Management of Toxicities Associated With Immune Checkpoint Inhibitors

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Abstract: Immune-related adverse events (irAEs) encompass a diverse range of toxicities following treatment with immune checkpoint inhibitors (ICIs), each with distinctive symptoms, severities, and outcomes. irAEs can affect any organ and are potentially fatal, so early diagnosis is key in preventing serious events. irAEs can be fulminant, requiring immediate attention and intervention. Management of irAEs involves the use of systemic corticosteroids and immunosuppressive agents in addition to any disease-specific therapeutics. Making the decision to rechallenge with ICIs is not always clear and involves weighing the risks and clinical benefits of continuing ICI therapy. Here, we review the consensus recommendations on managing irAEs and discuss current challenges in clinical care caused by these toxicities.

Keywords
Immune checkpoint inhibitors (ICIs), immune-related adverse events (irAEs), immunotherapy

Introduction

Immune checkpoint inhibitors (ICIs) have dramatically changed the therapeutic landscape of oncology over the last decade, with evidence supporting the use of ICIs in a growing number of cancers. ICIs act by modulating the immune system to attack cancer cells through inhibition of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed death 1 (PD-1), or programmed death ligand 1 (PD-L1), so their potential toxicities are distinct from those of cytotoxic chemotherapy. Immune-related adverse events (irAEs) can occur at any time after starting ICIs, even after ICI discontinuation, and occur with variable incidences and severities.[1] irAEs are graded using the Common Terminology Criteria for Adverse Events, with grade 1 irAEs generally allowing for continuation of ICIs, whereas grade 2 or higher irAEs may necessitate cessation of ICIs and treatment with corticosteroids or other immunomodulators.[2] Autoreactive T-cell activation by ICIs is associated with a wide spectrum of toxicities and can affect any organ. Given the range of clinical manifestations of irAEs, early diagnosis and timely management of irAEs are crucial in minimizing the risks for serious events (see the Figure).

