Review Article

Management of Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitor Therapy: a Minireview of Current Clinical Guidelines

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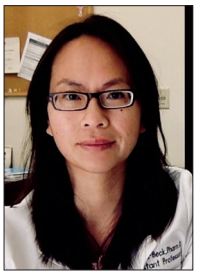

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ABSTRACT

Successful targeting and inhibition of the cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death-1 protein/programmed cell death ligand 1 immune checkpoint pathways has led to a rapidly expanding repertoire of immune checkpoint inhibitors for the treatment of various cancers. The approved agents now include ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, and cemiplimab. In addition to antitumor responses, immune checkpoint inhibition can lead to activation of autoreactive T-cells resulting in unique immune-related adverse events (irAEs). Therefore, it is imperative that oncology nurses, and other clinicians involved in the care of cancer patients, are familiar with the management of irAEs which differ significantly from the management of adverse events from cytotoxic chemotherapy. Herein, we review the mechanisms of irAEs and strategies for management of irAEs and highlight similarities as well as differences among clinical guidelines from the National Comprehensive Cancer Network, American Society of Clinical Oncology, Society for Immunotherapy of Cancer, and European Society for Medical Oncology. Understanding these similarities and key differences will facilitate the development and implementation of a practice site-specific plan for the management of irAEs.

Key words: Adverse events, atezolizumab, durvalumab, immune checkpoint, ipilimumab, management, nivolumab, pembrolizumab, side effects, toxicity

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Immune Checkpoints in Cancer

T-cell recognition and activation against tumor antigens require both binding of T-cell receptors to antigen peptides presented in the context of major histocompatibility complex and engagement of the costimulatory receptor CD28 on T-cells with CD80/86 on antigen-presenting cells or tumor cells.[1] However, antitumor immunity may be suppressed through activation of immune checkpoints that include the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 protein (PD-1) pathways. The CTLA-4 coinhibitory receptor competes with CD28 for CD80/86 and has superior binding affinity for CD80/86.[1] Activation of the CTLA-4 pathway signals for T-cell anergy instead of T-cell activation that results when CD28 binds to CD80/86.[1] Similarly, binding of PD-1 to its ligands – programmed cell death ligand 1 (PD-L1) or PD-L2 on antigen-presenting cells or tumor cells results in the inhibition of T-cell proliferation and reduction in cellular survival.[1] Successful targeting and inhibition of these immune checkpoint pathways was found to mitigate tumor-associated immunosuppression, and currently, there are 7 immune checkpoint inhibitors approved for the treatment of cancer [Table 1].

In the absence of cancer, both CTLA-4 and PD-1 serve to regulate the interaction between T-cells and self versus nonself antigens.[10] Therefore, their inhibition can lead to activation of autoreactive T-cells resulting in the unique immune-related adverse events (irAEs) associated with immune checkpoint inhibitors.[10] As a result, the management of irAEs differs significantly from the management of adverse events from cytotoxic chemotherapy. Herein, we review the mechanisms of irAEs and strategies for management of irAEs and highlight similarities as well as differences among the major clinical guidelines including the National Comprehensive Cancer Network (NCCN),[11] American Society of Clinical Oncology (ASCO),[12] Society for Immunotherapy of Cancer (SITC),[13] and European Society for Medical Oncology (ESMO)[14] guidelines for irAEs.

Patterns of Immune-Related Adverse Events

A meta-analysis comparing the PD-1 inhibitors – nivolumab and pembrolizumab to cytotoxic chemotherapy found that immunotherapy had significantly fewer adverse events overall.[15] However, the types of adverse events were markedly different between immune checkpoint inhibitor therapy and chemotherapy.[15] There was more asthenia, fatigue, nausea, diarrhea, and decreased appetite with immune checkpoint inhibitor therapy while chemotherapy was associated with more neutropenia, anemia, alopecia, stomatitis, and myalgia.[15] Similar adverse events occur with CTLA-4 inhibitors, suggesting that immune checkpoint inhibitors are generally more tolerable than cytotoxic chemotherapy. However, studies directly comparing CTLA-4 inhibitors with chemotherapy are lacking. Adverse events associated with immunotherapies may affect any organ system and are referred to as irAEs.[16]

