Chapter 2

# Management and Supportive Care of Patients Undergoing Immunotherapy

Bernardo L. Rapoport and Ronwyn van Eeden

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67372

**Abstract**

In many tumor types, where the prognosis was shown to be extremely dismal before, immunotherapy is now a new beacon of hope to many patients. Immunotherapy has been approved for use in a many different cancers including metastatic melanoma, advanced non-small cell lung cancer, metastatic renal cell carcinoma, refractory Hodgkin's lymphoma, metastatic bladder cancer advanced head and neck cancer, and the list keeps growing each day. It seems to be generally better tolerated in most patients and less toxic compared to what we have seen in different anticancer treatments from before. However, the toxicities here are termed immune-related adverse events. There is almost no prospective data on these toxicities, and guidelines or recommendations are mostly based on symptomatic management from the ongoing clinical trials. Treating oncologists need to be aware of the subtleties in presentation and the huge difference in the way we mange these side effects. Although most adverse events are low-grade and manageable, they have the potential to be life-threatening if not treated promptly. In this chapter, we address the different immune-related adverse events relating to the organ system they can involve, presentation and symptomatology, general recommendations of management, and individual toxicities. Keywords: immunotherapy, PD-1, CTLA-4.

**Keywords:** immunotherapy, PD-1, CTLA-4, immune-related adverse events, iRAE, supportive care

## 1. Introduction

Immunotherapy has emerged as the utmost oncological advance of 2016 [1]. It encompasses the enhancement, suppression, or induction of the body's own immune system to battle

cancer [1]. There has been a paradigm shift toward immunooncology therapy, and its side effects are often referred to as immune-related adverse events (irAEs). These side effects are in some cases unique and very different than those associated with chemotherapy or targeted drugs. The spectrum of irAEs is typically low-grade and manageable; however, the reporting of irAEs is generally suboptimal [2]. Therefore, oncologists should be aware that there is a broad range of additional toxicities and side effects that can be both unpredictable and even severe in nature. Early recognition of irAEs and aggressive management is crucial to reduce morbidity and mortality. Toxicities associated with PD-1 inhibitors are generally less severe than those associated with CTLA-4 inhibitors; however, grade 3–4 toxicities occur in about 21% of immunotherapy cases [3, 4].

Monoclonal antibodies that are currently registered include the following: anti-PD-1 (nivolumab and pembrolizumab), anti-PD-L1 (atezolizumab), and anti-CTLA-4 antibodies (ipilimumab) [5, 6].

## 2. Pathogenesis

The pathogenesis of irAEs is primarily based on and can be understood by the immune pathophysiology that leads to hyperactivation of T-cells. PD-1 and CTLA-4 are immune checkpoints that are expressed on the surface of antigen-presenting cells in the initiator and effector phase of T-cell activation, respectively. They are responsible for "switching off" the T-cell. Inhibition of these checkpoints allows for overexpression of the immune system, which is a powerful mechanism to defeat tumor cells.

Two signals are required by T cells to become fully activated [7]. The first signal originates from the interaction between T-cell receptors (TCR) and the antigen-peptide major-histocompatibility complex (MHC), which contributes to the specificity of the immune response. Additionally, T cells require a costimulatory antigen-dependent signal that occurs through the interaction between CD28 on T cells and B7-1 and B7-2 on the antigen-presenting cells (APC), to become entirely activated. On the other hand, expression of CTLA-4 by T cells constitutes a mechanism to prevent overstimulation of the immune system. CTLA-4 has a 100-fold higher affinity with the B7 complex than CD28, and this interaction is associated with an inhibitory function on the cell [8]. CTLA-4 inhibitors such as monoclonal antibodies ipilimumab and tremelimumab have been developed to block and release these breaks. Ipilimumab is currently approved for the treatment of metastatic malignant melanoma and is under investigation in the treatment of patients with nonsmall cell cancer (NSCLC).

Another well-established mechanism of immune-response evasion is regulated by expression of PD-L1 in the malignant cells. PD-L1 binds to PD-1 on the T cells and thus initiates a dual mechanism of inhibition by promoting apoptosis in antigen-specific T cells in lymph nodes and simultaneously reducing apoptosis in regulatory T cells referred to as T regs [9].

http://dx.doi.org/10.5772/67372

The mechanism of defeating tumor cells can be understood by the three phases of immunoediting [1]. The first phase, elimination, consists of the eradication of tumor cells by working with the innate and adaptive immune system. It activates several effector cells by inflammatory cytokines released by the tumor cells. The second phase, named equilibrium, is the development of resistance to the elimination phase by the tumour cells. Finally, the escape phase is where further resistance develops toward immune detection. The overactivation of the immune system, and blocking of suppressor checkpoints, also affects normal body tissues, which is the possible mechanism by which toxicities arise, although this remains largely unknown [1]. Checkpoint inhibitors CTLA-4, PD-1, and PD-L1 blockers are approved for use in metastatic melanoma, nonsmall cell lung cancer (NSCLC), renal cell carcinoma, head and neck cancer, Hodgkin's disease, and bladder cancer. They show improvement in overall survival in these tumor types.

## 3. irAEs' general concepts

The incidence of grade 3 or 4 adverse events is higher with CTLA-4 blockers, and PD-1 inhibitors appear to have better tolerability [2, 3, 10]. The grade of irAEs varies according to the dose of drug administered to patients, where smaller doses of drug are used, side effects are similar but are less frequent [11]. The incidence of irAEs can vary with tumor type and between different classes of drugs. The combination of PD-1 inhibitor with a CTLA-4 inhibitor was recently approved for the treatment of metastatic malignant melanoma; however, more adverse reactions were seen when the two drugs were used together. In combination, there are especially more grade 3 or 4 events (55%). It is important to point out that although greater overall response rates were seen, it was also noted that the combination led to a higher incidence of severe irAEs and treatment discontinuations due to severe toxicity [12–14].

