Managing Adverse Effects of Immunotherapy

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Abstract: Remarkable efficacy has been achieved in a variety of cancer types by targeting immune checkpoints. The cytotoxic T-lymphocyte–associated antigen 4 inhibitor ipilimumab, the programmed death 1 inhibitors nivolumab and pembrolizumab, and the programmed death ligand 1 inhibitors atezolizumab, avelumab, and durvalumab are the agents currently approved by the US Food and Drug Administration for the treatment of certain advanced malignancies. These agents mark a departure from both standard cytotoxic chemotherapy and targeted therapy. However, they are associated with a unique set of immune-related adverse events (irAEs), which can manifest as a wide range of autoimmune phenomena. The irAEs can affect any system in the body and in rare cases are life-threatening. It is critical for the practicing medical oncologist to recognize and promptly treat any irAEs that may develop.

Introduction

In the early 1890s, the surgeon William B. Coley hypothesized that infection could lead to tumor regression. He subsequently observed shrinkage of sarcomas after the intratumoral injection of bacteria that came to be known as "Coley's toxins."[1] Soon after, in 1909, the physician and scientist Paul Ehrlich hypothesized that the immune system plays a role in protection from carcinogenesis. The theory was revisited in the 1950s and 1960s by the immunologists Lewis Thomas and F. Macfarlane Burnet, who predicted the finding that immune surveillance eliminates early malignancies.[2] In the 1950s, allogeneic stem cell transplant was shown to induce a graft-versus-leukemia effect in mice,[3] and allogeneic transplants have been used in patients with leukemia since the 1960s. However, it was not until the development of monoclonal antibodies that the theoretical concept was experimentally validated.[4] An extensive and rapid effort was dedicated to the study of immunosurveillance, and the paradigm was subsequently refined in work by Robert Schreiber, who coined the term "cancer immunoediting" to refer to the process.[5,6] This physiologic system consists of 3 distinct phases—elimination, equilibrium, and escape. The escape phase involves the interaction of major histocompatibility complexes, cytokines,

and immunosuppressive molecules in the tumor microenvironment.[7] These insights laid the groundwork for the development of immunotherapy as a treatment for cancer. The first immunotherapeutic agent to be used in clinical practice was high-dose interleukin 2, which was shown to induce complete responses, and rarely long-term remissions, in selected cases of metastatic melanoma and renal cell carcinoma.[8,9] More recently, the role of immune checkpoint molecules, which normally serve to prevent autoimmunity and may be hijacked by tumor cells to allow immune escape, has generated excitement.[10,11] Inhibiting 2 major pathways—first, the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) pathway and second, the programmed death 1/programmed death ligand 1 (PD-1/PD-L1) interaction—by means of various monoclonal antibodies has improved clinical outcomes in subsets of patients across numerous tumor types.[12-15] Such agents include the CTLA-4 inhibitors ipilimumab (Yervoy, Merck) and tremelimumab (in development by AstraZeneca); the PD-1 inhibitors nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck); and the PD-L1 inhibitors atezolizumab (Tecentriq, Genentech), avelumab (Bavencio, EMD Serono/Pfizer), and durvalumab (Imfinzi, AstraZeneca), many of which have been approved by the US Food and Drug Administration (FDA) for the treatment of various advanced cancers.

Owing to the immunomodulatory nature of these agents, their toxicity profiles are distinct from those of typical cytotoxic chemotherapeutic agents.[16,17] Activation of the immune system can lead to off-target attacks on normal tissue, causing signs and symptoms that mimic those of autoimmune disease. Virtually any organ system in the body can be attacked, so that a wide variety of potential immune-related adverse events (irAEs) may occur, depending on which organ is affected.[16]

Factors Affecting Toxicity

The development of irAEs is difficult to predict in individual patients. However, interest is growing in how the gut microbiome affects the efficacy of immunotherapy and the development of irAEs. In mice, high levels of *Bifidobacterium* organisms in the intestines enhanced the antitumor activity of a PD-1 inhibitor.[18] In humans undergoing immunotherapy, greater microbial diversity in the gut and a relative abundance of Ruminococcaceae were found in responders vs nonresponders.[19] Additionally, recent reports have suggested that the presence of certain intestinal bacteria, specifically those of the Bacteroidetes phylum, correlates with resistance to colitis following treatment with a CTLA-4 inhibitor. On the other hand, the presence of microbiota-associated modules involved in bacterial polyamine transport may predict the development of colitis.[20] Other factors, such as baseline elevation of serum interleukin 17,[21] the presence of circulating autoantibodies,[22] and tissue expression of CTLA-4,[23] also may be implicated in the development of irAEs.

