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MELANOMA (RJ SULLIVAN, SECTION EDITOR)

Immune Checkpoint Inhibitor Toxicity

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Abstract

Purpose of review Immune checkpoint inhibitors have revolutionised the treatment of multiple malignancies and have a growing list of indications. As our familiarity with these agents grows, so does our understanding of their unique spectrum of toxicities. Here, we will review the literature regarding the toxicities of checkpoint inhibitors and address challenges encountered in day-to-day clinical practice.

Recent findings Inhibitors of the PD-1/PD-L1 axis are considerably less toxic than the anti-CTLA-4 antibody ipilimumab. The combination of ipilimumab and anti-PD-1 agents is being trialled in multiple malignancies and is associated with increased toxicity. There is accumulating evidence suggesting a potential correlation between a subset of toxicities and clinical benefit in several tumour types, although conflicting data exists. Retrospective series have shown that anti-PD-1 can be safely administered to patients with prior high-grade toxicity from ipilimumab or combination immunotherapy.

Summary The management of checkpoint inhibitor toxicity is complex and requires collaboration with our subspecialty colleagues. Identifying predictive biomarkers of both efficacy and toxicity would likely help guide treatment decisions, and should be a research priority in the years ahead.

Keywords Checkpoint inhibitors · CTLA-4 · PD-1 · Ipilimumab · Nivolumab · Pembrolizumab · Toxicity · Immune-related adverse events (irAEs)

Introduction

Immune checkpoints are a collection of inhibitory pathways built into the immune system, which are essential for the maintenance of self-tolerance and the regulation of physiologic immune responses. Dysregulation of immune checkpoints is an important mechanism by which some tumours evade host immunity. Immune checkpoint inhibitors (ICIs) are immunomodulatory antibodies that upregulate host antitumour immunity, and have demonstrated efficacy in multiple tumour types.

The primary targets for currently approved checkpoint inhibitors include cytotoxic T lymphocyte-antigen 4 (CTLA-4) and the programmed cell death receptor 1 (PD-1) and its ligand, PD-L1. The anti-CTLA-4 antibody ipilimumab has been shown to improve overall survival in patients with advanced melanoma, and was granted FDA approval in 2011 [1]. The anti-PD-1 antibodies pembrolizumab and nivolumab closely followed suit, and were approved for the treatment of advanced melanoma in 2014 [2•, 3•]. The indications for these antibodies and others in development has grown exponentially over the past 6 years, as they are trialled with varying success across most tumour types (Table 1).

As experience with checkpoint inhibition grows, so does understanding of the unique spectrum of side effects that can occur as a result of non-specific immunostimulation. Many toxicities mimic autoimmune diseases and have been predefined in clinical trials as immune-related adverse events (irAEs). Toxicities are graded using the National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) [4]. These criteria were developed primarily as a means to standardise reporting of AEs for clinical trials

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Table 1 FDA-approved checkpoint inhibitors

Drug	Indications	Pivotal trial/s
Ipilimumab	Metastatic melanoma	MDX010-20
	Adjuvant treatment resected stage III melanoma	EORTC 18071
Nivolumab	Metastatic melanoma	Checkmate-066
	Adjuvant treatment resected stage III/IV melanoma	Checkmate-238
	2L metastatic NSCLC	Checkmate-017 & 057
	2L metastatic RCC	Checkmate-025
	2L recurrent or metastatic SCCHN	Checkmate-141
	Locally advanced or metastatic UCC[a]	Checkmate-275
	Classical Hodgkin lymphoma[b]	Checkmate-205 & 039
	2L MSI-H or MMR deficient metastatic CRC[c]	Checkmate-142
	2L HCC	Checkmate-040
Ipilimumab + nivolumab	Metastatic melanoma	Checkmate-069
	1L metastatic RCC (intermediate/poor risk)	Checkmate-214
Pembrolizumab	Metastatic melanoma	Keynote-006
	1L metastatic NSCLC (PD-L1 ≥ 50%)	Keynote-024
	1L metastatic NSCLC in combination with carboplatin/pemetrexed	Keynote-021
	2L NSCLC (PD-L1 ≥ 1%)	Keynote-010
	2L recurrent or metastatic SCCHN	Keynote-012
	1L locally advanced or metastatic UCC (cisplatin-ineligible)	Keynote-052
	2L locally advanced or metastatic UCC[a]	Keynote-045
	Classical Hodgkin lymphoma[d]	Keynote-087
	2L metastatic gastric cancer (PD-L1 CPS ≥ 1)[e]	Keynote-059
	MSI-H or MMR deficient metastatic solid organ tumours[f]	Keynote-012, 016, 028, 158 & 164
Atezolizumab	1L locally advanced or metastatic UCC (cisplatin-ineligible)	IMvigor-210
	2L locally advanced or metastatic UCC[a]	IMvigor-210
	2L metastatic NSCLC	OAK, POPLAR
Durvalumab	2L locally advanced or metastatic UCC[a]	Study 1108
	Consolidation therapy, unresectable stage III NSCLC[g]	PACIFIC
Avelumab	Metastatic Merkel cell carcinoma	JAVELIN Merkel 200
	2L locally advanced or metastatic UCC[a]	JAVELIN Solid Tumour Trial