Generally, the most frequent irAEs are seen in the gastrointestinal (35%) and dermatological (44%) systems [11]. The incidence of hepatic and endocrine system involvement follows with about 5–6%. Other systems less frequently affected are neurological, ophthalmological, pulmonary, renal, hematological, cardiovascular, respiratory, and musculoskeletal [3, 11, 13]. IrAEs typically develop within 6–12 weeks of initial dosing and resolution occurs within 12 weeks of onset. irAEs may develop after the first dose administered [15, 16]. It has been also hypothesized that the severity of the adverse correlates positively with a response to treatment [4, 14, 17]. However, the correlation of response to treatment and toxicity remains controversial. When managed correctly and promptly and with close monitoring, most are irAEs are reversible [11, 12, 14]. In general, the optimal management of irAEs includes early recognition (by far being the most important), proper assessment of severity so that the choice of therapy, either supportive or immunosuppressive, can be quickly and correctly implemented. Usually, mild adverse events can be observed or treated symptomatically with supportive care. As a guide, with the exception of irAE endocrine moderate events, what is usually required is stopping the offending agent, implementing oral corticosteroid therapy, and restarting therapy again once symptoms have resolved. Severe irAEs warrant permanent discontinuation of the drug, patient hospitalization, and high-dose intravenous corticosteroids, with slow

weaning. In very severe cases, other immunosuppressive agents such as infliximab or mycophenolate mofetil may be necessary [18].

In the following chapter sections, the different systems will be discussed.

### 3.1. Dermatological

A diffused, erythematous maculopapular rash and pruritus can occur in up to 50% of patients treated with anti-CTLA4 or up to 37% of patients treated with anti-PD-1 [4, 13, 15, 17]. The rash can occur after the initial dose of treatment and can be ongoing (**Figure 1A–C**). However, symptoms on an average start 3–4 weeks after treatment. Vitiligo has also been reported [19, 20] (**Figure 2**). In severe cases, toxic epidermal necrolysis and Stevens-Johnson syndrome can occur, but in less than 1% of patients [15, 19]. Most of the dermatological eruptions and pruritus associated with these agents are managed symptomatically and usually do not require treatment delays or discontinuation. A recent meta-analysis of a total of 1208 patients demonstrated that the overall incidence of all-grade rash associated with ipilimumab was 24.3% (95% confidence interval [CI]: 21.4–27.6%), with a relative risk of 4.00 (95% CI: 2.63–6.08, $P < 0.001$). The overall incidence of high-grade rash was 2.4% (95% CI: 1.1–5.1%), with a relative risk of 3.31 (95% CI: 0.70–15.76, $P = 0.13$) [21]. A second meta-analysis from a total of nine clinical trials in patients receiving ipilimumab, nivolumab, tremelimumab, pidlizumab, and pembrolizumab was included. The relative risk of all-grade rash was 4.06 (95% CI: 3.35–4.91; $P < 0.0001$), vitiligo 16.3 (95% CI: 3.21–82.8; $P = 0.0008$), and pruritus was 3.4 (95% CI: 2.24–5.16; $P < 0.00001$) [22].

