Safety and Tolerability of Immune Checkpoint Inhibitors (PD-1 and PD-L1) in Cancer

Iosune Baraibar^{1,2} · Ignacio Melero^{1,2,3,4} · Mariano Ponz-Sarvisé^{1,2,4} · Eduardo Castanon¹

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Abstract

Immunotherapy has emerged in recent years and has revolutionized the treatment of cancer. Immune checkpoint inhibitors, including anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) agents, are the first of this new generation of treatments. Anti-PD-1/PD-L1 agents target immune cells by blocking the PD-1/PD-L1 pathway. This blockade leads to enhancement of the immune system and therefore restores the tumour-induced immune deficiency selectively in the tumour microenvironment. However, this shift in the balance of the immune system can also produce adverse effects that involve multiple organs. The pattern of toxicity is different from traditional chemotherapy agents or targeted therapy, and there is still little experience in recognizing and managing it. Thus, toxicity constitutes a real clinical management challenge and any new alteration should be suspected of being treatment-related. The most common toxicities occur in the skin, gastrointestinal tract, lungs, and endocrine, musculoskeletal, renal, nervous, haematologic, cardiovascular and ocular systems. Immune-mediated toxic effects are usually manageable, but toxicities may sometimes lead to treatment withdrawal, and even fulminant and fatal events can occur. Oncologists need to collaborate with internists, clinical immunologists and other specialists to understand, manage and prevent toxicity derived from immunotherapy. This review focuses on the mechanisms of toxicity of anti-PD-1/PD-L1 agents, and its diagnosis and management.

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✉ Eduardo Castanon
ecastanon@unav.es

- ¹ Departamento de Oncología. Clínica, Universidad de Navarra, Pamplona, Spain
- ² Centro de investigación médica Aplicada (CIMA), Pamplona, Spain
- ³ Centro Virtual de la Investigación Biomédica en red en Oncología (CIBERONC), Madrid, Spain
- ⁴ IdiSNA, Pamplona, Spain

Key Points

Enhancement of the immune system response by immunotherapy has provoked a total paradigm shift in the treatment of oncological malignancies.

Patients who receive immune checkpoint inhibitors, such as anti-programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) agents, may experience a unique set of adverse effects in comparison with traditional chemotherapy agents or monoclonal antibodies.

Although manageable, this toxicity may threaten the life of patients and constitutes a real clinical management challenge for oncological physicians and other specialists.

Knowledge of immune-mediated toxicity will allow prompt diagnosis and improve its management.

1 Introduction

The programmed cell death-1 (PD-1) pathway regulates the necessary balance between the stimulatory signals required for an effective immune response to external microorganisms and inhibitory signals for maintenance of self-tolerance [1]. This pathway also plays an important role in immune evasion from tumour-specific T cells [2].

PD-1 is a negative stimulatory surface receptor that is expressed on activated T cells [3]. The PD-1 ligands, PD-L1 and PD-L2, can be expressed on tumour cells or immune cells, including those infiltrating tumours. Activation of the PD-1/PD-L pathway leads to inhibition of the cytotoxic T cell response [4, 5].

Inhibiting the interaction of PD-1 and its ligands results in significant enhancement of T-cell function and therefore anti-tumour activity [6]. Anti-PD-1 antibodies such as nivolumab and pembrolizumab, as well as anti-PD-L1 antibodies such as avelumab, durvalumab and atezolizumab, have been developed. These anti-PD-1/PD-L1 agents have achieved great success over conventional treatments in many types of tumours and have been approved by the US FDA and the European Medicines Agency (EMA) [see electronic supplementary material]. In 2018, the Nobel Prize in Physiology was awarded to Tasuku Honjo and James P. Allison for discovering that immune regulation by PD-1 and CTLA-4 (cytotoxic T lymphocyte antigen-4) was a successful anti-cancer therapeutic approach.

