Review Article

Identifying and managing the adverse effects of immune checkpoint blockade

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Abstract: Immunotherapy has revolutionized the field of oncology. By inhibiting the cytotoxic T-lymphocyte-associated protein (CTLA-4) and programmed death-1 (PD-1) immune checkpoint pathways, multiple studies have demonstrated greatly improved survival in locally advanced and metastatic cancers including melanoma, renal, lung, gastric, and hepatocellular carcinoma. Trials in other malignancies are ongoing, and undoubtedly the number of drugs in this space will grow beyond the six currently approved by the Food and Drug Administration. However, by altering the immune response to fight cancer, a new class of side effects has emerged known as immune-related adverse events (irAEs). These adverse events are due to overactivation of the immune system in almost any organ of the body, and can occur at any point along a patient's treatment course. irAEs such as endocrinopathies (thyroiditis), colitis, and pneumonitis may occur more commonly. However, other organs such as the liver, heart, or brain may also be affected by immune overactivation and any of these side effects may become life threatening. This review presents an approach to promptly recognize and manage these toxicities, to hopefully minimize morbidity and mortality from irAEs.

Keywords: Checkpoint inhibitors; immunotherapy; toxicities

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Introduction

Immune evasion is one of the hallmarks of cancer growth; by avoiding detection malignant cells are able to spread uninhibited (1). Oncologists have long sought to harness the immune system to fight cancer, dating back to the late 19th century when intra-tumoral injections of live bacteria were noted to induce a durable response (2). With the more recent discovery and success of targeting the cytotoxic T-lymphocyte-associated protein (CTLA-4) and programmed death-1/programmed death ligand-1 (PD-1/PD-L1) pathways, immune checkpoint inhibitors have gained widespread use as trials continue to demonstrate dramatic improvements in survival (3-6). The anti-CTLA-4 antibody ipilimumab was approved in 2011 for the treatment of unresectable melanoma (7). Since that time, there has been an influx into the market of drugs targeting both pathways, including the approved PD-1/PD-L1 inhibitors nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab as well as the still investigational CTLA-4 inhibitor tremelimumab, and others are in development (8).

Unlike traditional chemotherapy, the toxicities of these medications are wholly different and continue to be defined. Despite the general consensus that checkpoint inhibitors are more easily tolerated than chemotherapy, their unique side effect profile is important to recognize given the possibility of life threatening adverse events (9). Stimulating the immune system to fight cancer can lead to the overactivation of T-lymphocytes in a target organ,

causing inflammation and a constellation of toxicities that have become known as immune-related adverse events (irAEs). The incidence of any grade irAE in clinical trials is reportedly is as low as 15% to as high as 90%, and toxicities severe enough to require drug discontinuation and the initiation of immunosuppressive medications occur 10–55% of the time (9,10). The reason for this huge variability may be due to the lack of agreed upon uniform definitions as to what constitutes a particular irAE, although recently there have been attempts to standardize grading and criteria for irAEs (11). Possible underreporting of toxicities within clinical trials may also lead to heterogeneity in the reported incidence of these adverse events (12). While overall the rate of irAEs is lower in patients treated with PD-1/PD-L1 inhibitors than the anti-CTLA4 antibody ipilimumab, trials are increasingly investigating the potential of using these drugs in combination, which has been shown to be more toxic than targeting either pathway alone (13). Therefore, recognizing and treating irAEs are paramount, and it is the aim of this review to highlight an approach to the toxicities of checkpoint inhibitors.

Pulmonary toxicities

Pneumonitis is the dreaded pulmonary complication of checkpoint inhibitors. Presentations can range from asymptomatic changes seen on imaging, to cough, mild dyspnea, or severe shortness of breath with life threatening hypoxia. In clinical trials of nivolumab, the median time from drug initiation to the development of pneumonitis was 2.6 months, although symptoms were seen in as little as 2 weeks or as late as 11.5 months after starting therapy and may occur even later (14). The incidence of pneumonitis in trials of PD-1/PD-L1 inhibitors is roughly 5%, with grade 3, 4, or 5 reactions occurring <2% of the time (11). While symptomatic pneumonitis occurs only between 1% and 5% of the time in patients treated with CTLA-4 inhibitors, combination PD-1/PD-L1 and CTLA-4 inhibition results in a significant increase of pneumonitis to roughly 10% (9,15).