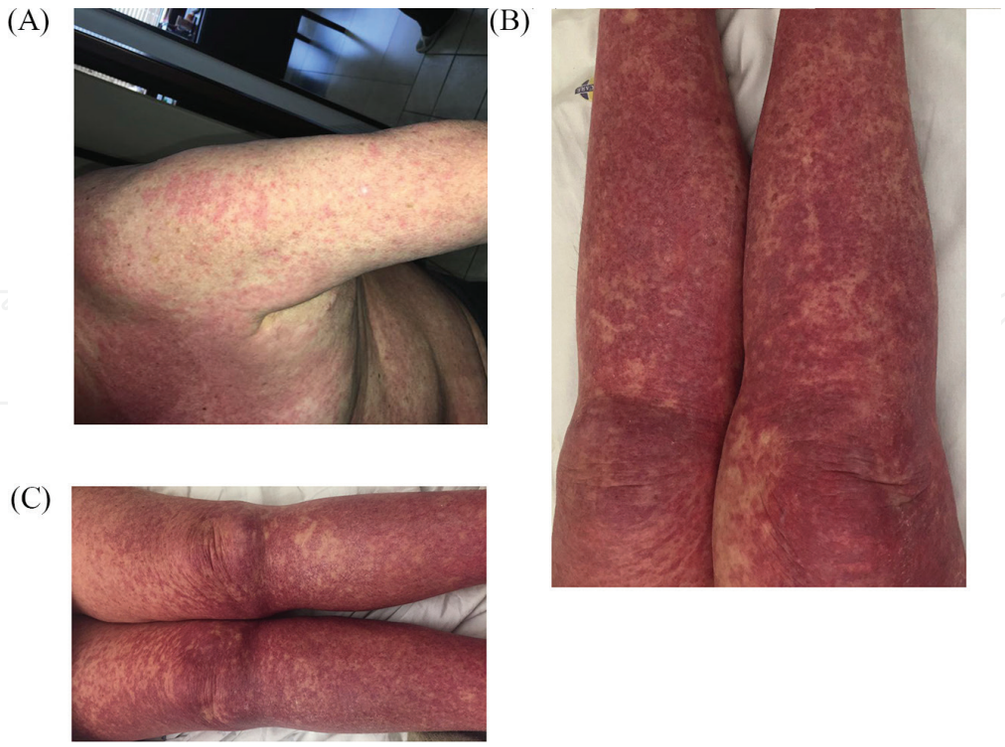


**Figure 1.** Severe generalized maculo-papular rash associated with a combination of ipilimumab and nivolumab.

http://dx.doi.org/10.5772/67372

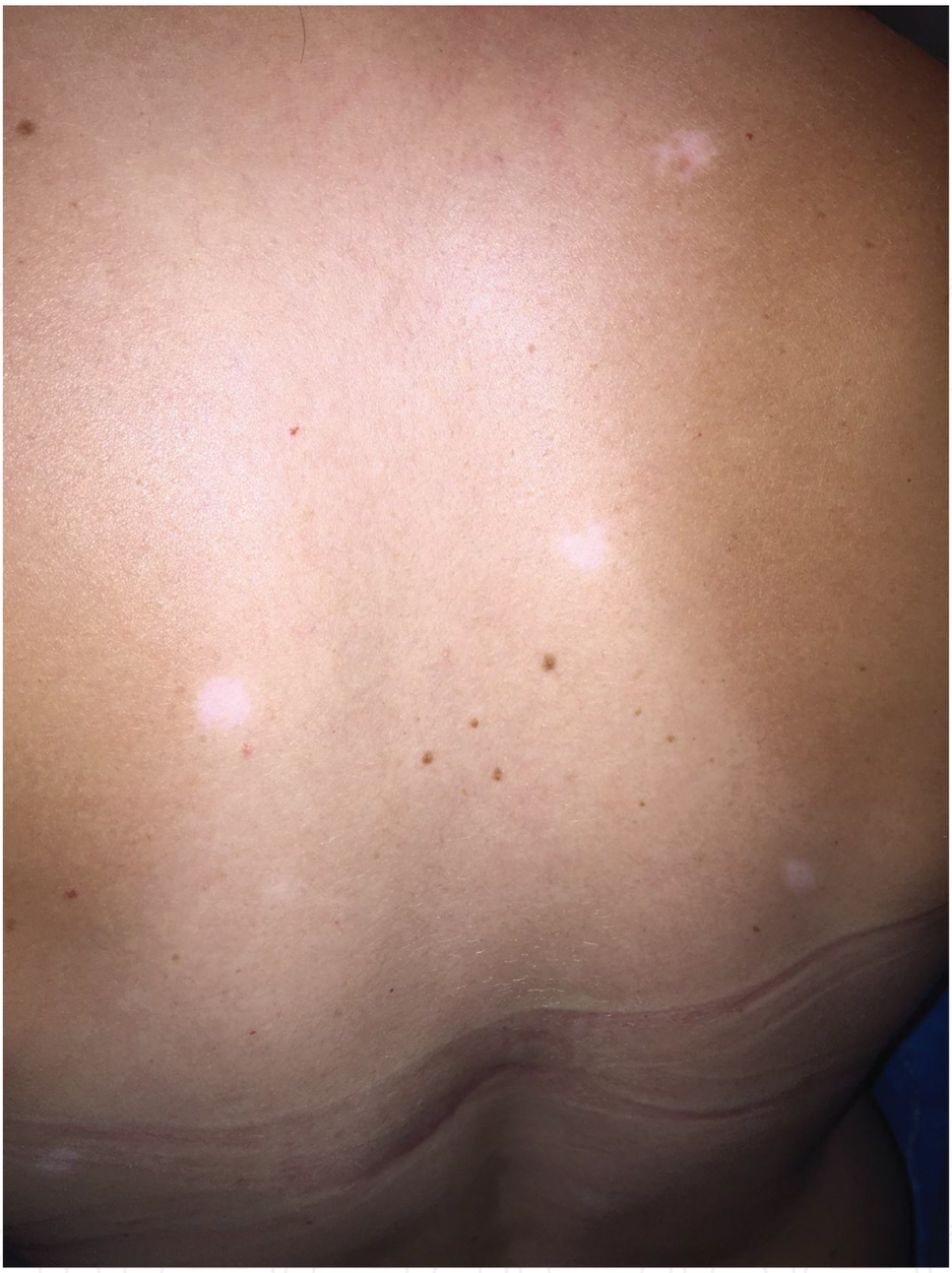

**Figure 2.** Vitiligo associated with Ipilimumab.

## Management

Topical glucocorticosteroids (e.g., betamethasone cream) or urea-containing creams in combination with oral antipruritics (e.g., diphen-hydramine HCl or hydroxyzine HCl) are recommended. The recommendation patients with a moderate rash, nonlocalized, and covers more than 50% of the skin surface area are to omit the offending agent. For grade 3 dermatological irAEs, hold treatment and administer a 3–4-week course of oral corticosteroids in the form of prednisone at a dose of 1 mg/kg or dexamethasone at a dose of 4 mg four times a day given orally daily. Treatment should be permanently discontinued for severe, life-threatening skin

toxicity and prednisone at a dose of 1–2 mg/kg orally or equivalent formulations given at least for 30 days [23]. When a high-dose corticosteroid therapy is used, once symptoms are controlled, tapering of the steroids should occur over a one-month period at least [18]. Vitiligo may be associated with clinical benefit. Although it occurs in a small percentage of patients undergoing immunotherapy, there is a clear survival benefit in patients who do develop vitiligo during treatment [19, 20]. In some patients, vitiligo is associated with long-term survival [19, 20].

### 3.2. Gastrointestinal

Side effects can occur anywhere along the gastrointestinal tract, ranging from mucositis, aphthous ulcers, gastritis, and abdominal pain. More commonly, diarrhea related to colitis can be observed. This will be elaborated on in the next section [4, 13, 15].

#### *3.2.1. Diarrhea and colitis*

Diarrhea and colitis are very common side effects of checkpoint inhibitors. It is more frequently seen when using CTLA-4 inhibitors than when using PDL-1 inhibitors. It is reported in about 30% of patients receiving CTLA-4 therapy, whereas it is as little as only 1–2% of patients receiving PDL-1 therapy [2, 4, 10, 24]. There is a higher incidence and a greater severity in grade when bigger doses are used as seen in the initial trials of ipilimumab when comparing 10 mg vs. 3 mg [4, 11, 24]. It is also more frequently seen and with a higher incidence in grade 3 and grade 4 events when the two checkpoint inhibitors are used in combination [2, 3, 12, 14]. This irAE is most likely to manifest within the first 6 weeks after checkpoint inhibitor therapy has been initiated, slightly later than dermatological irAEs, although this is not absolute, as it can also occur anywhere in the treatment course [15, 16, 24]. Diarrhea, which is an increase in the frequency of stool is related to, but a different clinical entity from colitis. The CTCAE states that symptoms related to colitis are associated with abdominal pain and include patients who have blood or mucus in their stool. If there is evidence of inflammation on endoscopic investigation or radiographically, it is also then defined as colitis. It is important to exclude other infectious causes of diarrhea, for instance, *Clostridium difficile* infection in all cases [4, 13, 15]. In very selected cases, where patients have accompanying symptoms of high fevers, leukocytosis, and those who have been on immunosuppressive therapy for long periods of time rendering them more susceptible to infections, prophylactic antibiotics can be considered [15]. A colonoscopy can be considered in patients with severe or persistent symptoms or if the cause is unclear [13, 15, 24] (**Figure 3**).

In severe conditions, perforation can occur and lead to death and must be excluded in patients with symptoms of peritonitis. These patients may require surgery and possible colostomy [3, 15].