2 Immune-Related Adverse Events

Although anti-PD-1/PD-L1 have provoked a total paradigm shift in the treatment of oncological malignancies, a different pattern of toxicity has arisen in comparison with traditional chemotherapy agents or monoclonal antibodies. Toxic effects associated with immune checkpoint inhibitors are usually manageable, but toxicities may sometimes lead to treatment withdrawal, and fulminant and fatal events can also occur [7]. This constitutes a real clinical management challenge for oncological physicians and other specialists (Fig. 1). Collaboration between oncologists, internists, clinical immunologists and other specialists is essential for improving patient care. The main oncology societies (European Society for Medical Oncology [ESMO], American Association for Cancer Research [AACR], National Comprehensive Cancer Network [NCCN], and Society for Immunotherapy of Cancer [SITC]) have proposed extensive recommendations to guide optimal management of this novel toxicity. Many recommendations are largely based on case reports, case series, personal experience, and expert consensus. As a general rule, it is recommended that treatment with PD-1/PD-L1-blocking agents be interrupted if the adverse events are grade 2 or higher. Careful risk-to-benefit balance should be considered given the underlying disease. In severe cases, immunotherapy must be permanently discontinued, while, in other cases, re-institution of treatment may be attempted once the immune-related adverse event is resolved.

Fig. 1 Fundamental pillars of diagnosis and treatment of immune adverse events

It is also important to remark that most immunotherapy clinical trials exclude patients with pre-existing autoimmune and/or inflammatory disease (AID) because of the possible increase of immune-related adverse events. However, anti-PD-1 agents have been studied in patients with AID or previous major toxicity with ipilimumab, and they seem to be as safe and effective as in AID-free patients [8].

2.1 Endocrinological Disturbances

Endocrinological alterations are among the most frequent adverse events reported with immune checkpoint inhibitors [9–11]. Although all the endocrine glands may be affected, the thyroid, hypophysis and adrenal glands are among the most frequently affected organs. Most of the cases may be asymptomatic and only biochemistry alterations are observed, however sometimes there are critical situations that may jeopardize patient safety.

2.1.1 Thyroid Alterations

Although not completely understood, the underlying pathophysiology of immune-related thyroid dysfunction involves silent inflammatory thyroiditis with destruction of the thyroid gland, mediated by T-cell cytotoxicity, natural killer cells and perhaps PD-1/PD-L1 expression in thyroid tissue [12, 13]. Commonly, a distinction between hypothyroidism, hyperthyroidism or thyroiditis cases is made, but these are rather part of the same disease process: an acute but transient stage of thyroiditis, biochemically accompanied by thyrotoxicosis, and followed by progression to clinical or subclinical hypothyroidism [14].

Thyroid peroxidase autoantibodies are often negative, suggesting an antibody-independent mechanism, closer to postpartum silent thyroiditis than autoimmune thyroiditis unrelated to pregnancy [13]. In contrast, other investigations have found a high frequency of positive anti-microsomal and anti-thyroglobulin antibodies [15]. Either anti-thyroid antibodies being the cause of thyroid dysfunction or a humoral immunological response to thyroid antigens released during the destruction of the gland have been proposed in those cases [13].

2.1.1.1 Hypothyroidism In a recent meta-analysis, the incidence of hypothyroidism in patients receiving anti-PD-1/PD-L1 in both monotherapy and combination treatment was 6.6% [9]. Patients are regularly asymptomatic, although a minority may present symptoms such as fatigue, constipation, weight gain or bradypsychia. When hypothyroidism is suspected, a thyroid biochemistry panel, including thyroid-stimulating hormone (TSH), free T4 and free T3, should be demanded. If TSH is over 10 IU with a paired decrease of T4 and T3, substitution therapy should be started (e.g. oral

levothyroxine 1.6 µg/kg/day) [16, 17]. In severe cases, differential diagnosis should include central hypothyroidism, which can present isolated or as part of hypophysitis [11].

2.1.1.2 Hyperthyroidism Even though it is less frequent than hypothyroidism, hyperthyroidism has been described with anti-PD-1/PD-L1 agents [18]. Barroso-Sousa et al. reported a higher prevalence of hyperthyroidism in those patients receiving anti-PD-1 agents than those receiving anti-PD-L1 agents (odds ratio [OR] 5.36, 95% confidence interval [CI] 2.04–14.08) [9]. Patients who develop hyperthyroidism usually present with tachycardia, hyperhidrosis, diarrhoea, tremors, or even exophthalmos. Blood tests reveal a low concentration of TSH with a normal or high presence of T4 and/or T3. Thyroid-stimulating immunoglobulin and/or anti-thyroid peroxidase antibodies may sometimes be detected in peripheral blood. If cardiac symptoms are present, β-blockers such as propranolol or atenolol should be used [19]. When symptoms are severe or a ‘thyroid storm’ is suspected, the use of other drugs such as intravenous corticosteroids, potassium iodide in fluid therapy or anti-thyroid drugs such as thioamides may be considered [17]. Nevertheless, isolated hyperthyroidism is rare and often presents as a transient phase that preludes the development of a hypothyroid status [20].

