Taylor & Francis
Taylor & Francis Group

Expert Review of Quality of Life in Cancer Care

ISSN: (Print) 2380-9000 (Online) Journal homepage: https://www.tandfonline.com/loi/terq20

The management of immune-related adverse events associated with immune checkpoint blockade

André P. Fay, Raphael Brandão Moreira, Paulo R. S. Nunes Filho, Caroline Albuquerque & Carlos H. Barrios

To cite this article: André P. Fay, Raphael Brandão Moreira, Paulo R. S. Nunes Filho, Caroline Albuquerque & Carlos H. Barrios (2016) The management of immune-related adverse events associated with immune checkpoint blockade, Expert Review of Quality of Life in Cancer Care, 1:1, 89-97, DOI: 10.1080/23809000.2016.1142827

To link to this article: https://doi.org/10.1080/23809000.2016.1142827

Published online: 12 Feb 2016.

EXPERT REVIEW OF QUALITY OF LIFE IN CANCER CARE, 2016
VOL. 1, NO. 1, 89–97
http://dx.doi.org/10.1080/23809000.2016.1142827

Taylor & Francis
Taylor & Francis Group

REVIEW

The management of immune-related adverse events associated with immune checkpoint blockade

André P. Fay[a,b], Raphael Brandão Moreira[c], Paulo R. S. Nunes Filho[a], Caroline Albuquerque[a] and Carlos H. Barrios[a,b]

[a]Department of Medical Oncology, PUCRS School of Medicine, Porto Alegre, Brazil; [b]Department of Medical Oncology, Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [c]Department of Medical Oncology, Centro Oncológico Antônio Ermínio de Moraes, São Paulo, Brazil

ABSTRACT

Immunotherapy has become an important component of modern oncology therapy. Recently methods of immune checkpoint blockade include; anti-CTLA-4, anti-PD-1/PD-L1, or a combination of both therapies and have been developed with the objective of restoring immune system T-cell responses against cancer. This strategy has demonstrated important clinical activity in different tumor types and is currently approved for the treatment of several malignancies worldwide. However, the experience gathered so far with this strategy has revealed emerging immune-related adverse events (irAEs) that deserve particular attention. irAEs can affect any organ or system and require adequate diagnosis, rapid recognition and appropriate management as they may have an impact on the outcome of patients receiving these therapies.

ARTICLE HISTORY
Received 7 December 2015
Accepted 13 January 2016

KEYWORDS
immunotherapy; immune-related adverse events; toxicity; CTLA-4 inhibitors; PD-1 inhibitors; PD-L1 inhibitors

Introduction

Over the past few decades, the immune system has been recognized as having an important role in cancer progression and treatment [1]. Improved understanding of the biology underlying the anti-tumor immune response has brought new life to immunotherapy. The discovery of immune checkpoint molecules that regulate T-cell responses has led to the development of therapeutic strategies that restore the immune response against tumor cells [2]. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and Programmed Death-1 (PD-1) are among the first recognized checkpoints that negatively regulate T-cell immune responses [3,4].

Ipilimumab is a fully human monoclonal antibody against the T-cell co-inhibitory pathway CTLA-4. CTLA-4 acts as an immune brake to prevent T-cell overstimulation. Blockade of the CTLA-4 pathway by the administration of ipilimumab can shift the immune system balance toward T-cell activation [4]. Ipilimumab was the first immune checkpoint inhibitor to demonstrate prolongation of overall survival in patients with advanced melanoma [4]. In addition, long-term follow-up has demonstrated a plateau in survival curves indicating the potential of durable responses resulting from this strategy [5].

Similarly, PD-1 is an immune checkpoint expressed on the surface of T-lymphocytes, B-lymphocytes, and monocytes [6]. PD-L1 and PD-L2 are the ligands for PD-1 and are expressed in tumor cells or tumor infiltrating immune cells at different levels. The binding of PD-L1 or PD-L2 to PD-1 results in negative regulation of T-cell signaling and activation. PD-1 and PD-L1 inhibitors are antibodies, which restore the T-cell-mediated anti-tumor response [7]. Recently, PD-1 inhibitors have shown to be more effective compared to ipilimumab in advanced melanoma and have been associated with a better toxicity profile [8–11]. In addition, the blockade of the PD-1/PD-L1 axis has demonstrated antitumor activity in a variety of tumor types including non-small-cell lung carcinoma (NSCLC), renal cell carcinoma [12], urothelial carcinoma [13], Hodgkin's lymphoma [14], head and neck carcinoma [15], and mismatch-repair-deficient colorectal cancer [16]. Furthermore, emerging evidence suggests that the combination of immune checkpoint inhibitors appears to be more effective when compared to single immune agents. However, combination therapy seems to be associated with increased toxicity [17–19].

While immunotherapy can lead to a significant clinical benefit in many tumor types, it has been associated with a unique profile of side effects, labeled 'immune-related adverse events' (irAEs), which are different from the chemotherapy-associated AEs [2]. The toxicity profile of these drugs in pivotal clinical trials is summarized in Tables 1–6.

