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REVIEW

Immune Checkpoint Inhibitors and Systemic Side Effects: Overview for the Inpatient Dermatologist

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Abstract

Purpose of Review Immune checkpoint inhibitor (ICI) therapy has changed the landscape of cancer treatment and now represents part of the treatment regimen for approximately half of all cancer patients in high-income countries. The non-specific immune activation of ICIs creates a myriad of adverse effects, most commonly of the skin but also affecting other organ systems with potentially devastating consequences. We aim to highlight the most common or life-threatening systemic toxicities associated with ICIs such that oncodermatologists may be more able to recognize their early clinical signs and symptoms. This knowledge will be helpful in effectively managing follow-up testing and coordinating with other specialty services to improve patient outcomes on ICIs.

Recent Findings In the past 5 years, immune checkpoint inhibitor safety profiles have been updated in several studies and case reports. Multiple guideline statements published by the American Society of Clinical Oncology, the Society for Immunotherapy of Cancer, and the Multinational Association of Supportive Care in Cancer have been recently released on the toxicity management for patients on immune checkpoint inhibitors. These organizations have updated what is known about adverse events for ICIs ranging from gastrointestinal, pulmonary, and hepatic to endocrine complications, as well as immune-mediated cardiovascular, rheumatic, and renal toxicities.

Summary Cutaneous immune-related adverse events to immune checkpoint inhibitor therapies are the most common and earliest complications of these treatment modalities. For the oncodermatologist, recognizing symptoms and signs of rare but dangerous systemic toxicities across various organ systems is important to improve patient outcomes on these therapies.

Keywords Immune checkpoint inhibitors · Immune checkpoint blockade · Oncodermatology · Immune checkpoint inhibitors/adverse effects · PD-L1 inhibitors · CTLA-4 inhibitors

Introduction

Immune checkpoint inhibitors (ICIs) have emerged as the keystones of modern cancer therapy. They have changed the landscape of tumor management in a wide variety of malignancies and in both neoadjuvant and metastatic settings. Among the variety of mechanisms used to harness the immune system to attack cancer, therapies targeted towards two checkpoints, the programmed death-1 (PD-1)/its ligand (PD-L1) and the cytotoxic T lymphocyte associated antigen 4 (CTLA-4), have found great success after their approval from the US Food and Drug Administration (FDA). Demonstrating their wide use, approximately half of all cancer patients in high-income countries have received ICIs as either monotherapy or in combination with other ICIs or systemic cytotoxic agents [1]. However, ICIs are associated with a host of immune-related adverse events (irAEs) due to their nonspecific activation of immune cells. The side effect profile of the checkpoint inhibitors can range from mild to debilitating and even fatal and in some cases necessitates the need to reduce or terminate ICI treatment. Immune-related cutaneous adverse events (ircAEs) are among the most common immune-related events and are also often the earliest to manifest in patients receiving ICI therapies. Given the early presentation of ircAEs, the oncodermatologist may be the first to see systemic events related to ICIs. It is crucial for clinicians in oncodermatology practices to be familiar not only with ircAEs but also with the related systemic toxicities associated with ICIs to effectively manage and refer these patients in a timely fashion.

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Mechanistic Differences in CTLA-4 and PD-1/PD-L1 Inhibitors

Adverse events have been commonly associated with CTLA-4 inhibitors, specifically the agents ipilimumab and tremelimumab. Reports cite up to 90% of patients on these agents experience some degree of immune-related complication [2]. CTLA-4 is an inhibitory receptor on T lymphocytes that works to downregulate T cell activity [3, 4]. The inhibitors of the CTLA-4 receptor thus activate T cells in lymphoid tissue. Ipilimumab was the first ICI to be approved for clinical use and showed superior results to previous first-line treatments in foundational malignant melanoma trials [5]. Ipilimumab is typically prescribed for four cycles and has been dose-adjusted to become more tolerable for patients [6].