CTLA-4 inhibitors generally have higher rates and higher severity of irAEs than PD-1/L1 inhibitors,[16] occurring in 90% and 70% of patients, respectively.[17] There appears to be a correlation between certain toxicities and specific types of cancers such as vitiligo in melanoma patients.[18] The irAEs often manifest in a dose-dependent manner within 3–6 months of initiation of CTLA-4 or PD-1/PD-L1 inhibitor therapy although they have been reported to occur up to a year after the patient is exposed to PD-1 inhibitors.[18] Development of irAEs is unpredictable and

Table 1: Currently approved immune checkpoint inhibitors

Generic name	Trade name	Target	Indication (approval year)
Pembrolizumab	Keytruda	PD-1[2]	Melanoma, nonsmall cell lung cancer (2018), head and neck squamous cell cancer (2018), classical Hodgkin lymphoma (2018), primary mediastinal large B-cell lymphoma (2018), urothelial carcinoma (2018), microsatellite instability-high cancer (2018), gastric cancer (2018), cervical cancer (2018), hepatocellular carcinoma (2018), Merkel cell carcinoma (2018)[2,3]
Nivolumab	Opdivo	PD-1[4]	Metastatic small cell lung cancer (2018), unresectable or metastatic melanoma (2017), locally advanced or metastatic urothelial carcinoma (2017), adult and pediatric patients with microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (2017), hepatocellular carcinoma (2017), metastatic nonsmall cell lunch cancer (2016), advanced renal cell carcinoma (2016), classical Hodgkin lymphoma (2016), recurrent or metastatic squamous cell carcinoma of the head and neck (2016)[3,4]
Cemiplimab	Libtayo	PD-1[5]	Metastatic cutaneous squamous cell carcinoma (2018), locally advanced CSCC (2018)[3,5]
Atezolizumab	Tecentriq	PD-L1[6]	Urothelial carcinoma (2016), metastatic nonsmall cell lung cancer (2016)[3,6]
Avelumab	Bavencio	PD-L1[7]	Metastatic Merkel cell carcinoma (2017), locally advanced or metastatic urothelial carcinoma (2017)[3,7]
Durvalumab	Imfinzi	PD-L1[8]	Unresectable Stage III nonsmall cell lung cancer (2018), locally advanced or metastatic urothelial carcinoma (2017)[3,8]
Ipilimumab	Yervoy	CTLA-4[9]	Advanced renal cell carcinoma (2018), adults and pediatric with microsatellite instability-high or mismatch repair-deficient (2018) metastatic colorectal cancer (2018), cutaneous melanoma (2015), unresectable or metastatic melanoma (2014)[3,9]

CSCC: Cutaneous squamous cell carcinoma

does not appear to correlate with cumulative dose toxicity or anticancer efficacy.[17]

Management of Immune-Related Adverse Events

irAEs are managed according to severity assessed using the Common Terminology Criteria for Adverse Events grading system,[19] and this is summarized in Table 2. Corticosteroids are the mainstay for low-severity irAEs (e.g., Grades 1–2), administered at low (0.5–1 mg/kg/day), moderate (1–2 mg/kg/day), or high dosages (>2 mg/kg/day). After resolution of irAEs, patients will require tapering off corticosteroid therapy. Other immunosuppressants may be considered if there are severe irAEs (e.g., Grades 3–4) or when irAEs do not resolve with the use of corticosteroids. In general, immune checkpoint inhibitor therapy may be continued while most Grade 1 events are managed. For Grades 2–4 events, immunotherapy is usually withheld and can be reinitiated once irAEs resolve although permanent discontinuation is sometimes warranted. The similarities and differences among the clinical guidelines for the management of specific irAEs are discussed below.

Dermatologic

Dermatologic toxicities are the most common irAEs associated with immune checkpoint inhibition and can affect up to 50% of patients, the majority of which are low-grade severity. Typical presentations include pruritus, rash, dermatitis, and bullous dermatitis. However, Steven–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported.