2.1.2 Adrenal Gland Alterations

Primary adrenal insufficiency has been rarely observed with anti-PD-1/PD-L1 agents (< 1%) [21]. Patients with primary adrenal insufficiency usually present with symptoms such as fatigue, nausea/vomiting, weight loss and skin hyperpigmentation. Cortisol levels tend to be low, with a normal or higher concentration of adrenocorticotrophic hormone (ACTH). The pathogenesis of immune-mediated primary adrenal insufficiency remains unknown. Adrenal autoantibodies may play a role in pathogenesis, prediction or prognosis, but their real value is unknown. If suspected, anti-21-hydroxylase and adrenal cortex antibodies should be determined [22]. Adrenal crisis is always a medical emergency and intravenous hydration and corticosteroids should be started immediately [16].

2.1.3 Hypophysis

Hypophysitis is more prone to being developed in patients with anti-CTLA-4 regimens as an on-target effect of ectopic CTLA-4 protein expression in the pituitary gland, antibody-dependent cell-mediated cytotoxicity (ADCC) and activation of the complement pathway [23]; however, anti-PD-1/PD-L1 agents also have the potential to cause this pathology [24–26]. The pathogenesis of immune-related hypophysitis for anti-PD-1/PD-L1 therapy remains unknown. The

different capacity of the immunoglobulin (Ig) G subclass of immunotherapy agents to activate both ADCC and the complement pathway may contribute to a different potential to induce hypophysitis. Interestingly, the Fc region of the IgG1 subclass durvalumab and atezolizumab are modified to disable these agents to induce either ADCC or complement-dependent cytotoxicity.

Hypophysitis should be ruled out in those patients presenting with headache, nausea/vomiting, fatigue, orthostatic hypotension, loss of libido or muscle weakness. Blood tests may usually reveal a mild hyponatraemia with low concentrations of TSH and ACTH. Other central hormones, such as luteinizing hormone (LH), follicle-stimulating hormone (FSH) or prolactin, may not be affected. If highly suspected, a brain magnetic resonance image (MRI) with pituitary cuts should be ordered. Once confirmed, hormonal supplementation, as needed, is mandatory. When both thyroid and adrenal suppression are present, treatment with corticosteroids should be started, followed by thyroid substitution [17].

2.1.4 Diabetes

Although rare, type 1 diabetes may develop in patients receiving anti-PD-1/PD-L1 [27]. Upregulation of CD8+ T-cell response to type 1 diabetes mellitus (T1DM) antigen and T1DM-specific autoantibodies (GAD65) may be involved in immune-mediated diabetes [28]. If a patient presents with polydipsia with an increase in urine output frequency, diabetes should be ruled out. According to the American Diabetes Association, diabetes is diagnosed when one of the following are present: fasting glucose ≥ 126 mg/dL; a glucose level of > 200 mg/dL after an oral glucose tolerance test; a ciper of $A1c \geq 6.5\%$; or a random glucose level of > 200 mg/dL [29]. Insulin treatment should be started based on local standards of care [16, 17]. All measures should be started in order to avoid evolution to a diabetic ketoacidotic state.

2.2 Dermatologic Manifestations

Skin toxicity is one of the most common adverse effects seen in patients receiving anti-PD-1/PD-L1 agents [30]. Between 30 and 40% of patients may develop some type of skin toxicity, ranging from mild rash to severe epidermolysis [31]; however, the mechanism underlying dermatologic toxicity remains unclear. As a consequence of PD-1/PD-L1 pathway blockade, non-specific T cells might activate and target antigen-bearing keratinocytes and other skin cells.

2.2.1 Rash

Rash constitutes the most frequent cutaneous toxicity in patients treated with anti-PD-1/PD-L1 agents. It is usually

manifested by erythematous macules with or without papules [32], and usually affects the trunk and the extremities [33]. Furthermore, these lesions are usually accompanied by pruritus, the principal symptom patients complain of. Histologically, when a biopsy is performed there are usually signs of lichenoid dermatitis and spongiotic dermatitis features with a perivascular infiltrate rich in T lymphocytes [34]. Although rash is usually easily manageable with topical corticosteroids, corticosteroids such as prednisone 1–2 mg/kg might be needed in some severe cases [17]. If pruritus is present, antihistamine drugs (ceterizine, hydroxyzine) have frequently been prescribed, although symptom control using these drugs has not been evaluated.

