TSH and free thyroxine levels at baseline and routinely during ICI therapy. In addition, baseline testing of serum ACTH and cortisol can be considered, especially in patients with preexisting endocrine disease.\textsuperscript{59-11} Unlike other irAEs, which resolve with treatment, endocrinopathies are almost always permanent and require lifelong hormone replacement.\textsuperscript{11} Patients should be managed in close collaboration with endocrinology.

**Thyroid toxicity**

Hypothyroidism is more common with ICI therapy than hyperthyroidism.\textsuperscript{58} The overall incidence of hypothyroidism is 6.6%, with the lowest incidence (3.8%) reported in patients treated with ipilimumab and the highest incidence (13.2%) in patients treated with combination therapy. Hyperthyroidism is less common than hypothyroidism, with an overall incidence 2.9%; the lowest incidence is 0.6% with anti–PD-L1, and the highest is 8% with combination therapy.\textsuperscript{58}

Most patients with ICI-induced thyroid dysfunction are asymptomatic or present with hypothyroidism or mild thyrotoxicosis. A retrospective series including 45 patients who developed thyroid dysfunction after either anti–PD-1 monotherapy or combination anti–PD-1/anti–CTLA-4 therapy for multiple tumor types found that 22% of patients initially presented with hypothyroidism, and the remaining 78% initially presented with thyrotoxicosis.\textsuperscript{63} Of the patients with thyrotoxicosis, 80% later developed hypothyroidism. Thyroid storm\textsuperscript{64} and myxedema crisis\textsuperscript{65} have rarely been reported in patients treated with ICI. The median onset of thyroid dysfunction occurs 4 weeks after starting therapy.\textsuperscript{66} Elderly patients and patients with cardiovascular disease, who are often excluded from clinical trials, are at higher risk of cardiovascular events secondary to thyroid disorders;\textsuperscript{67} the frequency of these presentations may increase as indications for ICI expand.
Patients who develop hypothyroidism should be treated with thyroid hormone replacement after adrenal insufficiency has been ruled out.5,9-11 Thyroiditis should be managed conservatively during the thyrotoxic phase; however, other causes of thyrotoxicosis, including Graves disease, should be ruled out with laboratory tests, imaging, and endocrinology referral. Patients with symptoms of thyrotoxicosis, including tachycardia and tremor, can receive symptom-directed management with \( \beta \)-blockers.

**Pituitary toxicity**

The highest incidence of hypophysitis occurs with anti–CTLA-4 monotherapy and combination therapy. Incidence is dose-dependent (1%-4% with ipilimumab at a dose of 3 mg/kg and 16% with a dose of 10 mg/kg).33,61,68,69 The median onset occurs after 8 or 9 weeks or the third dose of ipilimumab.5 Hypophysitis is rare with anti–PD-1 monotherapy.58 The median onset of hypophysitis with nivolumab monotherapy occurs at 4.9 months (range, 1.4-11 months).70 Symptoms of hypophysitis may vary based on the region of the pituitary affected and may result from dysfunction of the thyroid, adrenal, or gonadal axis,70 with ACTH and TSH deficiency most commonly described in anti–CTLA-4–associated hypophysitis.71 Hypogonadotropic hypogonadism has been described, although the incidence is difficult to characterize given the effect of severe illness on the gonadal axis.71 Diabetes insipidus is rare.71 Enlargement of the pituitary gland is usually mild; therefore, symptoms of mass effect, such as vision loss, are rare.71

Patients who develop clinical or laboratory features of hypophysitis should undergo testing of thyroid, adrenal, and gonadal axes.5 The diagnosis of hypophysitis should be considered in patients found to have central hypothyroidism, characterized by low free thyroxine with low or inappropriately normal TSH.71 Laboratory and imaging studies are consistent with hypophysitis if there is deficiency of at least 1 pituitary hormone with magnetic resonance imaging (MRI) abnormality or if there is a deficiency of \( \geq \)2 pituitary hormones in the presence of symptoms.71 MRI findings may include diffuse pituitary enlargement, enlargement of the infundibulum, and homogeneous or heterogeneous pituitary enhancement after gadolinium administration, which may precede laboratory or clinical findings.72 Adrenal insufficiency secondary to ICI–induced hypophysitis is usually permanent and requires lifelong hormone replacement.71 Recovery of secondary hypothyroidism and hypogonadism has been described with frequency varying from 6% to 64% and 11% to 57%, respectively.71 A retrospective study of 25 patients with advanced melanoma and ipilimumab-induced hypophysitis found that high-dose steroid treatment did not improve the frequency of resolution or the time to resolution of hypophysitis.73 A large retrospective series including 98 patients with melanoma and ipilimumab–induced hypophysitis examined the effect of glucocorticoid dose on survival and found that patients who received low-dose glucocorticoids (maximum average daily dose, 7.5 mg of prednisone during the first 2 months after diagnosis) had longer overall survival and time to treatment failure compared with patients who received higher doses of glucocorticoids.74 These differences remained when adjusted for other prognostic factors, including performance status and lactate dehydrogenase levels. There was no improvement in the recovery of pituitary function noted with higher doses of steroids. Furthermore, patients who developed hypophysitis and were treated with either high-dose or low-dose glucocorticoids had improved overall survival compared with patients who received ipilimumab but did not develop hypophysitis.74 Future studies will be needed to clarify the effect of high doses of glucocorticoids on clinical outcomes in hypophysitis. Because the currently available data do not show that high-dose steroids lead to improved recovery of pituitary function, guidelines recommend careful consideration of the risks and benefits of high-dose steroids.10 Patients with headache, compressive symptoms, or adrenal crisis should be treated with methylprednisolone or prednisone at a dose of 1 to 2 mg/kg daily until symptom resolution; however, patients without these symptoms can be managed with physiologic replacement doses.