CONTACT André P. Fay andre.fay@pucrs.br [PUCRS School of Medicine, Av. Ipiranga 6690 – Building 60 (HSL) - 3rd Floor, 302, Porto Alegre, RS 90610-000, Brazil]

Table 1. Nivolumab and pembrolizumab irAE in phase III melanoma trial.

	Pembrolizumab 2 mg/kg q3w *N*: 277		Nivolumab 3 mg/kg q2w *N*: 313	
Adverse event	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Diarrhea	14.4	1.1	19.2	2.2
Colitis	3.6	2.5	1.3	0.6
Rash	13.4	0	25.9	0.6
Pruritus	14.1	0	18.8	0
Hypothyroidism	8.7	0	8.6	0
Arthralgia	11.6	0.4	7.7	0
Pneumonitis	1.8	0.4	NR	NR
Hypophysitis	0.7	0.4	NR	NR
Uveitis	1.1	0	NR	NR

Source: Robert et al. [8] and Larkin et al. [18] .

Table 2. Nivolumab and pembrolizumab irAE in phase III lung cancer trial.

	Pembrolizumab NSCLC		Nivolumab NSCLC, squamous	
Adverse event	Total (%)	G3/4 (%)	Total (%)	G3/4 (%)
Diarrhea	8.1	0.6	8.0	0
Pruritus	10.7	0	NR	NR
Rash	9.7	0.2	4.0	0
Hypothyroidism	6.9	0.2	NR	NR
Pyrexia	4.2	0.6	5.0	0
Arthralgia	9.1	0.4	5.0	0
Pneumonitis	3.6	1.8	5.0	0
Transaminases elevation	3.0	0.6	NR	NR
Fatigue	19.4	0.8	16.0	1.0

Source: Garon et al. [11] and Borghaei et al. [20].

Table 3. Nivolumab irAE in phase III kidney cancer trial.

	Nivolumab kidney (*N*: 406)	
Adverse event	Total (%)	G3/4 (%)
Diarrhea	12	1
Pruritus	14	0
Rash	10	0
Cough	9	0
Anemia	8	2
Pneumonitis	4	1
Fatigue	33	2
Mucositis	3	0
Fatigue	13	0
Peripheral edema	4	0

Source: Motzer et al. [12].

Table 4. Nivolumab irAE in phase II refractory Hodgkin disease trial.

	Nivolumab refractory Hodgkin (*N*: 23)	
Adverse event	Total (%)	G3/4 (%)
Diarrhea	13	0
Pruritus	13	0
Rash	22	0
Cough	9	0
Thrombocytopenia	17	0
Lymphonepnia	9	0
Hypothyroidism	9	0
Mucositis	9	0
Fatigue	13	0
Myelodysplastic syndrome	4	4
Pancreatitis	4	4

Source: Ansell et al. [14].

Table 5. Ipilimumab irAE in MDX-020 trial.

	Ipilimumab + gp100 *N*: 380			Ipilimumab *N*: 131			Gp100 *N*: 132		
Adverse event	Total (%)	G3	G4	Total (%)	G3	G4	Total (%)	G3	G4
Pruritus	67 (18)	1	0	32 (24)	0	0	14 (11)	0	0
Rash	67 (18)	5	0	25 (19)	1	0	6 (5)	0	0
Vitiligo	14 (3.7)	0	0	3 (2)	0	0	1 (1)	0	0
Diarrhea	115 (30)	14	0	36 (28)	6	0	18 (14)	1	0
Colitis	20 (5)	11	1	10 (8)	7	0	1 (1)	0	0
Endocrine	15 (4)	4	0	10 (8)	3	2	2 (2)	0	0
ALT	3 (2)	2	0	2 (2)	0	0	3 (2)	0	0
AST	4 (1)	1	0	1 (1)	0	0	2 (2)	0	0
Hepatitis	2(1)	1	0	1 (1)	0	0	0	0	0
Total	338 (89)	62	4	105 (80)	25	5	104 (79)	15	0

Source: Hodi et al. [4].

Table 6. Ipilimumab irAE in phase II dose-ranging trial.

	0.3 mg/kg		3.0 mg/kg		10.0 mg/kg	
Adverse event	Total	G3/4	Total	G3/4	Total	G3/4
Diarrhea	12	–	18	1	28	10
Colitis	–	–	4	1	4	2
Rash	3	–	17	1	16	–
Pruritus	2	–	15	1	23	2
Hepatitis	–	–	–	–	2	2
Endocrine	–	–	4	2	3	1
Others	1	–	1	–	5	2
SAE-IR	6		13		19	

Source: Wolchok et al. [21].

Briefly, among patients with metastatic melanoma treated with various doses of ipilimumab, more than 70% of patients experienced AEs of any grade [4]. Initially, 25% of these events were grade 3 or 4 toxicities, such as dermatitis, colitis, hepatitis, and hypophysitis as defined by Common Terminology Criteria for Adverse Events (CTCAE).

