Immunotherapy-Related Adverse Events: A Primer for the Non-Oncologist

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have significantly improved the overall survival of patients with many different types of cancer since they were first approved by the United States in 2011. However, patients who are treated with ICIs can develop a variety of toxicities, known as immunotherapy-related adverse events (irAEs), that have the potential to affect essentially any organ system. Due to the growing use of ICIs in the field of oncology, it is likely that non-oncologist clinicians will increasingly encounter irAEs in both inpatient and outpatient environments. This review will provide an overview of both common and rare irAEs for the non-oncologist clinician, in addition to providing information about several guidelines developed by multiple organizations that can aid the non-oncologist clinician with the initial work-up and diagnosis of irAEs.

KEYWORDS: immunotherapy; immune checkpoint inhibitors; immunotherapy-related adverse events; immunotoxicity

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of both solid-organ and hematologic malignancies in the United States since they were first approved by the Food and Drug Administration in 2011.[1] Immune checkpoints, a normal part of the immune system, describe a variety of inhibitory pathways that work to maintain self-tolerance by preventing the immune system from indiscriminately attacking its own cells. Unfortunately, some cancer cells have been able to exploit immune checkpoint pathways in order to evade the immune system.[2] ICIs work by blocking immune checkpoint receptors and ligands (such as CTLA-4, PD-1, PDL-1, and LAG3) from binding to one another, thereby preventing signaling that would otherwise dampen the endogenous immune response against cancer cells.[3]

The advent of ICIs have improved both response rates and overall survival for patients diagnosed with advanced malignancies, particularly in those with previously refractory cancers such as metastatic melanoma, lung cancer and renal cell carcinoma. However, the blockade of immune self-tolerance mechanisms can lead to the development of toxicities that have the potential to affect essentially any organ system.[4] These inflammatory side effects are known as immunotherapy-related adverse events (irAEs).[5] Due to the growing use of ICIs in the field of oncology, non-oncologist clinicians will increasingly encounter irAEs, which differ from traditional chemotherapy-related side effects, in both inpatient and outpatient practice. This review will provide an overview of both common (cutaneous, gastrointestinal, hepatic, endocrine, pulmonary) and rare irAEs.

Cutaneous Toxicities

The skin is the organ system that is most frequently affected by irAEs.[4,6] The overall incidence of cutaneous irAEs is commonly estimated to be 25%, though some literature describes an incidence as high as 40–60%.[7-11] The most common cutaneous irAEs are maculopapular rashes and pruritus, which can be seen with or without an associated cutaneous eruption. These reactions most commonly occur on the trunk and extremities.[4] Less common cutaneous irAEs include psoriasiform, eczematous, and lichenoid dermatoses, vitiligo-like skin hypopigmentation/depigmentation, and bullous pemphigoid. Severe reactions, such as SJS, TEN, and DRESS, can also occur.[12]

Gastrointestinal and Hepatic Toxicities

The development of gastrointestinal and hepatic toxicities are also commonly associated with ICI therapy. The lower gastrointestinal tract is more frequently affected than the upper gastrointestinal tract, and diarrhea and colitis are the most common gastrointestinal irAEs with estimated incidences of 30–40% and 8–22%, respectively.[13,14] While ICI-associated colitis is most often associated with watery diarrhea, other symptoms include hematochezia, abdominal pain, fevers, nausea/vomiting, and weight loss. Although rare, it can also be associated with severe complications such as intestinal perforation.[13] In patients who present with these symptoms, infectious etiologies should be ruled out with laboratory studies and stool samples prior to establishing the diagnosis of a gastrointestinal irAE.[15]

Although less frequent than ICI-associated colitis, hepatitis is another common complication of ICI therapy with an estimated incidence of 15%.[16] ICI-associated hepatitis is

most often asymptomatic and identified on routine monitoring based on laboratory markers of hepatocellular injury (elevations of ALT or AST with or without associated elevations in bilirubin).[17] Although rare, symptomatic ICI-associated hepatitis can mimic liver failure and patients can present with jaundice, coagulopathies, abdominal pain, and dark urine.[13] Both infectious (viral hepatitis) and noninfectious (alcohol-induced or drug-induced liver injury, biliary obstruction, autoimmune, etc.) etiologies of liver injury should be ruled out prior to establishing the diagnosis of a hepatic irAE.[13]

Endocrine Toxicities

A variety of endocrine glands and organs can be affected by ICIs, including the thyroid gland, pituitary gland, endocrine pancreas, and adrenal glands.[12] Endocrine irAEs have an estimated incidence of 5–10%, though some literature describes an incidence closer to 20%.[18,19] Thyroid toxicity is the most common endocrine irAE and typically presents similarly to hypothyroidism. Hypophysitis, or inflammation of the pituitary gland, can present with a wide variety of symptoms, including fatigue, headache, nausea, vomiting, anorexia, loss of libido, erectile dysfunction, and confusion.[12] Though less common, endocrine pancreas toxicity typically presents similarly to type I diabetes mellitus (with polyuria, polydipsia, and fatigue) and adrenal toxicity can present similarly to primary adrenal insufficiency. Endocrine toxicities can often be difficult to diagnose as many of these symptoms are nonspecific in nature. However, clinicians must maintain a high index of suspicion for these irAEs as a delayed diagnosis can result in life- threatening conditions such as diabetic ketoacidosis and adrenal crisis.[20]