Incidence of Adverse Events

The irAEs associated with CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors are similar across the various agents. The incidence and patterns are distinct, however, especially when CTLA-4 inhibitors and PD-1/PD-L1 inhibitors are compared. The rates of irAEs are significantly higher with ipilimumab and other CTLA-4 inhibitors than with PD-1 and PD-L1 inhibitors. A pooled analysis of 325 patients treated with ipilimumab reported total drug-related adverse events in 84.6% of patients, with irAEs in 72.3% and grade 3 or 4 irAEs in 25.2%.[24,25] A dose-dependent effect has been observed; rates of irAEs with ipilimumab are significantly higher at a dose of 10 mg/kg and lower at doses of 0.3 mg/kg and 3 mg/kg.[25] Toxicity rates are lower with the PD-1/PD-L1 agents than with CTLA-4 inhibitors; grade 3 or 4 irAEs have been observed in 10% to 30% of patients.[25] The highest incidence of all irAEs has been seen in trials combining CTLA-4 inhibitors with PD-1 or PD-L1 inhibitors, with rates of any irAE as high as 95% and a 55% incidence of grade 3 or 4 events.[26]

Timing of Adverse Events

No markers are currently used in the clinic to predict in whom or when an irAE may develop, but some patterns are emerging related to the timing of irAEs. Most of the published data specifically on irAEs are obtained from the experience with ipilimumab in melanoma.[25,27] In a detailed safety analysis of a phase 3 trial of ipilimumab for advanced melanoma, it was found that the vast majority of irAEs occurred within 12 weeks after initial ipilimumab dosing, during the induction phase.[25] Skin reactions to ipilimumab tend to be early, occurring at an average of 2 to 3 weeks after the initiation of therapy. Diarrhea, colitis, and hepatitis occur on average after 6 to 7 weeks.[27] Hypophysitis was reported to occur at a median of 8 to 9 weeks after the start of ipilimumab therapy in a retrospective institutional study.[27,28] The timing of the other major autoimmune endocrinopathies, thyroiditis and hypothyroidism, is more variable and can be idiosyncratic, with the time of onset ranging from within 5 months to up to 5 years after ipilimumab induction therapy.[25] Uveitis, a rare phenomenon occurring in fewer than 1% of patients, occurs at a median of 8 weeks.[29] Nephritis, which is even

Table. Selected Toxicities of Anti–PD-1/PD-L1 and Suggestions for Treatment

	Definition	Incidence	Treatment
Colitis	Grade 1: increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline Grade 2: increase of 4-6 stools per day over baseline; moderate increase in ostomy output; mucus or blood in stool Grade 3: increase of ≥7 stools per day over baseline; incontinence, severe increase in ostomy output, abdominal pain Grade 4: life-threatening sequelae of increased stool output	Anti–PD-1 - Any grade: 8% - Grade 3-4: 1% Anti–CTLA-4 - Any grade: 44% - Grade 3-4: 18% Combination - Any grade: 12%	Grade 1: - Continue agent with close follow-up for changes/progression; workup for other causes Grade 2: - Hold agent - Workup for other causes - Initiate prednisone 1 mg/kg/d if no improvement after 2-3 days and taper slowly - Refer to SITC/ESMO guidelines for rechallenge Grade 3-4: - Hold agent - Sigmoidoscopy - Rule out infectious causes - IV administration of agent equivalent to prednisone 1-2 mg/kg/d (consider PJP and GI prophylaxis) - Refer to SITC/ESMO guidelines for cases refractory to rechallenge: infliximab 5 mg/kg q2wk
Pneumonitis	Grade 1: asymptomatic, may show on imaging Grade 2: symptomatic Grade 3: severe symptoms impairing ADLs and requiring oxygen Grade 4: life-threatening	Anti–PD-1 - Any grade: 5% - Grade 3-4: 1% Anti–CTLA-4 - Any grade: <1% Combination - Any grade: 10%	Grade 1: - Hold agent until resolution on repeated imaging Grade 2: - Hold agent - Bronchoscopy with BAL - Initiate prednisone 1 mg/kg/d with slow taper after improvement - Consider rechallenge Grade 3-4: - Permanently discontinue agent - Hospitalize, consider ICU - Bronchoscopy - Rule out infectious causes - IV methylprednisolone 2 mg/kg/d (consider GI and PJP prophylaxis) - Refractory cases: infliximab 5 mg/kg q2wk; consider adding cyclophosphamide, mycophenolate mofetil, and IVIG
Hepatitis	Grade 1: AST/ALT between ULN and 3 × ULN, or bilirubin between ULN and 1.5 × ULN Grade 2: AST/ALT between 3 and 5 × ULN, or bilirubin between 1.5 and 3 × ULN Grade 3: AST/ALT between 5 and 20 × ULN, or bilirubin between 3 and 10 × ULN Grade 4: AST/ALT >20 × ULN, or bilirubin >10 × ULN	Anti–PD-1 - Any grade: 5% Anti–CTLA-4 - Any grade: 3%-10% Combination - Any grade: 25%-30%	Grade 1: - Continue agents - Monitor laboratory tests weekly and if stable, increase monitoring interval Grade 2: - Hold agent until resolution - Rule out other causes - Initiate prednisone 0.5-1.0 mg/kg/d with slow taper - Resume agent when grade ≤1 Grade 3-4: - Permanently discontinue agent - IV administration of agent equivalent to prednisone 1-2 mg/kg/d - Refractory cases: consider mycophenolate mofetil or antithymocyte globulin