In a recent report summarizing the experience of a single institution, 85% of patients receiving ipilimumab had an AE of any grade and 19% had to discontinue therapy due to toxicity. Interestingly, clinical outcomes were not affected neither by the occurrence of irAEs nor by the use of systemic corticosteroids, the treatment for many of these toxicities [22]. In their experience, 35% of patients required high-dose of corticosteroids, and out of these, 30% required another type of immunosuppressive agents to control irAEs.

Recent advances in immune therapeutics create a new set of challenges for clinicians, who must develop specific skills to identify and manage these AEs. Prompt recognition, and adequate management of irAEs is essential to maximize the clinical benefit associated with these agents [23]. Immune checkpoint inhibitors have been now approved in several countries, and as a consequence, the experience in recognizing and managing AEs is increasing. In this review, we sought to summarize the toxicity profile of the available immune checkpoint inhibitors highlighting the management of irAEs.

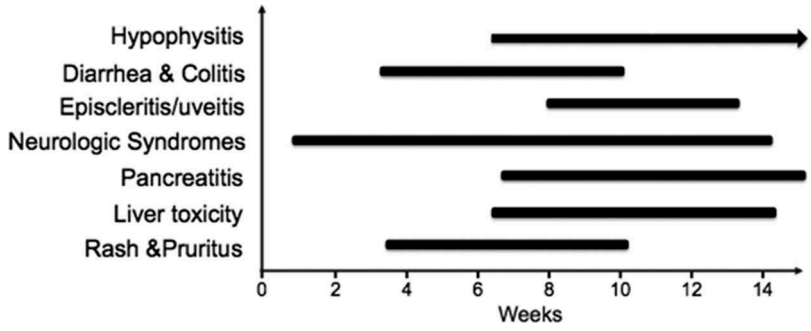

Figure 1. Time of start and duration of specific irAEs

Mechanism of action of immune-related toxicities

Mechanisms of irAEs are not completely understood. Immune-related toxicities are, generally, related to the inflammatory reaction produced by immune system responses against specific organs and tissues. Presumably immune-related T-cell activation leads to the secretion of high levels of CD4 T-helper cell cytokines and cytolytic CD8 T-cell tissue infiltration [24]. As T-cell immune responses are not necessarily tissue specific, the hyperactivity leads to cross-reactivity breaking tolerance. In the case of checkpoint inhibitors, we induce an active immune cross-reaction generating populations of T-cells that interact with specific tissues potentially leading to AEs [25].

General principles

Immune-related toxicities are different from toxicities related to cytotoxic chemotherapy and targeted agents. Education of both clinicians and patients is an essential aspect of management. A high index of suspicion and early recognition are essential and allow for the implementation of easier treatment measures assuring patient compliance. In addition, due to the nature of some of these toxicities other subspecialties may need to be consulted to optimally diagnose and manage irAEs. Therefore, in many instances, a multidisciplinary approach is needed.

While we must recognize that some of the toxicities associated with immunotherapy can be severe, it is important to note that discontinuation rates have been low in most studies reported so far. Anti-CTLA4 treatment seems to have a dose-related toxicity profile that has not been seen with blockade of the PD1/PD-L1 axis [21]. Conversely, toxicities related to PD1 or PDL1 inhibition may take longer to resolve [23].

One important emerging aspect that should be noted is that several toxicities seem to happen earlier in the course of treatment. This is particularly important considering the protracted administration of PD1 and PDL1 inhibitors. Usually, most AEs are not expected to occur before the first four weeks of treatment [26]. Furthermore, there seems to be a predictable pattern of appearance of the different immune toxicities with skin and gastrointestinal toxicities generally appearing in the first 4–6 weeks, while liver and endocrine manifestations tend to occur later, after the third month (Figure 1).

Definitive data defining optimal management of irAEs is still lacking, although experience so far allows for some broad recommendations. In general, based on completed clinical trials and in the experience of large cancer centers, grade 2 toxicities are managed with a treatment break until symptoms recover or toxicity returns to grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day or equivalent) (Table 7) should be started if symptoms do not resolve after a few days. Severe toxicities (grade 3 or 4) should be treated with high doses of corticosteroids (prednisone 1–2 mg/kg/day or equivalent) and occasionally may require permanent immunotherapy discontinuation. Overall, steroids can be tapered over a few weeks if symptoms are recovered and toxicity decreases to grade 1 (Table 8).

Infusion-related reactions

Infusion-related reactions (IRR) such as flushing, chills, pruritus, rash, nausea, dyspnea, cough, bronchospasm, fever, malaise, headache, hypotension/hypertension, diaphoresis, tachycardia, and pain are common during the infusion of monoclonal antibodies. Interestingly, few IRRs have been described with ipilimumab or nivolumab in

Table 7. Steroids equivalence.

Agent	Equivalent dose (mg)
Hydrocortisone	1
Dexametasone	26
Prednisone	3
Prednisolone	3
Methylprednisolone	6
Fludrocortisone	12

Table 8. Special key points in the management of adverse events.