Pulmonary Toxicities

Immune checkpoint inhibitor-associated pneumonitis is a serious irAE that is associated with significant morbidity and mortality. The overall incidence of ICI-associated pneumonitis is estimated to be between 3–6%, though some literature describes an incidence as high as 20%.[21-24] The clinical presentation of ICI-associated pneumonitis can range from asymptomatic to symptomatic, with symptoms including dyspnea (at rest or with exertion), cough, and hypoxemia.[22] Findings on CT imaging varies but literature has shown that approximately 50% of cases have been associated with ground-glass opacities and consolidations.[25] As with other irAEs, alternative diagnoses such as infection, pulmonary hemorrhage, pulmonary embolism, interstitial lung disease, obstructive lung disease exacerbations, and cancer progression should be ruled out prior to establishing the diagnosis of a pulmonary irAE.[22]

Rare Toxicities

Although cutaneous, gastrointestinal, hepatic, endocrine, and pulmonary toxicities are the most common irAEs, nearly any organ system can be affected by treatment with ICIs. Various hematologic irAEs have also been described in literature, including ITP, aplastic anemia or pancytopenia, hemolytic anemia, and HLH.[26] The estimated incidence of hematologic irAEs is 0.04–3.6%.[27] Neurological irAEs are estimated to occur in 1–5% of patients treated with ICIs and can affect both the peripheral nervous system and the central nervous system.[28,29] Peripheral neurologic irAEs include myositis, peripheral neuropathies, Guillain-Barré syndrome, and myasthenia gravis and central neurologic irAEs include encephalitis, aseptic meningitis, and cranial neuropathies.[30,31] Cardiovascular irAEs, such as myocarditis, pericardial disease, and arrythmias, have an estimated incidence of 0.4–1.4%.[32,33] Although ICI-associated myocarditis is rare, it has one of the highest reported irAE mortality rates.[34] Presentation can range from asymptomatic with cardiac biomarker elevations with or without EKG abnormalities to severe decompensation with associated end organ damage.[35] A rare overlap syndrome that is comprised of both neurologic and cardiovascular irAEs is the triad of myasthenia gravis, myositis, and myocarditis. It is recommended that the identification of any one of these irAEs should lead to an investigation for the other two as this triad has been shown to have increased mortality when compared to these presentations in isolation.[36,37]

DISCUSSION

As the indications for cancer immunotherapy expands to include new types of cancer and earlier-stage malignancies, the incidence and clinical significance of irAEs will also continue to increase.[38] In addition to their physical manifestations, irAEs can be associated with ICI non-compliance, discontinuation, and dose modifications. Therefore, the early identification of irAEs, by the oncologist and the non-oncologist alike, can lead to earlier management of irAEs, which can improve both immunotherapy compliance and treatment continuation.[3] Multiple organizations, such as the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Society for Immunotherapy of Cancer (SITC), have published guidelines to assist clinicians with the diagnosis and management of irAEs.[3,39-41] A brief summary of these guidelines for a selection of common irAEs is depicted in **Tables 1–4**. For the non-oncologist, these guidelines may prove useful for aiding with the initial work-up of irAEs and for determining whether an oncologist should be contacted or when an escalation of care should be recommended.

Table 1. Basic Work-Up and Management of Common Cutaneous irAEs[3,39-41]

irAE	Work-Up	Management
Rash/Pruritus	• Pertinent history and physical examination • Rule out other etiologies (such as infection, drug reaction, unrelated primary skin disorder etc.) via basic labwork (including autoimmune serologies), medication review, and/or skin biopsy as clinically indicated	**Grade 1:** symptoms do not affect quality of life • Continue ICI • Treat with topical emollients and/or topical corticosteroids **Grade 2:** symptoms affect quality of life • Hold ICI • Treat with topical emollients, topical corticosteroids, and/or oral antihistamines **Grade 3:** symptoms affect quality of life and have not responded to prior interventions • Hold ICI and consult dermatology • Treat with topical emollients, topical corticosteroids, and/or oral antihistamines • Initiate systemic corticosteroids **Grade 4:** intolerable symptoms that have not responded to prior interventions • Hold ICI, admit to hospital, and consult dermatology • Initiate systemic corticosteroids • Consider alternative antineoplastic therapy if the reaction does not improve to Grade 1 or less

