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REVIEW

A Review of Cancer Immunotherapy Toxicity: Immune Checkpoint Inhibitors

Neeraj Chhabra [1,2] · Joseph Kennedy [1,2]

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Abstract

Cancer immunotherapy, which leverages features of the immune system to target neoplastic cells, has revolutionized the treatment of cancer. The use of these therapies has rapidly expanded in the past two decades. Immune checkpoint inhibitors represent one drug class within immunotherapy with its first agent FDA-approved in 2011. Immune checkpoint inhibitors act by disrupting inhibitory signals from neoplastic cells to immune effector cells, allowing activated T-cells to target these neoplastic cells. Unique adverse effects associated with immune checkpoint inhibitors are termed immune-related adverse effects (irAEs) and are usually immunostimulatory in nature. Almost all organ systems may be affected by irAEs including the dermatologic, gastrointestinal, pulmonary, endocrine, and cardiovascular systems. These effects range from mild to life-threatening, and their onset can be delayed several weeks or months. For mild irAEs, symptomatic care is usually sufficient. For higher grade irAEs, discontinuation of therapy and initiation of immunosuppressive therapy may be necessary. The management of patients with irAEs involves multidisciplinary care coordination with respect to the long-term goals the individual patient. Clinicians must be aware of the unique and sometimes fatal toxicologic profiles associated with immunotherapies to ensure prompt diagnosis and appropriate management.

Keywords Immunotherapy · Checkpoint inhibitor · Chemotherapy · Toxicity · Adverse events

Background

The pharmacologic treatment of cancer has evolved in the last two decades as agents with novel mechanisms of action have successfully transitioned from the bench to the bedside. Traditional cytotoxic chemotherapy, which nonspecifically targets cell proliferation, is associated with sometimes serious adverse effects to multiple organ systems. The immune system is a commonly affected organ system and cytotoxic chemotherapy frequently results in immunosuppression in addition to anti-tumor effects. Targeted therapies have since been developed which leverage features of the body's innate immune system to direct immune cells to target neoplastic cells [1]. These therapies are collectively termed immunotherapy.

Since the introduction of rituximab as the first FDA-approved monoclonal antibody for the treatment of cancer in 1997, immunotherapy agents, mechanisms, and indications have expanded [2]. Given the rapid growth of immunotherapy, clinicians must be aware of the unique adverse effects associated with their use to ensure timely diagnosis and appropriate management. The purpose of this two-part narrative review is to mechanistically categorize the immunotherapy agents used in the treatment of cancer, examine their respective toxicities, and describe treatment considerations. This first part of a two-part series will focus on immune checkpoint inhibitors.

Methods

Relevant articles were identified through PubMed using the following query: "Drug-Related Side Effects and Adverse Reactions""[Mesh]) AND ""Antineoplastic Agents""[Mesh])

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✉ Neeraj Chhabra
NChhabra@cookcountyhhs.org

[1] Cook County Health, Department of Emergency Medicine, Division of Medical Toxicology, 1950 W Polk Street, 7th Floor, Chicago, IL 60612, USA

[2] Toxikon Consortium, Chicago, IL, USA

AND ""Immunotherapy""[Mesh]. The database was queried for all article types, including clinical trials, meta-analyses, reviews, and practice guidelines. We searched through the date August 8, 2020. Additional references were identified through the search of publications' bibliographies. For the purposes of this two-part review, immunotherapy will be subcategorized as immune checkpoint inhibitors, adoptive cellular therapies, kinase inhibitors, other monoclonal antibodies, and oncolytic viruses [1].

Immune Checkpoint Inhibitors

Ipilimimab became the first FDA-approved immune checkpoint inhibitor (ICI) in 2011 for the treatment of advanced melanoma [3]. Since then, 6 other ICIs have been approved for use in the United States (Table 1), with several others in clinical trials. Initial studies indicated improved mortality in patients with advanced-stage melanoma [3–5]. Subsequent studies have highlighted the efficacy of these medications, even in patients who were previously considered untreatable [6–10]. Indications continue to expand and include Hodgkin's lymphoma and several solid tumors such as non-small cell lung cancer, colorectal cancer, and renal cell cancer [11]. ICIs are used either as monotherapy or in conjunction with other agents, including other ICIs (dual immune checkpoint blockade). They are typically dosed in cycles every 2-3 weeks [12].

Mechanism of Action

ICIs are monoclonal IgG antibodies, which act by disrupting inhibitory signals which inactivate cellular immune effector cells. The physiologic role of immune checkpoints is to limit the immune response and therefore allow self-tolerance by turning cytotoxic T-cells "off" [13]. Native cells use these checkpoints to avoid tissue damage from activated T-cells. Some cancer cells exploit these checkpoints by interacting with receptors on cytotoxic T-cells in order to evade host immunity. Immune checkpoints are therefore both a mechanism by which cancer cells can escape immuno-surveillance and also a promising therapeutic target [14]. By disrupting the interaction between immune checkpoints and cancer cells, ICIs allow T-cells to remain activated and target these cells (Fig. 1). Current surface receptor and ligand targets for ICIs include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death receptor 1 (PD-1), and its ligand, programmed death-ligand 1 (PD-L1). These receptors and ligands are overexpressed in certain tumor microenvironments, explaining their efficacy in cancer therapy [15].