1. Education of the medical team and patients is an essential aspect of management
2. High index of suspicion and early recognition are mandatory
3. Supportive treatment, a careful monitoring of patients need to be applied to all patients with irAEs
4. In grade 1 or 2 toxicity: steroids (prednisone 0.5 mg/kg/day or equivalent) may be started if symptoms do not resolve after 3 days
5. In grade 3 or 4 toxicity: Treatment should start with high doses of steroids (prednisone 1 to 2 mg/kg/day or equivalent)
6. Multidisciplinary approach should be always considered
7. Facing an irAEs, infection should be excluded
8. Withhold immunotherapy until symptoms are resolved or toxicity returns to grade 1 or less
9. Steroids should be tapered in at least 4 weeks in grade 3 or 4 toxicities
10. Steroids tapering: we suggest to reduce 25% of the steroid dose every 7–10 days
11. Other immunosuppressive agents may be considered in refractory cases

pivotal clinical trials [27]. IRRs caused by monoclonal antibodies are usually managed slowing the rate of infusion and rarely require medical therapy [28,29].

Immune-related adverse events by organ system

Dermatological immune-related adverse events

Dermatological irAEs have been observed in up to 44% of patients. However, less than 2% of these have been considered severe (grade 3 or 4). However, Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported and must be considered in rapid-onset cases of skin toxicity.

A maculopapular rash is reported in up to 20% of patients receiving ipilimumab. Usually, it occurs after the third week of therapy, with its peak at the sixth week. Most toxicities affecting the skin are grade 1 (involvement of less than 10% of body surface area) and may be accompanied by symptoms, such as pruritus [30].

Blocking the PD-1/PD-L1 axis, a maculopapular rash is most commonly observed. Interestingly, rarer rashes have been described, including lichenoid [31], bullous pemphigoid [32], Stevens–Johnson syndrome, and toxic epidermal necrolysis [33], which are of special interest due to their severity and potentially life-threatening consequences. The underlying mechanism for the development of this toxicity is most likely the blockade of common antigens, co-expressed on a patient's tumor cells, and those that are present on the dermo-epidermal junction and/or other layers of the skin [33].

Skin rash restricted to a small portion of the body surface area may be observed, or occasionally treated with topical corticosteroids, such as betamethasone 0.1%, or clobetasol 0.05%. No changes in the immunotherapy dose or schedule are necessary. On the other hand, patients with symptomatic lesions and involvement of a larger (10–30%) proportion of the body surface (grade 2) should be treated with topical or oral steroids (prednisone, up to 0.5 mg/kg/day, or equivalent). Rapid improvement is expected and the steroid should be tapered according to the treatment response. To proceed with subsequent infusions skin involvement should be grade 1 at the most, otherwise, treatment must be postponed. Rare events of grade 3 skin rash (greater than 30% of body surface area involved) must be treated with IV steroids (methylprednisolone 1–2 mg/kg/day, or equivalent). Upon improvement, oral steroids may replace IV steroids with a careful tapering plan. Permanent discontinuation of therapy due to dermatologic toxicity has been reported in <5% of patients in clinical studies [30].

Gastrointestinal immune-related adverse events

Immune-related AEs affecting the gastrointestinal tract have been frequently reported in clinical trials using immune-checkpoints inhibitors. The rate of gastrointestinal irAEs with ipilimumab has ranged from 18 to 27.5% at the dose of 3 mg/kg and from 27 to 32.8% at the dose of 10 mg/kg [21]. Regarding the anti-PD-1 agents, diarrhea has been reported in approximately 18% of the cases, 2–3% of them classified as grade 3 or 4 [19,22].

Diarrhea is the most common gastrointestinal irAE, usually starting around week 6 or 7 of treatment and recovering around week 10 [23]. Endoscopy and biopsies have revealed an autoimmune colitis most frequently involving the distal colon and sparing the rectum with different degrees of severity. Macroscopic abnormalities identified with colonoscopy are erythema, edema, erosion, and bleeding. Histological examination of the affected colonic mucosa shows neutrophil invasion with destruction of the epithelial surface and crypts [19].

Management of grade 1 or 2 diarrhea is accomplished with usual antidiarrheal drugs (such as loperamide, atropine sulfate, and diphenoxylate hydrochloride), oral hydration, and electrolyte supplementation if needed. Dietary modification and antimotility agents can be helpful in controlling symptoms and should be included in the initial treatment plan. Persistent grade 2 diarrhea, defined as 4–6 stools per day over baseline for more than 3 days of symptoms, is an indication for treatment with steroids (0.5 mg/kg of prednisolone or equivalent dose). Generally, improvement is seen in 48–72 hours and corticosteroids can be tapered slowly during approximately 4 weeks.