Mild symptoms can be treated symptomatically with rehydration, replacing electrolyte losses, and loperamide [3, 4, 18, 24]. Grade 2 irAEs require the offending immunotherapy agent to be omitted. If symptoms are ongoing for more than one week, there should be an immediate commencement of oral corticosteroid therapy at a dose of 1 mg/kg/day. When symptoms are resolved, the immunotherapy drug can be recommenced [4, 6, 13, 15, 24].

http://dx.doi.org/10.5772/67372

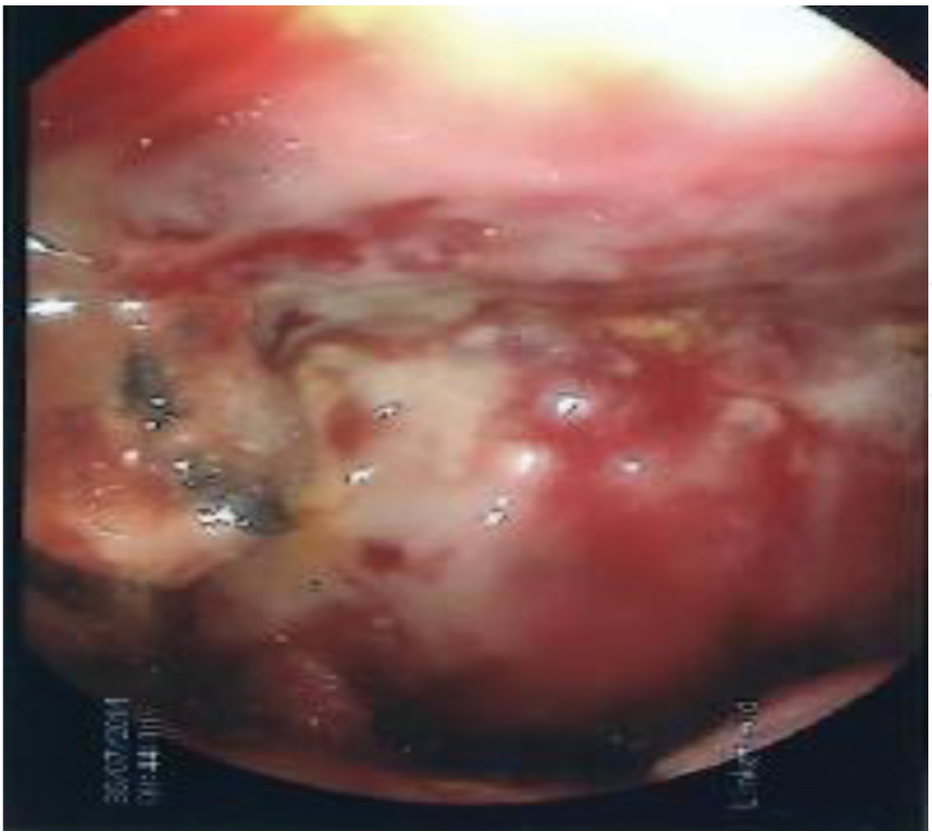

**Figure 3.** Severe colitis associated with ipilimumab.

Severe or life-threatening colitis and symptoms consistent with perforation, ileus, or fever is a serious complication. High-dose intravenous corticosteroids commencing at a starting dose of 2 mg/kg/day must be initiated promptly [15, 18].

If symptoms persist, a single dose of immunosuppressive infliximab therapy at 5 mg/kg must be considered unless there is a contraindication [15, 18, 24]. The dose of infliximab be repeated after 2 weeks if symptoms persist [13, 15, 24]. Mycophenolate mofetil can also be considered in severe and refractory cases [15]. The most important part of management of a patient with colitis is recognition and early initiation of aggressive treatment. Diarrhea treatment guidelines have been shown to reduce bowel perforation and colectomy rates and serious irAEs by up to 50% when this is done. There is anecdotal evidence that shows that high-dose therapy initiated for irAEs does not affect efficacy of treatment [2, 12]. Furthermore, it is postulated that the severity of the adverse event correlates with a better response to treatment [11, 14, 17].

### 3.3. Hepatic

Hepatotoxicity can be observed following treatment with anti-CTLA4 or anti-PD-1/anti-PDL1 therapy usually at about 6 weeks after initiation. It frequently manifests as an asymptomatic increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or total bilirubin. Hepatotoxicity has been observed in 3–9% of patients receiving ipilimumab [25, 26]. A meta-analysis of a total of nine randomized controlled trials in patients with solid tumors

demonstrated that the use of PD-1 inhibitors, when compared to the control group of chemotherapy or everolimus, significantly increased the risk of developing all, but high-grade hepatic AEs. Additionally, the risk of all grades of hepatic AEs was considerably higher when a nivolumab and ipilimumab combination was used compared to ipilimumab monotherapy. No significant differences in the risk of all-grade and high-grade hepatic irAEs were found between PD-1 inhibitors monotherapy and ipilimumab monotherapy [27].

*3.3.1. Management*

The differential diagnosis of immune-related hepatotoxity includes progressive metastatic liver disease, viral hepatitis, or another drug-specific toxic reaction. Diagnostic workup includes viral hepatitis studies, liver imaging, and excluding other drug-related causes for abnormal liver functions. A liver biopsy is indicated when the etiology is unclear [15]. It is important to point out that hepatic toxicity can occur in the absence of symptoms. Baseline liver functions should be obtained before commencement of therapy [15, 18]. When derangements are documented, other infectious causes, concurrent medications used by patients and disease progression must be excluded by appropriate investigations [15, 18].

Severe hepatotoxicity requires permanent discontinuation of the drug. Additionally, high-dose intravenous glucocorticosteroids for 24–48 hours followed by an oral steroid taper with dexamethasone at a dose of 4 mg every 4 hours or prednisone at 1–2 mg/kg tapered over not less than 30 days. If the levels of serum transaminase do not decrease 48 hours after commencement of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours should be considered [28]. Infliximab is associated with hepatotoxicity and should be avoided in this clinical setting.

### 3.4. Endocrine

Endocrine irAEs are in general inconstantly described in recent published data. Assessment and reporting of endocrine irAEs in clinical trials should be done using standardized diagnostic criteria and terminology. Unfortunately, as a consequence of the lack of standardization, the true incidence of endocrine adverse events on patients undergoing anti-CTLA-4 and antiPD-1/PD-L1 pathway blockades is unknown. Thyroid dysfunction is the most common irAE reported. Hypophysitis has merged as a distinctive side effect of CTLA-4-blocking antibodies [2, 13, 29]. The spectrum of endocrine disease in patients treated with ipilimumab includes hypophysitis, and occasionally primary adrenal insufficiency. This complication, if not promptly diagnosed, can be life-threatening (due to secondary hypoadrenalism). Hypopituitarism caused by CTLA-4-blocking antibodies is rarely reversible, and prolonged or lifelong hormonal replacement treatment is often required. The mechanism of injury and pathogenesis to the endocrine system triggered by ipilimumab needs to be clarified.