Table 1 FDA-approved immune checkpoint inhibitors and indications.

Drug	Trade name	Year	Target	Location	Indications*
Ipilimumab	Yervoy®	2011	CTLA-4	T-lymphocyte	Melanoma, RCC, colorectal carcinoma
Nivolumab	Opdivo®	2014	PD-1	T-lymphocyte	Melanoma, NSCLC, SCLC, RCC, Hodgkin lymphoma, SCC of H&N, urothelial carcinoma, colorectal carcinoma, HCC
Pembrolizumab	Keytruda®	2014	PD-1	T-lymphocyte	Melanoma, NSCLC, Hodgkin lymphoma, SCC of H&N, urothelial carcinoma, gastric tumors, bladder cancer, head and neck cancer, esophageal cancer, cervical cancer, HCC, RCC, Merkel cell carcinoma, breast cancer, colorectal carcinoma
Atezolizumab	Tecentriq®	2016	PD-L1	Tumor cell	NSCLC, urothelial carcinoma, SCLC, breast cancer
Durvalumab	Imfinzi®	2017	PD-L1	Tumor cell	Urothelial carcinoma, NSCLC
Avelumab	Bavencio®	2017	PD-L1	Tumor cell	Merkel cell carcinoma, urothelial carcinoma, RCC
Cemiplimab	Libtayo®	2018	PD-1	T-lymphocyte	Cutaneous SCC

* Some indications represent second and third-line treatment options or are only indicated in the presence of specific biomarkers or in combination with other agents. FDA, Food and Drug Administration; CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SCC of H&N, squamous cell carcinoma of the head and neck; HCC, hepatocellular carcinoma.

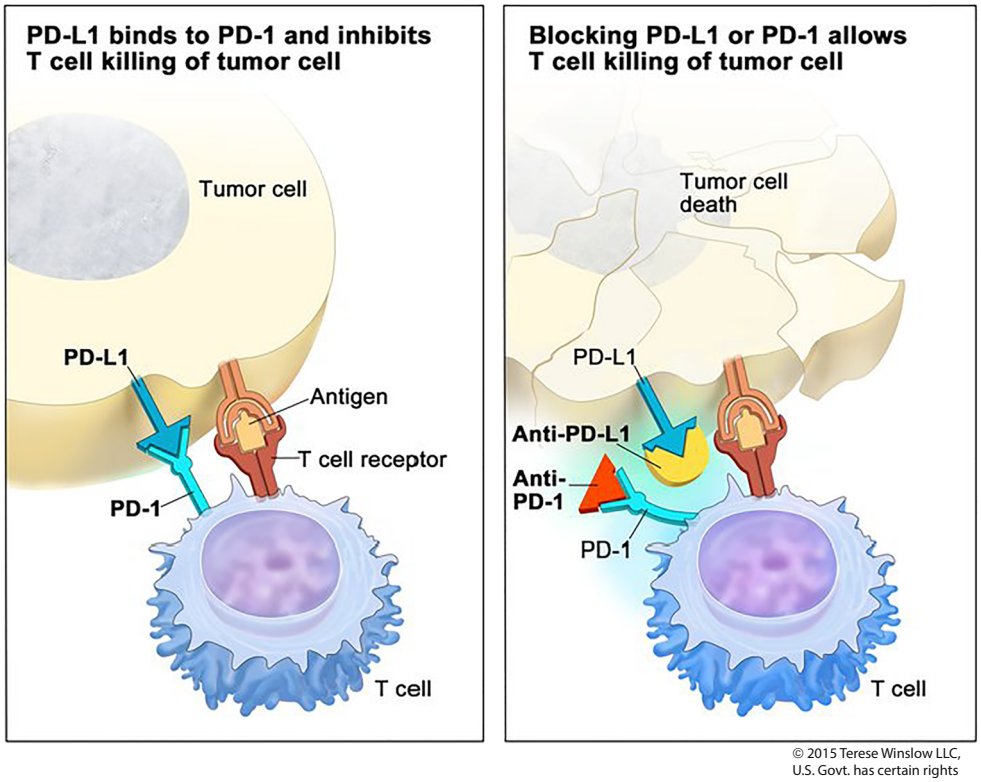

Fig. 1 Immune checkpoint inhibitor mechanism of action (PD-1) (reproduced with permission from Terese Winslow LLC). PD-1, programmed death receptor 1; PD-L1 programmed death-ligand 1.

PD-1, programmed death receptor 1; PD-L1 programmed death ligand 1

Overview of Toxicity

In clinical trials for several cancer types, checkpoint inhibitors have shown favorable outcomes in both tumor regression and patient survival. However, unique adverse effects are common due to non-specific immunostimulation which may cause organ-specific inflammation, tissue damage, and autoimmunity [11]. Non-cancerous tissue infiltration by dysregulated T-lymphocytes is a likely mechanism of toxicity, although increased production of antibodies has been described [16–20]. Clinical experience with ICIs and their unique adverse effects, termed immune-related adverse effects (irAEs), has increased since 2011 [21]. To date, there are no well-described reports of ICI overdose in the medical literature.