Given the potentially fatal nature of this toxicity, pneumonitis must be recognized promptly (16). Imaging characteristics of immunotherapy-induced pneumonitis on CT are non-specific and vary widely, from a pattern consistent with cryptogenic organizing pneumonia most commonly, to acute respiratory distress syndrome (ARDS), non-specific interstitial pneumonia (NSIP), and hypersensitivity pneumonitis (HP) (14,17). Therefore, one must maintain a high index of suspicion in patients with even subtle pulmonary complaints.

Treatment of pneumonitis depends on the grade. All patients with this complication should establish care with a pulmonologist. Grade I pneumonitis, in which patients are asymptomatic and pulmonary inflammation is detected by imaging or on clinical exam can be managed simply by withholding the drug. Close follow-up is recommended until documented resolution, at which point re-challenging the patient with the checkpoint inhibitor is reasonable if warranted. Patients are symptomatic with grade II pneumonitis, and steroids should be initiated at a dose of 1 mg/kg/day of methylprednisolone or its oral equivalent (11). A bronchoscopy with lavage to assess for infection should be considered in any patient with pneumonitis grade II or higher given that imaging findings are often indistinguishable between checkpoint inhibitor-related pneumonitis and various pulmonary infections (18). Steroids must be tapered slowly over weeks as abrupt withdrawal of immunosuppression may cause pneumonitis to flare. Re-challenge with a checkpoint inhibitor may be considered if complete resolution of inflammation is documented and steroids are able to be tapered to <10 mg/day. Grade III and IV reactions warrant urgent hospitalization as patients are symptomatic and often hypoxic. They may decline rapidly, and intubation should not be delayed if necessary. Steroids should be given at doses of 2–4 mg/kg/day of methylprednisolone. If there is no improvement within 48 hours, additional immunosuppression with infliximab, mycophenolate mofetil, or cyclophosphamide should be considered (10,18). The offending checkpoint inhibitor should be permanently discontinued in the event of a grade III or IV adverse reaction.

Sarcoidosis is another pulmonary manifestation described as a consequence of therapy with checkpoint inhibitors (10,17). Imaging findings include hilar lymphadenopathy, but a transbronchial biopsy showing non-caseating granulomas is recommended to confirm the diagnosis. Once histologically confirmed, management of immunotherapy-related sarcoidosis is extrapolated from guidelines for patients with non-immunotherapy related sarcoidosis. Patients should obtain baseline pulmonary function tests (PFTs) and a baseline CT as well as a 6-minute walk test. Resting O_2 saturation should be monitored frequently. Patients with hypercalcemia, progressive symptoms, declining lung function, or evolving radiographic changes should all initiate treatment. Extrapulmonary manifestations may also be seen including cardiac sarcoidosis and ocular

sarcoidosis, therefore a baseline electrocardiogram (EKG) and eye exam should be obtained, and a pulmonology referral should be made early (11).

Gastrointestinal toxicities

Gastrointestinal toxicities of immune checkpoint blockade include diarrhea, colitis, and hepatitis, and can be life threatening. Diarrhea is one of the more frequently reported adverse events in trials of checkpoint inhibitors, and is more commonly associated with the CTLA-4 inhibitors. When ipilimumab was used at a dose of 3 mg/kg, the rate of grade 3 or 4 diarrhea requiring hospitalization was roughly 5% (19,20). When doses of 10 mg/kg were used, grade 3 or 4 diarrhea occurred in 10–15% of patients and similarly, trials with tremelimumab saw 15% of patients develop diarrhea requiring hospitalization (7,21,22). PD-L1 inhibitors are notably less toxic in terms of diarrhea, with grade 3 or higher symptoms occurring roughly 1–2% of the time (4,5). Grade 1 diarrhea (<4 bowel movements/day) can typically be managed as an outpatient with anti-motility agents including loperamide, diphenoxylate/atropine, and tincture of opium, as well as increasing fiber intake. However, this should only be done after checking for infection, including testing for *clostridium difficile*, as well as other common bacterial and parasitic pathogens, and only starting anti-motility agents if the work-up is negative (11). The question of enteric steroid prophylaxis using budesonide versus placebo was studied in melanoma patients undergoing treatment with 10 mg/kg of ipilimumab. With a median follow-up of over 12 months, the rate of grade 2 or higher diarrhea was 32.7% in the budesonide group and 35.0% in the placebo group which was not significant, and therefore budesonide prophylaxis to prevent check-point inhibitor induced diarrhea is not recommended (23).