2.2.2 Vitiligo

Vitiligo and vitiligo-like lesions are usually observed in melanoma patients who are receiving anti-PD-1/PD-L1 agents [33]. Vitiligo-like lesions are usually bilaterally and symmetrically distributed [35, 36]. Indeed, vitiligo correlates with a better clinical outcome in melanoma patients, and, although asymptomatic, it may have a social impact on a patient's life.

2.2.3 Other Skin Disturbances

Many other dermatologic alterations have been diagnosed under therapy with anti-PD-1/PD-L1 agents, and entities such as bullous pemphigoid [37], Stevens–Johnson syndrome [38] or psoriasis [39] have been described. Fluent collaboration with dermatologic teams should be encouraged in order to avoid skin complications.

2.3 Cardiac Toxicity

Although present in $< 1\%$ of patients, cardiologic events may occur when using anti-PD-1/PD-L1 agents [40]. This toxicity may be life-threatening and lead to fulminant situations [41]. The precise mechanism by which cardiac toxicity is produced is not well understood; however, hyperactivated cytotoxic T cells may be involved.

CTLA-4 and PD-1 regulate potential autoreactive lymphocytes in the myocardium. Mouse models of T-cell-mediated myocarditis have demonstrated that PD-1 deficiency predisposes to spontaneous myocarditis [42], and deletion of PD-L1 in Murphy Roths Large mice genetically predisposed to autoimmunity resulted in lethal autoimmune myocarditis [43]. Autoantibodies against cardiac troponin I were observed in PD-1-deficient mice that presented with dilated cardiomyopathy [44]. These in vivo experiments led to the hypothesis that blockade of the PD-1/PD-L1 pathway may disbalance the immune homeostasis in the myocardium and enhance the T-cell reactivity to myocardial cells. Similar

T-cell populations have been reported in tumour cells and cardiomyocytes. Patients with rhythm disturbances present with lymphocytic infiltration into the sinoatrial and atrioventricular nodes, and, in immune-mediated pericarditis, pathological evaluation of pericardial fluid indicates lymphocyte infiltration without any cytologic signs of malignant invasion or microorganisms [45].

2.3.1 Myocarditis

Myocarditis may appear in <1% of patients [46]. Fulminant myocarditis has been described with anti-PD-1/PD-L1 agents, alone or in combination with other agents, and presents as a severe toxic effect with the highest fatality rate (approximately 40%) [7, 41]. This clinical situation may be very subtle, and symptoms may vary, ranging from palpitations, dyspnoea or chest pain to arrhythmias or pericardial/pleural effusion. Blood tests may reveal an elevation in serum troponin levels, as well as in BNP (Brain Natriuretic Peptide), and patients should undergo serial electrocardiograms (ECGs) and cardiac image studies [47]. Cardiac MRI is preferred over echocardiogram as the former can provide unique information regarding left ventricular function and chamber sizes, myocardial strain, focal and diffuse fibrosis, inflammation, and edema [48]. Nevertheless, endomyocardial biopsy remains the gold standard for diagnosis and should be performed when diagnosis is not clear or response to immunosuppressive therapy fails. Differential diagnosis with myocardial ischaemia is usually a key point and should always be considered ahead of arrhythmia in patients treated with checkpoint inhibitors.

Specific guidelines for the treatment of immune-mediated myocarditis have not yet been published. Patients should be started on methylprednisolone 1–2 mg/kg if myocarditis is suspected. Immunosuppressive agents such as infliximab [16], calcineurin inhibitors such as tacrolimus, mammalian target of rapamycin (mTOR) inhibitors such as mycophenolate or antithymocyte globulin may be used in severe or steroid-refractory cases given their success in treating cardiac allograft rejection [49–53].

2.3.2 Rhythm Disturbances

Isolated rhythm disturbance in the context of structural cardiopathies may be diagnosed in patients receiving anti-PD-1/PD-L1 agents [54]. In case conduction abnormalities are observed in the ECG, other immune-mediated toxicities such as myocarditis should be ruled out due to their potential lethality. Patients should be kept in observation in special coronary units under ECG monitor and with means to reverse cardiac arrest at hand. Anti-arrhythmic drugs should be used under expert cardiology surveillance. Methylprednisolone 1–2 mg/kg may be useful in severe disturbances

[17], whereas other immune suppressors such as infliximab, cyclophosphamide or mycophenolate may be useful in refractory situations [17].