While ICIs typically produce more mild toxicity than traditional cytotoxic chemotherapy, irAEs can still cause significant morbidity and are sometimes fatal [22, 23]. Up to 85% of patients report irAEs after treatment with ipilimumab, which targets CTLA-4, and up to 70% of patients report irAEs after treatment with inhibitors of the PD-1 axis [16, 24]. High grade organ-specific toxicities for agents which act on the PD-1 axis are similar between agents but some organ systems appear to be more sensitive to certain agents [25]. These specific agents are discussed in more detail in the sections corresponding to specific organs. Toxicity is dose-related for certain agents, and patients receiving combination ICI therapy appear to have an increased incidence of toxicity [22, 26]. Severe irAEs were nearly 40% higher with dual checkpoint blockade compared to monotherapy in one study [7]. Typically, irAEs are organ-specific with certain organ systems displaying increased vulnerability, such as the skin and gastrointestinal tract. Additionally, there is variability in the likelihood of individual organ irAEs based on the specific ICI. In general, colitis and hypophysitis are more common with anti-CTLA-4 antibodies, and thyroid dysfunction and pneumonitis are more common with antibodies impairing the PD-1 axis [27, 28].

Toxicities due to ICIs are due to immunostimulation and mimic autoimmune diseases [11]. In order to standardize reporting of irAEs, they are graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Table 2). Although these criteria were primarily developed to standardize reporting of AEs for clinical trials, they are used clinically to direct management [13]. In general, patients with grade 1 or 2 toxicity can either continue treatment with an ICI or have a brief interruption for treatment and monitoring. Patients with severe toxicity (grades 3 or 4) should have their ICI stopped and are generally not re-challenged with ICIs in the future due to the risk of toxicity recurrence [30, 31]. Patients with grade 3 and 4 irAEs are typically managed in a hospital setting. Any decision to restart an ICI should be made following a discussion between the patient and their oncologist with consideration of their organ-specific toxicity, likelihood of recurrence, prognosis, and potential alternative therapies.

Table 2 Grading and general acute management of immune-related adverse events caused by immune checkpoint inhibitors adapted from Brahmer et al. [29].

CTCAE severity grade	Description	Setting	Corticosteroids	Other immunosuppressive drugs	ICI continuation
1	Mild or asymptomatic	Ambulatory	Not recommended	Not recommended	Continue
2	Moderate, minimal, or local	Ambulatory	Topical or systemic oral 0.5-1 mg/kg/day	Not recommended	Suspend temporarily*
3	Severe or medically significant	Hospital	Systemic steroids oral or intravenous 1-2 mg/kg/day	Consider if symptoms unresolved in 3-5 days	Discontinue permanently†
4	Life-threatening	Hospital or intensive care setting	Systemic steroids oral or intravenous 1-2 mg/kg/day	Consider if symptoms unresolved in 3-5 days	Discontinue permanently
5	Death	NA	NA	NA	NA

* May be continued for dermatologic or endocrine systems. † In select cases, ICI may be restarted after discussion of risks and benefits between the patient, their oncologist, and any relevant subspecialists. CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor; NA, not applicable.

The development of immunostimulation, as evidenced by the presence of irAEs, appears to be associated with a beneficial cancer response and prolonged survival. Several irAEs, including vitiligo, hypophysitis, enterocolitis, and pneumonitis, have been associated with favorable tumor response or prolonged survival [32]. These findings, however, should be interpreted with caution due to potential survivorship bias as patients with a positive response to ICI therapy survive longer and therefore have a longer time course in which to develop and report irAEs [13, 33].

Management of irAEs is organ-specific and requires a multidisciplinary approach to ensure the best clinical outcome with respect to the long-term goals of individual patients. General management is with immunosuppression typically using corticosteroids with or without cessation of the ICI depending on the organ involved and severity of toxicity. For grade 2 irAEs, topical or oral corticosteroids may be appropriate initially. For high-grade irAEs, systemic intravenous corticosteroids are recommended. Although corticosteroid response may be immediate, treatment is typically needed for a month or longer for severe irAEs [26]. Although consideration of the adverse effects due to the prolonged use of corticosteroids is necessary for clinicians, they are beyond the scope of this review. There is emerging evidence that as many as one-third of patients with severe irAEs may not respond to systemic corticosteroids [24]. While evidence is limited to case reports and case series, other immunomodulatory agents may be indicated in the management of severe corticosteroid refractory irAEs [34]. Agents such as anti-thymocyte anti-globulin, infliximab (anti-TNF-alpha mAb), tocilizumab, and rituximab have all been used for their immunosuppressive effect [29, 34–36]. Given the organ-specific nature of toxicity, this review will use an organ system-based approach to describe potential complications of ICI therapy.