Patients with hypophysitis should be managed in conjunction with endocrinology 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 before thyroid hormone replacement to prevent adrenal crisis.11 Patients with adrenal insufficiency should be educated about the potential life-threatening nature of adrenal crisis and should be provided with stress doses of hydrocortisone in case of infection, trauma, or illness.11

**Pneumonitis**

Pneumonitis is the most common pulmonary toxicity of ICI therapy.11 Although the overall incidence of pneumonitis is low, it is potentially life-threatening and should be considered in any patient who develops new respiratory symptoms. A meta-analysis of fatal AEs of ICI found that 35% of anti–PD-1/anti–PD-L1–related fatalities resulted from pneumonitis.29 The incidence of pneumonitis is slightly higher with PD-1 monotherapy versus CTLA-4 monotherapy and increases with dual checkpoint inhibition.75,76 A large retrospective series that included 915 patients treated for multiple tumor types with anti–PD-1/anti–PD-L1 monotherapy or combination therapy reported an overall 5% incidence of pneumonitis, with 1% to 2% grade 3 and 4 pneumonitis.77 Pneumonitis secondary to anti–PD-1/anti–PD-L1 therapy is more common and more severe in patients who have NSCLC compared
with those who have melanoma. For instance, a meta-analysis that included 20 trials of anti–PD-1 therapy for melanoma, NSCLC, and RCC found that the incidence of all-grade and grade ≥3 pneumonitis was higher in patients who had NSCLC (4.1% and 1.8%, respectively) compared with those who had melanoma (1.6% and 0.2%, respectively). The incidence of all-grade pneumonitis, but not grade ≥3 pneumonitis, was higher in patients who had RCC compared with those who had melanoma. Patients with NSCLC may be at higher risk of pneumonitis given underlying lung pathology, including chronic obstructive pulmonary disease and pulmonary fibrosis. Another meta-analysis that included 19 trials of PD-1 and PD-L1 therapy for NSCLC found that the incidence of any grade and grade ≥3 pneumonitis was higher with PD-1 inhibitors compared with PD-L1 inhibitors (3.6% vs 1.3% and 1.1% vs 0.4%, respectively). The incidence of pneumonitis was also higher in treatment-naïve patients compared with previously treated patients (4.3% vs 2.8%). Larger studies are needed to determine risk factors for pneumonitis, including the relationship between smoking history and the risk and role of the PD-1/PD-L1 pathway in development of pneumonitis.

The presentation of pneumonitis varies in both severity and acuity of onset. Patients may develop cough, chest pain, wheezing, shortness of breath, new hypoxia, or fatigue. Some patients are asymptomatic, with a diagnosis made incidentally on imaging studies; in 1 series, 33% of patients were asymptomatic at diagnosis. In rare cases, hypoxia progresses rapidly, leading to respiratory failure. Imaging findings are variable and include cryptogenic organizing pneumonia, nonspecific interstitial pneumonitis, hypersensitivity pneumonitis, or usual interstitial pneumonitis/pulmonary fibrosis. Imaging findings consistent with cryptogenic organizing pneumonia are more common in patients with NSCLC and have been associated with an increased likelihood of requiring immunosuppression compared with other imaging subtypes. In addition, pulmonary and extrapulmonary sarcoid have been reported in patients treated with anti–PD-1/anti–PD-L1 and anti–CTLA-4 therapy and should be considered when chest imaging shows mediastinal or hilar lymphadenopathy or reticulonodular opacities. A retrospective series of patients with multiple tumor types treated with anti–PD-1/anti–PD-L1 monotherapy or in combination with anti–CTLA-4 therapy reported a median onset at 2.8 months, although the timing of onset was variable, ranging from 9 days to 19.2 months. Onset occurred earlier in patients treated with combination therapy. Given the variable clinical presentation and imaging findings with potential for the rapid development of respiratory failure, a high index of suspicion for pneumonitis should be maintained in patients on ICI therapy who develop respiratory symptoms. Baseline pulmonary function tests can be considered in patients who are at high risk of developing pulmonary toxicity. Guidelines recommend concurrent broad-spectrum antibiotics and immunosuppression during workup because of the potential for overlapping presentation of pneumonitis and infection. In patients with grade ≥2 pneumonitis, ICI should be withheld, pulmonology should be consulted for bronchoscopy with bronchoalveolar lavage, high-dose steroids should be started, and hospitalization may be needed.

Limited data exist regarding the management of steroid-refractory pneumonitis. Additional immunosuppression with infliximab, cyclophosphamide, or mycophenolate mofetil can be considered. In the largest retrospective series of patients with ICI-induced pneumonitis, 5 of 12 patients with grade ≥3 pneumonitis were treated with infliximab or infliximab and cyclophosphamide in addition to high-dose steroids. None of these patients survived; 3 of the deaths were attributed to infection resulting from prolonged immunosuppression, one was attributed to pneumonitis, and one was attributed to progression of cancer. The optimal choice, timing, and duration of immunosuppression in cases of ICI-induced pneumonitis are the subjects of ongoing study.