FDA, Food and Drug Administration; *1L*, 1st line; *2L*, second line; *NSCLC*, non-small cell lung cancer; *RCC*, renal cell carcinoma; *SCCHN*, squamous cell carcinoma of the head and neck; *UCC*, urothelial carcinoma; *MSI-H*, microsatellite instability-high; *MMR*, DNA mismatch repair; *CRC*, colorectal cancer; *HCC*, hepatocellular carcinoma; *CPS*, combined positive score

[a] Locally advanced or metastatic UCC who have disease progression during or following platinum-containing chemotherapy, or progression within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy

[b] Classical Hodgkin lymphoma that has relapsed or progressed after autologous haematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT

[c] Patients ≥12 years old with MSI-H or MMR deficient metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

[d] Adult and paediatric patients with refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more prior lines of therapy

[e] Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 CPS ≥1 with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy

[f] Adult and paediatric patients with unresectable or metastatic, MSI-H or MMR deficient solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

[g] Unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy

rather than to guide clinical care, though are frequently used in toxicity management algorithms. IrAEs can affect any organ system, and differ in their pattern and severity depending on which checkpoint is targeted (Fig. 1) [5•]. Management is with

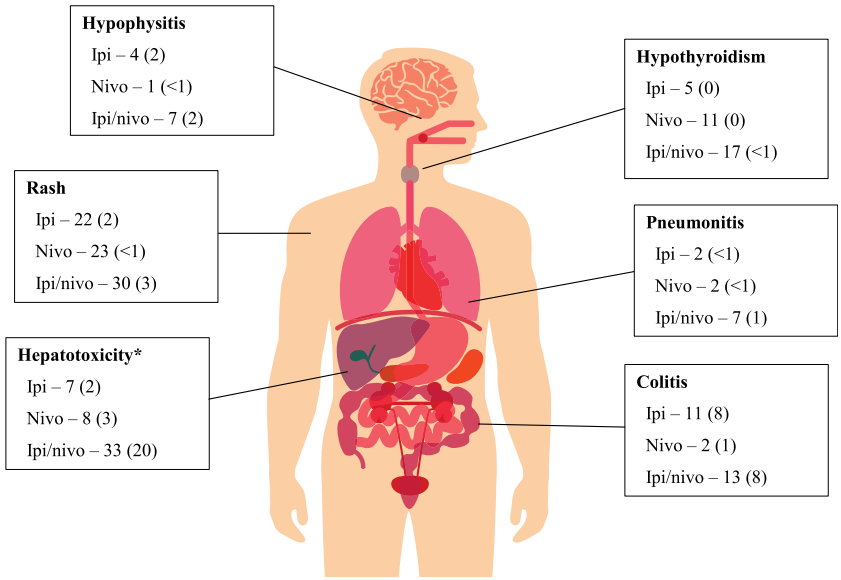

Fig. 1 The frequency of irAEs per organ system [% (G3/4)] in patients with advanced melanoma receiving ipilimumab (ipi), nivolumab (nivo) or a combination of both agents (ipi/nivo). Based on data from Checkmate 067 [4]. The asterisk denotes hepatic treatment-related adverse events of potential immunologic aetiology, including elevations in aspartate and alanine aminotransferases, alkaline phosphatase, gamma-glutamyltransferase and bilirubin. Image courtesy of Eveleen/shutterstock.com

immunosuppression using corticosteroids and less commonly other immunomodulatory agents. No prospective trials have tested management strategies for specific irAEs, though several professional groups have developed consensus guidelines to assist with their management [6•, 7•].

This review will focus on the toxicities of ipilimumab and anti-PD-1 antibodies (hereafter referred to as anti-PD-1) using an organ system-based approach, and will address some challenges encountered in day-to-day practice.

Systemic Adverse Effects

Systemic AEs of ICI therapy include fatigue and less commonly infusion reactions. Fatigue is the most commonly reported AE across studies using anti-PD-1 and ipilimumab, occurring in 16–37% and 42% of patients respectively [1, 8]. Important causes of fatigue to consider in patients receiving ICI include hypothyroidism, hypophysitis and less commonly primary adrenal insufficiency. Infusion reactions may manifest as fever, pruritus, dyspnoea, wheeze, urticaria, hypotension, angioedema and even anaphylaxis. These are relatively uncommon, though occur in up to 25% of patients receiving the anti-PD-L1 antibody avelumab [9]. US prescribing information for avelumab recommends premedication with acetaminophen and an antihistamine for at least the first four cycles of treatment [10].