Time-Course

It is important for both patients and clinicians to appreciate the time-course associated with irAEs. Compared to cytotoxic chemotherapy, the development of irAEs can be delayed. The average time to onset for irAEs is 6 to 12 weeks from the initial dose, although rarely some may occur up to one year from last administration [18, 37–39]. Dermatologic and gastrointestinal toxicities are among the first to develop, while endocrine toxicity often arises after more than 6 weeks from the last administration [30]. Clinicians must maintain a high index of suspicion for irAEs in patients who have had ICIs within the past year. In patients who have had ICI therapy, any symptom must be considered as a potential irAE [40]. Similarly, patients should be counseled on irAEs and be aware that initial symptoms may be vague or mild [41]. Predictive biomarkers for the development of specific irAEs are not commonly used clinically but represent a promising future area of research, which may potentially allow for earlier recognition of mild irAEs [42–44].

Cardiac

ICI-related cardiotoxicity is rare but potentially fatal, requiring a high index of suspicion by treating clinicians. It has been estimated to occur in approximately 0.09% of patients receiving ICI therapy although the true incidence may be higher [17, 35, 45]. Combination ICI therapy is associated with a 5 times higher risk for ICI-related cardiotoxicity when compared to monotherapy [17]. Both PD-1 and PD-L1 are expressed in human cardiomyocytes, lending plausibility to lymphocyte-medicated cardiac toxicity [46]. Myocarditis, dilated

cardiomyopathy, pericarditis, pericardial effusion, and arrhythmias have all been described along with fatal cases of heart failure [35, 46, 47]. The median time to onset is 17 to 34 days from treatment initiation but may occur 6 weeks or longer into treatment [48–51]. Mortality due to ICI-associated cardiotoxicity is high, with estimates as high as 27%-50% [49, 52].

Symptoms of ICI-related cardiotoxicity vary widely and include fatigue, myalgias, chest pain, dyspnea, and syncope [45]. Diagnosis is aided by the presence of cardiac biomarker elevation, which is almost universally present in cases of ICI-related myocarditis [35, 49]. Elevations in serum troponin levels may be predictive of major cardiac sequelae such as cardiac arrest or cardiogenic shock in patients with ICI-related myocarditis [47, 49]. The median admission troponin elevation in patients with ICI-related myocarditis and major adverse cardiac event was almost forty times the upper limit of normal [49]. Additional laboratory testing with brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) may be helpful in the evaluation of volume overload due to heart failure but is neither diagnostic nor prognostic in the setting of ICI-related myocarditis [45, 52]. Electrocardiogram (ECG) changes are common but not always present. Echocardiography may show left ventricular systolic dysfunction in up to 79% of patients with ICI-associated cardiotoxicity and should be performed in all patients with suspected ICI-associated cardiotoxicity given the risk for pericardial effusion and cardiac tamponade [52]. Cardiac MRI may not have adequate sensitivity for the evaluation of ICI-related myocarditis [53]. Endomyocardial biopsy is the gold standard for diagnosis of ICI-associated myocarditis but the decision to perform a biopsy should be made after weighing potential benefits in diagnosis against potential risks of the procedure including myocardial perforation, arrhythmia, and heart block [35]. In general, biopsy should only be performed if the diagnosis is in question after other diagnostic studies and will impact treatment decisions. A T-cell predominant lymphocytic infiltration of the myocardium is the expected finding if biopsy is performed [49]. However, due to the patchy involvement of ICI-associated myocarditis, negative results should be interpreted with caution [45].

Patients should be closely monitored for life-threatening complications, including arrhythmias and heart failure, and managed in consultation with a cardiologist. Pericardial effusion with tamponade physiology warrants prompt pericardial drainage. Given the potential for sudden cardiac death, ICI cessation and immediate initiation of systemic high-dose corticosteroid treatment are critical [54]. An initial dose of 1-2 mg/kg/day of intravenous methylprednisolone is likely sufficient in the acute setting followed by a slow taper of oral prednisone or prednisolone in the outpatient setting [35, 53, 54]. Corticosteroid therapy may increase the likelihood of left ventricular function recovery by up to 50% [52]. For patients without an immediate response to corticosteroids, dose escalation to methylprednisolone 1 gram/day should be considered [54]. Other immunosuppressive agents such as mycophenolate mofetil, anti-thymocyte globulin (ATG), and tacrolimus, as well as plasmapheresis have been proposed for the treatment of steroid-refractory myocarditis but there is currently a dearth of evidence supporting their use [35]. Infliximab, a monoclonal antibody against the inflammatory cytokine TNF-alpha, has also been proposed but carries the potential to precipitate new-onset congestive heart failure, possibly worsening the course of ICI-associated cardiotoxicity [55]. In contrast to most other irAEs, it is recommended that ICI therapy be temporarily discontinued for grade 1 toxicity and permanently discontinued for cardiac adverse events of grade 2 or higher [29, 56].