Presenting symptoms of hypothyroidism, such as fatigue, weakness, depression, memory loss, cold intolerance, and cardiovascular abnormalities, may be incorrectly attributed to the primary malignant disease. The onset of hypothyroidism is variable and can occur within the first 5 months and up to 2 years following immune-therapy. Some patients may develop autoimmune thyroiditis [30]. The prevalence of abnormal thyroid tests in one series was 15%

http://dx.doi.org/10.5772/67372

[31]. A recent meta-analysis of ten clinical trials showed that relative risk of all grades hypothyroidism 8.26 (95% CI: 4.67–14.62; $P < 0.00001$), hyperthyroidism 5.48 (95% CI: 1.33–22.53; $P = 0.02$), hypophyisitis 22.03 (95% CI: 8.52–56.94; $P < 0.00001$), and adrenal insufficiency 3.87 (95% CI: 1.12–13.41; $P = 0.03$) [32].

Baseline thyroid function tests are also recommended. Pituitary hormones, in the presence of symptoms, are indicated if thyroid functions are normal. Primary adrenal and primary pituitary insufficiency can be differentiated with an early morning cortisol [4, 13, 15]. MRI can be obtained to visualize the pituitary gland to confirm the diagnosis of hypophysitis [4, 15]. MRI findings can be nonspecific, but can show a general enlargement of the pituitary gland [33, 34]. In a review, about 85% of patients had pituitary gland abnormality on MRI [5]. Treatment of hypothyroidism usually requires replacement of thyroid hormone, and in mild cases of adrenal insufficiency, oral corticosteroid therapy can be used [4, 8]. Adrenal insufficiency or crisis is a medical emergency. This warrants hospitalization, high-dose intravenous corticosteroids with mineralocorticoid activity. Infection or sepsis should be excluded in these cases. A consultation with an endocrinologist is needed to ascertain if long-term hormone replacement is necessary [13, 15, 18].

### 3.5. Pulmonary

Immune-related pneumonitis is a serious IrAE associated with immunotherapy. This is more common with PD-1 blockers, although the incidence is <1% and presents far later into treatment phase [13]. Patients undergoing immunotherapy, experiencing new symptoms of cough or dyspnea, should arouse suspicion for the development of pneumonitis (**Figure 4**). In a nivolumab monotherapy, early dose-finding study (CA209-003) that evaluated various tumor types, three treatment-related deaths (1%) due to pneumonitis were reported in two patients with NSCLC and one patient with colorectal cancer [36]. A recent meta-analysis of 11 clinical trials showed that the odds ratio was 3.96 (95% confidence interval [CI]: 2.02–7.79; $P < 0.0001$) for all-grade pneumonitis and 2.87 (95% CI: 0.90–9.20; $P = 0.08$) for high-grade pneumonitis. Additionally, the odds ratio of all grades of pneumonitis with a nivolumab and ipilimumab combination vs. ipilimumab monotherapy was 3.68 (95% CI: 1.59–8.50; $P = 0.002$), and for high-grade pneumonitis, it was 1.86 (95% CI: 0.36–9.53; $P = 0.46$). Subgroup analysis did not demonstrate a significant difference between lung cancer patients and other types of cancer in the risk of pneumonitis. This is an irAE that can occur both with anti-CTLA-4 or anti-PD-1 agents. It has been reported in approximately 1% of patients treated with anti-PD-1 agents and occurs more frequently than with anti-CTLA-4 agent ipilimumab. Deaths related to immune-onset pneumonitis have been reported in NSCLC patients. Pneumonitis management involves prompt initiation of high-dose corticosteroids, close symptoms monitoring, and oxygen requirements. Immunosuppressive interventions may be required in a minority of patients [37]. Radiological findings should be monitored closely.

A second meta-analysis comprised 20 PD-1 inhibitor trials in 4496 patients with malignant melanoma (12 trials), NSCLC (5 trials), and RCC (3 trials). The overall incidence of pneumonitis during PD-1 inhibitor monotherapy was 2.7% (95% CI, 1.9–3.6%) for all-grade and 0.8% (95% CI, 0.4–1.2%) for grade 3 or higher pneumonitis. The incidence was higher in NSCLC for all-grade