**Rheumatologic Toxicity**

The incidence of rheumatologic irAEs in patients treated with ICI is not well characterized, reflecting the difficulty in distinguishing between these irAEs and other musculoskeletal complaints in a population with a high baseline frequency of musculoskeletal symptoms. A systematic review of rheumatologic and musculoskeletal irAEs, which included 33 clinical trials, 3 observational studies, and 16 case reports or series, reported a prevalence of 1% to 43% for arthralgia and 2% to 20% for myalgia, highlighting significant variability in symptom reporting and diagnosis of rheumatologic irAEs. Only 2 of the studies included in this systematic review used combination therapy, and it was not possible to investigate an association between different regimens and rheumatologic irAEs.

Variable presentations of rheumatologic irAEs have been reported, including arthritis, which may present with 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 uveitis. Other rheumatologic irAEs include sicca syndrome; myositis, which resembles polymyositis; giant-cell arteritis; polymyalgia rheumatica; systemic lupus erythematosus; and sarcoidosis. Symptoms may persist beyond cessation of checkpoint blockade. A retrospective series that included 30 patients with multiple tumor types who developed ICI-induced inflammatory arthritis found that patterns of presentation varied by treatment regimen.
with combination therapy were more likely to develop knee arthritis and a reactive arthritis–like phenotype and to have had a previous irAE. In contrast, patients treated with monotherapy were more likely to present with small joint involvement and were less likely to have another irAE.

A high index of suspicion should be maintained for rheumatologic toxicity in patients with acute muscle–skeletal symptoms, as erosion and irreversible joint damage can occur within weeks. Grade 1 toxicity is managed with nonsteroidal anti-inflammatory drugs, followed by prednisone if no improvement occurs. Grade ≥2 toxicity is treated with prednisone, and patients should be managed in close collaboration with rheumatology. Additional immunosuppression, including methotrexate, sulfasalazine, leflunomide, or anticytokine therapy, can be considered in steroid-refractory cases. The IL–6 receptor antibody tocilizumab is approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis and has been investigated for use in rheumatologic irAEs. A case series that included 3 patients with metastatic melanoma who developed severe polyarthritis secondary to ICI therapy described significant clinical improvement in all 3 patients in addition to durable antitumor response in 1 of 3 patients after treatment with tocilizumab.

Rare Immune-Related Adverse Events
Neurologic toxicity
An analysis using a pharmacovigilance database reported an overall incidence of 0.93% of serious neurologic irAEs in patients who had melanoma who were treated with nivolumab with or without ipilimumab. The median time to onset was 45 days, and the time to resolution was 32 days. Thirty-two of 43 observed neurologic events were grade 3 or 4, and 1 case of encephalitis was fatal. Another analysis of a pharmacovigilance database identified different patterns of neurologic toxicity, depending on class of immunotherapy. For instance, myasthenia gravis was associated with anti–PD-1/anti–PD-L1 therapy. Noninfectious encephalitis/myelitis was more common with anti–PD-1/anti–PD-L1 therapy than with anti–CTLA-4 therapy and with combination therapy versus monotherapy. Guillain–Barre syndrome and noninfectious meningitis were more common with anti–CTLA-4 compared with anti–PD-1/anti–PD-L1 therapy and with combination therapy compared with monotherapy. Myasthenia gravis had an earlier onset (median, 29 days) compared with other neurologic toxicities (median, 61–80 days), and was often associated with myocarditis and myositis. Furthermore, myasthenia gravis was associated with a higher fatality rate compared with other neurologic toxicities, with the highest fatality rate noted in patients who had myasthenia gravis in addition to myositis and myocarditis.

The presentation of neurologic irAEs can be diverse, with potential for involvement of any aspect of the central or peripheral nervous system. Diagnoses may include autoimmune encephalitis, myasthenia gravis, Guillain–Barre syndrome, peripheral neuropathy, posterior reversible encephalopathy syndrome, aseptic meningitis, and transverse myelitis. Most neurologic toxicities are low grade, with a higher incidence of grade 3 and 4 toxicity after anti–CTLA-4 treatment (0.7%) compared with anti–PD-1 treatment. The differential diagnosis for patients who develop neurologic symptoms on ICI therapy is broad and includes irAE, infection, central nervous system (CNS) metastasis or leptomeningeal spread, paraneoplastic syndromes, vitamin B12 deficiency, and diabetic neuropathy. Because there is potential for variable timing of onset and for rapid clinical deterioration, neurologic irAE and early neurology consultation should be considered in patients who develop new neurologic symptoms. For patients with grade ≥2 neurologic symptoms, ICI should be withheld and steroids started while diagnostic evaluation is pursued. Patients who require hospitalization for neurologic irAEs should be managed in close collaboration with neurology.

In steroid-refractory or rapidly progressive cases, additional lines of immunosuppression can be considered, although data are limited and current recommendations are drawn from case reports. Case reports have been published describing the successful use of plasmapheresis and intravenous immunoglobulin in patients with neurologic irAEs. Natalizumab, an α4-integrin antibody approved for the treatment of multiple sclerosis, has been used to treat a patient who developed autoimmune encephalitis with anti–Hu antibodies after treatment with ipilimumab–nivolumab.