Cytokine Release Syndrome

Cytokine release syndrome is a systemic inflammatory response characterized by the systemic release of cytokines. Patients will typically develop fever, chills, hypotension, and tachycardia [11]. It is a rare complication of ICI therapy. Case reports have described the spectrum of symptoms and complications seen with cytokine release syndrome associated with ICI therapy [57–62]. An international registry study found that cytokine release syndrome represented only 0.14% of all ICI-related adverse drug reactions [63]. This contrasts with adoptive cellular therapies, another type of cancer immunotherapy, where cytokine release syndrome is far more common. The timing of cytokine release syndrome following ICI therapy ranges from 1 to 18 weeks with a median of 4 weeks [63]. Severe cases may be life-threatening. The diagnosis of ICI-related cytokine release syndrome is difficult due to its rarity, similarity with other disease processes such as sepsis, and potentially delayed onset. It is therefore vital for clinicians to elicit a history of ICI therapy and maintain a broad differential diagnosis. Simultaneous treatment for cytokine release syndrome and sepsis may therefore be prudent until a definitive diagnosis can be established. Further discussion of the diagnostic considerations and management of cytokine release syndrome is provided in part II of this review in the section on adoptive cellular therapies.

Dermatologic

Dermatologic toxicities are the most common irAEs, occurring in 40-50% of patients treated with ipilimumab and 30-40% of patients treated with ICIs which target the PD-1 axis [64]. Of agents acting on the PD-1 axis, nivolumab carries the highest risk [25]. While rarely life-threatening, they may greatly diminish the quality of life for patients [65]. Common skin irAEs include erythema, pruritus, vitiligo-like hypopigmentation, lichenoid reactions, eczema, and

morbilliform eruptions. The presence of vitiligo appears to only occur in patients with melanoma and is associated with a favorable cancer prognosis [66, 67]. Rarely, eruptions such as papulopustular eruptions and ulcerations mimicking pyoderma gangrenosum may occur. Low-grade dermatologic irAEs include any of the above eruptions which occupy less than 10% of total body surface area (grade 1) or between 10% and 30% of total body surface area (grade 2). Grade 3 reactions affect over 30% of the total body surface area or significantly affect activities of daily living. Grade 4 reactions are life-threatening [68]. Grade 3 and 4 reactions are rare (1-4% of dermatologic irAEs) but include exfoliative diseases such as Stevens-Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) [64, 68, 69]. Hair re-pigmentation and alopecia have also been reported with ICI therapy but are of unclear clinical significance [70, 71]. Dermatologic complications will typically appear 3 to 8 weeks after the initiation of therapy and are dose-dependent [3, 65].

Skin toxicity is typically mild and managed with symptomatic therapies and topical agents. Patients should be counseled on photoprotection with clothing, hats, and sunscreens to avoid sunburn, especially if vitiligo is present. If the diagnosis of a dermatologic irAE is in question, consultation with a dermatologist should be sought. Skin biopsy may assist in the diagnosis, particularly for a prolonged course of rash or for a persistent rash unresponsive to treatment [66]. Grade 1 and grade 2 skin toxicity can be managed with topical corticosteroids, skin emollients, and antihistamines without interruption of the ICI treatment schedule [31, 72]. For grade 1 and 2 skin toxicity that does not improve with this approach, ICI treatment should be temporarily interrupted and a systemic corticosteroid considered [66]. For rare grade 3 or 4 toxicity, systemic corticosteroids should be initiated and the ICI therapy permanently discontinued.

Endocrine

Endocrine dysfunction following ICI therapy is common and potentially severe. While the thyroid gland is most commonly affected, dysfunction of the pituitary gland is often life-threatening. Other endocrine irAEs include diabetes mellitus and adrenal insufficiency, but these are less common [73]. Thyroid dysfunction can manifest as hypothyroidism, hyperthyroidism, or thyroiditis. Hypothyroidism may be primary, due to thyroid dysfunction, or secondary, due to pituitary gland dysfunction. ICI-related thyroid dysfunction is reported in up to 20% of patients on ICI therapy and is more common in patients treated with anti-PD-1 therapy [74]. This is possibly due to the expression of PD-1 on all B cell surfaces including those of IgM-secreting memory B cells [43]. As such, antibody-mediated thyroid dysfunction is common in patients undergoing therapy with PD-1-based ICIs. Anti-thyroid antibodies have been detected in up to 80% of patients with ICI-related hypothyroidism, highlighting the similarities with autoimmune thyroid disease [75]. Hyperthyroidism is often transient, likely underdiagnosed due to lack of symptoms, and typically requires no treatment unless the patient is significantly symptomatic [76, 77]. ICI-related hyperthyroidism will typically lead to a permanent hypothyroid state within 3 to 6 weeks [78–80]. Preventative corticosteroids have not been shown to prevent progression to hypothyroidism in patients with ICI-related hyperthyroidism. Diagnosis of thyroid dysfunction can be confirmed with laboratory testing for serum thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). Lifelong thyroid hormone replacement is necessary in patients with symptomatic immune-related hypothyroidism as thyroid gland dysfunction is typically permanent [79].