The NCCN, ASCO, ESMO, and SITC guidelines all recommend the use of topical steroids, oral antihistamines, and topical emollients for low-grade rash/inflammatory dermatitis, and immune checkpoint inhibitors should be continued for Grade 1 cases. For Grade 2 dermatitis, ESMO and SITC recommend continuing immunotherapy and adding on antihistamines, topical steroids, and emollients, whereas NCCN and ASCO recommend that clinicians consider holding therapy and starting high-dose systemic

Table 2: General approach for management of immune-related adverse events

irAE	ICI therapy	Immunosuppressants	Other treatment
Grade 1	Discontinue if hypophysitis, pneumonitis, and/or sarcoidosis Consider holding if renal Hold if neurologic, aplastic anemia, acquired hemophilia Continue for all others	Prednisone 0.5-1 mg/kg/day if acquired hemophilia	Topical steroids[a], oral antihistamines[b], topical emollients if dermatologic Loperamide if gastrointestinal[c] Thyroid hormone supplementation[d] if hypothyroidism Beta-blockers for symptomatic hyperthyroidism[e]; insulin therapy if hyperglycemia Oral fluids, loperamide, hormone replacement therapy[f] if hypophysitis Consider artificial tears if ocular Analgesics[g] if rheumatologic
Grade 2	Considering holding if dermatologic, rheumatologic, or lymphopenia Hold for all others	Prednisone 0.5-1 mg/kg/day[h] Prednisone 1-2 mg/kg/day if hypophysitis[i] Prednisone 2 mg/kg/day if transverse myelitis[k]	In addition to the above, consider: Adding infliximab if gastrointestinal[j] Empiric antibiotics if pulmonary Adding ATG and cyclosporine if aplastic anemia Adding GABA agonist[l] or duloxetine for pain if peripheral neuropathy Adding ophthalmic prednisone if ocular
Grade 3	Discontinue if hepatitis, renal, ocular, neurologic, cardiovascular, rheumatologic, and/or hematologic Hold for all others	Prednisone 1-2 mg/kg/day Prednisone 2-4 mg/kg/day if peripheral neuropathy or Guillain-Barre syndrome Consider plasmapheresis, intravenous immunoglobulin therapy, methotrexate, azathioprine, or mycophenolate mofetil through Grade 4 if myositis; Consider methotrexate or tocilizumab through Grade 4 if Consider rituximab or cyclophosphamide if acquired hemophilia	In addition to the above, consider: Adding omalizumab, GABA agonistl if pruritis Plasmapheresis or immunoglobulin if neurologic Pyridostigmine[m] if myasthenia gravis Antirheumatic drugs[n], methotrexate, infliximab or tocilizumab if refractory arthritis or polymyalgia-like syndrome Infliximab, mycophenolate mofetil, intravenous immunoglobulin if pulmonary or renal Rituximab if autoimmune encephalopathy infliximab if cardiovascular[o]
Grade 4	Discontinue	Prednisone 2-4 mg/kg/day	In addition to the above, consider: Adding mycophenolate mofetil if hepatitis[p] empiric antivirals[q] if aseptic meningitis and/or encephalitis rituximab if acquired TTP[r] rituximab or cyclophosphamide if acquired hemophilia rituximab, intravenous immunoglobulin, cyclosporine A, or mycophenolate mofetil if autoimmune hemolytic anemia eculizaumab[s] if hemolytic uremic syndrome intravenous immunoglobulin, rituximab, or thrombopoietin receptor agonists if immune thrombocytopenia