In refractory, persistent, or grade 3 or 4 diarrhea, defined as at least seven diarrheal bowel movements

in 24 hours over baseline, colonoscopy, or CT abdomen can be considered to confirm colitis. Importantly, infection must be excluded through examination of stools testing for the presence of leucocytes and germ cultures. More intensive management is recommended for grade 3 or 4 diarrhea, including parenteral hydration, nutritional support and early intravenous corticosteroids (methylprednisolone 125 mg, IV, bolus) followed by high doses of oral corticosteroids (prednisone 1–2 mg/kg or equivalent doses). If there is no improvement in 48–72 hours, treatment with infliximab at a dose of 5 mg/kg every 2 weeks may be considered. Glucocorticoid therapy should be tapered along 6–8 weeks [19–23].

Although the incidence of severe complications such as perforation and obstruction is low (<1% in pivotal clinical trials), consequences can be life threatening and require immediate evaluation and surgical consultation [19,23].

Endocrine immune-related adverse events

The most common endocrine AEs associated with checkpoint inhibition are thyroiditis, hypophysitis, and adrenal insufficiency but other alterations have been described such as low testosterone levels and type 1 diabetes mellitus [34–38]. It is recommended that all patients receiving checkpoint inhibitors should be followed carefully regarding endocrine dysfunctions. Monitoring thyroid-stimulating hormone (TSH) levels is recommended before each ipilimumab infusion according to the US FDA. In addition, thyroid function studies at intervals of 6–12 weeks should be monitored for the first 6 months after completing treatment. Adrenocorticotropic hormone, cortisol, and testosterone (in men) should also be checked in patients who develop fatigue and nonspecific symptoms [23]. As most of the clinical manifestations of early endocrine dysfunction are non-characteristic, a high index of suspicion is important to identify and treat these conditions.

CTLA-4 blockade has been reported to cause endocrinopathies in 3–20% of patients. The most common are: hypophysitis, thyroiditis, and adrenal insufficiency [23,21,39]. Similarly, endocrinopathies with the use of PD-1/PD-L1 blockade occur in 5–20% of cases and are similar to those described with ipilimumab. Endocrine toxicities tend to occur late and are generally diagnosed between weeks 12 and 24 [23].

Hyperthyroidism or hypothyroidism may occur in 10–15% of patients and usually hyperthyroidism precedes a prolonged period of hypothyroidism [23]. Thyroid dysfunction may take 6–10 months to resolve.

An important concern is the delivery of subsequent immunotherapy in patients with adrenal dysfunction on replacement corticosteroids and caution should be taken while treating them [23]. Long-term follow-up of patients who had endocrine toxicities suggests that some thyroid function may be restored over time but that dysfunctions of the corticosteroid and gonadal axes are likely permanent [34,37]. In our experience, after dealing with acute adrenal insufficiency and tapering hormone replacement to the maintenance dose (7.5 mg/day of prednisone or equivalent) the treatment with immunotherapy can be cautiously resumed. Further clinical data on the safety and efficacy of this approach is needed.

Symptoms of hypophysitis are characteristically nonspecific, and this diagnosis requires a high index of suspicion. Headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment have also been reported. Symptoms rarely start before 6 weeks and some cases have been reported to occur many months later [24]. Low levels of hormones define the diagnosis: adrenocorticotropic hormone, TSH, follicle-stimulating hormone, luteinizing hormone, growth hormone, and prolactin. Magnetic resonance imaging of the hypophysis is helpful to identify enlargement of the gland; however, some cases are diagnosed in the absence of radiological findings. The cornerstone of management of hypophysitis is hormone replacement. Similarly, prompt management improves symptoms and allows for continuation of the immune agent but endogenous hormone secretion may not completely recover [23].

Hepatic immune-related adverse events

Hepatotoxicity related to immunotherapy is a relatively rare event, occurring in less than 10% of cases with both anti-CTLA4 and anti-PD-1. Moreover, serious AEs are detected in less than 1% of patients [19]. The main manifestation consists in elevation of transaminases or bilirubin. Fever is present in a minority of patients. Biopsy studies have shown diffuse lymphocyte infiltration [18]. Liver function tests need to be monitored before each administration of immunotherapy. In case any degree of liver dysfunction is detected, other causes, such as neoplastic progression, viral hepatitis or toxicity induced by other drugs should be investigated [23]. The management of this adverse event consists on drug discontinuation in case of hepatotoxicity grade 2 until improvement to grade <1. Grade 3 or 4 hepatotoxicity, should lead to discontinuation of immunotherapy and treatment with intravenous corticosteroids at high doses followed by oral prednisone therapy 1–2 mg/kg (or equivalent dose of

dexamethasone). In the absence of improvement in 48 hours, mycophenolate mofetil may be considered. In these cases, infliximab should be avoided for its hepatotoxic potential. Glucocorticoid therapy should be titrated for at least 4 weeks and, in the case of ipilimumab, recurrence of hepatitis has been reported during weaning of steroids [19,23].

Pancreatic immune-related adverse events

Immune-related pancreatitis has been reported in less than 1.5% of patients receiving anti-CTLA-4 antibodies [40]. Although some patients complain of unspecific symptoms like abdominal pain, pancreatitis is usually diagnosed by an asymptomatic increase of amylase and lipase with associated radiographic changes [41–43]. It is important to note that an increase of amylase and/or lipase alone does not confirm diagnosis of pancreatitis. Therefore, the routine monitoring of amylase and lipase values in otherwise asymptomatic patients treated with checkpoint blockade is not recommended. For symptomatic patients, treatment with prednisone or dexamethasone can be considered [23].