Pituitary gland inflammation, termed hypophysitis, was previously a rare disease characterized by immune-cell infiltration of the pituitary gland. Since the approval of ipilimumab, hypophysitis has become more common. The incidence of hypophysitis ranges from 1-4% with low-dose ipilimumab therapy to up to 17% with high-dose therapy [81, 82]. The incidence with other ICIs is less than 0.5% [28]. The exact pathophysiologic mechanism for this discrepancy remains unclear, but is possibly related to CTLA-4 expression in human pituitary cells as well as an increased production of antibodies against pituitary cells [83]. It is more common in males, but this may be partially attributable to the greater incidence of melanoma in males [76, 81]. The typical time from ICI-initiation to the diagnosis of hypophysitis is 6-12 weeks but it has been reported up to 16 weeks after ICI treatment [76]. In patients receiving low-dose ipilimumab, the median time of onset is more delayed (11 weeks) than with high-dose therapy, indicating a potential cumulative effect following repeated doses [84]. Hypophysitis presents in most patients with vague and nonspecific symptoms such as headache, fatigue, and malaise, making early diagnosis difficult especially in older adults [11, 85]. More severe symptoms include confusion, lethargy, and altered mental status [73, 79]. Visual complaints due to optic pathway disruption are rare with ICI-related hypophysitis compared with other causes.

The diagnosis should be confirmed with laboratory findings of hypopituitarism and MRI abnormalities, given the nonspecific symptoms and potentially insidious onset [86]. MRI evaluation of will typically reveal pituitary enlargement, heterogeneous enhancement, and stalk thickening, although imaging be normal in some cases [86–88]. One or multiple pituitary hormone axes may be affected. Deficiencies in TSH and adrenocorticotropic hormone (ACTH) are the most common and lead to central hypothyroidism and central adrenal insufficiency, respectively [73, 79]. Central adrenal insufficiency may be life-threatening if untreated. Less commonly,

gonadotrophin and growth hormone deficiencies may be seen [73]. If endocrine dysfunction is suspected, patients should undergo laboratory evaluation including serum TSH, T3, T4, and ACTH.

Physiologic hormone replacement in consultation with an endocrinologist is the mainstay of treatment for ICI-associated hypophysitis following a thorough evaluation of endocrine hormone dysfunction. Systemic high-dose steroids should be commenced prior to thyroid hormone replacement to prevent an adrenal crisis. While adrenal recovery is rare, thyroid and gonadal function does recover in some patients. ICI therapy should be permanently discontinued in patients with hypophysitis.

Gastrointestinal and Hepatic

Immune checkpoint inhibitors are frequently associated with both luminal gastrointestinal (GI) adverse effects as well as hepatic effects. Immune-related pancreatitis is rare but has also been described in patients with melanoma as well as those with solid tumors [89, 90]. The GI effects mimic idiopathic inflammatory bowel disease and differentiation between these conditions is difficult [91]. Colitis is a common irAE and may be severe. In patients treated with ipilimumab, diarrhea occurs in approximately one-third of patients with 8-23% experiencing colitis [92]. GI irAEs are less common with ICIs which act on the PD-1 axis, with colitis occurring in fewer than 4% of patients [92]. An exception to this is nivolumab, which carries an incidence for diarrhea of 10-13% [25]. The onset of symptoms is highly variable and ranges from 11 days to 4 months with a median of 34 days following ICI-therapy [93, 94]. Diarrhea is the most common symptom of colitis, and additional symptoms can include abdominal pain, emesis, fever, weight loss, and hematochezia [95]. Electrolyte abnormalities including hypokalemia and hyponatremia may occur [96]. In addition to an immunostimulatory mechanism of colitis, there is evidence that alterations in the gastrointestinal microbiome may predispose patients to colitis [43, 97, 98]. Patients and providers should therefore be cautious in initiating antibiotic therapy unless clearly indicated. Colonic perforation is a rare complication and possibly dose-dependent [93, 99]. The differential diagnosis for patients on ICI therapy with diarrhea is broad, and patients should be evaluated for other causes including *Clostridium difficile* toxin and other diarrhea-causing pathogens.

Definitive diagnosis is with biopsy, although frequently unnecessary as other diagnostic modalities such as computed tomography (CT) may provide evidence of colitis [22]. CT findings share a similar appearance with inflammatory bowel disease [100]. Specific findings include diffuse colitis involving more than one segment of the colon, mural bowel wall thickening, and submucosal edema [88]. Treatment of grade 1 toxicity is largely supportive, with fluid and electrolyte repletion. The addition of corticosteroids should be considered with grade 2 colitis and commenced in all cases of grade 3 or 4 colitis [95]. Gastroenterologist consultation and endoscopic evaluation are recommended in cases of grade 2 toxicity that do not respond to supportive measures and in most cases of grade 3 and 4 toxicity if the diagnosis is uncertain [93]. Endoscopic examination typically shows a continuous pattern of inflammatory changes with exudates, granularity, and ulcerations [91]. Biopsy can be performed during endoscopy if the diagnosis is in doubt but must be weighed against the risk for perforation [101]. For grade 3 and 4 colitis, ICI therapy should be permanently discontinued and systemic corticosteroids commenced (1-2 mg/kg/day of methylprednisolone or its equivalent) [93]. A single dose of infliximab (5 mg/kg) has been used successfully in cases where there is a failure to respond to corticosteroids after 3-5 days [102–104]. Relapses of colitis are common. As such, corticosteroids should be tapered over a period of 6 to 8 weeks. Prophylactic corticosteroids have not been shown to prevent the development of diarrhea or colitis [105, 106].