Renal toxicity
Renal irAEs are rare, with an estimated incidence of 2% with ICI monotherapy and 5% with combination therapy in a review of published phase 2 and 3 trials that included data on renal outcomes. More recent studies have suggested that the incidence of acute kidney injury in patients treated with ICI is higher than that initially reported; this increased incidence could reflect either checkpoint inhibitor toxicity or other more common causes of acute kidney injury, such dehydration and other nephrotoxic medications. Future studies will clarify the real-world incidence of renal irAEs. Presentation varies and may include worsening hypertension, electrolyte imbalance, altered urinary output, or rising creatinine.

Acute interstitial nephritis (AIN) is the most commonly reported pathology. In a series of 13 patients with biopsy-confirmed, ICI-induced acute kidney injury, for instance, AIN was the primary pathologic finding in 12 of 13 patients; in the final patient, the primary lesion was acute thrombotic microangiopathy with no evidence of AIN.
Other pathologies that have been reported include minimal change disease and lupus-like nephritis. Renal toxicity occurs earlier with ipilimumab therapy (2-3 months) compared with anti–PD-1 therapy (3-10 months); however, in the cohort of 13 patients, the time to onset ranged from 21 to 245 days, with 1 diagnosis of renal irAE made 63 days after the last ICI dose.

The differential diagnosis of acute kidney injury in patients receiving ICI therapy includes dehydration, sepsis, and other medications. Workup includes urinalysis and renal ultrasound. ICI should be withheld for cases of grade ≥2 nephrotoxicity, and steroids can be given if there is no other identifiable cause. There are limited data regarding the efficacy of glucocorticoids in the treatment of ICI-induced AIN. For example, small case series have shown recovery of renal function with glucocorticoids in the majority of cases; however, the optimal dose and duration of glucocorticoids are not known.

**Ocular toxicity**

Ophthalmologic toxicity occurs in <1% of patients treated with ICI, and few case reports describing the ocular toxicities of ICI have been published to date. Manifestations vary and include uveitis, peripheral ulcerative keratitis, Vogt-Koyanagi-Harada syndrome, choroidal neovascularization, melanoma-associated retinopathy, thyroid-associated orbitopathy, and idiopathic orbital inflammation. The median onset occurs at 2 months. Presentation varies, and patients may develop worsening vision, floaters, or conjunctival injection.

Ocular toxicity is often seen in combination with extraocular irAEs, particularly colitis. A prospective case series that included 745 patients who were treated with anti–PD-1/anti–PD-L1 therapy described a total of 8 cases of ocular irAEs. Five of 8 patients with ocular irAEs had additional extraocular irAEs. Because ocular irAEs can be vision-threatening, patients with new visual symptoms should be referred promptly to ophthalmology. Grade 2 toxicity can be managed with topical corticosteroids, whereas grade 3 and 4 toxicities often require systemic corticosteroids.

**Cardiovascular toxicity**

A retrospective and prospective multicenter registry of patients with ICI-induced myocarditis estimated an incidence of 1.14% with a median onset at 34 days. An earlier analysis using a pharmacovigilance database for patients receiving nivolumab with or without ipilimumab reported 18 cases of severe drug-related myocarditis among 20,594 patients (0.09%), with a higher incidence in patients who received ipilimumab-nivolumab (0.27%) compared with nivolumab alone (0.06%). However, a recent review of the World Health Organization database observed an increased incidence of reported cases of ICI-induced myocarditis over time, with 75% of reported cases from 2017, suggesting that the higher incidence of ICI-induced myocarditis reported in the more recent multicenter registry is likely closer to the true incidence. It is hypothesized that the increased incidence of myocarditis is related to the increasing use of checkpoint inhibitors and improved recognition of ICI-induced myocarditis. Concurrent severe AEs are common in patients with cardiac irAEs and occurred in 42 of 101 patients with myocarditis, most commonly myositis (25 patients) and myasthenia gravis (11 patients).

The presentation of cardiac irAEs varies and can include dyspnea, chest pain, or acute cardiovascular collapse. Cardiac irAEs include myocarditis, pericarditis, cardiac fibrosis, arrhythmias, and new-onset heart failure. Myocarditis can be rapidly fatal; in the multicenter registry of patients with ICI-induced myocarditis, 16 of 35 patients with myocarditis experienced a major adverse cardiac event at a median follow-up of 102 days, including 6 cases of cardiovascular death, 3 of cardiogenic shock, 4 of cardiac arrest, and 3 of complete heart block, highlighting the potentially life-threatening nature of this irAE and the importance of vigilant monitoring.