Diarrhea may be a symptom of more severe bowel inflammation (enterocolitis), which can be accompanied by abdominal pain, hematochezia or ileus and typically presents within 2 months of beginning a checkpoint inhibitor (12). If symptoms are grade 2 (4–6 bowel movements/day with or without abdominal pain or bloody stools) the checkpoint inhibitor should be held and steroids should be started at an equivalent of prednisone 1–2 mg/kg/day, and should be tapered over 4–6 weeks as long as improvement is seen (11,20). If diarrhea remains grade 2 or less and improves, then re-challenging the patient with the offending agent can be considered.

In cases of more severe grade 3 or 4 diarrhea, the patient should be hospitalized, and an endoscopic evaluation of the enteric tract should be considered in consultation with a gastroenterologist. Interestingly, in a study where investigators biopsied the colon and small bowel of patients with CTLA-4 inhibitor-induced enterocolitis, results showed inflammatory mucosal changes consistent with severe inflammatory bowel disease (24). It is therefore no surprise that cases refractory to treatment with conventional steroids have been effectively treated with the anti-TNFα monoclonal antibody infliximab at a dose of 5 mg/kg every 2 weeks, usually in consultation with gastroenterology (24,25). There is also data for the use of the anti-integrin α4β7 antibody vedolizumab which acts by preventing the adhesion and migration of memory T-lymphocytes into the gut endothelium, and has been effective in some patients with enterocolitis refractory to infliximab (26). Of course, the offending drug should be discontinued permanently in any patient who suffers grade 3 or 4 gastrointestinal symptoms, or a patient with a lower grade with inability to taper steroids to the equivalent of <10 mg of prednisone/day.

Liver function testing is recommended prior to beginning any immune checkpoint inhibitor and then regularly prior to each infusion, so that the development of hepatitis can be recognized early. Rates of hepatitis or elevated transaminases are drug and dose dependent. In trials of ipilimumab 3 mg/kg, 2% of patient developed evidence of liver inflammation versus 10–15% at the 10 mg/kg dose (7,20,21). In contrast, PD-1/PD-L1 inhibitors have a much lower rate of hepatitis which occurs 1–2% of the time although combination PD-L1/CTLA-4 blockade yields the highest rate of hepatitis, which can occur in 15–30% of patients (12,13,16,27,28). In patients with an AST or ALT >3 times the upper limit of normal or a total bilirubin >1.5 times the upper limit of normal that persists, holding the drug and initiating a work-up to rule out infectious or malignant causes is appropriate. If no alternative cause is found, initiating steroids at a dose roughly 0.5–1 mg/kg is recommended (16,29). For more severe transaminitis or hyperbilirubinemia, hepatology should be involved and a higher dose of steroids should be attempted. A biopsy could be considered which should be significant for bile duct or hepatocyte injury with inflammation and immune infiltrate, findings seen in autoimmune hepatitis. For cases refractory to steroids, mycophenolate mofetil has been used with some success (11).

Cardiac toxicities

One of the more uncommon organs to be adversely affected

by check point inhibition, cardiotoxicity of PD-L1 and CTLA-4 blockade has been increasingly recognized in the last few years as a potentially fatal complication (30). In the initial trials that led to the approval of ipilimumab in melanoma, the rate of any grade 3 or 4 adverse event was 40–45% (6,19). Despite the high rate of toxicity, cardiac events were not commonly seen, with only one case of fatal myocarditis reported (21). Similarly, large phase III trials of PD-1 or PD-L1 antibodies did not describe cardiac toxicity in the list of adverse events (3,4,31). However, as use of these drugs has become more widespread, reports have emerged defining a wide variety of potential cardiac complications.