Dermatologic Adverse Effects

Skin toxicities occur in 40–50% of patients treated with ipilimumab and 30–40% of patients treated with anti-PD-1 [1,2•,3•, 8, 11, 12]. Ipilimumab is most commonly associated with a morbilliform eruption and pruritus. Ipilimumab skin toxicity tends to occur earlier and is dose-dependent [13]. Skin toxicity following anti-PD-1 is less severe and tends to occur later. Lichenoid reactions, eczema, vitiligo and pruritus are the most commonly reported following anti-PD-1 monotherapy [13, 14]. Bullous dermatoses, psoriasis, lichenoid reactions of the mucous membranes and hair re-pigmentation have also been described [13, 15, 16]. The majority of skin toxicities are low-grade and easily managed with emollients, topical corticosteroids and oral antihistamines. ICI therapy can be continued with caution for CTCAE grade 2 skin toxicity, though interrupted if the AE does not resolve to ≤ grade 1 within a week or two. ICI therapy should be interrupted for ≥ grade 3 skin toxicity and systemic corticosteroids commenced [7•]. Although rare, exfoliative conditions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported and may be fatal. In these settings, ICI therapy should be permanently discontinued [6•].

Endocrine Adverse Effects

Thyroid Disease

Thyroid dysfunction (hypothyroidism, hyperthyroidism and thyroiditis) was reported in 6–20% of patients in large phase 3 clinical trials of ICI therapy [17]. Hypothyroidism is more common than hyperthyroidism. The latter is often transient and precedes a permanent hypothyroid state, inferring a mechanism akin to destructive thyroiditis [17]. In a prospective analysis of 51 patients with NSCLC treated with

pembrolizumab in the Keynote-001 study, anti-thyroid antibodies were detected in 80% of patients who developed hypothyroidism compared to 8% of patients who did not develop thyroid dysfunction [18]. This suggests that autoimmune thyroid disease and thyroid dysfunction as an irAE may have a similar pathogenesis.

Thyroid dysfunction is considerably more common in patients treated with anti-PD-1 monotherapy or combination ipilimumab/nivolumab than ipilimumab alone [6•]. In a systematic review, the incidence of hypothyroidism following treatment with ipilimumab, nivolumab or pembrolizumab and combination ipilimumab/nivolumab was 3.8, 7.0 and 13.2% respectively. Hyperthyroidism occurred in 1.7, 3.2 and 8.0% respectively [19•], though its incidence may be underreported due to its predominantly transient nature. The development of Graves' disease is rare.

Management of hypothyroidism is with thyroid hormone replacement. Patients with symptomatic hyperthyroidism should be treated with beta-blockers. Rarely, carbimazole or corticosteroids are required, though it should be noted that the latter has not been shown to prevent the onset of hypothyroidism due to thyroid gland destruction [7•].

Hypophysitis

Prior to the introduction of ipilimumab, hypophysitis was rare. The incidence of hypophysitis is 1–4% with ipilimumab 3 mg/kg, 16% with ipilimumab 10 mg/kg and 7% with combination ipilimumab/nivolumab [1, 5, 20, 21]. It is rare with anti-PD-1 monotherapy (incidence < 1%) [22]. The median time from commencing ipilimumab to the diagnosis of hypophysitis is 8–9 weeks, or after the third dose of treatment [23]. Hypophysitis manifests with non-specific symptoms such as fatigue, headache and weakness, with less frequent symptoms including confusion, insomnia, temperature intolerance and loss of libido. Visual impairment due to optic pathway involvement is rare compared to classic lymphocytic hypophysitis [22]. The diagnosis is confirmed by biochemical evidence of hypopituitarism and with MRI abnormalities including pituitary enlargement, stalk thickening and heterogeneous enhancement (Fig. 2a) [6]. Multiple anterior pituitary hormone deficiencies can occur, with central hypothyroidism and central adrenal insufficiency the most commonly observed [6•, 24]. The true incidence of hypogonadotropic hypogonadism is difficult to estimate given the effect of severe illness on the gonadal axis [25]. The growth hormone axis is not significantly affected and diabetes insipidus is rare [26].

Management of confirmed hypophysitis involves physiologic hormone supplementation in consultation with an endocrinologist. When adrenal insufficiency and hypothyroidism co-exist, steroids should always be commenced prior to thyroid hormone to avoid precipitating an adrenal crisis. High-dose steroids should be administered to patients presenting with adrenal crisis, headaches and visual disturbance [6•], though this has not been shown to affect the frequency or timing of pituitary recovery [22, 27]. Thyroid and gonadal function recovers in a proportion of patients (37–50% and 57% respectively), though adrenal recovery is rare [22, 28, 29]. All patients with adrenal insufficiency should be instructed to carry a medical alert bracelet.

Rare Endocrine Adverse Events

Primary adrenal insufficiency and insulin-deficient diabetes are rare, with a reported incidence of 0.7 and 0.2% respectively. The former is more commonly observed with combination ICI therapy and the latter with anti-PD-1/PD-L1 monotherapy, though small patient numbers limit data interpretation [19•, 30]. C-peptide and antibodies against islet cells (ICA) and glutamic acid decarboxylase (GAD) should be measured to help distinguish between type 1 and type 2 diabetes [7•].