Immune-related hepatitis resembles an autoimmune-like drug-induced liver injury and consists of asymptomatic elevations of hepatic transaminases [107]. Rarely, serious hepatitis and liver failure can occur [108, 109]. ICI-associated hepatitis is most often panlobular with a hepatocellular injury pattern [110, 111]. Hepatic irAEs are less common than luminal irAEs, occurring in around 4% of patients [112]. The risk is higher in patients receiving ICI therapy for the treatment of hepatocellular carcinoma [113, 114]. CTCAE grading for hepatitis is based on serum transaminase and total bilirubin measurements [85]. Transaminase levels of 3-5, 5-20, and 20x the upper limit of normal are categorized as grades 2, 3, and 4, respectively. Similarly, total bilirubin concentrations of 1.5-3, 3-10, and 10x the upper limit of normal are categorized as grades 2, 3, and 4, respectively. The risk for severe (grade 3 or 4) hepatitis is dose-dependent and more frequent with dual immune checkpoint inhibition [115]. Immune-related hepatitis typically presents 8 to 12 weeks after initiation of ICI therapy [91]. The diagnosis of ICI-related hepatitis may be suggested by histologic examination of the liver [116–118]. Alternative causes of hepatitis, including viral hepatitides and other drug-induced hepatitides, should be excluded [118]. For grade 2 hepatitis, ICI therapy should be temporarily interrupted until serum transaminase levels are declining [36]. For grade 3 or 4 hepatitis, ICI should be stopped and systemic corticosteroids (methylprednisolone 1-2 mg/kg/day) commenced. Corticosteroids should be tapered over a time period of at least one month or until toxicity is downgraded to grade 1 [113]. Based on published case reports, mycophenolate mofetil is recommended in cases unresponsive to corticosteroids [29, 36]. Other agents, such as anti-thymocyte globulin, have been used but available evidence is currently limited to case reports. Infliximab should be avoided due to the potential provocation of fulminant hepatitis [119].

Neurologic

Neurologic irAEs occur in 6 to 12% of patients on ICI therapy and are generally of low grade. Mild neurologic irAEs include nonspecific symptoms such as headache, dizziness, and sensory impairment [120]. High-grade neurologic AEs are rare, occurring in fewer than 1% of patients, and should be managed in consultation with a neurologist [121]. These include meningitis, encephalitis, Bell's palsy, Guillain-Barre syndrome, central nervous system demyelination, and myasthenia gravis [69, 122]. Seizure activity is a common presenting symptom of encephalitis [120]. Antibodies to the N-methyl-D-aspartate and Hu receptors have been detected in some patients with encephalitis associated with ICI therapy [123, 124]. Diagnosis may be difficult as progression of cancer should also be on the differential diagnosis in any patient with malignancy and a neurologic abnormality. Central nervous system imaging studies and cerebrospinal fluid analysis (CSF) should be performed as needed to evaluate for alternative causes for the clinical presentation. In cases of ICI-related aseptic meningitis, a lymphocyte predominance will be noted on CSF analysis [125, 126]. If a neurologic irAE is suspected and severity is grade 2 or higher, ICI therapy should be interrupted and systemic corticosteroids (methylprednisolone 0.5-1 mg/kg/day for grade 2, greater than 1 mg/kg/day for higher grades) commenced, even for conditions for which corticosteroids are not typically administered (e.g., Guillain-Barre syndrome) [127]. For the treatment of myasthenia gravis and Guillain-Barre syndrome, intravenous immunoglobulin (400 mg/kg for 5 days) or plasmapheresis should be commenced along with pyridostigmine (myasthenia gravis) in consultation with a neurologist [34, 120, 122, 128]. Rituximab, an anti-CD20 monoclonal antibody, has been used in cases of ICI-associated encephalitis unresponsive to corticosteroids and intravenous immunoglobulin but available literature is limited to case reports [124, 129].

Ocular

Ocular irAEs in patients receiving ICI therapy are rare (<1% of patients) [130]. The most commonly reported irAE is dry eyes but several others have been described including uveitis, ulcerative keratitis, choroidal neovascularization, and orbital inflammation [131–133]. Mild irAEs can be treated with ocular lubricants and topical corticosteroids, while systemic corticosteroids are reserved for severe inflammation or for those who do not respond to topical therapy. Ophthalmologic evaluation should be arranged for all visual complaints.