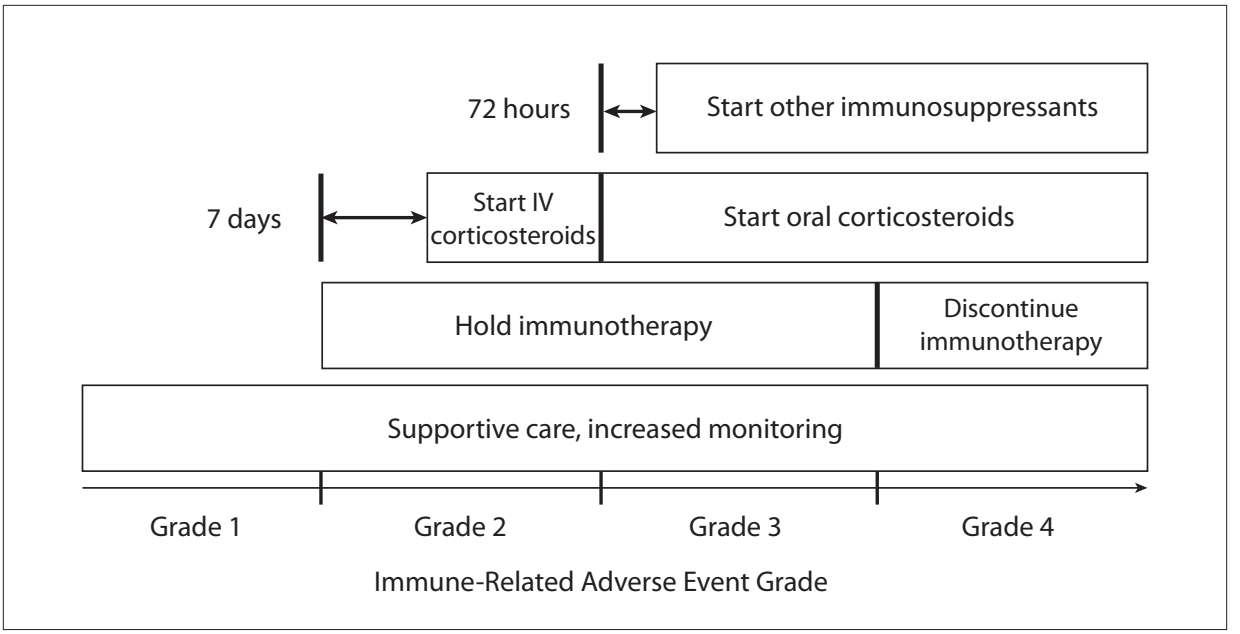

Figure. General approach to the management of immune-related adverse events.

IV, intravenous.

Dermatologic Toxicities

Cutaneous toxicities are the most common irAEs, occurring in approximately 20% to 60% of patients treated with monotherapy ICIs, and 60% to 70% of patients receiving combination anti–PD-1/PD-L1 and anti–CTLA-4 agents.[3,4] irAEs of the skin encompass a variety of clinical conditions, including maculopapular rash, pruritus, vitiligo, bullous dermatitis, lichenoid dermatitis, psoriasis, and rarely alopecia or vasculitis.[3,4] Of the dermatologic irAEs, the most common are rash and pruritus, which generally are low-grade. Oral antihistamines, topical emollients, and corticosteroids are used to treat grades 1 and 2 rash and pruritus.[5,6] Guidelines recommend holding immunotherapy, consulting dermatology, and treating severe grade 3 toxicities with oral corticosteroids.[5]

On the other hand, autoimmune bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms are potentially life-threatening dermatologic irAEs that require early cessation of immunotherapy, the introduction of systemic corticosteroids, and urgent dermatologic consultation.[5] One option in patients with bullous pemphigoid refractory to systemic corticosteroids is rituximab. In a phase 3 clinical trial, a combination of rituximab and corticosteroids demonstrated superior complete remission rates to corticosteroids alone (89% vs 39%) for patients with pemphigus.[7] Other immunosuppressants such as intravenous immunoglobulin (IVIG) can be given as an adjunct to rituximab or as a corticosteroid-sparing approach for bullous dermatitis. Additionally, IVIG is a treatment alternative for severe or corticosteroid-refractory Stevens-Johnson syndrome and toxic epidermal necrolysis.[5,6] Given the concerns for safety with ICI rechallenge, the National Comprehensive Cancer Network (NCCN) advises permanent discontinuation of ICIs for severe bullous dermatitis and all cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.[5]

Gastrointestinal Toxicities

Gastrointestinal (GI) irAEs, consisting of diarrhea, colitis, gastritis, enterocolitis, hepatitis, and pancreatitis, are common in patients treated with ICIs. Diarrhea and colitis are the most prevalent toxicities among the GI irAEs. Immune-mediated diarrhea and colitis (IMDC) is diagnosed based on symptoms, with diarrhea defined as an increase in frequency of watery stools over baseline and colitis defined as symptoms of abdominal pain, mucous, or blood in the stools.[8] Abdominal imaging, fecal inflammatory markers, and endoscopic evaluation are not routinely performed in patients with IMDC. Nonetheless, fecal inflammatory markers such as calprotectin and lactoferrin may serve as surrogate predictive markers to invasive endoscopies in evaluating response to treatment in patients with moderate to severe IMDC.[9] One study demonstrated that low fecal calprotectin at the onset of symptoms corresponded with clinical remission. Another

study showed that low fecal calprotectin concentrations before and after treatment for IMDC correlated with endoscopic and histologic response.[10,11]