Gastrointestinal Adverse Events

Hepatitis

Hepatic AEs with ICI therapy consist mainly of asymptomatic elevations of alanine and aspartate transaminase, though more serious autoimmune-like hepatitis with elevated bilirubin and acute liver failure can occur. Like most other irAEs, the risk of hepatotoxicity with ipilimumab is dose-dependent. In studies using ipilimumab 3 mg/kg, the incidence of hepatitis ranges from 1.2–3.9% (all grades) and 0.8–1.6% (≥ grade 3) [1, 2•, 5•, 20]. In the EORTC 18071 study of adjuvant ipilimumab 10 mg/kg, hepatitis occurred in 17.6% (all grades) and 4.3% (≥ grade 3) respectively [21]. A higher incidence of ≥ grade 3 hepatitis (up to 20% depending on definition) is observed when ipilimumab 3 mg/kg and nivolumab 1 mg/kg are combined [5•]. Severe hepatitis is rare with anti-PD-1 monotherapy (1.1–1.3% ≥ grade 3) [2•, 3•, 5•, 20].

Alternative causes of hepatic inflammation should be excluded including viral infections, medications, alcohol, thromboembolic disease and disease progression [6•]. ICI therapy should be interrupted for ≥ grade 2 hepatitis, and corticosteroids commenced immediately for ≥ grade 3 hepatitis or grade 2 toxicity that is slow to resolve. Mycophenolate mofetil (MMF) is recommended in steroid-refractory cases [7•]. Anti-thymocyte globulin (ATG) has been used successfully to treat a case of fulminant ICI-related hepatitis [31].

Colitis

Diarrhoea is one of the most common toxicities in patients treated with ipilimumab, and severe colitis is a frequent reason

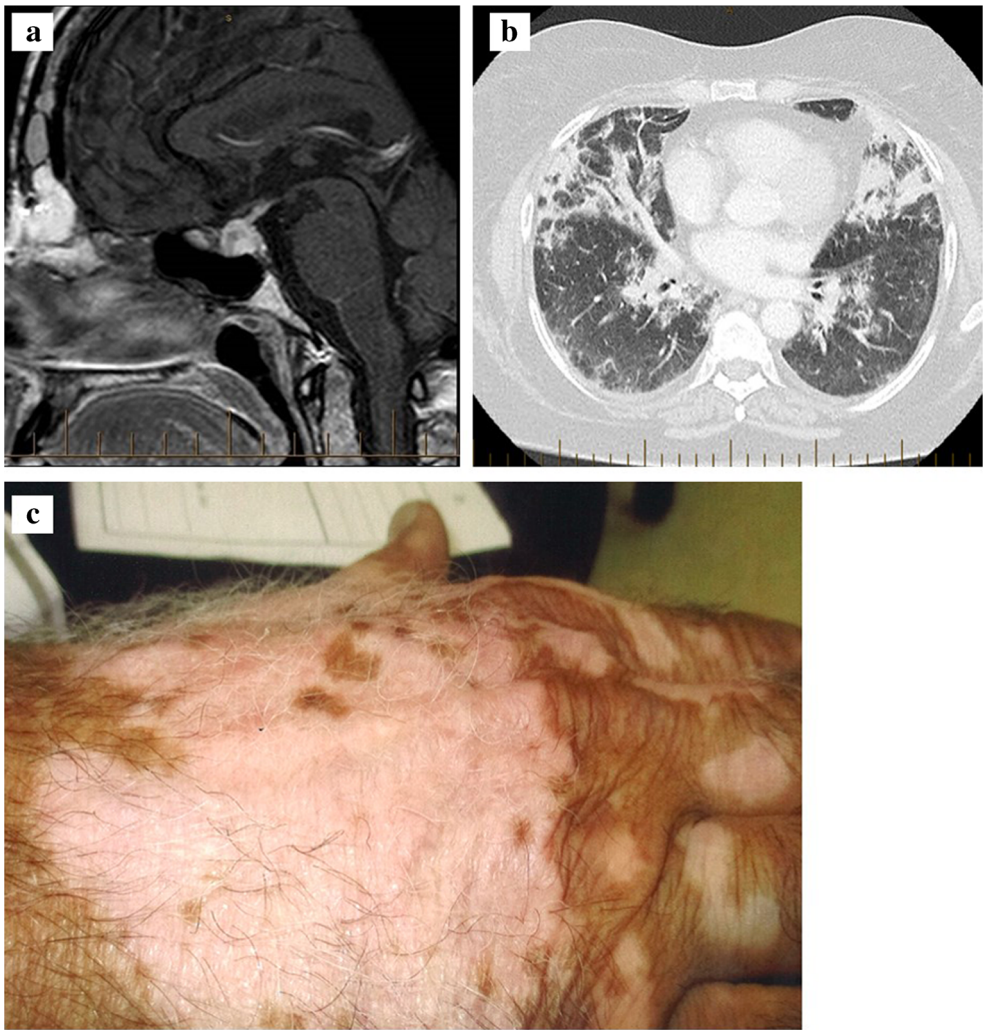

Fig. 2 **a** Pituitary enlargement and heterogeneous enhancement in a patient with hypophysitis following their second dose of ipilimumab. **b** Pneumonitis in a patient receiving nivolumab for metastatic NSCLC. **c** Vitiligo in a patient receiving pembrolizumab for metastatic melanoma