(Table continued on next page)

Table. *(Continued)* Selected Toxicities of Anti–PD-1/PD-L1 and Suggestions for Treatment

	Definition	Incidence	Treatment
Thyroid disorder	Hyperthyroidism: low TSH, elevated free T_4 Hypothyroidism: high TSH, low free T_4, or TSH >10 with normal free T_4 Subclinical hypothyroidism: high TSH, normal free T_4	Anti–PD-1 - Any grade: 5%-10% Anti–CTLA-4 - Any grade: 1%-5% Combination - Any grade: 20%	Symptomatic hyperthyroidism: - Beta blocker or methimazole - Hold agent only if patient clinically unwell Hypothyroidism: - Levothyroxine supplementation - Continue agent unless severe symptoms
Hypophysitis	Pituitary inflammation with depressed pituitary axis hormones (eg, TSH, FSH/LH, GH, ACTH)	Anti–PD-1 - Any grade: 0.5% Anti–CTLA-4 - Any grade: 1%-6% Combination - Any grade: 8%	MRI pituitary protocol to confirm and rule out another process - IV methylprednisolone 1 mg/kg for severe mass effect symptoms or severe hypoadrenalism - Oral prednisone 0.5-1.0 mg/kg/d for moderate symptoms - Replace cortisol and thyroxine as needed - Withhold agent only for moderate to severe symptoms
Skin toxicity	Grade 1: rash <10% BSA Grade 2: rash 10%-30% BSA, affects IADLs Grade 3: rash >30% BSA, affects ADLs Grade 4: life-threatening rash (ie, SJS)	Anti–PD-1 - Any grade: 15% Anti–CTLA-4 - Any grade: 24% Combination - Any grade: 40%	Grade 1-2: - Continue therapy, topical emollients, oral antihistamines, mild topical corticosteroids - Consider dermatology referral Grade 3-4: - Supportive care for severe skin rash - Systemic equivalent of prednisone 0.5-2.0 mg/kg/d - Withhold offending agent - Urgent dermatology consult

Source: Adapted from European Society for Medical Oncology (ESMO) and Society for Immunotherapy of Cancer (SITC) guidelines in Haanen JBAG et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142 and Puzanov I et al. *J Immunother Cancer*. 2017;5(1):95.[49,54]

ACTH, adrenocorticotropic hormone; ADLs, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAL, bronchoalveolar lavage; BSA, body surface area; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ESMO, European Society for Medical Oncology; free T_4, free thyroxine; FSH, follicle-stimulating hormone; GH, growth hormone; GI, gastrointestinal; IADLs, instrumental activities of daily living; ICU, intensive care unit; IV, intravenous; IVIG, intravenous immunoglobulin; LH, luteinizing hormone; MRI, magnetic resonance imaging; PD-1, programmed death 1; PJP, *Pneumocystis jiroveci* pneumonia; q2wk, every 2 weeks; SITC, Society for Immunotherapy of Cancer; SJS, Stevens-Johnson syndrome; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

less common with CTLA-4 antagonists than with anti–PD-1 therapy, has been reported to occur at between 6 and 12 weeks.