Case reports of patients treated with the CTLA-4 inhibitor ipilimumab have ranged from asymptomatic dilated cardiomyopathy to symptomatic heart failure with reduced systolic function on echocardiogram, myocardial fibrosis, and takotsubo cardiomyopathy with apical ballooning (32). In a large clinical trial of pembrolizumab in metastatic non-small cell lung cancer, myocardial infarction led to one fatality in a patient treated with 10 mg/kg of pembrolizumab (5). Both pericarditis and myocarditis, sometimes fulminant and rapidly fatal have been seen in patients treated with mono and dual checkpoint inhibition (33). Tachyarrhythmias including ventricular fibrillation and cardiac arrest as well as bradyarrhythmias including first, second, and third-degree heart block have also been reported in the literature (32,34). While data suggests that cardiac complications are more frequent in patients receiving dual PD-L1 and CTLA-4 blockade than in either therapy alone, the absolute incidence of cardiac toxicity remains low at <1% (33). However, markers of cardiac dysfunction such as left ventricular ejection fraction or cardiac cell death (troponin-I, CK-MB) are not routinely checked in patients on immunotherapy with checkpoint inhibitors, and thus the cardiac toxicity associated with these medications may be underestimated (35).

The pathogenesis of checkpoint inhibitor-induced cardiac toxicity is still under investigation. Studies suggest that the checkpoint pathway is crucial in preventing inflammation within the milieu of the cardiac microenvironment. PD-L1 is expressed in both human and murine heart cells, and expression can be influenced by immune signaling molecules such as IFN-γ (36). Expression of PD-1 and PD-L1 may help regulate the immune microenvironment and suppress overactivation of T cells within the heart. Indeed, dilated cardiomyopathy has been induced in mice deficient in PD-1 expression, and in studies of CD8+ T cell induced myocarditis, lack of PD-1/PD-L1 expression by inhibiting IFN-γ or genetically deleting PD-1 led to a rapidly fatal form of cardiac inflammation (37,38). CTLA-4 also provides an inhibitory signal to prevent T cell overactivation and inducing self-tolerance. Inhibition of this protein has led to overactivity of T cells and autoimmunity in the heart and elsewhere (39).

Treatment of an adverse cardiac event is related to the severity of the reaction, and given the potential seriousness of cardiac toxicities, some have advocated for routine troponin and EKG monitoring in patients being treated with checkpoint inhibitors (40). For mild grade I or II adverse events as defined by the Common Terminology Criteria for Adverse Events (CTCAE 4.0), such as asymptomatic arrhythmias or structural heart failure without symptoms, initiating routine cardiac monitoring with serial EKGs, troponins, and echocardiograms may be appropriate based on the finding (41). If symptomatic, holding the checkpoint inhibitor may also be considered until the symptom is stabilized, at which point one could consider reinitiating the drug with caution and after a discussion with the patient. For grade III–IV adverse events, including acute coronary syndrome, moderate-severe decompensated heart failure, or severe arrhythmias, the checkpoint inhibitor should be discontinued permanently. If myocarditis is suspected, prompt initiation of steroids is critical at a dose of at least 1 mg/kg of methylprednisolone. Some have advocated much higher doses of 1 g methylprednisolone given daily, similar to dosing used in giant cell myocarditis. Advanced heart failure and transplant services should also be consulted, and if the patient fails to stabilize, other immunomodulators can be used. Infliximab, which is commonly given to patients who fail to respond to steroids has a contraindication to use in patients with heart failure as it can worsen cardiac function. Therefore, anti-thymocyte globulin as well as other immunomodulators such as mycophenolate mofetil or tacrolimus could be tried first, although the evidence is limited (40).