2.3.3 Pericarditis

Although rarely associated with anti-PD-1/PD-L1 agents, patients may develop autoimmune pericarditis [45]. Traditional symptoms such as chest pain, fever, shortness of breath when reclining and the typical pericardial friction rub may be observed. To our knowledge, no cases of cardiac tamponade have been reported. Although there is no clear evidence, prednisone and colchicine may be useful, especially in symptomatic cases.

2.4 Pulmonary Toxicity

In a recent meta-analysis by Nishino et al. [55], approximately 4% of patients receiving anti-PD-1/PD-L1 agents developed pneumonitis. Although the precise underlying mechanism remains unclear, some authors declare that alveolar macrophages may be hyperactivated in patients receiving anti-PD-1 agents. This hypothesis is supported by the fact that interstitial macrophages and alveolar cells express repulsive guidance molecule B (RGMB) in their surface, which may act as a ligand to PD-L2 [56]. When anti-PD-1 agents are used, the ability of PD-L2 to bind to RGMB may be increased after PD-1 blockade.

Typical symptoms that should warrant further studies are dyspnoea and dry cough. If suspicion of pneumonitis is high, conventional chest radiology and a computed tomography (CT) scan should be performed. Different radiographic patterns are related to pneumonitis, including signs suggesting acute interstitial pneumonia, cryptogenic organizing pneumonia, hypersensitivity pneumonitis or non-specific interstitial pneumonia [57]. If the results of the CT scan are inconclusive, a bronchoscopy with bronchoalveolar lavage (BAL) should be performed. A BAL full of lymphocytes is typically observed in this case. In case BAL is inconclusive, transbronchial biopsy may show an inflammatory interstitial pattern. Clinicians are often faced with differential diagnosis with infectious pneumonitis, particularly in patients with pre-existing obstructive pulmonary disease. In case of doubt, the use of antibiotics following culture collection is a suitable option, particularly if there is fever, neutrophilia or elevated procalcitonin serum levels.

Corticosteroids (methylprednisolone 1–4 mg/kg/day) should be promptly started because, if left untreated, pneumonitis may lead to respiratory failure and may be lethal. In refractory cases, infliximab, cyclophosphamide or mycophenolate have been used [16, 17, 19, 58, 59].

If pneumonitis is managed with corticosteroids, very slow and cautious tapering of corticosteroids should be carried out as pneumonitis exacerbations may develop.

2.5 Gastrointestinal Disturbances

Digestive tract disorders are one of the most common toxicities derived from immunotherapy. The gastrointestinal mucosa must maintain permeability to absorb nutrients while defending against pathogenic microorganisms. Regulatory cells and receptors may play a central role in this homeostasis. Blockade of inhibitory signals of immune response shifts the balance to activation of immune response. Genetic and microbiota may also be involved in gastrointestinal toxicity induced by immunotherapy.

2.5.1 Colitis

Colitis, defined as colonic inflammation, is more common in patients receiving ipilimumab, alone or in combination, than in those treated with single-agent anti-PD-1/PD-L1 inhibitors [26]. Characteristically, immune-related colitis usually involves the descending colon. Patients typically present bloody or watery diarrhoea, abdominal pain and sometimes fever [60]. Abdominal CT scan imagery shows colon wall thickening and edematous changes [61], but colonoscopy is the gold-standard test to confirm immune-related colitis. Colonoscopy findings range from normal mucosa or mild erythema to severe inflammation with mucosal granularity, friability and/or ulceration [60, 62]. Histopathological features include lamina propria expansion, villous blunting and acute inflammation (intraepithelial neutrophils and increased crypt/gland apoptosis); however, in contrast to colitis induced by anti-CTLA-4 agents, intraepithelial lymphocytes are rarely prominent. Infectious diarrhoea, Crohn's disease, or ulcerative or pseudomembranous colitis must be considered in the differential diagnosis. Once these previous conditions are ruled out, corticosteroids (methylprednisolone 1–2 mg) should be promptly started. If there is no improvement in 72 h, tumour necrosis factor (TNF)- α antagonists such as infliximab, or $\alpha_4\beta_7$ integrin inhibitors such as vedolizumab, are indicated [16, 19].