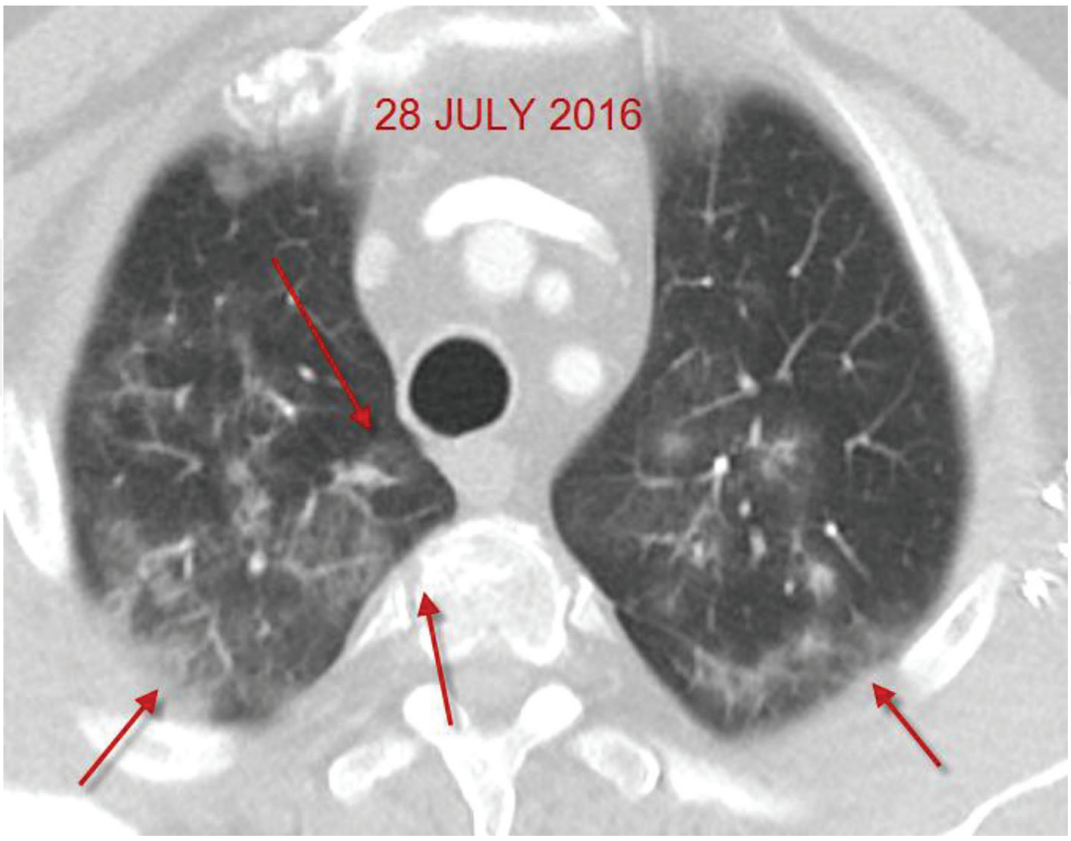


**Figure 4.** Pneumonitis associated with Nivolumab.

(4.1 vs. 1.6%; $P = 0.002$) and grade 3 or higher pneumonitis (1.8 vs. 0.2%; $P < 0.001$) compared with melanoma. The incidence in RCC was higher than in melanoma for all grades of pneumonitis (4.1 vs. 1.6%; $P < 0.001$) but not for grade 3 or higher. Four pneumonitis-related deaths were documented in patients with NSCLC in the monotherapy group. Pneumonitis was more frequent during combination immunotherapy than monotherapy for all grades (6.6 vs. 1.6%; $P < 0.001$) and for grade 3 or higher (1.5 vs. 0.2%; $P = 0.001$) in melanoma, with one pneumonitis-related death during combination therapy. Multivariable analyses demonstrated higher odds of pneumonitis in NSCLC for all-grade (odds ratio [OR], 1.43; 95% CI, 1.08–1.89; $P = 0.005$) and grade 3 or higher pneumonitis (OR, 2.85; 95% CI, 1.60–5.08; $P < 0.001$) and in RCC for all-grade pneumonitis (OR, 1.59; 95% CI, 1.32–1.92; $P < 0.001$) compared with melanoma. The combination therapy had significantly higher odds than monotherapy for all-grade (OR, 2.04; 95% CI, 1.69–2.50; $P < 0.001$) and grade 3 or higher pneumonitis (OR, 2.86; 95% CI, 1.79–4.35; $P < 0.001$). The authors concluded that the incidence of PD-1 inhibitor-related pneumonitis was higher in NSCLC and RCC and during combination therapy [38].

Several pulmonary inflammatory conditions have also been seen in patients treated with ipilimumab, including sarcoidosis [39, 40] and organizing inflammatory pneumonia [41].

In any patient undergoing anti-CTLA-4 or anti-PD-1/PD-L1 immunotherapy, presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, or shortness of breath, pneumonitis should be considered and evaluated with imaging. Because the onset and

http://dx.doi.org/10.5772/67372

symptoms of pneumonitis are often vague and diagnosis is often delayed, clinicians should be aware of this and consider diagnostic radiology (X-rays, CT scans) early. Bronchoscopy and lung biopsy should be considered to rule out other causes such as infectious etiologies before starting treatment, especially in moderate-to-severe cases [13, 15]. Differential diagnosis includes disease progression of cancer, lymphangitis carcinomatosis, opportunistic infections, severe pneumonitis, early cardiac failure, alveolar hemorrhage, or congestive cardiac failure. In severe cases, treatment should comprise high doses of corticosteroids such as intravenous methylprednisone at a dose of 2 mg/kg. Additional immunosuppression with infliximab, mycophenolate mofetil, or cyclophosphamide may be required and is a reasonable approach in nonresponding patients [13, 15].

### 3.6. Ophthalmological

Ophthalmological immune-related adverse events are extremely rare and occur in less than 1% of patients treated with anti-CTLA-4 therapy. The incidence with anti-PD-1 antibodies is unknown [42, 43]. Besides, from the direct toxicity of immunotherapy agents, the eye can also indirectly be affected via other immune-related adverse endocrinopathies such as hyperthyroidism form autoimmune thyroiditis [30, 43]. There have been case reports of Grave's opthalmopathy with symptoms and signs of proptosis associated with swelling of extraocular muscles and xeropthalmia [30, 42, 44]. Ophthalmological side effects include episcleritis, conjunctivitis, and uveitis [3]. A rare case of bilateral iridocyclitis and of bilateral choroidal neovascularization was reported [4, 42, 45]. Most cases can be managed with topical corticosteroids [34]. Systemic corticosteroids can be implemented in patients who do not respond to topical management or in grade 3 or in grade 4 cases. It is always recommended to consult an opthalomologist [43].

### 3.7. Neurological

Neurological symptoms can vary widely and present as a range of different conditions. It is postulated that neurological toxicity can occur in about 1–3% of patients from literature reviews [46]. Most information collected about neurological toxicity from immunotherapy is from case reports. Posterior reversible encephalopathy syndrome, Guillain-Barre, aseptic meningitis, enteric neuropathy, and transverse myelitis cases have been reported [4, 13]. There have also been isolated reports of chronic inflammatory demyelinating polyneuropathy and a Myasthenia-Gravis type syndrome [47]. Most times, if the adverse event is low-grade, stopping the offending agent until symptoms dissipate suffices or commencing low-dose oral corticosteroids [18, 47]. In grade 3 or grade 4 events, high-dose intravenous corticosteroids are warranted, and at times, plasmapheresis and intravenous immunoglobulin are warranted [4, 13]. It is worthwhile to involve neurologists to assist with diagnosis and what treatment is necessary for each individual case according to severity [4, 13].

### 3.8. Hematological

The evidence regarding hematological side effects is all anecdotal and based on case reports as well. Severe anemia requiring transfusions and febrile neutropenia requiring support

with granulocyte colony stimulating factor (GCSF) may occur [4, 48]. One case reported a patient with neutropenia receiving a CTLA-4 inhibitor that was refractory to GCSF therapy and required immunoglobulin therapy [49]. Red cell aplasia, acquired hemophilia A, and thrombocytopenia have all been described as well [4, 13]. Recently, cases of hemolytic-uremic syndrome occurring in a patient receiving ipilimumab have been reported [50]. Generally, hematological immune-related adverse events respond to steroid therapy, but in severe cases, may need more intense therapy.

### 3.9. Renal

Renal toxicity due to checkpoint inhibitors is extremely rare. A case series of thirteen patients provides information of different clinical presentations of patients with immune-related nephritis and different histological diagnoses [51]. It showed that the median time to develop kidney injury from immune checkpoint inhibitors was around 91 days though it ranged widely. It is estimated that about 1–2% of patients can have acute kidney injury from checkpoint inhibitors, with less than 1% of those patients having a serious grade 3 or 4 events [15, 51]. Histology in these patients showed a dominance of tubule-interstitial nephritis, and in one patient, showed a thrombotic microangiopathy [51, 52]. Initiating corticosteroid early therapy and stopping drug is the recommended treatment for acute kidney injury/interstitial nephritis from checkpoint inhibitor therapy. Most patients respond to steroid therapy [15]. Other causes of kidney injury such as infection or other medications should be excluded, and when etiology is in doubt, a renal biopsy should always be performed if not contraindicated. Close monitoring of patient's serum creatinine should be followed during treatment, especially if there is even a slight increase in creatinine. Grade 1 toxicity according to management guidelines is defined as an increase in creatinine up to 1.5 times above baseline, grade 2 or grade 3, defined as a creatinine above 1.5 times above baseline to 6 times above normal. Grade 4 events are life-threatening [15]. Mycophenolate Mophetil in refractory cases can be considered and potentially anti-TNF agents [51]. Data regarding management in these patients is very limited, and general supportive measure should be carried out as well such as fluid therapy and correcting electrolytes. Early involvement with a nephrologist is recommended as there were dialyses-requiring patients in the series as well [15, 51].