Table 2. Basic Work-Up and Management of Common Gastrointestinal and Hepatic irAEs[3,39-41]

irAE	Work-Up	Management
Colitis/Diarrhea	• Pertinent history and physical examination • Rule out other etiologies (such as infection or medication effect) via basic labwork, infectious work-up (stool culture, *C. diff* testing, etc.), and medication review • Can consider imaging, endoscopy, or colonoscopy as clinically indicated	**Grade 1:** <4 stools/day over baseline • Continue ICI • Symptom management with diet adjustments and anti-diarrheal agents **Grade 2:** 4-6 stools/day over baseline • Hold ICI • Initiate systemic corticosteroids • Consider gastroenterology consultation and endoscopic evaluation **Grade 3:** ≥7 stools/day over baseline, hospitalization indicated, or severity limits ADLs • Same management as Grade 2 with the following exceptions: increase systemic corticosteroid dosing, consider adding immunosuppressive agent, consider admission to hospital if dehydration or electrolyte imbalance **Grade 4:** life-threatening consequences • Same management as Grade 3 with the following exceptions: discontinue ICI permanently, admit to hospital
Hepatitis	• Pertinent history and physical examination • Rule out other etiologies (such as infection, alcohol use, medication toxicity, etc.) via basic labwork, imaging, medication and supplement review, and alcohol use history	**Grade 1:** asymptomatic; AST or ALT >ULN to 3x ULN or total bilirubin >ULN to 1.5x ULN • Continue ICI and monitor **Grade 2:** asymptomatic; AST or ALT 3-5x ULN or total bilirubin 1.5-3x ULN • Hold ICI and known hepatotoxic drugs • Initiate systemic corticosteroids and can consider adding immunosuppressive agent • Consider hepatology consultation **Grade 3:** AST or ALT 5-20x ULN or total bilirubin 3-10x ULN or symptomatic compensated liver dysfunction • Same management as Grade 2 with the following exceptions: discontinue ICI permanently, increase systemic corticosteroids dosing, consider liver biopsy, consider admission to hospital **Grade 4:** AST or ALT >20x ULN or total bilirubin >10x ULN or symptomatic decompensated liver dysfunction • Same management as Grade 3 with the following exceptions: increase systemic corticosteroid dosing

Table 3. Basic Work-Up and Management of Common Endocrine irAEs[3,39-41]

irAE	Work-Up	Management
Hypothyroidism	• Pertinent history and physical examination • Thyroid function tests	**Grade 1:** asymptomatic; TSH >4.5 and <10 • Continue ICI with routine monitoring of thyroid function tests **Grade 2:** moderate symptoms or TSH >10 • Hold ICI • Start thyroid hormone supplementation in symptomatic patients or in asymptomatic patients with persistent TSH >10 • Consider endocrine consultation **Grade 3-4:** severe symptoms or life-threatening consequences • Hold ICI, consult endocrine, and start thyroid hormone supplementation • Admit to hospital for developing myxedema
Hypophysitis	• Pertinent history and physical examination: • Obtain appropriate endocrine labwork including ACTH, cortisol, thyroid function tests, LH, FSH, testosterone (in males), and estrogen (in females) • Consider MRI Brain to evaluate for optic chiasm compression	**Grade 1:** asymptomatic or mild symptoms • Hold ICI until patient is stabilized on hormone replacement therapy • Consult endocrine for assistance with initiation of appropriate hormone replacement therapy **Grade 2:** moderate symptoms • Same management as Grade 1 with the following exceptions: consider oral pulse dose therapy in patients with MRI findings of threatened optic chiasm compression **Grade 3-4:** severe symptoms or life-threatening consequences • Same management as Grade 2 with th following exceptions: admit to hospital for consideration of stress dose steroids

Table 4. Basic Work-Up and Management of Common Pulmonary irAEs[3,39-41]

irAE	Work-Up	Management
Pneumonitis	• Pertinent history and physical examination • Pulse oximetry • Rule out other etiologies (such as infection, pulmonary embolus, cancer progression, pleural effusion etc.) via basic labwork, infectious work-up (sputum cultures, viral respiratory pathogen panel, etc.) and imaging	**Grade 1:** asymptomatic; involves one lobe of the lung or <25% of lung parenchyma • Hold ICI vs. continue ICI with close clinical monitoring to monitor for progression to Grade 2 **Grade 2:** symptomatic; involves more than one lobe of the lung or 25–50% of lung parenchyma • Hold ICI • Initiate systemic corticosteroids • Consider bronchoscopy or empiric antibiotics • Consider pulmonary and/or infectious disease consultation **Grade 3:** severe symptoms; involves all lung lobes or >50% of lung parenchyma; oxygen indicated • Discontinue ICI permanently and admit to hospital with strong consideration of pulmonary and/or infectious disease consultation • Initiate systemic corticosteroids and can consider adding immunosuppressive agent if no improvement • Start empiric antibiotics and consider bronchoscopy **Grade 4:** life-threatening respiratory compromise • Same management as Grade 3

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Disclosures

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