2.5.2 Hepatitis

Immune-related liver injury is usually observed in <5% of patients receiving anti-PD-1/PD-L1 agents in monotherapy, in contrast to 25% of patients when combined with ipilimumab [63]. Immune-related liver injury normally presents as an asymptomatic elevation of serum levels of hepatic alanine aminotransferase and/or aspartate aminotransferase enzymes, but fever, fatigue, malaise and even fulminant hepatitis and death have been reported [17].

If immune-related hepatitis is suspected, differential diagnosis should include disease-related causes, concomitant drug administration (including alcohol, statins or antibiotics), autoimmune hepatitis and infectious agents such as hepatitis A, B, C or E virus. Ultrasonography and CT scan usually show non-specific imaging patterns (steatosis, hepatomegaly, periportal edema, gallbladder edema and lymphadenopathy) [61, 64]. Liver biopsy should be considered for a conclusive diagnosis. The limited histological data published describing anti-PD-1/PD-L1-induced hepatitis report a similar pattern between anti-CTLA-4 and anti-PD-1/PD-L1 agents. Histopathologically, lobular hepatitis with scattered foci of patchy necrosis and acidophilic bodies with no confluent necrosis is observed. Bile ductular proliferation, cholangiolitis, focal endothelialitis and bile duct injury have also been described. Confluent necrosis and histiocytic aggregates are common in anti-CTLA-4-induced hepatic injury, but are rare in anti-PD-1/PD-L1 agents [62, 65]. If suspected, all hepatotoxic concomitant drugs should be stopped and treatment in collaboration with hepatologists should be started with corticosteroids (methylprednisolone 1–2 mg/kg). In refractory cases, other immune suppressors such as mycophenolate should be added [16, 17]. Infliximab is contraindicated in immune-related hepatitis due to its potential ability to provoke fulminant hepatitis [66].

2.5.3 Pancreatitis

Asymptomatic increase of pancreatic enzymes in patients receiving checkpoint inhibitors have been widely reported and usually do not require further immunosuppressive treatment. In fact, some authors do not recommend routine assessment of serum amylase and lipase since it is usually altered and may mislead the clinical approach and management [67]. However, cases of drug-induced pancreatitis have been reported as a rare complication of anti-PD-1/PD-L1 agents (<1%) 2–16 weeks after treatment initiation [68, 69]. Drug-induced pancreatitis is characterized by elevation of serum amylase and lipase in laboratory findings, as well as some typical findings in CT scan images, such as a swollen pancreas and reduced tissue contrast enhancement and lobulation [46, 64, 70]. Fluid collection, pancreatic necrosis or duct dilatation are usually absent. In 18F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT), peripancreatic fat stranding with diffuse increased FDG uptake is seen [46, 49, 64, 71]. Reactivation of autoimmune pancreatitis (including IgG4-related pancreatitis), obstructive pancreatitis, hepatitis, and bowel obstruction or perforation should be ruled out prior to starting treatment. If suspicion of an immune-mediated pancreatitis is strong, hospitalization should be strongly recommended and corticosteroid administration started.

2.6 Haematologic Disturbances

Even if haematologic disorders are rarely associated with anti-PD-1/PD-L1 therapy (<1%), T-cell activation can inappropriately occur against self-antigens, haematopoietic progenitors and blood cells, leading to immune-mediated haematologic toxicity [72]. To date, case reports of central (aplastic anaemia) and peripheral anaemia (autoimmune haemolytic anaemia [AHIA] and immune thrombocytopenic purpura [ITP]) immune toxicity associated with anti-PD-1 agents has been reported.

2.6.1 Aplastic Anaemia

When aplastic anaemia is suspected, blood tests should include a peripheral blood smear, Coombs test, reticulocyte count, and haemolysis assays (lactate dehydrogenase, haptoglobin and bilirubin), and a bone marrow aspiration/biopsy and flow cytometry should be performed in uncertain cases [17].