Guidelines recommend baseline electrocardiography and troponin in all patients, although the optimal monitoring frequency for troponin is not known. Diagnostic evaluation in patients who have symptoms consistent with cardiac irAE includes electrocardiogram, troponin, brain natriuretic peptide, echocardiogram, and chest x-ray. Patients with suspected myocarditis should be managed by a multidisciplinary team, with early cardiology consultation given the potential for fatal cardiac events. In cases of confirmed myocarditis, ICI should be stopped, and patients should be treated with high-dose corticosteroids. The timing of corticosteroid initiation is made on an individual basis, because there are no data available to establish a threshold (eg, cutoff troponin) for starting corticosteroids in patients with suspected myocarditis. In a retrospective series of patients with ICI-induced cardiotoxicity, complete reversibility of left ventricular dysfunction was observed in 8 of 12 patients who received corticosteroids compared with 1 of 6 patients who did not. Furthermore, in the retrospective and prospective multicenter registry of patients with ICI-induced myocarditis, higher starting doses of steroids were associated with lower serum troponin and lower rates of major adverse cardiac events. Therefore, guidelines recommend initial methylprednisolone pulse dosing (1 g/day for 3–5 days). In unstable patients and patients who do not respond to corticosteroids, additional immunosuppression should be considered, although the optimal agent is not known. Infliximab, antithymocyte globulin, intravenous immunoglobulin,
mycophenolate mofetil, and tacrolimus can be used. A case report describing the resolution of steroid-refractory myocarditis with abatacept, a CTLA-4 agonist, has been published.

**Hematologic toxicity**

Hematologic irAEs are rare; however, diverse manifestations, including hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, myelodysplasia, hemophilia A, aplastic anemia, and hemophagocytic lymphohistocytosis have been described. An analysis of the World Health Organization database identified 168 individual case-safety reports of hematologic toxicity secondary to ICI therapy. The most common hematologic irAEs were immune thrombocytopenic purpura (68 cases) and hemolytic anemia (57 cases), including 4 cases of concomitant immune thrombocytopenic purpura and hemolytic anemia. The median onset occurred at 40 days. An observational study that included 35 patients treated with anti–PD-1/anti–PD-L1 who had hematologic irAEs reported an overall incidence of <1%, although the majority (77%) of hematologic irAEs were grade 4, and there were 2 deaths secondary to febrile neutropenia.

The differential diagnosis for progressive cytopenias includes cancer progression, bone marrow involvement, gastrointestinal bleeding, and drug effect. Guidelines recommend treatment with corticosteroids on an individual basis in addition to hematology consultation.

**Patients with Autoimmune Disease Or Prior irAEs**

In patients with preexisting autoimmune disease or a history of prior irAEs, there is a risk of exacerbation of autoimmunity, redevelopment of prior irAEs, or development of de novo irAEs with ICI therapy. Although these populations were excluded from trials leading to FDA approval, studies have assessed the efficacy and safety of ICI in these populations. In a series of 30 patients with melanoma and preexisting autoimmune disease (including 6 patients with rheumatoid arthritis, 5 with psoriasis, and 6 with inflammatory bowel disease) who were treated with ipilimumab, 8 patients developed exacerbation of autoimmunity, and all were managed with corticosteroids. Ten patients developed conventional grade 3 through 5 irAEs, including a fatal case of colitis in a patient with skin–limited psoriasis; however, 15 of 30 patients had neither major irAEs nor flares. Another series included 119 patients with melanoma and either preexisting autoimmune disease or a prior significant irAE with ipilimumab who were treated with anti–PD-1 therapy. Among 52 patients with preexisting autoimmune disease, 20 developed a flare requiring immunosuppression. Only 2 patients discontinued treatment because of the flare; however, 15 patients developed de novo irAEs, and 4 of these required discontinuation of treatment. Among the 67 patients who had a prior irAE with ipilimumab, 2 patients developed a recurrence of the same irAE, and 23 developed de novo irAEs. Eight patients discontinued treatment, and there were no treatment-related deaths.

In a retrospective cohort study that included 93 patients who had multiple tumor types and prior grade ≥2 irAEs with combination or anti–PD-1/anti–PD-L1 monotherapy, 17 of 40 patients who were rechallenged with anti–PD-1/anti–PD-L1 developed a recurrent irAE, and 5 patients developed a de novo irAE. A multicenter, retrospective analysis that included 80 patients with melanoma who were rechallenged with anti–PD-1 therapy after experiencing an irAE with combination therapy reported recurrence of the irAE in 18% of patients and development of a de novo irAE in 21%. One grade 5 recurrence occurred in a patient who had had grade 2 rash with combination therapy and developed SJS/TEN with anti–PD-1. The variation in the rate of irAEs with rechallenge observed in these 2 studies may reflect differences in the initial immunotherapy leading to irAE, because patients in the study by Pollack et al transitioned from combination therapy to anti–PD-1 monotherapy, which has a lower overall toxicity profile, whereas many of the patients in the study by Simonaggio et al developed the initial irAE on anti–PD–1/anti–PD-L1 monotherapy and were later rechallenged with the same class of therapy. Studies have shown that patients with severe irAEs during combination therapy have high response rates and good clinical outcomes with observation alone, and guidelines recommend the consideration of close surveillance in patients with responding or stable disease.

Patients with preexisting autoimmune disease or prior irAEs encompass a diverse spectrum of disease pathophysiology and severity, and long-term prospective studies are needed to clarify the optimal approach to ICI therapy in specific clinical scenarios. Guidelines recommend permanent discontinuation of ICI after grade 4 irAEs, except for endocrine toxicity, which is managed with physiologic hormone replacement, and after grade 3 toxicity with a high risk of morbidity and mortality, including pulmonary, hepatic, pancreatic, ophthalmologic, and neurologic irAEs.