Current guidelines for the management of patients with mild or grade 1 IMDC advocate for close monitoring and supportive care. Conversely, grade 2 or higher IMDC requires holding immunotherapy, stool evaluation to assess for infectious causes, and systemic corticosteroids (1-2 mg/kg/day).[5,6] Clinical response typically occurs within 3 days of starting corticosteroids.[9] However, a subset of patients with IMDC are corticosteroid-refractory, in which case infliximab or vedolizumab (Entyvio, Takeda) can be added to corticosteroids.[5,6] Studies have not directly compared infliximab vs vedolizumab in corticosteroid-refractory IMDC, so the decision to choose infliximab or vedolizumab should be individualized depending on the risks for toxicities.[9] Infliximab, an anti–tumor necrosis factor α (TNF-α) agent, carries a risk for hepatitis B reactivation and tuberculosis activation, and should not be used in patients with concomitant ICI hepatitis owing to concerns over infliximab-induced hepatotoxicity.[5] On the contrary, vedolizumab is a monoclonal antibody against α4β7 integrin and a treatment option for patients with contraindications to anti–TNF-α therapy or those with infliximab-refractory IMDC.[10,12,13] Other agents, including tofacitinib (Xeljanz, Pfizer) or ustekinumab (Stelara, Janssen), can be considered in infliximab- or vedolizumab-refractory colitis, although data on these therapies are limited to case reports.[5,6,14,15]

Hepatitis is the second most common GI irAE, with an incidence of 1% to 7% among patients on single-agent PD-1/PD-L1 or CTLA-4 inhibitors and 13% to 30% among those on treatment with combination therapy.[16] A diagnosis of ICI-related hepatitis requires excluding all other causes of hepatitis, including viral etiologies. Corticosteroids are generally effective for ICI-related hepatitis; the American Society of Clinical Oncology (ASCO) and NCCN guidelines recommend prednisone at 0.5 to 1 mg/kg/day for grade 2 hepatotoxicity and corticosteroids at 1 to 2 mg/kg/day for grade 3 toxicities.[5,6] Of note, corticosteroid tapering should take place over a course of at least 4 weeks, or even longer for severe cases. Hepatitis takes approximately 8 weeks to resolve and relapses are high during corticosteroid tapering.[16] Infliximab should not be used in these patients owing to its risks for hepatotoxicity. Mycophenolate mofetil can be used in the corticosteroid-refractory setting, whereas antithymocyte globulin can be considered in corticosteroid- and mycophenolate mofetil–refractory patients.[5,17]

Acute pancreatitis related to immunotherapy is rare, whereas asymptomatic elevations in amylase and lipase are more frequently observed. Currently, the standard approach to ICI pancreatitis is similar to that in non-ICI pancreatitis and is centered on hydration and pain control. Although guidelines suggest the use of corticosteroids, one retrospective study did not find any improvements in symptoms, long-term outcomes (chronic pancreatitis, recurrent pancreatic injury, and diabetes), or survival with corticosteroids.[18]

Pulmonary Toxicities

Pneumonitis is less common than cutaneous and GI irAEs, and occurs in approximately 5% of patients receiving anti–PD-1/PD-L1 therapy and 10% of patients receiving combination anti–PD-1/PD-L1 and anti–CTLA-4 ICIs.[19] Early detection is imperative because pneumonitis carries the potential for fatal events. The median time to onset is 2.8 months; presenting symptoms may include dyspnea, cough, fever, or chest pain. High-resolution computed tomography scans can provide evidence for ICI pneumonitis, with the most common radiographic patterns showing ground-glass opacities (37%), organizing pneumonitis (19%), and hypersensitivity pneumonitis (22%).[19] Diagnostic bronchoscopy can be helpful to rule out other etiologies, such as infection or disease progression, and can be considered in patients with moderate to severe symptoms.