In contrast to chemotherapy, cytopenia is not a common adverse effect of immunotherapy. Anti-PD-1 drug-induced aplastic anaemia has been reported in the literature [73, 74]. Lethal aplastic anaemia has been described with nivolumab, both in monotherapy and in combination with ipilimumab [75, 76]. In these cases, pancytopenia with scattered lymphocytes is seen in the peripheral blood smear and hypocellularity with stromal edema, with no signs of fibrosis and a virtual absence of haematopoietic elements in the bone marrow biopsy or aspirate. In flow cytometry of bone marrow, lymphocytes usually represent 50% of the sample (mostly CD8-positive T cells). Blood transfusions, use of granulocyte colony-stimulating factor (G-CSF) or platelet transfusion should be considered in a case-by-case situation, guided by the affected cell line. In refractory cases, the use of anti-thymocyte globulin can be considered in collaboration with haematologists [17].

2.6.2 Autoimmune Haemolytic Anaemia

Reported AHIA secondary to anti-PD-1 usually shows elevated bilirubin, lactate dehydrogenase, reticulocyte count and reduced haptoglobin in serum, spherocytosis in the peripheral blood smear [77], and direct Coombs test positive for IgG or C3 [78, 79].

Treatment of this condition should include corticosteroids (methylprednisolone 1–2 mg/kg). Furthermore, administration of rituximab has also been reported [80]. Although its use has not been described in the literature as it is a rare entity, cyclosporine, mycophenolate, cyclophosphamide, azathioprine or intravenous immunoglobulins may be considered for severe situations [17].

2.6.3 Immune Thrombocytopenic Purpura

ITP has also been reported in patients receiving anti-PD-1 therapy and usually occurs within 12 weeks after treatment initiation. It presents with decreased platelet count, increased levels of platelet-associated IgG, normal white blood cell count and haemoglobin levels in the laboratory findings, as well as an increased number of megakaryocytes with a high percentage of immature platelets and without abnormal cells in the bone marrow biopsy [81–83]. Antiplatelet antibodies should be determined. This rare complication may be mediated by elevated PD-1 expression on B cells since B cells seem to play a predominant role in the pathogenesis of ITP [84]. If ITP is suspected, corticosteroids (methylprednisolone 1–2 mg/kg) should be initiated. In some severe cases, intravenous immunoglobulins, rituximab or thrombopoietin may be considered [17].

2.7 Nephrological Alterations

Acute interstitial nephritis (AIN) is an inflammatory disease characterized by an inflammatory infiltrate in the renal interstitium, which is usually associated with an acute kidney injury. AIN has been reported in patients receiving anti-PD-1/PD-L1 therapy [85, 86]. Tubular epithelial cells (TECs) can modulate immune response as they express major histocompatibility complex (MHC) class II, which allows them to act as antigen-presenting cells, and PD-L1, which acts as an inhibitory signal [87]. Thus, TEC PD-L1/T-cell PD-1 binding would have a protective role against immune-mediated tubulointerstitial injury, and, if anti PD1/PDL1 blockade occurs, T cells would be active against antigens presented by TECs [88]. An increase of cytokines is produced upon T-cell activation, which recruits other cells of immune response, such as lymphocytes, macrophages, monocytes, eosinophils and/or polymorphonuclear neutrophils [72]. Either a loss of acquired tolerance against endogenous kidney antigens [89] or a reactivation of exhausted drug-specific T cells previously primed by nephritogenic drugs, as well as an activation of memory T cells against the drug after loss of tolerance, have also been proposed as the pathophysiology mechanisms underlying [90].

Patients may present with haematuria, oliguria and/or hypertension. Up to 10% of patients with nephritis secondary to immunotherapy may develop fever, eosinophilia, and skin rash at the same time. Blood tests usually reveal a creatinine increase, eosinophilia and mild hyponatraemia. If diagnosis is uncertain, a renal biopsy may show inflammatory infiltrates (diffuse or patchy) involving the cortex more than the medulla. Other findings include interstitial edema with no involvement of the glomerulus or blood vasculature [91]. In moderate situations, treatment with prednisone 1 mg/kg would be sufficient, whereas in

severe cases, treatment with high-dose steroids (methylprednisolone 1 g) should be started [17]. Although there is little evidence, immune suppressors such as mycophenolate, cyclosporine or cyclophosphamide can be useful in refractory cases [16].