PD-1 and PD-L1 inhibitors are cited to cause immune-related side effects in up to 70% of patients treated with these therapies [2]. The mechanism of action relies on the PD-1 ligand, a protein on target cells, that binds to PD-1 receptors on cytotoxic CD8 + T cells. Ligand-receptor binding normally limits inflammation and protects healthy cells from premature apoptosis [7]. In cancer, malignant cells often overexpress PD-L1 and remain protected from cell death [8]. PD-1 inhibitors, such as pembrolizumab, nivolumab, cemiplimab, and PD-L1 inhibitors, such as atezolizumab, avelumab, and durvalumab, prevent tumor cells from evading the body's immune system. Proof-of-concept trials demonstrating effectiveness against refractory solid tumors allowed the FDA to approve these agents shortly after the approval of the CTLA-4 agents [9]. The PD-1/PD-L1 agents are generally better tolerated than ipilimumab/tremelimumab and are able to be given for extended periods of time compared to the shorter cycles of CTLA4 inhibitors, due to their less severe irAEs [10].

Because of their differing mechanisms of action, the types of immune activation–related adverse events and degree of effect are different depending on the ICI used. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 delineates severity of drug-related toxicities [11]. Grades range from 1 to 5 with mildest reactions (grade 1) involving asymptomatic or minimal symptoms that are based on clinical observation alone, to the more severe (grades 3–4) with medically significant complications possibly needing hospitalization or urgent intervention, to grade 5 representing death related to AE.

A subcategory of grades is present for each organ system of possible involvement. For example, the cutaneous complication grading scale goes from 1 to 4 + , where the mildest reactions (grade 1) involve < 10% body surface area (BSA) with or without symptoms. This escalates to more severe toxicities (grades 3–4) involving > 30% BSA and with potentially life-threatening consequences. These grades are specifically discussed elsewhere [12]. Overall, severe toxicities of any organ are reported more frequently in patients treated with CTLA-4 inhibitor monotherapies, at approximately ≤ 25% of these patients, compared with patients treated with PD-1/PD-L1 inhibitor monotherapy where rates are ≤ 20% [13, 14]. The skin is an important site for irAEs and is frequently implicated in ICI therapies due to the skin's high lymphocyte concentration [15]. Low-grade cutaneous toxicities may be harbingers to severe toxicities in the future for patients on ICIs. Immune-related cutaneous AEs occur at an average of 3.6 weeks after treatment initiation versus a 6- to 7-week latency for systemic toxicities [13, 16]. Ultimately, severe irAEs may lead to death in 2% of patients on these therapies [2]. Knowledge of the systemic toxicities associated with ICIs can help dermatologists improve patient care by intervening before any potentially damaging side effect profiles develop further.

Immune-Related Enteropathies and Gastrointestinal Pathologies

Immune activation of the gastrointestinal (GI) system has been reported in patients on both CTLA-4 inhibitors and PD-1/PD-L1 therapies. Drug-induced GI symptoms are particularly associated with anti-CTLA-4 therapy, where roughly one-third of these patients have irAEs of the GI tract [17]. The reported GI irAEs include aphthous ulcers, esophagitis, gastritis, diarrhea, enterocolitis, and microscopic colitis [17, 18]. Colitis in patients receiving anti-CTLA-4 therapy has a frequency of between 8 and 22% [19–21]. Of note, the highest rates of enterocolitis were reported in patients receiving ipilimumab for resistant prostate cancer, where the rate of immune-related enterocolitis and grade 3/4 colitis was found to be 22% and 16%, respectively [21]. Median onset of drug-induced enterocolitis occurs at 6 or 7 weeks (up to 19 weeks) after therapy initiation [22]. PD-1 and PD-L1 inhibition has also been associated with GI immune-related adverse events. However, the rate is much lower than in CTLA-4 inhibitors: the rate of grade 3/4 diarrhea in patients on PD-1/PD-L1 is reported between 1 and 2% [23–25]. Upper GI pathologies, such as gastritis and duodenitis, have been reported in relation to pembrolizumab, nivolumab, and atezolizumab [26–28]. Symptoms to monitor for include diarrhea, fecal urgency, abdominal pain, and mucus or blood in stool, and more severe symptoms may include peritoneal signs or ileus. Symptoms may resemble infection, thus ruling out infectious etiologies and pursuing biopsies of the GI tract may be warranted if symptoms are persistent or severe [29–31]. On endoscopy, colitis will appear as erythema, edema, and potentially ulcerated mucosa. On biopsy, features supporting irAE-related colitis include crypt abscess formation, neutrophil and lymphocyte infiltration, and nonspecific inflammation or epithelial necrosis [30–34].