Pulmonary immune-related adverse events

Inflammatory conditions affecting the lungs, such as sarcoidosis or organizing inflammatory pneumonia have been observed with ipilimumab as well as PD-1 inhibitors in less than 10% of patients receiving these agents [44,45]. New respiratory symptoms, such as cough or shortness of breath in patients receiving immunotherapy should be investigated with imaging and prompt a differential diagnosis to rule out infection among other conditions.

Severe pulmonary toxicities should be treated with 1–2 mg/kg of IV steroids. Additional immunosuppression with infliximab, mycophenolate mofetil, or cyclophosphamide may be considered if no resolution with steroids is seen.

Rare immune-related toxicities

Episcleritis, conjunctivitis, and uveitis have been described in less than 1% of patients receiving ipilimumab. Photophobia, pain, dryness of the eyes, and blurry vision may be present at the time of diagnosis. A multidisciplinary approach including an ophthalmologic consultation is recommended. Topical steroids are usually the treatment of choice for these situations [46].

Neurologic, renal [47,48], or hematologic toxicities are rare occurrences that should be assessed and managed in a multidisciplinary manner [49]. The safety of administering immunotherapy in patients with a previous diagnosis of autoimmune diseases is not well established as these situations have been excluded from most clinical trials. Exacerbations of underlying autoimmune conditions may be seen and this subgroup of patients should be followed carefully [50]. Clinical expansion of the use of these agents in wider populations should be able to inform our decision in this subject.

Immune-related adverse events associated with combination immunotherapy

The combination of CTLA-4 and PD-1 blockade has shown very encouraging results with improved clinical benefit compared with either CTLA-4 or PD-1/PD-L1 agents as single agents [17,51,52]. At the same time, the incidence of irAEs has been reported as numerically higher with the combination. Grade 3 or 4 irAEs have been reported in up to 50% of patients treated with combinations [18,19]. In addition, AEs could be even more frequent when combining immunotherapy with targeted agents [53].

Interestingly, no new toxicities have been observed with the combination of these agents that have not been described with both ipilimumab or nivolumab alone. These combinations are being tested in phase III studies for several malignancies such as kidney and bladder tumors. Forthcoming information will help in characterizing the toxicity profile and the specific management in these situations.

Considerations over the long-term and high-dose use of steroids

Corticosteroids play an important role in the management of inflammatory or immune-related conditions. The management of corticosteroid adverse effects is beyond the scope of this review; however, it is well established that this strategy may be associated with serious risks including osteoporosis, adrenal suppression, hyperglycemia, cardiovascular disease, Cushing's syndrome, psychiatric disorders, and immunosuppression [54].

Corticosteroids are the cornerstone of the treatment of irAEs and their use may be necessary for long periods of time. Corticosteroid-related AEs seem to be related to both the average dose and cumulative duration of the treatment. It is important to note that the ideal dose, the maximum dose or the appropriate treatment duration of corticosteroids have not been established and likely should be contingent on the disease being treated [55]. Corticosteroids-related AEs can be reduced through careful patient monitoring and implementation of preventive measures, such as the use of the

lowest dose required for an adequate management of the underlying condition.

Use of other immunosuppressive agents

Occasionally, corticosteroids may not be enough to adequately manage some irAEs. Infliximab (5 mg/kg) may be considered in patients with steroid-refractory diarrhea [56,57]. In addition, anti-tumor necrosis factor-alpha agents (anti-TNF-**α**) have been effective therapies in refractory irAEs, such as diarrhea and pneumonitis. As previously discussed in this manuscript, those agents should not be used in patients presenting with hepatotoxicity. However, clear guidelines for their application in these situations remain to be defined [58].

Expert commentary

Immunotherapy has dramatically changed the treatment landscape for several tumor types significantly improving clinical outcomes. As these agents are becoming widely used worldwide and the list of approved indications is increasing, the challenge of dealing with the associated complications needs to be recognized. irAEs are common and may be severe. The health care team involved in patient management needs to be educated, trained and prepared to rapidly recognize and manage irAEs. Immunosuppressive treatments are the basis of the therapeutic strategy. Steroids in various forms and regimens have been widely used successfully with symptomatic improvement and event resolution in most cases. However, no prospective data are available yet to define the best agent, regimen, and strategy.

Differently from our experience with targeted therapies such as vascular endothelial growth factor-tyrosine kinase inhibitors in kidney cancer, the appearance of irAEs has not been associated with efficacy parameters. At the same time, further data is required to address whether the use of steroids in the management of irAEs does have an impact on efficacy as well.

Presently, the management of these patients should follow established guidelines mostly based on completed clinical trials and real life experience of high-volume institutions reporting on the use of these promising therapies.