Pulmonary

Pneumonitis is an uncommon irAE but rapidly progressive and potentially fatal when present [22, 86]. With the exception of atezolizumab, it is more common following therapy with PD-1 and PD-L1 therapies compared to ipilimumab [25, 31]. The median time to onset is 10-12 weeks following ICI therapy and initial symptoms may be non-specific [134]. Clinicians must maintain a high index of suspicion for immune-related pneumonitis given the late onset and potentially catastrophic outcome. The most common presenting symptoms are dyspnea and cough. These symptoms in a patient with underlying cancer should prompt a broad diagnostic workup including laboratory analyses and chest imaging for diagnoses such as pulmonary embolism, pneumonia, viral infection, and cancer progression. Radiographic findings of ICI-related pneumonitis include interstitial pneumonia, organizing pneumonia, and hypersensitivity pneumonitis [135]. These findings often mimic those from infectious etiologies, making definitive diagnosis difficult. Bronchoscopy with bronchoalveolar lavage may assist in excluding infectious etiologies but lung biopsy is seldom required. If there is suspicion for pneumonitis, ICI therapy should be withheld and corticosteroids commenced [136]. As infection cannot always be promptly ruled out prior to the initiation of immunosuppressive therapy, it is reasonable to initiate broad-spectrum antibiotics in conjunction with corticosteroid therapy. Patients should have periodic monitoring of pulmonary function and continuous pulse oximetry. Supplemental oxygen may be necessary [22]. Patients with grade 3 or 4 toxicity should be admitted to the hospital, receive expert consultation, and receive high-dose systemic corticosteroid therapy [31]. Patients with grade 2 toxicity should also receive systemic corticosteroids and hospital admission if their symptoms progress during an initial observation period of 3 to 6 hours. If there is steroid-resistance after 48 hours, as evidenced by lack of clinical or radiologic improvement, the initiation of infliximab, mycophenolate mofetil, or cyclophosphamide therapy should be considered [137]. Pneumonitis can recur after reinstitution of ICI therapy in patients with grade 1 or 2 pneumonitis. Patients and providers should be aware of this risk when considering restarting ICI therapy.

Renal

Renal irAEs have been reported in 2.2% of patients following ICI therapy but may be underreported due to the high prevalence of kidney disease in patients with cancer [138, 139]. It is estimated that up to 29% of patients may have a low-grade irAE following ICI therapy [139, 140]. High-grade acute kidney injury necessitating hemodialysis, however, is rare [138, 141, 142]. Combination ICI therapy is a risk factor for immune-related renal toxicity when compared to monotherapy. The median onset of acute kidney injury ranges from 2 months with anti-CTLA-4 treatment to 3 to 10 months following ICIs which act on the PD-1 axis [140, 143]. Agents which act on the PD-1 axis have similar incidents of renal toxicity

[25]. Symptoms include oliguria, hematuria, or peripheral edema [144]. Acute interstitial nephritis is the most commonly reported cause of immune-related AKI, although lupus nephritis and thrombotic microangiopathy have also been described. Case reports have noted both proteinuria and the presence of anti-double-stranded DNA antibodies [142]. Renal biopsy with lymphocyte infiltration can confirm the diagnosis of immune-related kidney injury in patients taking ICI therapy [139, 145]. If suspected, ICI therapy should be interrupted and systemic corticosteroids initiated after consultation with a nephrologist [16].

Rheumatologic

Several rheumatologic complications have been described during ICI therapy including arthralgia, inflammatory arthritis, rheumatoid arthritis-like disease, inflammatory myopathy, scleroderma, and vasculitis [146, 147]. These complications are more common with ICIs which act on the PD-1 axis and tend to occur later than most other irAEs [148]. Clinicians should have a high suspicion for inflammatory arthritis and arrange prompt evaluation by a rheumatologist as permanent erosive joint damage can occur within weeks [143]. While typically managed with prednisone, steroid-resistant cases have been described and treated with disease-modifying anti-rheumatic drugs or TNF-alpha inhibitors such as infliximab. Duration of therapy can be prolonged and patients sometimes require chronic therapy [143, 149]. Suspected immune-related vasculitis should also be evaluated promptly given the concern for organ-specific complications which may lead to significant morbidity and mortality.

Conclusion

Immunotherapy has revolutionized the pharmacologic care of patients with cancer over the past two decades. Clinicians must be aware of these rapidly expanding classes of xenobiotics and their unique toxicologic profiles. Immune checkpoint inhibitors, first FDA-approved in 2011, block inhibitory signals from cancer cells to T-cells to allow the body's innate immune system to target cancer cells. Adverse effects unique to ICIs, termed irAEs, represent a heterogeneous classification of immunostimulatory effects to multiple organ systems. While most irAEs are mild, severe cases do occur and may be rapidly fatal. Management of moderate to severe irAEs often includes cessation of ICI therapy and initiation of immunosuppressive agents such as corticosteroids. Appropriate management of patients with irAEs involves multidisciplinary care coordination with respect to patients' individual long-term goals. Clinician recognition of irAEs and their sometimes delayed onset is critical to ensure appropriate and timely treatment.

Declarations All authors are listed above and comply with the ICMJE authorship criteria.

Conflicts of Interest None.

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