For PD-1/PD-L1 inhibitors, the published data are even sparser. In an abstract presented at the 2015 American Society of Clinical Oncology Annual Meeting, the authors reported a pooled analysis of 576 patients receiving nivolumab as part of 4 studies of melanoma, with 49% experiencing an irAE.[30] Skin irAEs occurred at a median of 5.0 weeks, with a wide range of onset times (0.1-57.0 weeks); gastrointestinal irAEs occurred at a median of 7.3 weeks (range, 0.1-37.6), hepatic irAEs at a median of 7.7 weeks (range, 2.0-33.8), pulmonary irAEs at a median of 8.9 weeks (range, 3.6-22.1), endocrine irAEs at a median of 10.4 weeks (range, 3.6-46.9), and renal irAEs at a median of 15.1 weeks (range, 3.9-26.4).[30] Thus, in general, the overall pattern of the timing of irAEs with nivolumab was similar to that previously reported with ipilimumab. The median onset times of certain irAEs with the combination of nivolumab and ipilimumab were also found to be similar in a combined analysis of melanoma trials, with skin irAEs occurring at a median of 3.1 weeks and renal irAEs at a median of 16.3 weeks.[31] Patterns observed in clinical practice suggest that irAEs can occur at any time during treatment with these agents and even after the cessation of therapy, so there should be a low threshold for suspicion when any patient presents with new symptoms regardless of the time frame.

Specific Adverse Events

Specific immune-related adverse events associated with immunotherapy include dermatitis, colitis, pneumonitis, hepatitis, hypophysitis, thyroiditis, adrenalitis, and myocarditis.

Dermatitis

One of the most common irAEs associated with immunotherapy is skin rash. Up to 50% of patients treated with ipilimumab and 30% to 40% of patients treated with PD-1 agents experience rash.[32] This most commonly manifests as dermatitis characterized by dry skin with mild erythema; a lymphocytic infiltrate is seen on microscopic examination after skin biopsy.[33] However, the skin manifestations are highly variable and may include papular or nodular components, scaling, mucosal erosion, and lichenoid features.[34] Autoimmune blistering disorders such as bullous pemphigoid have been observed,[35] as has extensive alopecia.[36] Stevens-Johnson syndrome and toxic epidermal necrolysis are rare and life-threatening toxicities that have been described in case reports.[37,38] Most dermatologic manifestations can be adequately managed with topical corticosteroids such as betamethasone 0.1% and hydrocortisone 1%, or with topical urea-based therapies.[39] Itching is a common complaint, and antipruritic agents are often helpful. Dose interruptions or modifications are not required if less than 50% of the total body surface area is affected. Skin biopsy should be considered for cases not responsive to topical corticosteroids. Severe irAEs such as Stevens-Johnson syndrome and toxic epidermal necrolysis require inpatient admission, discontinuation of the offending agent, and the intravenous administration of high-dose corticosteroids (1-2 mg of prednisone per kilogram or its equivalent), converted to oral administration once symptoms are controlled, with a long taper. Reintroduction of the offending agent in patients with severe toxicities should be avoided.

Colitis

One of the more common and potentially life-threatening irAEs is colitis.[40] Patients invariably present with diarrhea, which is frequently watery and can rapidly lead to dehydration. Colitis can be more difficult to diagnose in patients with ostomies owing to soft or watery stool at baseline. In patients treated with ipilimumab, the incidence of diarrhea of any grade was 44%, and grade 3 or 4 diarrhea occurred in 18%.[41] Observed rates are lower with PD-1/PD-L1 inhibitors, with diarrhea of any grade occurring in 8% and grade 3 or 4 diarrhea in 1% of patients.[12,40] Bowel perforation has been described but is rare, occurring in fewer than 1% of cases.[42] During initial management, it is imperative to confirm the diagnosis and rule out alternative causes of diarrhea. Ideally, sigmoidoscopy should be performed as soon as the diagnosis is considered for any patient with grade 2 or higher diarrhea, or if significant abdominal pain or hematochezia is present. A stool specimen should be tested for *Clostridium difficile*, and a stool culture should be obtained to evaluate for bacterial infection. For patients with grade 1 colitis, treatment may be continued; once grade 2 toxicity develops, treatment should be interrupted. Both grade 1 and grade 2 toxicity can initially be managed with antimotility agents and consideration of budesonide (9-12 mg by mouth daily).[43] Prophylactic budesonide is not recommended because lack of efficacy was demonstrated in a randomized phase 2 clinical trial in a cohort of 115 patients treated with ipilimumab.[44] If symptoms persist or progress, systemic corticosteroids may be required. Grade 3 or 4 colitis should be treated with high-dose corticosteroids (1 mg of prednisone per kilogram or the equivalent), preferably given intravenously. Once symptoms have resolved to grade 1, corticosteroids can be converted to the equivalent dose of an oral agent. Per recent guidelines from the American Society of Clinical Oncology, corticosteroid therapy should be tapered gradually over a period of 4 to 6 weeks.[45] Diarrhea that is refractory to high-dose corticosteroids has been managed successfully with anti–tumor necrosis factor alfa agents (eg, infliximab at 5 mg/kg given every 2 weeks until resolution).[46] Before starting infliximab, patients should be tested for hepatitis B as well as for tuberculosis with a purified protein derivative skin test or interferon gamma release assay (QuantiFERON-TB Gold); regular testing of liver function is warranted while this therapy is continued.