Systemic corticosteroids are the mainstay treatment for symptomatic ICI pneumonitis, with the NCCN and ASCO guidelines recommending prednisone or methylprednisolone at 1 to 2 mg/kg/day for grade 2 or higher toxicities. Immunotherapy should be held and corticosteroids continued until symptoms improve to at least grade 1, followed by careful tapering over 4 to 6 weeks.[5,6] Although a majority of patients rechallenged with ICIs do not experience a recurrence, subsequent episodes of pneumonitis occur in 25% to 33% of patients after ICI reinitiation. As a result, close monitoring of all patients with ICI pneumonitis is essential. Recurrences of ICI pneumonitis can be successfully managed by holding ICIs and restarting corticosteroids.[19–21] Additionally, a subset of patients (2%) develops chronic ICI pneumonitis, which is characterized by persistent bronchoalveolar lavage fluid lymphocytosis, organizing pneumonia on lung biopsy, and the need for at least 12 weeks of immunosuppression.[22]

Corticosteroid-refractory pneumonitis, which is characterized by a lack of clinical improvement after 48 hours of high-dose corticosteroids, carries a significant risk for mortality. One retrospective study reported an incidence of 18.5% for corticosteroid-refractory pneumonitis at a single institution and another retrospective study found a 90-day all-cause mortality or hospice referral rate of 50%.[23,24] Studies have not directly compared the efficacy of various immunosuppressive agents in this

setting. Guidelines suggesting the use of infliximab, IVIG, mycophenolate mofetil, cyclophosphamide, or tocilizumab (Actemra, Genentech) in corticosteroid-refractory pneumonitis are based on case reports and data from studies on other corticosteroid-refractory irAEs as well as immune-mediated pneumonitis.[5,6,25]

Endocrine Toxicities

Endocrine irAEs from ICIs can affect the thyroid gland, pituitary gland, adrenal glands, and pancreas, causing hypothyroidism, hyperthyroidism, hypophysitis, primary adrenal insufficiency, and type 1 diabetes. Hypothyroidism is the most common endocrine toxicity, with an overall incidence of 6.6% among all ICI regimens. Primary adrenal insufficiency and type 1 diabetes are rare endocrine toxicities, occurring in less than 1% of patients receiving ICI therapy.[26] Only routine monitoring of thyroid dysfunction with thyroid-stimulating hormone and free thyroxine is advised by guidelines.[5,6,25] A diagnosis of endocrinopathy is typically prompted by symptoms, with the clinical presentation of hypophysitis varying depending on the affected hormone axis. Hypophysitis may cause headaches or vision changes; primary adrenal insufficiency can be associated with hypotension, dehydration, and electrolyte abnormalities; and type 1 diabetes can occur with the rapid onset of hyperglycemia or diabetic ketoacidosis.[27,28]

Unlike other irAEs, endocrine toxicities often cause permanent organ damage that results in the need for lifelong hormone replacement. Management of endocrine irAEs is unique in that corticosteroids are not the mainstay therapies in these conditions, except for acute symptomatic hypophysitis and primary adrenal insufficiency. Immunosuppressants do not confer clinical benefits.[5,6] Levothyroxine is administered to patients with primary hypothyroidism, and insulin is indicated in treating patients with type 1 diabetes. A combination of corticosteroids, thyroid replacement hormone, and gonadal replacement hormone may be necessary in hypophysitis. Patients can continue ICIs despite acquiring endocrinopathies, given that hormone supplementation is generally effective and the organ dysfunction is irreparable.

Cardiovascular Toxicities

Cardiotoxicities from ICIs consist of myocarditis, cardiomyopathy, cardiac fibrosis, heart failure, and pericarditis.[29] Although myocarditis is rare, with an incidence of 0.06% to 1%, it can be fulminant and fatal in 46% of cases.[30,31] Acute cardiovascular disease and ICI myocarditis can share similar clinical features, so accurate diagnostic testing is required to distinguish between these.[32] According to guidelines, evaluation of any grade ICI myocarditis involves an examination of cardiac biomarkers (eg, troponin I, creatine phosphokinase, and B-type natriuretic peptide), along with ordering an electrocardiogram, chest x-ray, and echocardiogram. A cardiology consultation is also required, with consideration for cardiac catheterization, myocardial biopsy, and/or cardiac magnetic resonance imaging.[5,6] Endomyocardial biopsy is considered the gold standard in diagnosing ICI myocarditis, with inflammatory infiltrates and myocardial necrosis seen on histology.[32] An endomyocardial biopsy is not feasible in all cases, however, given its invasiveness and risks for complications, so diagnosing ICI myocarditis depends on clinical suspicion and the results of all other available studies.