[a]Clobetasol dipronate 0.05% or equivalent; [b]Cetirizine, hydroxyzine, or equivalent; [c]Avoid for *Clostridium difficile*; [d]Levothyroxine 1.6 mcg/kg or 25-50 mcg in elderly; [e]Atenolol 25-50 mg; [f]Thyroid, testosterone, estrogen; [g]Acetaminophen or nonsteroidal anti-inflammatory drugs; [h]Consider starting at 1 mg/kg/day if gastrointestinal; [i]Consider infliximab, MMF, tacrolimus, or loperamide through Grade 4; [j]Infliximab-refractory is noted if no response is seen in 2 days; [k]Intravenous immunoglobulin or plasmapheresis is strongly recommended; [l]Gabapentin, pregabalin, or equaivalent if neuropathic-related; [m]Pyridostigmine 30 mg three times a day; [n]Sulfasalazine, methotrexate, leflunamide; [o]High-dose prednisone for myocarditis; [p]Avoid infliximab for hepatitis; [q]Intravenous acyclovir; [r]Prednisone 1 g intravenously for TTP; [s]Eculizumab 900 mg weekly for four doses, 1200 mg week 5, then 1200 mg every 2 weeks. ATG: Antithymocyte globulin, GABA: Gamma-aminobutyric acid, TTP: Thrombotic thrombocytopenic purpura, ICI: Immune checkpoint inhibitor, MMF: Mycophenolate mofetil

steroids. A dermatological referral is warranted in these patients. Any cases of Grades 3 or 4 dermatitis require immediate discontinuation of immune checkpoint inhibitors and treatment with high-dose systemic corticosteroids until severity is less than or equal to Grade 1, at which time immune checkpoint inhibitors may be rechallenged. Pruritus is recognized by NCCN and SITC for which recommendations are similar to that of rash/inflammatory dermatitis. For Grade 3 pruritus, the addition of GABA agonists (e.g., pregabalin or gabapentin) may be helpful.

For bullous dermatitis, NCCN guidelines recommend holding immune checkpoint inhibitors and starting high-potency topical steroids for Grade 1 bullous dermatitis whereas ASCO guidelines recommend continuing therapy along with local wound care. For Grade 2 and above, both guidelines recommend high-dose oral or intravenous corticosteroids and discontinuation of immune checkpoint inhibitors therapy, along with wound care and topical corticosteroids. Severe skin reactions such as SJS and TEN can be fatal, and the consensus recommendation is high-dose corticosteroids with inpatient care and permanent discontinuation of immune checkpoint inhibitors.

Gastrointestinal

Gastrointestinal irAEs are divided into three major categories: colitis, hepatitis, and pancreatitis. Colitis usually presents as diarrhea and can affect up to 44% of patients, depending on the immune checkpoint inhibitor regimen. For Grade 1 colitis, all guidelines recommend close monitoring and changes in diet and continuation of immune checkpoint inhibitors therapy. Loperamide may be used; however, other causes such as *Clostridium difficile* infection need to be ruled out. For Grade 2 reactions, it is generally recommended to hold immunotherapy and start high-dose systemic corticosteroids. A gastrointestinal consult is recommended for Grade 2 toxicity and a negative infectious stool culture. At Grades 3 or above, inpatient hospitalization is warranted, and the addition of an immunosuppressant such as infliximab should be considered.

Up to 30% of patients receiving immune checkpoint inhibitors can develop hepatitis that usually presents as transaminitis (diagnosed by increased blood levels of alanine transaminase and aspartate transaminase), with or without hyperbilirubinemia. Transaminitis should be evaluated to rule out viral causes, disease or drug-related hepatic dysfunction, and hepatotoxic medications. Serial laboratories assessing blood levels of liver transaminases and bilirubin are necessary to monitor and assess recovery. Grade 1 hepatitis should be monitored, and all guidelines recommended to continue immune checkpoint inhibitors therapy. In those with Grades 2 or above, immune checkpoint inhibitor therapy should be discontinued and high-dose corticosteroids should be initiated. If there is no improvement after 3 days (i.e., steroid refractory), mycophenolate mofetil should be considered. Importantly, infliximab should not be used for hepatitis since it is associated with hepatotoxicity. Permanent discontinuation of immune checkpoint inhibitors is recommended for Grade 4 hepatitis, and patients should be treated inpatient.