Rheumatologic toxicities

Low grade musculoskeletal side effects of checkpoint inhibition occur relatively commonly; arthralgias and myalgias occur 2–12% of the time, and are more commonly associated with PD-1/PD-L1 inhibition than CTLA-4 blockade (16). In cases of grade I musculoskeletal pain, management with nonsteroidal anti-inflammatory drugs (NSAIDs) is reasonable, with escalation to low-dose

prednisone 10 mg if no improvement. If symptoms progress, holding the checkpoint inhibitor and increasing steroids to higher doses is recommended, and input from a rheumatologist may be reasonable (11,42).

For more severe joint pain and swelling that limits a patient's activities of daily living (ADLs), a more thorough work-up should be performed including sending inflammatory and rheumatologic tests such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-nuclear antibody (ANA) and cyclic citrullinated peptide antibody (anti-CCP). Imaging of affected joints should be obtained to assess for signs of inflammatory arthritis. In cases refractory or progressive despite steroid use, further immunosuppression in consultation with rheumatology should be considered, including the use of anti-TNF agents or methotrexate (42).

Of note, other rarer rheumatologic manifestations of checkpoint inhibition have recently been described, including myositis, lupus nephritis and vasculitis. If any of these conditions is suspected, even if only a mild grade, the patient should be referred to rheumatology immediately and checkpoint blockade should be held until a treatment course can be delineated to prevent end organ damage (43).

Renal toxicities

Renal immunotherapy related adverse events are relatively uncommon and thought to occur less than 2% of the time with single agent immunotherapy. This risk may be higher with combination treatments that includes an anti-CTLA-4 and PD-1 inhibitor (i.e., ipilimumab and nivolumab), though the incidence is still thought to be low at 5% (44). Such events are frequently diagnosed on routine lab work given that most patients tend to be asymptomatic despite an elevated creatinine. When patients are symptomatic, these symptoms may include hematuria, edema, and decreased urine output (11). Renal adverse events tend to occur earlier with an anti-CTLA-4 agent at approximately three months while with PD-L1/PD-1 inhibitors, events occur generally between 3 to 10 months after starting treatment (44). Given that toxicity is rarely symptomatic, it is important that serum renal indices are monitored from the start of treatment and reassessed at frequent intervals as treatment continues. If a rise in serum creatinine is noted, alternative causes for kidney injury should be excluded via a thorough history and appropriate urine and serum studies. Imaging to assess for post-obstructive causes should also be considered. If immunotherapy related kidney injury is suspected, a nephrology consult and renal biopsy is recommended to confirm diagnosis, if biopsy risk is low (44). Pathology is usually consistent with acute tubulointerstitial nephritis (45), though cases of thrombotic microangiography, lupus nephritis (46), and granulomatous nephritis have also been reported (47).

Use of corticosteroids in addition to stopping the immunotherapy agent is the usual mainstay of treatment for patients with severe kidney injury. A nephrology consult should be strongly considered for creatinine elevations that do not improve or recur with steroid treatment, or when metabolic derangements are observed from kidney failure (11). Reintroducing the immunotherapy agent may be possible, though this should be done cautiously with frequent checks of renal indices and avoiding any other offending medications that can cause kidney injury.

Endocrine and exocrine toxicities

A number of endocrinopathies can occur while on immunotherapy, the most common being thyroid disease. The incidence of hypothyroidism ranges from 4% with ipilimumab alone to 13% with dual CTLA-4 and PD-1 blockade (48). Classic symptoms of hypothyroidism include fatigue, hair loss, cold intolerance, constipation, and poor mood, though such symptoms are common in patients with cancers so laboratory testing is essential for diagnosis. Serial measurements of serum thyroid tests should be initiated at the start of immunotherapy treatment and should be followed as treatment continues. If lab tests reflect a hypothyroid state [e.g., high thyroid stimulating hormone (TSH) and low free T4], levothyroxine supplementation should be initiated and repeat TSH and T4 measurements should be drawn at 6 weeks. Further titration of levothyroxine should be performed until the patient has lab values that reflect a euthyroid state. A hyperthyroid state and even thyrotoxicosis is also possible though less common than hypothyroidism. Rates of hyperthyroidism range from 0.6% for PD-L1 inhibitors to 8% for combination treatment (48). Persistent immunotherapy related hyperthyroidism should be treated in the same way as primary hyperthyroidism. In cases of thyrotoxicosis, prior to reaching a hypothyroid state, giving corticosteroids is reasonable and B-blockers can also be helpful in controlling the symptoms of increased adrenergic activity (49).