Because cardiotoxicities can quickly progress, corticosteroids should be empirically started if there is a strong clinical suspicion for ICI myocarditis.[6] A retrospective observational study of 126 patients with ICI myocarditis observed the greatest risk reduction for major adverse cardiac events in patients receiving early high-dose corticosteroids. Individuals treated with corticosteroids within 24 hours of admission had the lowest rate of major adverse cardiac events (7.0%) compared with those receiving corticosteroids at 24 to 72 hours (34.3%) and more than 72 hours (85.1%; $P<.001$) of admission.[33] Corticosteroids can be gradually tapered after patients demonstrate clinical and cardiac biomarker response. Based on case reports and a small case series describing immunomodulator efficacy in ICI myocarditis, other immunomodulators, including abatacept, infliximab, mycophenolate mofetil, IVIG, alemtuzumab, antithymocyte globulin, and plasmapheresis, can be considered if there is no clinical response to corticosteroids.[5,32] Of note, infliximab can exacerbate heart failure and must be used with caution in patients with a reduced left ventricular ejection fraction.[32]

Given the risks for substantial morbidity and mortality with myocarditis, guidelines endorse interruption of ICI therapy for any suspicion of ICI myocarditis.[5,6,25,34] It is not clear whether ICIs can be safely restarted in patients with myocarditis, however, and recurrent myocarditis has been reported following ICI resumption.[31,35] Hence, it is reasonable and supported by guidelines to consider permanently discontinuing ICI therapy in patients with myocarditis associated with ICIs.[5,25,34]

Musculoskeletal and Rheumatic Toxicities

Arthralgia, myalgia, inflammatory arthritis, myositis, polymyalgia rheumatica, and sicca syndrome are musculoskeletal and rheumatic irAEs that may occur with ICI therapy. Arthralgia and myalgia are the most common, with a wide-ranging prevalence of 1% to 43% and 2% to 20%, respectively, whereas inflammatory arthritis, myo-

sitis, and polymyalgia rheumatica occur less frequently.[36] Symptoms of inflammatory arthritis include arthralgia, joint stiffness, and joint swelling. Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, may or may not be elevated, and a majority of patients with inflammatory arthritis are seronegative for rheumatoid factor and anti-citrullinated protein antibodies.[37] Similar to inflammatory arthritis, polymyalgia rheumatica presents with arthralgia and joint stiffness, mainly in the hips and shoulders, and can rarely be associated with giant cell arteritis.[38] Moreover, one potentially serious irAE is myositis, which primarily presents as muscle weakness and often appears with other conditions, such as myocarditis or myasthenia gravis.[25,38]

Generally, grade 1 musculoskeletal and rheumatic irAEs are managed with analgesia with nonsteroidal anti-inflammatory drugs or acetaminophen and continuation of immunotherapy. Systemic corticosteroids are reserved for grade 2 or higher toxicities, with the exception of any myositis in patients with muscle weakness and elevated creatine kinase levels as well as giant cell arteritis, in which case corticosteroids should be promptly initiated.[5,6,25]

Renal Toxicities

Acute kidney injury (AKI) directly related to ICIs occurs in approximately 5% of patients treated with combination ICI therapy and 2% of those treated with ICI monotherapy.[39] The median time from ICI initiation to AKI is 14 to 19 weeks, with most individuals developing acute tubulointerstitial nephritis.[39-41] Because there are no specific clinical features in ICI-related AKIs, a renal biopsy can help discern the causes of acute kidney damage, especially if other etiologies are possible.[41] However, the ASCO guidelines advise a renal biopsy only in AKIs that are refractory to corticosteroids or other immunosuppressants.[6]