for treatment discontinuation. Approximately one third of patients develop diarrhoea while colitis occurs in 8–22% [32]. Severe (≥ grade 3) colitis is uncommon in patients receiving anti-PD-1 monotherapy (1–3%) [2•, 3•, 20]. Onset is usually 10–12 weeks following the commencement of treatment, though can develop following the first infusion [33]. Symptoms include diarrhoea (92% of patients) [32], abdominal pain, haematochezia, passage of mucus, vomiting, fever and weight loss [34]. Extra-intestinal manifestations resembling those that occur in inflammatory bowel disease have been described [34]. Colonic perforation occurs in < 1% of patients treated with ipilimumab for advanced melanoma [32], though has been reported in up to 7% of patients receiving the same agent for advanced RCC [35].

Prompt recognition and treatment of colitis is crucial. In the setting of acute diarrhoea, the main differential diagnosis is gastrointestinal infection. Stool should be analysed for bacterial enteropathogens and *Clostridium difficile* toxin in all patients receiving checkpoint inhibitors who present with diarrhoea. Faecal calprotectin can help indicate whether there is an inflammatory aetiology [6•, 7•]. Flexible sigmoidoscopy and biopsy is usually sufficient to make a diagnosis as the rectosigmoid is involved in most cases [34]. Biopsy should be performed even when the bowel mucosa appears normal, as some types of colitis appear normal endoscopically. In the setting of persistent diarrhoea with a normal colonoscopy, examination of the small bowel with enteroscopy should be considered as cases of enteritis without colitis have been described [36]. Immunohistochemical staining for cytomegalovirus should also be routine [6, 7]. Screening tests for hepatitis B and C, human immunodeficiency virus (HIV) and tuberculosis should be performed pre-emptively in case a tumour necrosis factor-alpha (TNF-α) inhibitor is required [37].

ICI therapy should be interrupted for ≥ grade 2 colitis. Systemic corticosteroids should be commenced for patients with persistent grade 2 diarrhoea and all patients with ≥ grade 3 diarrhoea [6•, 7•]. If there is failure to respond to corticosteroids within 3–5 days, infliximab 5 mg/kg should be commenced in a similar fashion to inflammatory bowel disease management algorithms. Response to infliximab is usually

rapid (within 1–3 days) and a single dose is usually sufficient [32, 38–42]. An initial clinical response should be followed by a slow steroid wean over at least 8 weeks, as relapses are common. The development of a syndrome resembling chronic inflammatory bowel disease has been described [34].

Pulmonary Adverse Effects

Pneumonitis

Pneumonitis is an uncommon but potentially fatal toxicity of ICI therapy. The incidence is approximately 5% with anti-PD-1/PD-L1 monotherapy (1–2% ≥ grade 3) and up to 10% in those receiving combination immunotherapy [2•, 3•, 5•, 20, 43•]. Pneumonitis following ipilimumab monotherapy is rare. The most common symptoms are dyspnoea (53%) and cough (35%) [43•]. The median time to onset is 2.8 months [43•], with an earlier onset reported in NSCLC patients [44]. The rate of grades 3–4 pneumonitis is similar across tumour types, but there appears to be higher treatment-related mortality due to pneumonitis in patients with NSCLC [45].

Pneumonitis should be considered when any patient receiving ICI therapy develops new respiratory symptoms, and a chest CT requested. Radiographic findings are variable, with patterns resembling cryptogenic organising pneumonia, usual interstitial pneumonia, non-specific interstitial pneumonia and hypersensitivity pneumonitis observed [6•, 43•] (Fig. 2b). Diagnosis can be challenging given the overlap of clinical and radiographic findings with common problems such as pneumonia, lymphangitis carcinomatosis and cancer progression [6•]. Bronchoscopy with bronchoalveolar lavage may assist in excluding infectious aetiologies. Lung biopsy is seldom required, though may be useful in the setting of unexplained lymphadenopathy or if there is ongoing radiologic or clinical doubt as to the aetiology of pulmonary infiltrates [6•, 7•].

ICI therapy should be withheld and immunosuppressive treatment initiated promptly when there is a high degree of suspicion for pneumonitis. Infection should ideally be ruled out bronchoscopically prior to immunosuppression, though this is not always feasible. Acknowledging this difficulty, most treatment algorithms advocate for the administration of broad-spectrum antibiotics in conjunction with immunosuppressive treatment [7•]. Systemic corticosteroids should be initiated for ≥ grade 2 pneumonitis, and patients monitored with serial pulse oximetry, pulmonary function testing and chest radiography. In cases of ≥ grade 3 pneumonitis, patients should be admitted to hospital for parenteral corticosteroids and ICI therapy permanently discontinued. If there is no clinical or radiologic improvement after 48 h, the addition of infliximab, MMF or cyclophosphamide should be considered [7•].