Perhaps the most feared complication of the GI tract from ICI therapy is intestinal perforation leading to death. While near-fatal or fatal events are rare (<1% of patients), they have been reported as severe consequences of drug-related colitis [17]. Colitis complicated by bowel perforation represents the majority of life-threatening events under CTLA-4 inhibition and is the leading cause of ICI discontinuation [35]. Colitis-related fatalities due to PD-1 and PD-L1 therapies have also been documented as severe consequences [36].

Incidence and severity of GI irAEs appear to be dose-dependent. A phase II trial demonstrated that there may be some relation between ipilimumab dose and severity, as they showed that for patients receiving 0.3, 3, or 10 mg/kg of ipilimumab, the incidence of any irAE was 26%, 65%, and 70%, and the incidence of grade 3/4 GI irAE was 0%, 3% and 15%, respectively [37]. Studies have also shown an increase in frequency and severity when ipilimumab was used in combination with chemotherapy drugs such as dacarbazine, or biologics such as interleukin 2, for management of cancer [38, 39]. It is also more common in combination ICI regimens (e.g., ipilimumab plus nivolumab), where enterocolitis rates affect > 40% of patients [40–42].

In all cases where ICI is suspected to have a causal relationship with enterocolitis, and the irAE is grade 3 or higher, current recommendations support discussions with the oncologic team on discontinuation of ICI therapy. Checkpoint inhibitor–induced enterocolitis can also be treated with high-dose systemic corticosteroids as a first-line agent, then with infliximab or vedolizumab as second-line [33, 43]. Immunosuppressants such as mycophenolate mofetil and tacrolimus have also been employed as potential alleviating agents [22, 32, 44]. It should be noted that, while antibiotic therapy can be protective against ICI-mediated diarrhea and colitis, studies have shown that use of antibiotics, especially those with anaerobic activity, after ICI therapy was associated with increased risk of severe ICI-induced colitis [45]. Thus, caution should be exercised with starting patients on antibiotics surrounding induction of ICI therapy or in settings of new-onset GI symptoms in the context of ICI therapy.

Immune-Related Pulmonary Pathologies

Whereas colitis represents the most threatening of CTLA-4-associated irAEs, pulmonary disease represents the cause for the most severe PD-1/PD-L1-related adverse events. In some cases, severe damage to the lung by ICIs may warrant drug discontinuation. Pulmonary toxicity is important to recognize, and the initial symptoms may be mild [46]. Clinicians are advised to monitor for signs of ICI-induced pneumonitis, which typically present 3 months after ICI induction [47, 48]. Symptoms include dyspnea, nonproductive cough, tachypnea, fever, and fatigue [12, 49]. More severe manifestations include chest pain and hypoxemia, which can lead to respiratory failure. Current studies estimate that rates of all-grade and grade 3–5 pneumonitis are 2.7% (95% confidence interval (CI), 1.9–3.6%) and 0.8% (95% CI, 0.4–1.2%), respectively, of patients receiving PD-1 therapy for solid tumors [50]. PD-1 inhibitor–associated pneumonitis is reportedly higher in patients receiving the therapy to treat advanced NSCLC, where any-grade PD1-related pneumonitis rates are 4.1% and grade 3–5 rates are 1.8% [50].

The exact mechanism of action by which PD-1 inhibitors induce lung damage is not clear. It has been hypothesized that PD-1 could induce negative feedback to attenuate focal or diffuse innate inflammatory responses in instances where Toll-like receptors and cytokines attack tissue with high antigenic burden [51]. During lung infections, and in even mild irritating events, immune activation against lung tissue may be upregulated to a damaging extent by PD-1 and PD-L1 inhibitors, leading to ICI pneumonitis. More research is needed to elucidate the observation of PD-1 inhibitors being more frequently associated with lung damage than are anti-CTLA4 therapies. There is no significant association between CTLA-4 therapies and pneumonitis, though notably the rate of this complication is increased significantly in combination ICI therapy [52].