Holding ICI therapy can be considered for grade 1 AKIs, and systemic corticosteroids are recommended for patients with AKIs of grade 2 or higher or a creatinine increase of 2 or more times baseline.[5,6] Corticosteroids are effective for the majority of cases of ICI-related AKIs. A multicenter study of 138 patients with ICI-related AKIs showed complete, partial, or no kidney recovery in 40%, 45%, and 15% of patients treated with corticosteroids, respectively. Rechallenge with ICIs occurred in 22% of patients, and 23% of these patients developed recurrent ICI-related AKIs.[41] Other immunosuppressive agents, such as infliximab and mycophenolate mofetil, are treatment options for patients with ICI-related AKIs that are refractory to corticosteroids. One case series demonstrated complete or partial recovery in 8 out of 10 patients with corticosteroid-refractory AKIs treated with infliximab.[42] Alternatively, mycophenolate mofetil may be considered given its efficacy in non–ICI-related interstitial nephritis.[25,43]

Nervous System Toxicities

Neurologic irAEs span a broad range of disorders, including myasthenia gravis, Guillain-Barré syndrome (GBS), peripheral neuropathy, aseptic meningitis, encephalitis, cerebral vasculitis, optic neuritis, and transverse myelitis.[44,45] Overall, the incidence of neurologic irAEs is 4% with anti–CTLA-4 inhibitors, 6% with anti–PD-1 inhibitors, and 12% with combination therapy.[46] Neurotoxicities frequently arise in the first 3 months after starting ICIs. Myasthenia gravis can occur rapidly, with a median onset of 29 days, compared with 61 to 80 days for other neurologic events. Myasthenia gravis also confers the highest mortality rate (19%) among neurologic irAEs. The fatality rate is even higher when myasthenia gravis presents concurrently with myocarditis (33%) or with myocarditis and myositis (63%).[44]

As in many irAEs, corticosteroids are the first-line treatment for moderate to severe neurologic events. The ASCO and NCCN guidelines differ in their recommendations regarding permanent discontinuation of ICIs for grade 2 toxicities, except for GBS, where permanent discontinuation of immunotherapy is recommended by both groups.[5,6] Other therapeutic interventions specific to each neurologic irAE are extracted from the management of non–ICI-related events, such as pyridostigmine for myasthenia gravis, IVIG or plasmapheresis for GBS or myasthenia gravis, and empiric antimicrobials for meningitis or encephalitis.[45]

Current Challenges

Corticosteroids, immunosuppressive drugs, and holding ICI therapy are the cornerstones of treating significant irAEs. However, one of the current challenges with irAEs is deciding when and if ICI rechallenge should be attempted in patients with severe irAEs owing to concerns regarding serious or fatal irAE recurrences. Unfortunately, data from prospective trials assessing the safety of rechallenging with ICIs after an initial irAE are lacking. One retrospective study of 40 patients with various tumor types who developed irAEs and were rechallenged with the same anti–PD-1/PD-L1 inhibitors found an occurrence of the same or different irAE in 55% of patients. Specifically, the same irAE occurred in 17 patients (42.5%) and a different irAE occurred in 5 patients (12.5%). Hepatitis (18%), dermatologic toxicities (15%), pneumonitis (14%), colitis (12%), and arthralgia (7.5%) were the most common initial irAEs in this study. The incidence of

second irAEs was 38%, 48%, 14%, and 0% for grade 2, 3, 4 and 5 events, respectively.[47] Additionally, other retrospective studies have demonstrated that even with a class switch from anti–CTLA-4 to anti–PD-1/PD-L1 therapy or vice versa, a proportion of patients still experience irAE recurrence. One study of 67 patients with melanoma who switched from anti–CTLA-4 to anti–PD-1 therapy found recurrent irAEs in 37% of patients. Of the patients with recurring irAEs, 56% had grade 3 or higher events. Only 3% of patients had a recurrence of the same irAEs and 34% experienced de novo irAEs.[48]