Rechallenging patients with ICI following complete resolution of grade 1 or 2 pneumonitis appears to be reasonably safe, with only three of 12 patients developing a second pneumonitis event in a retrospective series. All three patients had low-grade recurrent pneumonitis that responded well to either drug holding or corticosteroids [43•]. That said, given the potentially catastrophic consequences of recurrent high-grade pneumonitis, patients must be well informed of the potential risks and clinicians must remain vigilant.

Sarcoidosis

Pulmonary sarcoidosis and sarcoid-like granulomatous reactions have also been reported following both anti-PD-1/PD-L1 and ipilimumab [46, 47]. The diagnosis is suspected when reticulonodular pulmonary opacities and/or symmetric mediastinal and hilar lymphadenopathy are visualised radiologically, and confirmed by visualisation of non-caseating granulomas histologically [6•]. Given the clinical and radiologic similarities to malignant disease progression, clinicians and radiologists need to be aware of this entity. Extra-pulmonary manifestations have also been reported [46]. Management strategies are extrapolated from sarcoidosis treatment algorithms for the general population.

Rheumatologic

Arthralgia has been reported in approximately 15% of patients receiving ICI therapy, but the incidence of true inflammatory arthritis has not been well defined [48]. Syndromes resembling rheumatoid arthritis and seronegative spondyloarthropathies have been described, with a small proportion of the former accompanied by elevated rheumatoid factor or anti-cyclic citrullinated peptide antibody titres [6•]. Cases of sicca syndrome, polymyalgia rheumatica, inflammatory myopathies, temporal arteritis and other vasculitides have also been reported [48–52].

All patients with suspected ≥ grade 2 inflammatory arthritis should be reviewed by a rheumatologist, because erosive and irreversible joint damage can occur within weeks of symptom onset. Patients with symptoms persisting for ≥ 6 weeks or those whose steroid dose cannot be tapered to ≤ 10 mg prednisone (or equivalent) within 4 weeks should also be referred, as the addition of disease-modifying anti-rheumatic drugs or biologics such as TNF-α inhibitors may be required. Due to their rarity and the potential for life- and organ-threatening consequences, all patients with suspected vasculitis or myositis should be reviewed by a rheumatologist immediately [6•].

Uncommon Adverse Effects

Neurologic

Neurologic irAEs are uncommon. A systematic review of 59 trials involving 9208 patients reported an incidence of 3.8% following anti-CTLA-4 therapy, 6.1% following anti-PD-1 and 12% following combination therapy [53]. The majority of these were low-grade and consisted of non-specific symptoms such as headache. High-grade (≥ grade 3) neurologic AEs occurred in < 1% of patients and included autoimmune encephalitis, aseptic meningitis, myasthenia gravis, Guillain-Barre syndrome (GBS), peripheral sensorimotor neuropathies and posterior reversible encephalopathy syndrome [53]. Investigations depend on the clinical presentation, but may include central nervous system imaging, lumbar puncture for cerebrospinal fluid analysis and nerve conduction studies [54]. Cancer progression, infection and paraneoplastic syndromes should be considered in the differential diagnosis. For all ≥ grade 2 neurologic symptoms, ICI therapy should be interrupted while investigation ensues and systemic corticosteroids commenced. Intravenous immunoglobulin or plasmapheresis should be considered for the treatment of GBS and myasthenia gravis [54]. Early neurology consultation is essential [6•, 7•, 54].

Renal

Acute kidney injury (AKI) was reported in 2.2% of patients following ICI therapy in a combined analysis of 3695 patients [55]. Grades 3–4 AKI or the requirement for dialysis occurred in 0.6%. AKI occurred more frequently in patients who received combination therapy with ipilimumab/nivolumab (4.9%) than in patients who received ipilimumab (2.0%), nivolumab (1.9%) or pembrolizumab (1.4%) alone [55]. Recently published data suggests that the incidence of renal irAEs may be underreported, with low-grade AKI occurring in up to 29% of patients ([56].

The onset of AKI following ipilimumab (2–3 months) is earlier than anti-PD-1 (3–10 months) [56]. Acute interstitial nephritis is the most commonly reported histologic finding [56]. Podocytopathies (minimal change disease, membranous nephropathy), lupus nephritis and thrombotic microangiopathies have also been reported following ipilimumab [56–59].

When immune-related renal disease is suspected, renal biopsy should be considered to confirm aetiology and guide management [6•]. When confirmed, ICI therapy should be interrupted and systemic corticosteroids administered [6•, 7•].

Cardiac

Cardiac irAEs are rare, occurring in < 1% of patients treated with ICI therapy. A higher incidence has been reported with combination ipilimumab/nivolumab (0.27%) than with nivolumab alone (0.06%) [60]. A range of toxicities including myocarditis, cardiomyopathy, cardiac fibrosis, arrhythmias and pericarditis have been described [60–64]. When suspected, early cardiology consultation is essential given the potential for sudden death. Interruption of ICI therapy and high-dose corticosteroids have successfully treated cardiac irAEs. Escalation to other immunosuppressive agents such as infliximab, MMF or ATG should be considered in steroid-refractory cases [6, 7].