Immune related effects on the pituitary gland or hypophysitis can lead to a range of disorders. Hypophysitis is more frequently seen with use of an anti-CTLA-4 agent such as ipilimumab or with combined CTLA-4 and PD-1

inhibition (48). It is frequently diagnosed when routine lab work indicates secondary hypothyroidism (i.e., low TSH and low free T4) or when patients present with symptoms such as fatigue and headache. Further work-up can include sending lab tests measuring levels of adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and cortisol, which would all be expected to be low in hypophysitis. In addition to hypothyroidism, central adrenal insufficiency can also be seen and when severe, this can lead to life threatening electrolyte abnormalities, hypoglycemia, dehydration, and hypotension. Imaging with brain MRI with special attention to the sella turcica region may reveal swelling and enhancement of the pituitary gland. If there is concern for hypophysitis and especially if adrenal crisis is suspected, high dose corticosteroids should be initiated immediately which should then be followed with an extended steroid taper of several weeks. This may reverse many of the immune mediated adverse effects, though in the long-term, the vast majority of patients will need some form of hormonal replacement with either levothyroxine for hypothyroidism or hydrocortisone supplementation for adrenal insufficiency (11,49). Endocrinology consultation in cases of hypophysitis is highly recommended as management of these hormonal imbalances require specialty expertise.

The exocrine functioning of the pancreas can also be affected by both anti-CTLA-4 agents and anti-PD1/PD-L1 treatments. In most of these cases, patients found to have elevated serum amylase and lipase values are not symptomatic from this and do not fit clinical criteria for pancreatitis. Monitoring serum pancreatic enzymes in the absence of symptoms is likely not to be of benefit and treatment of these elevations with corticosteroids without the clinical features of pancreatitis is not usually indicated.

An additional rare risk with immunotherapy is the development of autoimmune diabetes, leading to long-term insulin dependence. This uncommon adverse event is thought to occur in 0.2% of cases (48,50). Many patients may first present acutely in diabetic ketoacidosis or with significant hyperglycemia that requires insulin for correction (49). In addition to monitoring for symptoms of hyperglycemia, checking a glucose level, as would come standard with a basic or comprehensive metabolic panel, prior to each cycle of immunotherapy would be prudent.

Neurologic and ocular toxicities

A range of neurologic adverse events are associated with immune checkpoint inhibitors. The overall incidence of these events was found to be 3.8% with anti-CTLA-4 inhibitors, 6.1% with PD-1 inhibitors and 12.0% with the combination of both in one recent systematic review (51). Most of these events are grades 1–2 with the most frequent side effect being headaches. More severe events are rare with an incidence of less than 1% for all forms of checkpoint blockade. Both central and peripheral neurotoxicity can be seen.

Peripheral neuropathies have been reported as a side effect of both anti-CTLA-4 agents as well as for PD1/PD-L1 inhibitors and may manifest as either motor or sensory dysfunction. The majority of these cases are grades 1–2 and may not require intervention or treatment discontinuation if symptoms are stable and do not affect quality of life (52). Close follow-up and possible referral to neurology is still recommended. Higher grade peripheral neurotoxicity including cases of Guillain-Barre Syndrome (GBS) and myasthenia gravis have also been seen (53). While such cases are rare, the clinician should maintain a high level of awareness for any symptoms that include fluctuating or progressive muscle weakness, and ocular changes such as diplopia or ptosis. In suspected cases of GBS, a lumbar puncture to look for elevated protein levels, nerve conduction studies, and PFTs should be obtained. If there is concern for myasthenia gravis, a thorough physical exam that assesses for proximal muscle fatigue and ocular muscle dysfunction, as well as laboratory tests that include acetylcholine receptor and anti-MuSK antibodies is recommended (53). Neurology consultation in these cases are certainly warranted as they can assist in directing both further work-up as well as management. In addition to stopping the immunotherapy agent, high dose steroids plus plasmapheresis or intravenous immunoglobulin (IVIG) may be indicated.