Pneumonitis

Pneumonitis is relatively uncommon, occurring in 5% of patients treated with PD-1 inhibitors and 10% of those treated with the combination of a PD-1 inhibitor and a CTLA-4 inhibitor.[47] Grade 3 or 4 pneumonitis was observed in fewer than 1% of patients receiving a PD-1 inhibitor and has been fatal in rare cases. Unlike that of colitis, the clinical presentation of pneumonitis is highly variable and can be quite subtle. For example, patients can present with a dry cough and mild dyspnea on exertion, or with hypoxia noted only when vital signs are measured in the clinic. Many patients may be asymptomatic but found to have new abnormalities on chest radiography or computed tomography when these are ordered for routine re-staging. Rarely, patients present in extremis with hypoxic respiratory failure. Adding to the difficulty in diagnosis, the radiographic findings can also be subtle and variable; they may mimic those of cryptogenic organizing pneumonia, nonspecific interstitial pneumonia, acute interstitial pneumonia, or conditions with infectious etiologies.[48] An experienced radiologist and a high level of suspicion are required for the diagnosis.

When pneumonitis is suspected, the workup should include computed tomography of the thorax without contrast. Ideally, bronchoscopy with biopsy and washings should be performed to evaluate for an infectious cause of pneumonitis, such as *Pneumocystis jiroveci* pneumonia

(PJP) or respiratory syncytial virus pneumonia; however, this invasive procedure may not always be feasible. Even mild cases can progress rapidly; thus, administration of the offending agent should be halted during the workup.[49] Grade 1 pneumonitis can be managed with a dose interruption for 2 to 4 weeks. Grade 2, 3, or 4 pneumonitis should be treated with the prompt initiation of high-dose corticosteroids and 1 to 2 mg of prednisone per kilogram or the equivalent; in addition, the agent should be withheld. As with colitis, the intravenous administration of prednisone is preferred initially, with a long duration and slow taper of the treatment.[45] Infliximab with or without cyclophosphamide can be considered for refractory cases, although the effect of these agents on survival is uncertain.[47]

Hepatitis

Owing to the frequent laboratory monitoring of patients receiving antineoplastic agents, a mild elevation in both alanine aminotransferase and aspartate aminotransferase levels may incidentally be identified on routine blood testing, with or without an elevated bilirubin level. The incidence of true hepatotoxicity is low: 3% to 10% of patients treated with CTLA-4 inhibitors[50,51] and 5% of patients treated with PD-1 inhibitors.[52] The workup should include laboratory testing for viral hepatitis and an evaluation for autoimmune hepatitis with antinuclear antibody and anti–smooth muscle antibody. Imaging, if obtained, may show hepatomegaly with periportal edema or adenopathy.[53] The immunotherapeutic agent may be continued for patients with grade 1 toxicity,[54] but in those with grade 2 hepatitis, the offending agent should be withheld and liver function tests repeated frequently until resolution. Grade 3 or 4 hepatitis should be managed with the initiation of high-dose corticosteroids (1-2 mg of prednisone per kilogram or the equivalent) and frequent monitoring via liver function tests; the offending agent should be permanently discontinued. In cases that are refractory to corticosteroid treatment, mycophenolate mofetil[55] or antithymocyte globulin[27,56] are the preferred agents because infliximab can cause hepatotoxicity and is contraindicated.