Five-year view

Methods of immune checkpoint blockade including anti-CTLA-4, anti-PD-1/PD-L1, or a combination of both therapies represent a revolution in cancer treatment and will become widely internationally. This strategy has demonstrated important clinical activity in different tumor types, and durable responses have been reported. However, this arousal of the immune system against cancer has been associated with a distinct profile of AEs different from those associated with traditional cytotoxic chemotherapy or targeted therapies. Physicians and health professionals involved in cancer care will need to rapidly recognize, diagnose, and appropriately manage these new toxicities. The coming years will be marked by upcoming results of several important clinical trials associated with more experience of these agents in clinical practice. The establishment of guidelines to diagnose and manage irAEs is essential to maximize the clinical benefit of these agents.

Financial & competing interests disclosure

AP Fay has received honorarium from BMS, Pfizer, Novartis, Astellas and has served as a consultant for Janssen. CH Barrios has served on the advisory board and as a consultant for Boehringer-Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech, Eisai. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- The immune system has an important role in cancer progression and treatment.
- Immunotherapies have dramatically changed the treatment landscape of several types of cancer significantly improving clinical outcomes.
- Ipilimumab is a fully human monoclonal antibody against the T-cell co-inhibitory receptor CTLA-4. CTLA-4 acts as an immune brake preventing T-cell overstimulation.
- Anti-PD-1 and PD-L1 antibodies inhibit the PD-1/PD-L1 axis restoring T-cell-mediated anti-tumor response.
- Although immunotherapy leads to significant clinical benefits, immune checkpoint blockade has been associated with a unique profile of side effects (irAEs), which are different from the usual chemotherapy or targeted therapies associated AEs.
- Approximately 85% of patients receiving ipilimumab do report an AE of any grade, and 19% discontinue therapy due to toxicity.
- Advances in immunotherapy create a new set of challenges for clinicians, who must develop specific skills to rapidly identify and manage irAEs.
- Specific organ system-based toxicity management is recommended.
- Generally, grade 2 toxicities are managed with a treatment break until recovery of symptoms or until toxicity returns to grade 1 or less.
- Corticosteroids are useful in the management of irAEs.
- Generally, grade 3 or 4 irAEs should be treated with high doses of corticosteroids and occasionally may require permanent checkpoint inhibitor discontinuation.
- Steroids can be tapered over a few weeks if symptoms are recovered and toxicity decreases to grade 1.

References

1. Wolchok JD, Chan TA. Cancer: Antitumour immunity gets a boost. Nature. 2014;515(7528):496–498. doi:10.1038/515496a.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264. doi:10.1038/nrc3239.
3. Chambers CA, et al. CTLA-4-mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. Annu Rev Immunol. 2001;19:565–594. doi:10.1146/annurev.immunol.19.1.565.
4. Hodi FS, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–723. doi:10.1056/NEJMoa1003466.
5. Schadendorf D, et al. Pooled analysis of long-term survival data from phase ii and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33(17):1889–1894. doi:10.1200/JCO.2014.56.2736.
6. McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. Cancer Med. 2013;2(5):662–673. doi:10.1002/cam4.106.
7. Freeman GJ. Structures of PD-1 with its ligands: sideways and dancing cheek to cheek. Proc Natl Acad Sci U S A. 2008;105(30):10275–10276. doi:10.1073/pnas.0805459105.
8. Robert C, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–2532. doi:10.1056/NEJMoa1503093.
9. Weber JS, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375–384. doi:10.1016/S1470-2045(15)70076-8.
10. Brahmer J, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627.
11. Garon EB, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018–2028. doi:10.1056/NEJMoa1501824.
12. Motzer RJ, et al. Nivolumab for metastatic renal cell carcinoma: Results of a randomized phase II trial. J Clin Oncol. 2015;33(13):1430–1437. doi:10.1200/JCO.2014.59.0703.
13. Powles T, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558–562. doi:10.1038/nature13904.
14. Ansell SM, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311–319. doi:10.1056/NEJMoa1411087.
15. Segal NHOS, Balmanoukian AS, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol. 2015;33(15S).
16. Le DT, et al..PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–2520. doi:10.1056/NEJMoa1500596.
17. Valsecchi ME. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(13):1270. doi:10.1056/NEJMc1509660.
18. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(13):1270–1271. doi:10.1056/NEJMc1509660.
19. Postow MA, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006–2017. doi:10.1056/NEJMoa1414428.
20. Borghaei, et al. N Engl J Med. 2015;373(17):1627–39
21. Wolchok JD, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11(2):155–164. doi:10.1016/S1470-2045(09)70334-1.
22. Horvat TZ, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol. 2015;33(28):3193–3198. doi:10.1200/JCO.2015.60.8448.
23. Weber JS, et al. Toxicities of immunotherapy for the practitioner. J Clin Oncol. 2015;33(18):2092–2099. doi:10.1200/JCO.2014.60.0379.
24. Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo). 2013;2013:857519.
25. Quirk SK, Shure AK, Agrawal DK. Immune-mediated adverse events of anticytotoxic T lymphocyte-associated antigen 4 antibody therapy in metastatic melanoma. Transl Res. 2015;166(5):412–424. doi:10.1016/j.trsl.2015.06.005.
26. Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book. 2015;1(1):76–83.
27. Lacouture ME, et al. Ipilimumab in patients with cancer and the management of dermatologic adverse events. J Am Acad Dermatol. 2014;71(1):161–169. doi:10.1016/j.jaad.2014.02.035.
28. Momtaz P, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol. 2015;33(30):3454–3458. doi:10.1200/JCO.2015.61.0030.
29. Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. Oncologist. 2008;13(6):725–732. doi:10.1634/theoncologist.2008-0012.
30. Baurain JFSM, Pa A, et al. Outcomes of ipilimumab treatment-related adverse events in patients with metastatic melanoma (MM) who received systemic corticosteroids in a phase III trial. J Clin Oncol. 2012;30(ABSTR 8539).
31. Joseph RW, et al. Lichenoid dermatitis in three patients with metastatic melanoma treated with anti-PD-1 therapy. Cancer Immunol Res. 2015;3(1):18–22. doi:10.1158/2326-6066.CIR-14-0134.
32. Carlos G, et al. A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. Melanoma Res. 2015;25(3):265–268. doi:10.1097/CMR.0000000000000155.
33. Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book. 2015;35:76–83. doi:10.14694/EdBook_AM.2015.35.76.
34. Ryder M, et al. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. Endocr Relat Cancer. 2014;21(2):371–381. doi:10.1530/ERC-13-0499.