Concurrent immunosuppression with ICI rechallenge is a conceivable strategy to mitigate irAE recurrence, albeit with limited data, and requires further examination in prospective studies.[49] One case series (N=5) evaluated retreatment with ICIs in combination with infliximab as secondary prevention for IMDC. All patients tolerated ICI resumption with no recurrence of IMDC symptoms after follow-up of 2.5 to 10.5 months.[50] Another study retrospectively analyzed 102 patients who resumed ICI therapy and found lower IMDC recurrence rates in patients on concurrent maintenance immunosuppression compared with those not receiving immunosuppression (17% vs 37%). Overall survival was not significantly different between the 2 groups.[51] The phase 1b TICIMEL trial studied the approach of combining ipilimumab (Yervoy, Bristol Myers Squibb) and nivolumab (Opdivo, Bristol Myers Squibb) with either certolizumab or infliximab (both anti–TNF agents) as frontline therapy in advanced melanoma. Grade 3 and 4 drug-related AEs occurred in 65% of patients in the certolizumab group and 31% of those in the infliximab group. The objective response rate (ORR) was 60% in the certolizumab cohort and 46% in the infliximab cohort.[52] Compared with historical cohorts, the incidence of severe drug-related AEs and ORR with certolizumab in the TICIMEL study were equivalent, whereas AEs and ORR were less with infliximab.[52,53] Hence, the safety and efficacy of concurrent ICI therapy with immunosuppression as primary or secondary prevention of irAEs needs to be fully elucidated in larger studies. Of significance is understanding the effects of combination ICI and immunosuppression on tumor response and long-term outcomes.

Given the subset of patients who invariably develop irAEs with ICIs, there is a need to identify biomarkers that are associated with the occurrence and recurrence of irAEs. Studies have suggested the predictive value of circulating blood markers, although none of these have been sufficiently validated in the clinical setting.[54-58] One retrospective analyses of 60 patients with advanced non–small cell lung cancer (NSCLC) demonstrated a low baseline neutrophil-to-lymphocyte ratio (odds ratio, 2.2) and platelet-to-lymphocyte ratio (odds ratio, 2.8) to be implicated in irAE occurrence.[58] Meanwhile, a study using a human proteome microarray found specific pretreatment antibody profiles to be associated with the development of severe irAEs.[59] Serum cytokines and chemokines, such as elevated baseline interleukin 17 levels, correlated with the development of grade 3 IMDC in melanoma patients receiving ipilimumab, whereas low baseline interleukin 6 in melanoma patients treated with ipilimumab and high baseline chemokine ligand 5 in NSCLC patients treated with nivolumab corresponded with irAE onset in other studies.[55–57]

Undoubtedly, deciding to initiate or rechallenge with ICI therapy is complicated and ought to account for the inherent characteristics, risks for severity of irAEs, and anticipated clinical benefits of ICI therapy.[60] Close monitoring for irAEs is important in patients receiving ICIs and requires pretreatment assessments as well as routine clinical and laboratory examinations during therapy. One should evaluate for underlying autoimmune diseases, endocrinopathies, or infections before starting ICIs, and consider baseline pulmonary function and cardiac testing in high-risk patients.[5] The general consensus across guidelines supports restarting ICIs after adequate treatment of initial irAEs with some exceptions to certain irAEs where the chance of recurrence poses an extreme risk.[5,6,25,34] Amid the advances and growing use of ICIs in oncology, predictive biomarkers of irAEs and prophylaxis strategies need further exploration and validation.

Conclusion

As indications for ICI therapy expand, so will the number of patients who develop irAEs. Early detection and management are critical, given that irAEs may progress and result in serious or fatal outcomes. Systemic corticosteroids and immunosuppressive agents are at the core of treating moderate to severe irAEs, whereas temporary or permanent discontinuation of ICIs is generally recommended for high-grade events. Challenges with irAEs include prevention, the treatment of corticosteroid-refractory cases, and determining whether ICIs can be safely rechallenged after the occurrence of severe irAEs. Ongoing efforts to find predictive biomarkers of irAEs are paramount to inform treatment plans that optimize the clinical benefits of ICIs while reducing the risks for toxicities.

Disclosures

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