Pancreatitis presents with elevations in amylase/lipase in addition to clinical symptoms. According to NCCN guidelines, patient assessment should include an abdominal computed tomography (CT) with contrast and consider magnetic resonance cholangiopancreatography if clinical suspicion of pancreatitis is present with no radiological evidence on CT. A gastroenterology consult should be considered for all grades. Immunotherapy should be held and low-dose corticosteroids should be initiated for Grade 2. For Grades 3 or higher, permanently discontinue immunotherapy and give moderate-dose corticosteroids. Additional immunosuppression with mycophenolate mofetil may be considered for Grades 2 through 4.

Endocrine

NCCN, ASCO, ESMO, and SITC all recognize new-onset hyperglycemia as an irAE. Patients with Grade 1 hyperglycemia (fasting blood glucose <200 mg/dL) and/or history of type 2 diabetes mellitus with low suspicion of diabetic ketoacidosis, may continue immunotherapy along with monitoring of blood glucose and dietary or lifestyle modifications as needed. If hyperglycemia with fasting blood glucose >200 mg/dL or random blood glucose >250 mg/dL, or if there is a history of type 2 diabetes mellitus with fasting/random glucose >250 mg/dL, then consider holding immunotherapy until hyperglycemia is controlled. Oral therapy or insulin should be initiated to treat low-grade hyperglycemia; however, management should start with insulin therapy for Grade 3 or 4. ESMO guidelines also recommend inpatient care for Grades 3–4 hyperglycemia. An endocrinologist should be consulted if the patient is symptomatic and blood glucose is uncontrolled. SITC guidelines specifically address type 1 diabetes mellitus and recommend holding immunotherapy and management with insulin.

For hypothyroidism, both NCCN and SITC guidelines recommend thyroid hormone supplementation with monitoring of TSH and free T4 levels every 4–6 weeks for any grade event, whereas ESMO and ASCO recommend thyroid hormone therapy in symptomatic patients. In general, immunotherapy may be continued for Grade 1 or asymptomatic hypothyroidism, and Grade 2 events should be handled based on the specific patient scenario since the guidelines diverge with regard to whether or not to hold immunotherapy. Immune checkpoint inhibitors should be held for Grades 3–4 events until symptoms resolve.

Hyperthyroidism, including thyrotoxicosis, is recognized by ASCO, ESMO, and SITC. For Grade 1, ASCO and SITC suggest continuing immunotherapy along with symptomatic treatment with beta-blockers as needed, whereas ESMO suggests holding immunotherapy and restarting immunotherapy when asymptomatic. For Grades 2–4, all guidelines recommend holding immunotherapy until symptoms return to baseline, with administration of beta-blocker for supportive care. Monitoring should include thyroid function tests every 4–6 weeks until recovery. If TSH >10, this could indicate the development of hypothyroidism requiring administration of thyroid replacement therapy.

Hypophysitis, inflammation of the anterior lobe of the pituitary gland, is recognized by NCCN, ASCO, and ESMO. The main approach to management of hypophysitis of any grade is to hold immune checkpoint inhibitors until resolution of the irAE and administer supportive care (e.g., oral fluids, loperamide, avoidance of high fiber and lactose diet) and hormone replacement therapy (e.g., thyroid, testosterone, and estrogen) as needed. Recommendations for the administration of corticosteroids vary between the guidelines; corticosteroids may be initiated for Grade 1 (NCCN) or Grade 2 (ASCO) for moderate symptoms. ESMO recommends corticosteroids for Grade 2 symptoms that persist for more than 14 days or for 3 days and worsen. For Grades 3–4, if there is no improvement within 72 h of corricosteroid intiation, it is recommended to start infliximab, mycophenolate mofetil, or tacrolimus.

Pulmonary

Pneumonitis is recognized by NCCN, ASCO, ESMO, and SITC as an irAE. For any grade pneumonitis, immunotherapy should be discontinued. Grade 2 pneumonitis should be treated with corticosteroids and empiric antibiotics (NCCN, ASCO, and ESMO). SITC guidelines similarly recommend starting corticosteroids but not empiric antibiotic treatment for Grade 2 events. For Grades 3–4, all guidelines suggest permanently discontinuing immunotherapy. If patients do not improve on corticosteroid therapy after 48 h, then infliximab, mycophenolate mofetil, or intravenous immunoglobulin may be added. Severe pneumonitis (Grades 3 or 4) may require inpatient care, and infectious workup is warranted (NCCN).