Central neurological adverse events have also been seen with checkpoint blockade including immune mediated encephalitis (54), aseptic meningitis (53), and posterior reversible encephalopathy syndrome (PRES) (55,56). Symptoms are wide ranging and can include altered mental status, headaches, fevers, confusion, receptive and expressive aphasia, and motor or sensory changes. When a central process is suspected, the work-up should include both central nervous system (CNS) imaging as well as lumbar puncture to exclude alternative causes for neurologic symptoms such as metastatic disease to the brain, infectious causes, and leptomeningeal disease. High-dose steroids are once again the mainstay of treatment though infectious causes should ideally be ruled-out prior to starting of

steroids. Involvement of neurology in these cases would also be reasonable.

Ocular toxicities such as episcleritis, uveitis, and conjunctivitis are known to be associated with ipilimumab, though such adverse events are rare with less than 1% of patients affected (57). Symptoms can include ocular pain, dryness, photophobia, and vision changes. PD-1 inhibitors like nivolumab may also cause ocular side effects such as uveitis (58) though the risk for this is also thought to be low at less than 1% of patients affected. Ophthalmology consultation is advised and the majority of mild cases can be treated with topical steroids, such as 1% prednisolone drops. More severe cases may require discontinuation of the immunotherapy agent and the initiation of systemic high dose corticosteroids (59).

Dermatological toxicities

Dermatologic side effects are some of the most common adverse events associated with checkpoint blockade. The incidence of all-grade rashes has been reported to be 24% for ipilimumab in one recent meta-analysis (60), while nivolumab and pembrolizumab have rates of 14% and 17%, respectively (61). Higher grade toxicities are more commonly associated with ipilimumab and thought to occur in approximately 2% of patients (60). Rashes with CTLA-4 inhibitors are usually morbilliform or maculopapular and pruritic, which is typical of most drug-related rashes. Areas typically involved are the trunk and extremities while palms and soles are less often affected. In severe cases, toxic epidermal necrolysis can occur or patients can have other systemic symptoms (62). PD-1/PD-L1 inhibitors can produce similar skin findings, though these may be generally less severe than those seen with CTLA-4 inhibitors (63,64). Combination treatment with ipilimumab and nivolumab can also lead to dermatological adverse events and these may occur at a greater frequency and severity when compared to treatment with a single agent (65).

Grades 1–2 rashes with mild pruritus can be treated with topical steroids and oral antihistamines if needed. The immunotherapy agent in these mild cases may not necessarily need to be discontinued. Grade 3 skin reaction may require systemic high-dose steroids with temporary discontinuation of checkpoint blockade until rash improves. Grade 4 reactions typically require permanent discontinuation of the immunotherapy drug and high-dose systemic steroids (62,63).

Conclusions

The discovery and utilization of checkpoint blockade has revolutionized the field of oncology. Treatments involving the use of PD-1 and PD-L1 inhibitors are now FDA approved therapies for a range of malignancies, including non-small cell lung cancer and melanoma, as well as for tumors with microsatellite instability, agnostic of histology. Ipilimumab, while previously investigated in its role for treating metastatic melanoma, is now being studied for its potential to treat lung cancer either as a single agent or as a combination treatment with a PD-1/PD-L1 inhibitor. While these therapies hold great promise and many patients have already greatly benefited from immunotherapy agents, there are numerous immune-mediated adverse events that can occur with use of these drugs. While many of these toxicities are rare, clinicians need to be vigilant in monitoring for adverse events. If such adverse events go unrecognized, this can lead to significant morbidity and mortality. Many of these severe toxicities can be reversed with prompt recognition, discontinuation of the immunotherapy agent, and administering high-dose steroids. Adverse events can be complicated, causing severe organ dysfunction not normally managed by oncologists, so a multi-disciplinary approach with specialty consultation is strongly recommended in many cases. As the use of immune checkpoint inhibition grows, more immune-mediated adverse events are likely to be seen, so further research is needed on how to best identify and manage these toxicities.

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Footnote

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