Hypophysitis

Hypophysitis—inflammation of the pituitary gland—is relatively rare, occurring in 1% to 6% of patients treated with CTLA-4 inhibitors[27,42] and 0.5% of patients treated with PD-1 inhibitors.[57] The clinical syndrome consists of headache and fatigue, although nausea, vertigo, visual changes, and weakness have also been reported.[27] Diagnostic evaluation should include magnetic resonance imaging of the brain with and without contrast, which often demonstrates a swollen and enhancing pituitary gland.[58] Laboratory testing be sent to evaluate levels of thyroid-stimulating hormone (TSH), free thyroxine (free T_4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), and adrenocorticotropic hormone (ACTH). The cortisol level should be measured to evaluate for secondary adrenal insufficiency, and the testosterone level should be assessed in men. Initial management consists of high-dose corticosteroids (1-2 mg of prednisone per kilogram daily or the equivalent), as complete resolution of the irAE may be possible in some cases. Most patients require long-term supplementation of the deficient hormone(s): thyroid hormone, cortisol, and/or testosterone. Consultation with an endocrinologist is helpful for selection of the initial dose and titration to effect.

Thyroiditis

Thyroid disease is one of the most common irAEs; hypothyroidism is encountered most frequently, but thyroiditis and Graves disease have also been described.[59] Of the irAEs, thyroid disease is often the most straightforward to diagnose and manage. The incidence is 8% to 13% for PD-1 inhibitors, 2% to 8% for CTLA-4 inhibitors, and 15% to 25% for the combination.[28,57,60] Patients most often present with fatigue; rarely, they will present with florid hypothyroidism and have symptoms of constipation, weight gain, and peripheral edema. It is recommended to test thyroid function before and regularly during treatment with an immunotherapeutic agent; testing should also be done at intervals after the completion of therapy and per the medication package insert to monitor for subclinical disease.

In contrast to other irAEs, a diagnosis of hypothyroidism does not require discontinuation of the offending agent unless grade 4 toxicity occurs. The mainstay of treatment is thyroid hormone replacement. Subclinical disease, defined as an elevated TSH level with a normal free T_4 level, does not require treatment until the free T_4 drops below the normal range. Typical doses of thyroid hormone replacement are similar to those used to treat primary hypothyroidism, with an initial dose of levothyroxine of 1.6 µg/kg/d in young patients and lower doses (25-50 µg/d) in older patients or those with coronary artery disease. The serum TSH level should be monitored for 4 to 6 weeks after the initiation of therapy and the dose of levothyroxine titrated by 12 to 25 µg/d.[61] Consultation with a specialist in endocrinology is helpful. Corticosteroids are not indicated except for grade 4 toxicity, given that destruction of the thyroid gland is generally not reversible. Beta blockade may be beneficial if a patient presents initially with an acute hyperthyroid phase. Graves disease should be managed with methimazole, propylthiouracil, or radioiodine ablation in consultation with an endocrinologist.

Adrenalitis

Patients in whom primary adrenal insufficiency develops as a result of immunotherapeutic agents can present with fatigue, hyperkalemia, hyponatremia, and in severe cases severe hypotension and distributive shock. The incidence ranges from 0.6% to 2.6% across all agents.[57] Random testing of the serum cortisol level can be suggestive of the diagnosis, but ACTH stimulation testing, if feasible, is the gold standard. Management consists of dose interruption, the initiation of a stress-dose corticosteroid (eg, 15 mg of hydrocortisone in the morning and 10 mg at night) and a mineralocorticoid (eg, 0.1 mg of fludrocortisone daily), and the intravenous administration of fluids if hypotension is present.[57] As in patients with thyroiditis, the loss of gland function may be irreversible, and thus re-initiation of the offending agent is reasonable once symptoms are controlled.

Myocarditis

A recent report described 2 patients treated with the combination of nivolumab and ipilimumab, each of whom presented in cardiogenic shock. Both incidents were fatal despite aggressive management. At autopsy, a lymphocytic infiltrate of the myocardium with CD8-positive T cells was found in both patients, a finding highly suggestive of myocarditis due to immunotherapy.[62] Patients in whom myocarditis develops should be monitored closely for arrhythmias or conduction abnormalities and treated with supportive care and high-dose intravenous corticosteroids as previously outlined.

Additional Considerations

Flare of a pre-existing rheumatologic or other autoimmune disorder, fatigue, and infusion reactions are additional considerations with immunotherapy, as is the question of whether transplant recipients of solid organs and hematopoietic stem cells can be safely treated with these agents.