Sarcoidosis is a rare pulmonary toxicity in patients receiving immune checkpoint inhibitors. SITC is the only guideline that addresses sarcoidosis, and management is based on clinical experience and case reports. For any grade, immunotherapy should be discontinued and the patient should be closely monitored. For Grade ≥2, consider corticosteroid therapy, with taper over 2–4 months.

Renal

Renal adverse events may occur in 2%–5% of patients. These irAEs were reported within the first 3–10 months of anti-PD1 therapy and within 2–3 months of anti-CTLA4 therapy. Renal toxicities may present as oliguria, hematuria, peripheral edema, and anorexia. Grade 1 events may continue immune checkpoint inhibitors with close monitoring. However, patients with Grades 2–3 events should hold immune checkpoint inhibitors and initiate low to moderate doses of corticosteroids. Immune checkpoint inhibitor treatment may resume when renal events resolve. Grade 4 patients should prompt the permanent discontinuation of immune checkpoint inhibitors and initiation of moderate-dose corticosteroids. Persistent Grades 2 or higher toxicities should involve a nephrology consult. SITC recommends that patients with recurrent toxicities receive prophylactic corticosteroids following immune checkpoint inhibitor administration.

Ocular/ophthalmic

Ophthalmic irAEs have an incidence of <1%. These toxicities may present as vision changes, optic nerve swelling, uveitis/iritis, episcleritis, and/or blepharitis. For Grade 1 patients, immune checkpoint inhibitors may be continued. Grade 2 patient should hold immune checkpoint inhibitors therapy. For Grades 3–4, immune checkpoint inhibitors therapy should be permanently discontinued. Artificial tears are recommended for all grades, and ophthalmic and systemic corticosteroids may be considered starting with Grades 2 or higher events. A complete ophthalmic evaluation is recommended within a few days of symptom onset, and SITC also suggests that treatment of ophthalmic irAEs should be withheld until an eye examination is conducted unless the toxicity is believed to be unrelated to the use of immune checkpoint inhibitors.

Nervous/neurologic

Neurologic irAEs are uncommon, and the incidence of Grades 3 or higher events is <1%. These toxicities include myasthenia gravis, Guillain–Barre syndrome, peripheral neuropathy, aseptic meningitis, encephalitis, and transverse myelitis, and immune checkpoint inhibitors should be held for any grade event. In the case of myasthenia gravis, immune checkpoint inhibitors should be discontinued, and systemic corticosteroids should be initiated. Pyridostigmine should be administered once the immune checkpoint inhibitor is held. Grades 3–4 patients should permanently discontinue immune checkpoint inhibitors and initiate moderate to high dose of corticosteroids. Plasmapheresis or intravenous immunoglobulin may be considered for Grades 3 and higher events according to ASCO guidelines although NCCN only recommends adding on plasmapheresis or intravenous

immunoglobulin if there is no improvement or worsening symptoms despite corticosteroids.

Patients with peripheral neuropathy may require low dose of corticosteroids, and immune checkpoint inhibitor therapy should be discontinued. GABA agonists, such as gabapentin and pregabalin, or duloxetine may be considered for peripheral neuropathy. Patients with aseptic meningitis or encephalitis may require moderate dose of corticosteroids; empiric antivirals, such as acyclovir, may be started for aseptic meningitis and encephalitis. If patients are confirmed for aseptic meningitis, low to moderate dose of corticosteroids may be initiated. Patients with transverse myelitis or Guillain–Barre syndrome may require high dose of corticosteroids. Plasmapheresis or intravenous immunoglobulin has been considered for patients with transverse myelitis. Rituximab may be considered for Grades 3 and higher, as well as in patients positive for autoimmune encephalopathy. Frequent pulmonary function assessment and neurologic evaluation are advised.