The data suggest that some patients with preexisting autoimmune disease or irAEs can safely be treated with ICI; however, caution should be used, and patients should be managed in close multidisciplinary collaboration, because severe and fatal events can occur. Considerations in the decision to challenge or rechallenge should include the nature and severity of the autoimmune disease or irAE, the organ system affected, goals of treatment, therapeutic alternatives, and the expected clinical benefit of additional ICI therapy.
Adoptive Cellular Therapy

CAR-T Cells

CAR-T cells are autologous T cells that have been genetically engineered to express the intracellular domain of a T-cell receptor fused to the antigen-binding domain of a B-cell receptor. When reinfused, these reprogrammed T cells recognize and attack tumor cells bearing the tumor-specific antigen. Current clinical use of CAR-T cells targets CD19, the pan-B-cell antigen, in the treatment of hematologic malignancies. Two CD19-specific CAR-T–cell products are currently in clinical use: tisagenlecleucel, which is approved for the treatment of refractory B-cell precursor acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma, and axicabtagene ciloleucel, which is also approved for relapsed diffuse large B-cell lymphoma. Studies have shown the potential to induce durable complete remissions in subsets of patients.106–108 Because of the specific toxicity profile and the potential for life-threatening, treatment-associated AEs, CAR-T–based therapies are available only at centers with special certification through a risk evaluation and mitigation strategy.

Cytokine Release Syndrome

CRS results from T-cell activation after engagement of CAR-T cells with their targets, leads to a systemic inflammatory response, and is the most common AE after an infusion of CD19 CAR-T cells.109 Activated T cells produce cytokines and chemokines, such as IL-2, soluble IL-2R-α, IFN-γ, IL-6, soluble IL-6R, and granulocyte-macrophage colony-stimulating factor.8 Surrounding immune cells, including monocytes, macrophages, and dendritic cells, also produce cytokines, contributing to a generalized state of immune activation.

Clinical trials of adult and pediatric patients with various hematologic malignancies who are treated with CD19 CAR-T have a reported variable incidence of CRS, with the incidence of any-grade CRS ranging from 35% to 100% and severe CRS ranging from 1% to 28%.109 The reported incidence and severity vary between trials; however, comparison between trials is limited by different patient populations, malignancies, CAR-T products, and CRS grading systems. Less is known about the incidence of CRS with CAR-T cells targeting antigens other than CD19; however, the use of different target antigens or CAR-T structures may influence the risk of developing CRS.110

Patients initially develop constitutional symptoms, of which fever is the diagnosis of CRS.111 Other nonspecific symptoms include malaise, myalgias, fatigue, and rash. CRS may be self-limited and can resolve with supportive care or may become life-threatening, with capillary leak leading to peripheral and pulmonary edema, hypotension, multiorgan failure, and circulatory collapse.8,109

The onset of CRS is variable and occurs 1 to 14 days after infusion, with timing dependent on the CAR-T product and patient population.109 Some patients with severe CRS develop a presentation similar to hemophagocytic lymphohistiocytosis or macrophage-activation syndrome, characterized by hepatosplenomegaly, hepatic dysfunction, hyperferritinemia, hypofibrinogenemia, and coagulopathy.111 Symptoms of CRS are manifestations of a profound immune response, which could have multiple causes; therefore, patients who have received CAR-T and develop symptoms consistent with CRS should be evaluated for other causes of fever, hypotension, and respiratory failure, including overwhelming infection and progression of malignancy.111

Several risk factors for CRS have been described. Different CAR-T manufacturing techniques may lead to variable safety and efficacy profiles. The incidence of CRS is higher in patients treated for ALL compared with those treated for non-Hodgkin lymphoma and chronic lymphocytic leukemia.109 Clinical trials of CD19 CAR-T cells have reported a higher incidence of CRS in patients with a higher ALL disease burden112,113 and in patients who received higher infusion doses.114,115 However, multiple factors are involved in the in vivo expansion of CAR-T cells, and the total infused dose may underestimate the total active dose, because a high burden of malignancy may lead to increased antigen stimulation.

Consensus guidelines with recommendations for standardized grading of CRS have been developed by the American Society for Transplantation and Cellular Therapy, with severity of CRS dependent on the degree of hypotension and hypoxia.111 Because the management of CRS depends on grade, and because multiple institutions had independently developed different CRS grading systems before the publication of consensus guidelines, these guidelines have helped standardize the management of CRS. An overview of the grading system is provided in Table 2.

NCCN guidelines with recommendations for the management of CAR-T toxicity, including CRS, hemophagocytic lymphohistiocytosis/macrophage-activation syndrome, and neurotoxicity, have also been published.5

NCCN guidelines recommend at least twice-daily assessment for CRS in patients who are at risk, in addition to baseline C-reactive protein (CRP) and ferritin with repeat CRP and ferritin 3 times per week for 2 weeks after infusion. CRP, ferritin, and other markers of inflammation, including IFN-γ, IL-6, and IL-10, are elevated in patients with CRS.109,112,113 Patients with grade 1 CRS should be treated with broad-spectrum antibiotics along with other workup and supportive care, depending on the end-organ toxicities observed. Patients with grade...
≥2 CRS should be treated with tocilizumab at a dose of 8 mg/kg intravenously for a maximum of 4 doses; steroids should be added in cases of grade 3 and 4 toxicity and in cases of grade 2 toxicity with persistent hypotension after anti–IL-6 therapy.5