### 3.10. Pancreatitis

There have been reports of elevated amylase and lipase levels in clinical trials with unknown clinical significance. It is not recommended in general guidelines to monitor pancreatic enzymes unless there is a clinical suspicion of active or acute pancreatitis. There have been very few case reports of patients who developed fulminant pancreatitis. General guidelines for immune-related adverse events should be followed with close monitoring in these patients [15, 43, 53].

### 3.11. Cardiac

This is also extremely rare. There are case reports of varying cardiac conditions in patients with toxicity form checkpoint inhibitors. In a series, eight cases of immune-related cardiac toxicity were reviewed. Patients were asymptomatic of any cardiac-related issues before

http://dx.doi.org/10.5772/67372

initiating treatment with checkpoint inhibitors. Cases ranged from myocarditis and cardiomyopathy that responded well to corticosteroid therapy as well as cases that were fatal and refractory to treatment. Myocardial fibrosis was found in one patient's autopsy findings, in combination with multiorgan failure. The patients in this series were both very young and very old with no cardiac history and included patients with predisposing cardiac dysfunction. A patient also suffered a cardiac arrest. A total of 63% of patients had other organ systems involved in combination with the cardiac toxicity [54]. The review can allude to many hypotheses about cardiac related toxicity. There is a possibility of higher risk to develop cardiac toxicity if there are predisposing conditions and a higher incidence if there are other systems involved. As with other rare irAEs, more prospective data are needed. More case reports are emerging and include fulminant myocarditis and pericardial effusions with tamponade [55, 56]. It is clear that treating physicians need to be aware of the possibility of this irAEs and to start treatment with supportive and corticosteroid therapy promptly to avoid serious complications and death. There is currently no recommendations regarding monitoring of cardiac enzymes during therapy [54].

## 4. Conclusion

When managing a patient with suspected irAEs, the patients should be treated as individuals, and a thorough workup of each side effect should be done to ascertain whether or not there is truly an irAE and not other treatable causes. Most importantly, a high index of suspicion must always be kept in mind even though most are self-limiting and low-grade in severe cases if treatment is not given promptly and correctly, it can be life-threatening and result in death. Early recognition and aggressive treatment with immunosuppression is vital to prevent morbidity and mortality.

## Author details

Bernardo L. Rapoport* and Ronwyn van Eeden

*Address all correspondence to: brapoport@rosebankoncology.co.za

The Medical Oncology Centre of Rosebank, South Africa

## References

[1] K. Ryungsa, E. Manabu and T. Kazuak. Cancer immunoediting from immune surveillance to immune escape. Immunology. Vol: 121, No: 1, pp. 1-14, 2007.

[2] T. Chen, A. Razak, P. Bedard et al. A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors. Ann Oncol. Vol: 26, No: 9, pp. 1824-1829, 2015.

[3] A. Bertrand, M. Kostine, T. Barnetche. Immune-related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta analysis. BMC Med. Vol: 13, p. 211, 2015.

[4] A. Tarhini. Immune-mediated adverse events associated with Ipilimumab CTLA-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo). Vol: 2013, p. 857519, 2013.

[5] J. M. Redman, G. T. Gibney, M. B. Atkins. Advances in immunotherapy for melanoma. BMC Med. Vol: 6, pp. 14-20, 2016.

[6] M. Tsiatas, P. Grivas. Immunobiology and immunotherapy in genitourinary malignancies. Ann Transl Med. Vol: 4, No: 14, p. 270, 2016.

[7] K. J. Lafferty, H. S. Warren, J. A. Woolnough. Immunological induction of T lymphocytes: role of antigen and the lymphocyte costimulator. Blood Cells. Vol: 4, No: 3, pp. 395-406, 1978.

[8] D. M. Pardoll. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. Vol: 12, No: 4, pp. 252-264, 2012.

[9] C. Blank, T. F. Gajewski, A. Mackensen. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother. Vol: 54, No: 4, pp. 307-314, 2005.

[10] J. Weber, K. Kahler, A. Hauschild. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. Vol: 30, No: 21, pp. 12691-12697, 2015.

[11] J. Weber, R. Dummer, V. de Pril et al. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. Vol: 119, No: 9, pp. 1675-1682, 2013.

[12] J. Larkin, V. Chiarion-Sileni, R. Gonzalez. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. Vol: 373, No: 1, pp. 23-34, 2015.

[13] M. Postow. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book. pp. 76-83, 2015.

[14] J. Liu, S. Blake, M. Smyth et al. Improved mouse models to assess tumour immunity and irAEs after combination cancer immunotherapies. Clin Transl Immunol. Vol: 3, No: 8, e22, 2014.

[15] J. Villadolid, A. Amin. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res. Vol: 4, No: 5, pp. 560-575, 2015.

[16] Y. Bronstein, C. Ng, P. Hwu et al. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti–CTLA-4 antibody therapy. AJR Am J Roentgenol. Vol: 197, No: 6, pp. W992-W1000, 2011.

[17] B. Teply, E. Lipson. Identification and management of toxicities from immune checkpoint-blocking drugs. Oncology (Williston Park). Vol: 28 Suppl 3, pp. 30-38, 2014.

[18] Yervoy (ipilimumab). Princeton, NJ: Bristol-Myers Squibb, 2013 (package insert).

[19] C. Hua, L. Boussemart, C. Mateus et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol. Vol: 152, No: 1, pp. 45-51, 2016.

[20] H. Teulings, J. Limpens, S. Jansen et al. Vitiligo-Like depigmentation in patients with stage III–IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol. Vol: 33, No: 7, pp. 773-781, 2015.

[21] K. Minkis, B. C. Garden, S. Wu et al. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. J Am Acad Dermatol. Vol: 69, No: 3, pp. e121-e128, 2013.