Cardiovascular

Cardiovascular irAEs have an incidence <1% and may include myocarditis, pericarditis, arrhythmias, and impaired ventricular function that typically occurs within the 1st month of treatment. For all-grade irAEs, immune checkpoint inhibitors should be permanently discontinued and moderate- to high-dose corticosteroids are recommended as treatment. According to NCCN guidelines, infliximab may be considered for life-threatening symptoms. Although myocarditis is extremely rare, it can be fatal, and suspected cases should be admitted for monitoring. If myocarditis is confirmed, high-dose corticosteroids should be administered. Evaluation of cardiovascular irAEs should include chest imaging to rule out pulmonary embolism, pneumonitis, or pulmonary edema. Electrocardiograms should also be monitored closely, and cardiac biomarkers should be tested at baseline and repeated if symptoms arise. A two-dimensional echocardiogram may be considered for patients experiencing significant dyspnea or abnormal cardiac safety screening test.

Rheumatologic/musculoskeletal

The incidence of musculoskeletal toxicities is 2%–12% and can present as inflammatory arthritis, myalgias, myositis, and polymyalgia-like syndromes. Grade 1 patients may continue immune checkpoint inhibitors therapy with the initiation of analgesics (e.g., acetaminophen or nonsteroidal anti-inflammatory drugs). Grade 2 patients should consider holding immune checkpoint inhibitors and starting low-dose corticosteroids for 4–6 weeks. Grades 3–4 patients should permanently discontinue immune checkpoint inhibitors, and moderate-dose corticosteroids should be initiated. Infliximab or tocilizumab may be considered for refractory/severe arthritis, and antirheumatic drugs (e.g., sulfasalazine, methotrexate, or leflunomide) may be considered if there is no improvement after 2 weeks (NCCN). Grades 3–4 patients with myositis may be offered plasmapheresis, intravenous immunoglobulin therapy, or immunosuppressant therapy with methotrexate, azathioprine, or mycophenolate mofetil if symptoms do not improve or worsen after 4–6 weeks. Grades 3–4 patients with polymyalgia-like syndrome without improvement from corticosteroids may be offered methotrexate or tocilizumab.

Hematologic

Hematologic irAEs are rare and should be supported by changes in laboratory values. Generally, Grade 1 patients should continue immune checkpoint inhibitors, Grade 2 patients should hold immune checkpoint inhibitors, and Grades 3 or higher patients should permanently discontinue immune checkpoint inhibitors. Grades 1–2 toxicities may be treated with low-dose corticosteroids, while Grades 3–4 may require moderate-dose corticosteroids.

For autoimmune hemolytic anemia with no improvement after moderate-dose corticosteroid therapy, consider rituximab, intravenous immunoglobulin, cyclosporine A, or mycophenolate mofetil. In acquired thrombotic thrombocytopenic purpura, corticosteroids should be initiated, and rituximab may be offered. For hemolytic uremic syndrome, therapy with moderate-dose corticosteroid and eculizumab may be initiated. For lymphopenia, immune checkpoint inhibitors may be continued unless Grade 4, in which case immunotherapy should be held. For thrombocytopenia, discontinue immune checkpoint inhibitors and initiate moderate-dose corticosteroids; intravenous immunoglobulin, rituximab, or a thrombopoietin receptor agonist may also be considered. For aplastic anemia and acquired hemophilia, immune checkpoint inhibitors should be permanently discontinued, and patients should be treated with low to moderate dose of corticosteroids; the addition of rituximab or cyclophosphamide may be considered. Moreover, antithymocyte globulin equine with cyclosporine is an option for aplastic anemia.

Conclusion

The expanding repertoire of immune checkpoint inhibitors and their clinical applications makes it imperative that oncology nurses, and other clinicians involved in the care of cancer patients, are familiar with the management of irAEs which differ significantly from the management of adverse events from cytotoxic chemotherapy. Understanding the similarities and key differences in the management of irAEs across the available clinical guidelines will facilitate

the successful development and implementation of a practice site-specific plan for the management of irAEs.

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Conflicts of interest

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