Tocilizumab is an IL-6 receptor antagonist that has been shown to lead to rapid resolution of CAR-T–induced CRS116 and is FDA-approved for the treatment of severe CRS based on a retrospective analysis of 45 patients (median age, 12 years) who were treated with CD19 CAR-T cells and received tocilizumab for CRS; the response rate was 69%.117

The ideal timing of tocilizumab, including the benefit of early use in patients at high risk and the effect of steroids and tocilizumab on the durability of remission, are subjects of ongoing study. For example, a study of 16 patients with B-ALL who received CD19 CAR-T therapy reported the ablation of CAR-T cells by peripheral blood analysis in 3 patients who were initially treated for CRS with high-dose steroids, suggesting that high doses of steroids may decrease the effectiveness of CAR-T therapy.113 The next 3 patients with CRS were treated instead with tocilizumab, which led to an improvement in symptoms within 1 to 3 days and did not lead to reduced expansion of CAR-T cells in peripheral blood. There was a 5-fold decrease in bone marrow CAR-T cells in patients who received high-dose steroids compared with tocilizumab or supportive care alone. In a phase 1 trial of

### TABLE 2. Overview of Common Chimeric Antigen Receptor T-Cell Toxicities

| TOXICITY | BASELINE MONITORING | PRESENTATION | DIAGNOSIS | GRADING |
|----------|---------------------|--------------|-----------|---------|
| CRS      | Cardiac monitoring  | Fever (required for diagnosis) | Consider evaluation for other causes of fever, hypotension, and respiratory failure, including infection and progression of malignancy | Grade 1: fever (temperature ≥38°C) |
|          | Daily CBC           | Malaise      | Grade 2: fever with hypotension not requiring vasopressors or hypoxia requiring up to 6 L/min nasal cannula | |
|          | CMP, including magne- | Myalgias     | Grade 3: fever with hypotension requiring one vasopressor or hypoxia requiring high-flow nasal cannula, facemask, nonbreather, or venturi mask | |
|          | sium and phosphorous, | Fatigue      | Grade 4: fever with hypotension requiring more than one vasopressor, not including vasopressin, and/or hypoxia requiring positive pressure ventilation | |
|          | coagulation profile  | Rash         |           |         |
|          | CRP and ferritin at baseline and 3 times per wk for 2 wk | Pulmonary edema |           |         |
|          | Twice-daily assessment for CRS during the period of highest risk | Hypotension |           |         |
|          |                     | Organ failure |           |         |
|          |                     | Circulatory collapse |           |         |
| HLH/MAS  | Monitoring for CRS, as above | Consider HLH/MAS if the following features are present in patients with CRS: | | |
|          |                     | • Rapidly rising ferritin (>5000 ng/mL) | | |
|          |                     | • Cytopenias | | |
|          |                     | • Grade ≥3 elevation in AST, ALT, or bilirubin | | |
|          |                     | • Grade ≥3 elevation in creatinine | | |
|          |                     | • Grade ≥3 pulmonary edema | | |
|          |                     | • Presence of hemophagocytosis in bone marrow or other organs | | |
| ICANS    | Neurologic assessment twice daily, including cognitive and motor function | Tremor | Grade ≥2: Brain MRI, EEG | ASTCT consensus grading includes the following: |
|          |                     | Dysgraphia | | • ICE score |
|          | Consider baseline brain MRI | Expressive aphasia | | • Level of consciousness |
|          |                     | Apraxia | | • Seizure |
|          |                     | Impaired attention | | • Motor findings |
|          |                     | Subclinical or clinical seizures | | • Elevated ICP/cerebral edema |
|          |                     | Diffuse cerebral edema | | • Grade is assigned based on the most severe event that is not attributable to another cause |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASTCT, American Society for Transplantation and Cellular Therapy; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CRS, cytokine release syndrome; EEG, electroencephalogram; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; MRI, magnetic resonance imaging.
axicabtagene-ciloleucel that included 111 patients, 43% of patients received tocilizumab and 27% received glucocorticoids with no observed difference in the overall response rate.\textsuperscript{118}

To clarify the role of tocilizumab in preventing severe CRS, in a recent study of 78 patients aged 1 to 24 years with B-ALL, those with a high tumor burden received a single dose of tocilizumab at the time of first fever, because tumor burden is known to be a risk factor for the development of CRS.\textsuperscript{119} A clinically meaningful reduction in severe CRS was observed, suggesting that the early administration of tocilizumab may allow for the prevention of high-grade CRS while maintaining the efficacy of treatment. However, the administration of tocilizumab may predispose to neurologic toxicity. Cases have been described in which tocilizumab leads to the rapid resolution of hemodynamic instability; however, some patients develop neurotoxicity shortly after treatment with tocilizumab.\textsuperscript{120} Steroids and tocilizumab for the treatment of CRS have not been compared in a randomized trial, and management guidelines are based on the available data, which vary widely based on patient population, types of malignancy, CRS grading scale, definition of response to treatment, and CAR-T product.