Ocular

Ocular irAEs occur in < 1% of patients receiving ICI therapy [7•, 65], and include uveitis, peripheral ulcerative keratitis, Vogt-Koyanagi-Harada syndrome, choroidal neovascularisation and melanoma-associated retinopathy [65]. Thyroid-associated orbitopathy, idiopathic orbital inflammation, episcleritis, blepharitis and optic nerve swelling have also been reported [6•, 65, 66]. Prompt ophthalmologic assessment including dilated fundoscopy and slit lamp examination is necessary for all visual complaints [6•, 7•]. Generally speaking, mild irAEs can be treated with topical corticosteroids whereas systemic corticosteroids and discontinuation of ICIs are indicated for more severe ocular and orbital inflammation [65].

Haematologic

Reported haematologic irAEs include aplastic anaemia, autoimmune haemolytic anaemia, immune thrombocytopenic purpura, neutropenia, acquired haemophilia A and cryoglobulinaemia [67–72]. The optimal treatment of these rare and potentially severe AEs is not known. High-dose corticosteroids should be commenced in consultation with a haematologist [7•].

Association Between Immune-Mediated Toxicity and Response to Treatment

There is accumulating evidence that the development of irAEs may be associated with a response to immunotherapy and prolonged survival. An association between vitiligo and both tumour regression and prolonged survival has been observed in patients with melanoma for several decades, even before the advent of modern immunotherapies [73–76]. Vitiligo-like depigmentation results from anti-melanoma immunity that also targets healthy melanocytes, as a result of the shared expression of melanocyte differentiation antigens (Fig. 2c) [77]. In a recent systematic review and meta-analysis of 27 studies reporting individual patient data, the development of vitiligo was significantly associated with both progression-free

survival (PFS) (hazard ratio [HR] 0.51) and overall survival (HR 0.25), indicating that these patients have a 2–4 times lower risk of disease progression and death compared to patients who do not develop vitiligo [77]. In a prospective observational study of 67 patients treated with pembrolizumab as part of a phase 1 study, the development of vitiligo was associated with a higher objective response rate (ORR 71% with vitiligo vs 28% without vitiligo) [78].

Several recent studies have shown an association between irAEs other than vitiligo and favourable outcomes. In a single-centre prospective review of thyroid dysfunction in 51 patients with advanced NSCLC treated with pembrolizumab, the median overall survival was significantly longer in those who developed thyroid dysfunction compared to those who did not (median 40 vs 14 months, HR 0.29; 95% CI 0.09–0.94) [18]. In a retrospective review of 163 patients with advanced melanoma and RCC who received anti-CTLA-4 antibodies as part of three separate trials, 5 of the 8 patients (62.5%) who developed hypophysitis had objective tumour responses, which is considerably higher than the expected ORR of 10–20% in the population as a whole [79]. In another retrospective review of 198 patients with metastatic melanoma or RCC treated with ipilimumab, ORR in patients who developed enterocolitis was 36% for melanoma and 35% for RCC, compared with 11 and 2% respectively in those without enterocolitis [39]. The administration of corticosteroids and/or infliximab does not appear to affect the response and overall survival of patients treated with ipilimumab for melanoma [80, 81]. In the largest published series of patients with pneumonitis following anti-PD-1/PD-L1, the majority of patients with pneumonitis were also responders to immunotherapy. As noted by the authors, however, the variety of diseases, treatments and methods of assessment makes the assumption of a causal relationship problematic [43]. Case reports also suggest that the development of sarcoidosis may be associated with prolonged tumour response [47, 82].

Despite the data presented above, the relationship between irAEs and clinical benefit is yet to be resolved. Several large retrospective studies have failed to show a relationship between irAEs and response rates, time to treatment failure and survival [81, 83, 84]. The possibility of confounding between increased time on ICI therapy and a higher likelihood of both irAEs and clinical benefit from treatment must be acknowledged. Nevertheless, the observed associations between irAEs and clinical benefit are intriguing.

Risk of Toxicity Based on Patient Clinical Factors

Disease burden may have a bearing on toxicity following ICI therapy. In a pooled analysis of data from the Checkmate 069 and 067 trials in which patients with advanced melanoma received combination ipilimumab/nivolumab for 4 cycles (induction) followed by nivolumab monotherapy (maintenance), patients who discontinued treatment at any time due to an AE were less likely to have M1c disease (49 vs 61%) or an elevated lactate dehydrogenase (27 vs 39%) [85•]. Similarly, greater immune-related toxicity is seen with high-dose ipilimumab (10 mg/kg) in the adjuvant [21] versus metastatic [86] settings. It has been hypothesised that ICI therapy may be associated with greater toxicity in patients with early-stage disease, as a result of the immunosuppressive effects of a higher disease burden in the metastatic setting [87].