35. Blomhoff A, et al. Polymorphisms in the cytotoxic T lymphocyte antigen-4 gene region confer susceptibility to Addison's disease. J Clin Endocrinol Metab. 2004;89 (7):3474–3476. doi:10.1210/jc.2003-031854.
36. Ueda H, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature. 2003;423(6939):506–511. doi:10.1038/nature01621.
37. Albarel F, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol. 2015;172(2):195–204. doi:10.1530/EJE-14-0845.
38. Min L, et al. Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. Clin Cancer Res. 2015;21(4):749–755. doi:10.1158/1078-0432.CCR-14-2353.
39. Min L, Ibrahim N. Ipilimumab-induced autoimmune adrenalitis. Lancet Diabetes Endocrinol. 2013;1(3):e15. doi:10.1016/S2213-8587(13)70031-7.
40. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30(21):2691–2697. doi:10.1200/JCO.2012.41.6750.
41. Robert C, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109–1117. doi:10.1016/S0140-6736(14)60958-2.
42. Di Giacomo AM, et al. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. Cancer Immunol Immunother. 2009;58(8):1297–1306. doi:10.1007/s00262-008-0642-y.
43. Banks PA, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102–111. doi:10.1136/gutjnl-2012-302779.
44. Barjaktarevic IZ, et al. Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. Chest. 2013;143(3):858–861. doi:10.1378/chest.12-1467.
45. Eckert A, et al. Anti-CTLA4 monoclonal antibody induced sarcoidosis in a metastatic melanoma patient. Dermatology. 2009;218(1):69–70. doi:10.1159/000161122.
46. Robinson MR, et al. Cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma: a new cause of uveitis. J Immunother. 2004;27 (6):478–479.
47. Izzedine H, et al. Kidney injuries related to ipilimumab. Invest New Drugs. 2014;32(4):769–773. doi:10.1007/s10637-014-0092-7.
48. Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody-induced lupus nephritis. N Engl J Med. 2009;361(2):211–212. doi:10.1056/NEJMc0904283.
49. Voskens CJ, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. PLoS One. 2013;8(1):e53745. doi:10.1371/journal.pone.0053745.
50. Wang HB, et al. Anti-CTLA-4 antibody treatment triggers determinant spreading and enhances murine myasthenia gravis. J Immunol. 2001;166(10):6430–6436.
51. Hans J, Hammers ERP, Jeffrey R, et al. Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). J Clin Oncol. 2014 2014;32(suppl; abstr 4504):5s. doi:10.1200/JCO.2013.54.6911
52. Johnson DB, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol. 2015;3:1–7.
53. Asim Amin ERP, Infante JR, Ernstoff MS, et al. Hammers, Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC). J Clin Oncol. 32:5s. 2014suppl; abstr 50102014 doi:10.1200/JCO.2013.54.6911.
54. Liu D, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9 (1):30. doi:10.1186/1710-1492-9-30.
55. Da Silva JA, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis. 2006;65 (3):285–293. doi:10.1136/ard.2005.038638.
56. Pages C, et al. Ipilimumab-induced acute severe colitis treated by infliximab. Melanoma Res. 2013;23(3):227–230. doi:10.1097/CMR.0b013e32835fb524.
57. Merrill SP, et al. Early administration of infliximab for severe ipilimumab-related diarrhea in a critically ill patient. Ann Pharmacother. 2014;48(6):806–810. doi:10.1177/1060028014528152.
58. Stidham RW, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014;39 (12):1349–1362. doi:10.1111/apt.12749.