Flare of a Pre-existing Autoimmune Disorder

The vast majority of clinical trials evaluating checkpoint inhibitors excluded patients with pre-existing autoimmune diseases. However, as the agents have moved into clinical practice, experience has been acquired in treating patients with pre-existing psoriasis, rheumatoid arthritis, or inflammatory bowel disease. A retrospective review of 30 patients who had pre-existing autoimmune disease and melanoma treated with ipilimumab found that 50% had no flare or irAEs; the overall response rate was 20%.[63] A second retrospective review, of 52 patients who had pre-existing autoimmune disorders and were treated with PD-1 inhibitors, reported disease flare requiring immunosuppression in 38% of them.[64] Thus, a pre-existing autoimmune condition need not be a contraindication to treatment with these agents, so long as the possibility of disease flare is discussed with the patient. Collaboration with a specialist, such as the patient's rheumatologist, gastroenterologist, or neurologist, is imperative for management in such cases.

Treatment of Transplant Recipients

Recipients of solid organ transplants require special consideration. Immunotherapy in such patients may lead to graft rejection or failure. Alhamad and colleagues reported on the use of ipilimumab and pembrolizumab in a kidney transplant recipient in whom unresectable melanoma had developed. The patient had worsening renal failure and eventually required hemodialysis.[65] Lipson and colleagues reported a similar case of graft failure in the recipient of a kidney transplant who was being treated with nivolumab for metastatic squamous cell carcinoma of the skin.[66] In contrast, Barnett and colleagues described a kidney transplant recipient who was treated with nivolumab for metastatic adenocarcinoma of the duodenum and experienced no end-organ toxicity.[67] There remains a paucity of data regarding the use of these agents in the recipients of solid organ transplants.

Another population of patients requiring special consideration, because of concerns about worsening graft-versus-host disease (GVHD), includes those who have received an allogeneic hematopoietic stem cell transplant (HSCT). Haverkos and colleagues described 31 patients with lymphoma who were treated with PD-1 inhibitors following allogeneic HSCT. Treatment-emergent GVHD developed in a total of 55% of the patients, with grade 3 or 4 GVHD in 9 patients. The condition was refractory to treatment in 15 patients. Amazingly, the overall response rate to PD-1 inhibitors was 77%.[68] Thus, the use of immunotherapy after allogeneic HSCT is efficacious but may cause severe GVHD.

Rare Immune-Related Adverse Events

Immunotherapy agents can cause an autoimmune attack in any organ or organ system in the body. Reports in the literature have documented type 1 diabetes,[69] nephritis,[70] pancreatitis,[71] Guillain-Barré syndrome,[72] vasculitis,[73] myasthenia gravis,[74] encephalitis,[75,76] central nervous system demyelination,[77] inflammatory arthritis,[78] and immune-related cytopenias[79] associated with the use of immunotherapy. These irAEs should be managed by withholding the offending agent and treating the patient with a prolonged course of high-dose corticosteroids. The decision to restart treatment with the checkpoint inhibitor should depend on the severity of the irAE. Although the incidence of these diseases is quite low, the clinician should remain vigilant in picking up on rare signs and symptoms that may represent irAEs.

Fatigue

Fatigue has been a remarkably common irAE across multiple trials, with rates approaching 20%.[12] The cause is not known, and the condition appears unlikely to be immune-mediated. Patients experiencing fatigue should undergo testing to rule out reversible causes (eg, anemia, hypothyroidism, and hypocortisolism). They should be screened for depression, which can manifest as fatigue and anhedonia. As with chemotherapy-induced fatigue, exercise should be recommended; evidence supports its ability to relieve symptoms.[80]

Infusion Reactions

Infusion reactions are uncommon with most checkpoint inhibitors, occurring in approximately 1% of patients. The exception is avelumab, which is an immunoglobulin G1 monoclonal antibody directed against PD-L1; unlike the other PD-1 and PD-L1 inhibitors, it induces antibody-dependent cell-mediated cytotoxicity. This agent carries a significantly higher risk for infusion reaction, reaching 22%.[81] Thus, the package insert for avelumab specifies that an antihistamine should be given as premedication. Severe reactions should be managed with corticosteroids, dual antihistamine blockade, and acetaminophen per institutional standards.