Tumour type may also influence toxicity. In a systematic review incorporating 6938 patients across 48 prospective ICI monotherapy trials, the authors sought to identify patterns and incidence of irAEs based on tumour type and ICI class [88]. Melanoma patients treated with anti-PD-1 had a higher frequency of gastrointestinal and skin irAEs and a lower frequency of pneumonitis than NSCLC patients treated with anti-PD-1. Arthritis and myalgia were more common in melanoma compared with RCC, where pneumonitis was more prevalent. In some instances (e.g. vitiligo in melanoma) there is a sound immunologic hypothesis for the pattern of toxicity observed. Other proposed explanations for the different toxicities observed in different tumour types include differences in the tumour microenvironment and neoantigen expression [88]. In patients with NSCLC treated with anti-PD-1, comorbidities such as chronic obstructive pulmonary disease and prior thoracic radiation may help account for the higher incidence of pneumonitis in this population [88].

Some patients have been excluded from or underrepresented in the seminal clinical trials of checkpoint inhibitors, due to concerns about safety and excess toxicity. Examples include those with pre-existing autoimmune diseases, chronic viral infections, organ dysfunction, brain metastases, organ transplant recipients and those at the extremes of age. As summarised in a review by Johnson et al., there is accumulating data challenging the notion that ICIs are contraindicated in such patients [89•].

Recommencing ICI Following Prior Immune-Related Toxicity

The decision to recommence ICI therapy following resolution of high-grade irAEs represents a challenge for clinicians. With the exception of endocrine toxicities which can be treated with physiologic hormone replacement, guidelines recommend permanent discontinuation of ICIs following a CTCAE grade 4 toxicity [6•, 7•]. Due to the potential for morbidity and mortality, permanent discontinuation is recommended for grade 3 hepatitis, pneumonitis, neurologic and ophthalmologic toxicities [6•].

In general, the toxicity profile of anti-PD-1 is considerably more favourable than that of their anti-CTLA-4 counterparts. There has until recently been little data on their safety in patients with previous high-grade irAEs following ipilimumab. To clarify this, Menzies et al. performed a retrospective analysis of 119 patients with advanced melanoma and pre-existing autoimmune diseases and/or major irAEs with ipilimumab that went on to receive anti-PD-1 [90•]. In patients with prior ipilimumab toxicity requiring immunosuppression ($n = 67$), recurrence of the same irAE was rare (2 of 67 patients, i.e. 3%). In contrast, new irAEs occurred frequently and were often high-grade. Twenty-three patients (34%) developed new irAEs, and 14 of these (61%) were ≥ grade 3. Notably, recurrence of colitis was rare (2%), even in those with severe colitis requiring TNF-α inhibitors.

In a retrospective review of 40 patients with metastatic melanoma who received ipilimumab after progression on anti-PD-1, grades 3–4 irAEs occurred in 35% of patients, which is higher than observed in the anti-PD-1-naïve population [1, 91]. No association between toxicity and response was observed in this study [91].

The safety of resuming anti-PD-1 in patients who develop high-grade irAEs during combination ipilimumab/nivolumab has also been explored. In a study of 88 patients with metastatic melanoma who discontinued combination therapy due to clinically significant irAEs, all patients were re-challenged with anti-PD-1 [92•]. Approximately 40% of patients developed clinically significant recurrent (18%) or distinct (21%) irAEs upon PD-1 re-challenge. Of the 14 patients with recurrence of the same irAE, 7 were grades 3–4 and 10 (71%) discontinued treatment due to the recurrent irAE. There was one grade 5 event, a recurrent rash which progressed to fatal SJS/TEN. Certain toxicities appeared more or less likely to recur than others. Colitis, a classic ipilimumab-associated toxicity was less likely to recur, with only 2 of 33 (6%) patients experiencing recurrent colitis or diarrhoea with anti-PD-1 resumption.

There is accumulating evidence that patient outcomes are not compromised when ICIs are discontinued due to toxicity. In a retrospective analysis designed to assess the efficacy and safety of combination ipilimumab/nivolumab in patients with metastatic melanoma who discontinued treatment because of AEs, the response rate in those who discontinued treatment was numerically higher than in those who did not (58.3 vs 50.2%). Median PFS non-significantly favoured patients who did not cease treatment for an AE (8.4 vs 10.8 months) as did an 18-month landmark PFS (38 vs 49%), though longer follow-up is required to see if these potential differences widen [85•, 87]. Prospective studies are required to determine whether resumption of maintenance anti-PD-1 is beneficial for patients who cease combination therapy due to toxicity.

Conclusion

ICI therapy has revolutionised the treatment of multiple malignancies. While the toxicity profile is generally favourable, irAEs can develop and may occasionally be life-threatening. Management is with immunosuppression and requires close collaboration with our subspecialty internal medicine colleagues.

As the number of patients treated with ICI therapy around the world grows, we continue to learn more about the intricacies of managing immune-related toxicity. Collaboration between groups is required to continue gathering real-world patient data, to help inform the challenging decisions we make on a day-to-day basis regarding patients who frequently differ from those included in landmark clinical trials. Identifying predictive biomarkers of both efficacy and toxicity would help guide treatment decisions, and should be a research priority in the years ahead.

Compliance with Ethical Standards

Conflict of Interest Matteo S. Carlino has received compensation from MSD, Bristol-Myers Squibb, Novartis, and Amgen for service on advisory boards.

David J. Palmieri declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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