If clinicians suspect ICI-pneumonitis, future workup will likely include a chest x-ray, chest CT, and bronchoscopy with bronchoalveolar lavage for culture [49]. Bronchoscopy is especially indicated to rule out other causes of pneumonitis, such as opportunistic infections which can present similarly. Pulmonary function tests and pulse oximetry during rest and exercise may also be necessary. PD-1-associated pneumonitis presents differently on imaging but progressive, diffuse infiltrates and blunting of the costophrenic angle on CXR are supportive of the diagnosis. On CT imaging, pneumonitis may appear as isolated or diffuse lung consolidation with air bronchograms, pleural effusions, ground-glass or reticular opacities, nodularity in the central lobes, septal thickening between lobules, honeycombing, and/or traction bronchiectasis [53].

For any grade of pneumonitis, oncology should be consulted, and ICI treatment is typically discontinued. Hospitalization, close observation, and for severe cases, treatment in intensive care may follow while lung damage resolves. Treatment of ICI-associated pneumonitis consists of immunosuppression via corticosteroids and infliximab [47, 48, 54].

Immune-Related Hepatic Toxicities

Hepatoxicity is a commonly reported side effect of ICI therapy and has been associated with CTLA-4 inhibitors, PD-1 inhibitors, and anti-PD-L1 therapies [55–58]. In terms of timeline, hepatic toxicities present later than dermatologic consequences

of ICIs, and typically appear in the first 6 to 12 weeks after treatment initiation. Roughly 2 to 10% of all patients on ICI monotherapy will experience some form of hepatic inflammation [59]. Incidence and severity of immune-mediated hepatitis appear to be dose-dependent [5]. In addition, combination therapy of CTLA-4 combined with anti-PD-1/anti-PD-L1 has been observed to have the highest frequency of drug-induced hepatitis. While sometimes patients may be asymptomatic, they may present clinically with signs of hyperbilirubinemia. Cutaneous signs of hyperbilirubinemia can include jaundice and pruritus. Clinical manifestations of hepatotoxicity may also include fever, fatigue, nausea, vomiting, anorexia, and abdominal pain. In more severe cases of hepatotoxicity-induced veno-occlusive disease, patients may develop ascites, varices, and hepatic encephalopathy [60]. If suspected, serum AST, ALT, and total bilirubin concentrations can be ordered and patients should be assessed for manifestations of hepatotoxicity. Further evaluation may be needed to exclude infectious and autoimmune etiologies, depending on patient history and potential predisposing factors or exposures. Liver biopsy is the gold standard to formally diagnose this irAE, and ICI-associated hepatitis is typically responsive to systemic corticosteroids. Patients may also require secondary immune suppression [59].

Immune-Related Endocrinopathies

All major classes of ICI therapy have been associated with cases of drug-related endocrine pathologies. These side effects involve the pituitary, thyroid, and adrenal glands. A meta-analysis of 38 randomized trials demonstrated an overall incidence of endocrinopathies in 10% of patients receiving any ICI [61]. The most common ICI-associated endocrinopathy is hypothyroidism, which has been reported after initiation with all classes of ICIs [55–58, 62]. Hyperthyroidism is much less frequent after anti-PD-1/PD-L1 agents [55–58]. Autoimmune thyroiditis, though rare, has been reported in patients receiving the anti-CTLA4 agent ipilimumab [62]. When present, hyperthyroidism is typically treated for 2 to 3 months with symptomatic control to ensure it is persistent and not merely an early manifestation of hypothyroidism [63]. Hypopituitarism with concomitant adrenal insufficiency is less common than thyroid dysfunction, but has also been reported with ipilimumab, pembrolizumab, nivolumab, and atezolizumab [55–58] and hypogonadism is seen in some patients on ipilimumab [57]. Immune-mediated type I diabetes, with the potentially fatal complication of diabetic ketoacidosis, has presented after initiation of anti-PD-1 and anti-PD-L1 therapies [55, 56, 58].