**Immune Effector Cell-Associated Neurotoxicity Syndrome**

ICANS may present with a diverse range of neurologic symptoms; however, patients often develop a characteristic evolution of neurologic features.\textsuperscript{111} Patients initially develop tremor, dysgraphia, mild expressive aphasia, apraxia, and impaired attention. Expressive aphasia is a specific symptom of ICANS. In a phase 1 study of adult patients treated with CD19 CAR-T for B-ALL, expressive aphasia developed in 21 of 22 patients who had severe neurotoxicity and was the earliest neurologic symptom in 19 of 22 patients.\textsuperscript{121} Expressive aphasia evolved over a period of hours to global aphasia, with both expressive and receptive difficulty; patients were awake but mute and akinetic. This characteristic finding of an awake patient who is mute and unable to follow commands can help distinguish ICANS from other causes of encephalopathy. As neurotoxicity progresses, patients may develop subclinical or clinical seizures and, rarely, diffuse cerebral edema.\textsuperscript{111} Fatal cerebral edema has been reported.\textsuperscript{122} Onset has been described from 1 day to 3 or 4 weeks after CAR-T infusion.\textsuperscript{3,115} A single-center study of CAR-T neurotoxicity in patients who received CD19 CAR-T for B-ALL, non-Hodgkin lymphoma, or chronic lymphocytic leukemia reported grade ≥1 toxicity in 40% of patients, with a median time to onset of 4 days after CAR-T infusion and a median duration of reversible neurotoxicity of 5 days.\textsuperscript{123} Delayed-onset neurotoxicity occurring 3 to 4 weeks after CAR-T therapy has been described in up to 10% of patients.\textsuperscript{3}

Neurologic toxicity has been reported in clinical trials of multiple immune effector cell therapies, including CD19 CAR-T cells, CAR-T cells targeted to non-CD19 antigens, and bispecific antibody therapy.\textsuperscript{112,118,124,125} In a phase 1 study of 53 adult patients who received CD19 CAR-T cells for B-ALL, grade 1 and 2 neurotoxicity was observed in 11 patients, and grade 3 and 4 neurotoxicity was observed in 22 patients.\textsuperscript{121} The incidence of neurotoxicity resulting from CAR-T cells specific for solid tumor antigens is less well characterized and may vary based on the specific target antigen.

Two potential mechanisms have been proposed to account for the development of ICANS, although the precise physiology leading to its development is unknown. First, neurotoxicity may arise from the diffusion of cytokines into the CNS. Higher serum levels of IL-15, IL-6, IL-10, and IP-10 have been described in patients who develop high-grade neurotoxicity.\textsuperscript{126} Second, trafficking of CAR-T cells into the CNS may lead to the development of neurotoxicity. For example, a phase 1 study that included 21 children or young adults with hematologic malignancies who were treated with CD19 CAR-T reported higher concentrations of cerebrospinal fluid CAR-T cells in patients who developed neurotoxicity compared with those who did not.\textsuperscript{114}

Several studies have examined risk factors for the development of ICANS. For example, an analysis of neurologic adverse events in 133 adults who received CD19 CAR-T cells for multiple types of hematologic malignancies found that neurotoxicity was more common in younger patients, patients with B-ALL, those with high tumor burden, and those who received a high CAR-T cell dose.\textsuperscript{123} A higher CAR-T dose was also associated with the development of more severe neurotoxicity. Furthermore, levels of serum cytokines, including IL-6, IFN-γ, MCP1, IL-15, IL-10, and IL-2, were higher during the 36 hours after CAR-T infusion in patients who developed grade ≥4 neurotoxicity, suggesting that measurement of both the rate of rise and the peak levels of serum cytokine profiles could identify patients at the highest risk of severe ICANS.\textsuperscript{121} A study of 53 adult patients with ALL reported similar risk factors for the development of neurotoxicity, including high tumor burden, high in vivo CAR-T-cell expansion, and earlier and higher elevation of serum cytokines.\textsuperscript{121} Furthermore, there was a correlation between the development of ICANS and CRS, and all patients who developed neurotoxicity had at least grade 1 CRS, which developed before neurotoxicity.

Consensus guidelines with recommendations for the standardized grading of ICANS have been published by the American Society for Transplantation and Cellular Therapy.\textsuperscript{111} This grading system uses a 10-point screening tool, the Immune Effector Cell-Associated Encephalopathy
score, to provide an objective measurement of the pattern of neurotoxicity observed with CAR-T. Workup for causes of neurologic symptoms may include an MRI of the brain, an electroencephalogram, a neurology consultation, and a review of medications for drugs that can cause sedation. Unlike CRS, neurotoxicity often does not respond to tocilizumab, and guidelines recommend high-dose steroids for patients with grade ≥2 neurotoxicity. Unlike CRS, neurotoxicity often does not respond to tocilizumab, and guidelines recommend high-dose steroids for patients with grade ≥2 neurotoxicity, with the addition of tocilizumab if concurrent CRS is present. Risk evaluation and mitigation strategy guidelines for the currently available CAR-T products have been published to assist with the management of neurotoxicity and should be referenced when applicable.

Conclusions
Cancer immunotherapies, including ICIs and CAR-T, have transformed the treatment landscape for multiple solid and hematologic malignancies. Clinical trials continue to expand the indications for these therapies and to explore new methods of harnessing the immune system to treat cancer. The growing clinical application of immunotherapy highlights the importance of the recognition and management of its unique toxicity profile. Further studies are needed to develop risk stratification models and to characterize the pathophysiology leading to toxicity, which will improve current preventive and treatment approaches. The cornerstone of toxicity management is often steroids or immunosuppression, and ongoing studies are evaluating the effect of immunosuppression on antitumor efficacy.

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