Immune-Related Adverse Events as Predictors of Response to Treatment

An intriguing aspect of irAEs is that their development may confirm immune activation secondary to the therapy being administered. Therefore, many have raised the question of whether irAEs are predictive of or correlate with response to immunotherapeutic agents. Most published data come from the experience with ipilimumab in melanoma. In a pooled analysis of 3 phase 2 clinical trials of patients with melanoma who received ipilimumab, a trend toward improved disease control rates (34%-43%) was noted in those with irAEs of at least grade 2 compared with those who experienced no or only mild irAEs (20%-24%).[82] In an analysis of patients with melanoma receiving ipilimumab in combination with vaccines in 2 separate clinical trials, the development of an irAE was significantly associated with the likelihood of a response, and all 3 complete responses occurred in patients who experienced irAEs.[83] Other studies that specifically addressed cutaneous adverse events in patients with melanoma have likewise shown an association between irAEs and response.[84] However, the data are not uniform: a retrospective analysis of all patients with melanoma receiving standard-of-care ipilimumab therapy at Memorial Sloan Kettering Cancer Center failed to find an association between the occurrence of irAEs and overall survival or time to treatment failure.[85]

With anti–PD-1 agents, there is also a question regarding the association between the development of irAEs and response. In a retrospective analysis of patients with melanoma receiving nivolumab, a statistically significant improvement in overall response rates was observed in the patients who experienced irAEs of any grade compared with those who did not (48.6% vs 17.8%). There was no difference in median progression-free survival, however.[86] In another study, which pooled data from patients who had melanoma treated with nivolumab with or without peptide vaccine, the occurrence of irAEs of any grade was associated with a statistically significant benefit in overall survival. When subset analyses were performed, cutaneous irAEs were most strongly associated with benefit; other irAEs (eg, endocrinopathy, colitis, and pneumonitis) did not correlate with the survival rate.[87] In an analysis of patients with non–small cell lung cancer, renal cell carcinoma, or head and neck squamous cell carcinoma receiving anti–PD-1 monotherapy at Fox Chase Cancer Center, only low-grade irAEs were associated with a higher overall response rate or longer time to next treatment or death. This study found a 3-fold likelihood of treatment response in those who experienced a low-grade irAE.[88] One criticism of such retrospective analyses is that they are subject to bias because irAEs are more likely to develop in long-term responders, who have greater drug exposure. A Japanese study of patients receiving nivolumab, which used a 6-week landmark analysis for irAEs, found that the development of irAEs was positively associated with progression-free survival and overall survival. Prospective data are required to determine whether irAEs may actually be predictive of a response.[89]

Complications of Long-term Corticosteroid Use

Patients who have irAEs subsequently treated with high-dose corticosteroids for prolonged periods are at high risk for various toxicities: opportunistic infections (eg, PJP), stomach ulcers, hyperglycemia, fluid retention, and corticosteroid myopathies. Rare opportunistic infections have been reported, such as *Aspergillus fumigatus* pneumonia in a patient treated with systemic corticosteroids and infliximab for an irAE due to ipilimumab.[90] According to the American Thoracic Society guidelines, patients treated with a dose equal to or greater than 20 mg of prednisone (or its equivalent) daily for 1 month or longer should be prescribed PJP prophylaxis (eg, sulfamethoxazole/trimethoprim, dapsone, atovaquone, or pentamidine).[91] An acid suppressant (histamine$_2$ antagonist or proton pump inhibitor) can be considered to prevent gastritis.[92] Adrenal insufficiency may result, which can complicate corticosteroid discontinuation and necessitate a prolonged

taper. Elderly patients may also be at risk for osteoporosis depending on the length of corticosteroid use; courses longer than 90 days have been associated with increased risk for fracture.[93]

Conclusion

Significant advances have been made in our understanding of the role of the immune system in the development of cancer, culminating in the development of the checkpoint inhibitors. These agents augment the immune destruction of tumor cells and provide significant clinical benefit for patients with a variety of cancer types. The irAEs associated with immunotherapy are distinct from those of cytotoxic chemotherapy. Immune attack can occur in any body organ, leading to sometimes rare and life-threatening complications. The presentations are highly variable, and a high index of suspicion for these irAEs is paramount. Management generally consists of withholding the offending agent and administering high-dose corticosteroids for grade 3 or 4 toxicity. Hormone replacement may be indicated in cases of thyroiditis, hypophysitis, or adrenalitis. Efficacy does not appear to be compromised when corticosteroids are used, and re-treatment with the agent in question may be possible for patients who have mild irAEs. Excellent expert guidelines from various professional organizations have recently been published to help guide the management of these novel toxicities.[49,54]

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