Symptoms associated with ICI-induced endocrinopathies are often nonspecific. Therefore, a high level of clinical suspicion is necessary to elucidate these irAEs. Symptoms include fatigue, headache, photophobia, mental status changes, dizziness, and visual field defects [62]. Median onset of ICI-induced endocrinopathies is at 11 weeks post-induction of therapy [62]. Baseline thyroid function tests are low-cost and effective in monitoring patients for abnormal thyroid function. It is important to screen for endocrine AEs, especially in patients with signs of other irAEs, because endocrine irAEs can persist even after treatment discontinuation [62]. Patients with immune-related endocrinopathies may require long-term or permanent hormone replacement, such as with corticosteroids, insulin, or levothyroxine.

Less Frequent Immune-Related Adverse Events

ICI-Related Neurologic Consequences

Neurologic irAEs are estimated to affect 3–12% of patients on ICI therapy, with high-grade manifestations affecting less than 1% [64]. Neurological sequelae have been reported with CTLA-4, PD-1, and PD-L1 agents [55–58]. While rare, the consequences can be severe. They include myasthenia gravis, aseptic meningitis, encephalitis, Guillain–Barre syndrome, peripheral motor and sensory neuropathies, facial and abducens nerve paralysis, and demyelinating disorders [65, 66]. If it occurs, symptom onset is approximately 6 to 12 weeks after treatment initiation [65, 66]. Patients should be monitored for any unilateral or bilateral weakness, sensory alterations, and paresthesia. Signs of encephalitis may include headache, fever, confusion, memory loss, hallucinations, fatigue, seizures, and meningismus. Such complaints should be believed to be immune-mediated unless work-up reveals another etiology. Neurology should be consulted, and further diagnostic management may include brain MRI and lumbar puncture to rule out infection. If ICI-induced neurologic dysfunction occurs, immunotherapy may need to be held or discontinued depending on the severity of the AE. Management plans for ICI therapy are discussed in detail by grade and specific neurotoxicity by the American Society of Clinical Oncology, though there is generally a low threshold to discontinue ICI therapy due to the relatively higher fatalities associated with neurotoxicities compared to other irAEs [12, 67].

Immune-Related Renal Toxicities

Nephropathies have been associated with PD-1 inhibitors, PD-L1 inhibitors, and very rarely CTLA-4 inhibitors [55–58]. Interstitial nephritis can cause acute kidney injury in patients receiving ICIs. Additionally, patients have been reported to experience nephritis like in systematic lupus, or granulomatous nephritis [66]. These events are rare, only occurring in 1 to 5% of patients on ICI therapy. Patients on immune checkpoint inhibitors should be monitored for changes in renal function, and ICI may need to be withheld if serum creatinine dramatically rises or threatens renal integrity.

Immune-Related Cardiovascular Adverse Events

Cardiovascular toxicity is extremely rare, occurring in less than 0.1% of all patients on ICI therapy; however, it is important to be aware of such events as they can be life-threatening [68]. Cardiovascular irAEs include myocarditis, myocardial fibrosis, pericarditis, and conduction abnormalities. They are more common in patients receiving combination therapy, and the timeline for their occurrence is highly variable. Toxicities may manifest from 2 weeks post-induction to 32 weeks after therapy has begun [68]. If suspected, ECG and cardiac biomarkers should be promptly obtained. Guidelines for management of cardiotoxicity depend on the grade of the toxicity and are discussed in detail elsewhere [67, 69].

Other ICI-Associated Toxicities

Briefly, patients on anti-CTLA-4 and anti-PD-1/PD-L1 may experience a myriad of irAEs in other organ systems. Ocular irAEs include uveitis, iritis, conjunctivitis, blepharitis, episcleritis, and scleritis. Systematic corticosteroids can be used to prevent permanent visual loss, though ophthalmology consult is necessary [67]. Hematologic AEs to be aware of include hemolytic anemia, immune thrombocytopenic purpura, aplastic anemia, and lymphopenia. Vessel disease is more often seen in association with anti-CTLA-4 agents than anti-PD-1 and includes temporal arteritis and other leukocytoclastic vasculitides. In rarely documented cases, pancreatitis and sarcoidosis have been attributed to be due to ICI therapy.