[22] O. Abdel-Rahman, H. ElHalawani, M. Fouad. Risk of cutaneous toxicities in patients with solid tumors treated with immune checkpoint inhibitors: a meta-analysis. Future Oncol. Vol: 11, No: 17, pp. 2471-2484, 2015.

[23] J. S. Weber, S. P. D'Angelo, D. Minor 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. Vol: 16 No: 4, pp. 375-384, 2015.

[24] C. Friedman and M. Postow. Managing immunotherapy-related side effects. Oncol Hematol Rev. Vol: 11, No: 2, pp. 143-144, 2015.

[25] F. S. Hodi, S. J. O'Day, D. F. McDermott, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. Vol: 363, No: 8, pp. 711-723, 2010.

[26] C. Robert, L. Thomas, I. Bondarenko et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. Vol: 364, No: 26, pp. 2517-2526, 2011.

[27] X. Zhang, Y. Ran, K. Wang, et al. Incidence and risk of hepatic toxicities with PD-1 inhibitors in cancer patients: a meta-analysis. Drug Des Devel Ther. Vol: 10, pp. 3153-3161, 2016.

[28] R. Cheng, A. Cooper, J. Kench et al. Ipilimumab-induced toxicities and the gastroenterologist. J Gastroenterol Hepatol. Vol: 30, No: 4, pp. 657-666, 2015.

[29] S. M. Corsello, A. Barnabei, P. Marchetti et al. Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab. Vol: 98, No: 4, pp. 1361-1375, 2013.

[30] L. Min, A. Vaidya, C. Becker. Thyroid autoimmunity and ophthalmopathy related to melanoma biological therapy. Eur J Endocrinol. Vol: 164, No: 2, pp. 303-307, 2011.

[31] M. Ryder, M. Callahan, MA Postow et al. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. Endocr Relat Cancer. Vol: 21 No: 2, pp. 371-381, 2014.

[32] O. Abdel-Rahman, H. ElHalawani, M. Fouad. Risk of endocrine complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Future Oncol. Vol: 12, No: 3, pp. 413-425, 2016.

[33] K. Carpenter, R. Murtagh, H. Lilienfeld et al. Ipilimumab-induced hypophysitis: MR imaging findings. AJNR Am J Neuroradiol. Vol: 30, No: 9, pp. 1751-1753, 2009.

[34] T. Tokudome. Anti-CTLA-4 antibodies immunotherapy of cancer. Chapter 18, pp. 263-282, Kurashiki, Japan. Springer.

[35] Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary. Vol:19, pp 82-92, 2016.

[36] S. L. Topalian, F. S. Hodi, J. R. Brahmer et al. Safety, activity, and immune correlates of anti-PD-1 anti-body in cancer. N Engl J Med. Vol: 366: No: 26, pp. 2443-2454, 2012.

[37] O. Abdel-Rahman, M. Fouad. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis. Vol: 10, No: 3, pp. 183-193, 2016.

[38] M. Nishino, A. Giobbie-Hurder, H. Hatabu et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol. Vol: 2, Published online August 18, 2016. doi:10.1001/jamaoncol.2016.2453.

[39] C. Kim, J. Gao, VR Shannon et al. Systemic sarcoidosis first manifesting in a tattoo in the setting of immune checkpoint inhibition. BMJ Case Rep. Vol: 18, 2016 Oct 26;2016. pii: bcr2016216217.

[40] K. C. Suozzi, M. Stahl, C. J. Ko, et al. Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. JAAD Case Rep. Vol: 2, No: 3, pp. 264-268, 2016.

[41] P. Fragkou, M. Souli, M. Theochari et al. A case of organizing pneumonia (OP) associated with pembrolizumab. Drug Target Insights. Vol: 10, pp. 9-12, 2016.

[42] M. R. Robinson, C. C. Chan, J. C. Yang et al. Cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma: a new cause of uveitis. J Immunother. Vol: 27, No: 6, pp. 478-479, 2004.

[43] M. Postow, J. Wolchok. Toxicities associated with checkpoint inhibitor immunotherapy. UPTODATE http://www.uptodate.com/contents/toxicities-associated-with-checkpoint-inhibitor-immunotherapy.

[44] T. Hager and B. Seitz. Ocular side effects of biological agents in oncology: what should the clinician be aware of?. Onco Targets Ther. Vol: 7, pp. 69-77, 2014.

[45] B. S. Modjtahedi, H. Maibach, S. Park. Multifocal bilateral choroidal neovascularization in a patient on ipilimumab for metastatic melanoma. Cutan Ocul Toxicol. Vol: 32, No: 4, pp. 341-343, 2013.

[46] L. Spain, G. Walls, M. Julve et al. Neurotoxicity from immune-checkpoint inhibition in the treatment of melanoma: a single centre experience and review of the literature. Ann Oncol. Published online October 25, 2016.

[47] B. Liao, S. Shroff, C. Kamiya-Matsuoka et al. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro Oncol. Vol: 16, No: 4, pp. 589-593, 2014.

[48] E. Simeone, A. M. Grimaldi, A. Esposito et al. Serious haematological toxicity during and after ipilimumab treatment: a case series. J Med Case Rep. Vol: 8, p. 240, 2014.

[49] M. Akhtari, E. K. Waller, D. L. Jaye et al. Neutropenia in a patient treated with ipilimumab (anti-CTLA-4 Antibody). J Immunother. Vol: 32, No: 3, pp. 322-324, 2009.

[50] R. Nair, S. Gheith, S. Nair et al. Immunotherapy-associated hemolytic anemia with pure red-cell aplasia. N Engl J Med. Vol: 374, No: 11, pp. 1096-1097, 2016.

[51] F. B. Cortazar, K. A. Marrone, M. L. Troxell et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. Vol: 90, No: 3, pp. 638-647, 2016.

[52] N. Murakami, T. J. Borges, M. Yamashita et al. Severe acute interstitial nephritis after combination immune-checkpoint inhibitor therapy for metastatic melanoma. Clin Kidney J. Vol: 9, No: 3, pp. 411-417, 2016.

[53] A. M. Di Giacomo, R. Danielli, M. Guidoboni 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. Vol: 58, No: 8, pp. 1297-1306, 2009.

[54] D. B. Johnson, J. M. Balko, M. L. Compton et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. Vol: 375, No: 18, pp. 1749-1755, 2016.

[55] I. Kushnir, I. Wolf. Nivolumab-induced pericardial tamponade: a case report and discussion. Cardiology. Vol: 136, No: 1, pp. 49-51, 2016.

[56] L. Heinzerling, P. A. Ott, F. S. Hodi et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer. Vol: 4, p. 50, 2016.

IntechOpen