Muscle and joint manifestations of ICI therapy, while more common especially in association with PD-1/PD-L1 inhibitors, are typically mild [70]. They include arthritis, arthralgias, myositis, polymyalgia rheumatica, and rhabdomyolysis in severe cases. Rates of incidence as they relate to PD-1 inhibitors vary by report or intervention group: from 10 to 26% for arthralgia, 6 to 14% for general musculoskeletal pain, and 2 to 12% for myalgia [70]. The pathophysiology of such pains is hypothesized to be that they arise from systemic inflammation in reaction to immunotherapy with most sensitivity in the joints or muscle [71]. Because the majority of musculoskeletal irAEs are mild, they are typically managed symptomatically without change in ICI regimen. However, if there is concern for more severe toxicities (i.e., rhabdomyolysis), then creatinine phosphokinase, urine studies, BUN/Creatinine, myoglobin, and arterial blood gas tests may be considered and concurrent drugs should be examined [67].

General Management of Systemic irAEs

Systemic irAEs may require modification of treatment schedule for patients experiencing toxicities. Dose adjustment of immune checkpoint inhibitors or discontinuation is a significant decision that may ultimately be made as shared decision-making between the patient and the treatment team. The dermatologist may be the first clinician to observe systemic toxicities, as cutaneous irAEs frequently occur before toxicities in other organ systems [2]. After referral to the primary oncologic treatment team, it may be helpful from the dermatologist perspective to understand general guidelines that the treatment team and patient may pursue.

For mild to moderate irAEs, patients may sometimes be able to tolerate irAEs while staying on their current regimen. Otherwise, the immunotherapy agent may be withheld for a period of time, and patients may be able to restart ICIs once symptoms resolve or the patient is back to their baseline. For severe irAEs, the immunotherapy agent should be immediately discontinued. Systemic corticosteroid therapy at a dosage of 1–2 mg/kg per day of prednisone (or equivalent) should be initiated to mitigate immune-mediated toxicities. Prednisone can be tapered over the course of 1 or more months once patients' symptoms are controlled [55–58]. In some cases, steroid-sparing immunosuppressants or immunomodulators may be used. In general, long-term use of corticosteroids in the setting of immunotherapy should be avoided Table 1.

For all patients starting or already on ICI therapies, we underscore the importance that dermatologists take a thorough review of systems, especially for patients coming in for cutaneous irAEs. The review of systems may then necessitate a more comprehensive physical exam to evaluate for features such as but not limited to jaundice, cyanosis, mucosal ulcerations, and purpuric eruptions that may be key to recognizing other organ involvement Table 2.

Table 1 Most common organ systems involved in CTLA-4 checkpoint inhibitor adverse events. Percentages reported as fractions of all patients who experienced irAE due to CTLA-4 monotherapy [72]

Organ of involvement	% of irAEs
Skin	44
Gastrointestinal tract	35
Endocrine	6
Liver	5
Other (cardiac, ocular, neurological, etc.)	10

Table 2 Most common organ systems involved in PD-1/PD-L1 checkpoint inhibitor adverse events. Percentages reported as fractions of all patients who experienced irAE due to PD-1/PD-L1 monotherapy [73]

Organ of involvement	% of irAEs
Skin	36
Musculoskeletal	24
Endocrine	12
Gastrointestinal	6
Pulmonary	5
Other (cardiac, renal, neurological, etc.)	4

Table 3 Rates of immune-related adverse events in patients on monotherapy compared to combination therapy. irAEs reported from any grade and any organ, adapted from data across several studies [74, 78]

Therapy	% of patients experiencing irAEs (any)
Monotherapy with PD-1/PD-L1 inhibitors	22–27.72 [74–76]
Monotherapy with CTLA-4 inhibitors	22 [77]
Combination therapy	56.69 [74]

Conclusion

Our understanding of both the benefits of ICIs and their specific side effect profiles has widened dramatically since the use of immunotherapies has become more mainstream. As oncodermatology continues to evolve and patients continue to be placed on ICI therapy for management of their cancer, dermatologists will be increasingly faced with patients in the clinic being treated with immune checkpoint therapies. The awareness of possible organs of involvement and symptoms to elucidate on history taking will become an important component of high-quality oncodermatology patient care in order to catch irAEs early in their course and prevent long-term adverse consequences of ICI therapy (Table 3).

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Compliance with Ethical Standards

Ethical Approval Not applicable.

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