2.8 Ocular Syndromes

Ophthalmologic immune-related adverse events are infrequent, affecting up to 1% of patients, and have been mostly described in patients receiving anti-CTLA-4 agents [92]. The eye prevents invasion of infectious agents and inflammation to protect the visual function. This phenomenon, known as ocular immune privilege, is mediated by upregulation of transforming growth factor (TGF)- β and Fas ligand to cause immune cell death and convert T cells into regulatory T cells, and expression of CD86 and PD-L1 by retinal pigment epithelial cells to downregulate inflammatory T-cell activity. The consequences of immunotherapy on this environment are not well known [93]. Uveitis, uveal effusion, peripheral ulcerative keratitis, Vogt–Koyanagi–Harada syndrome, and retinopathy have been reported [94–100]. In general, referral to an ophthalmologist with experience in the treatment of uveitis is highly recommended.

2.8.1 Uveitis

Anti-PD-1/PD-L1-induced uveitis presenting with conjunctival redness, eye pain, photophobia, floaters, and blurry vision has been reported [101]. Complete ophthalmologic examination, funduscopy examination, fluorescein angiography, optical coherence tomography, ultrasound biomicroscopy, and electrophysiological examination must be considered. Topical corticosteroids and mydriatic agents may be considered for mild to severe cases [16, 17]. In some severe posterior uveitis cases, transscleral cryotherapy and vitrectomy may be an option.

2.8.2 Vogt–Koyanagi–Harada Syndrome

Vogt–Koyanagi–Harada-like syndrome, also known as uveomeningitis syndrome, is a multisystemic disorder that has also been reported with nivolumab [99]. It is usually associated with blurry vision, bilateral uveitis with exudative retinal detachments, and neurologic and cutaneous manifestations. For the ophthalmologic alterations, mydriatic agents may be taken into consideration.

2.8.3 Other Ocular Toxicity

Uveal effusion has been reported with nivolumab, atezolizumab and pembrolizumab [102]. Clinical presentation is blurry vision, redness and ocular pain 3–8 weeks after drug initiation. To confirm diagnosis, a B-scan ultrasonographic image showing serous choroidal detachment, and spectral-domain optical coherence tomography confirming the presence of subretinal and intraretinal fluid involving the fovea, are recommended.

Retinopathy secondary to anti-PD-1/PD-L1 agents causing blurry vision has been described [101–103]. In these cases, cancer-associated retinopathy must be ruled out.

2.9 Rheumatologic Disorders

Immune-mediated rheumatologic adverse events are underestimated as many clinical studies did not report this type of adverse event [103]. To date, the pathophysiological mechanisms underlying immune-mediated rheumatologic disorders have not been fully elucidated. Upregulation of MHC class I on muscle fibres, and loss of self-tolerance to muscle antigens after blocking PD-1/PD-L1 signalling, seem to be involved in some type of rheumatologic adverse effects, such as myositis [104–106].

2.9.1 Arthralgia/Myalgia

Arthralgia and myalgia have been widely reported with anti-PD-1/PD-L1 agents (approximately 10%), especially anti-PD-1 drugs [107]. These are generally mild and symptomatic, not usually requiring treatment discontinuation. Inflammatory signs suggesting either arthritis or myositis should be ruled out. Treatment with mild analgesics may be sufficient to palliate these symptoms; however, in severe cases, corticosteroids (prednisone 10–15 mg) may be considered [16].

2.9.2 Arthritis

Arthritis in patients treated with anti-PD-1/PD-L1 agents in monotherapy and in combination with anti-CTLA-4 appears in < 1% of patients (up to 10% in patients treated with pembrolizumab). Patients present with joint tenderness, warmth, swelling, redness, arthralgia, and morning stiffness [108–110]. Diagnosis is based on physical examination, signs of inflammation in joint radiography and ultrasonography, and blood tests including rheumatoid factor, anticyclic citrullinated peptide antibodies, antinuclear antibodies (ANA) and extractable nuclear antigens [111, 112]. Less than 1% of patients treated with anti-PD-1/PD-L1 therapy present with polymyalgia rheumatica and rheumatological assessment is recommended in those situations [108]. In

moderate cases, treatment with corticosteroids (prednisone 10–20 mg) may be sufficient. In severe situations, immunomodulators (hydrochloroquine, salazopyrine, leflunomide or methotrexate) may be considered. In refractory cases, biological agents such as infliximab, tocilizumab or abatacept may be useful [16, 17, 19].

2.9.3 Myositis

De novo myositis following anti-PD-1/PD-L1 therapies is seen in <1% of patients. Clinical presentation differs from minimal creatine kinase (CK) elevation, mild myalgia and weakness to life-threatening rhabdomyolysis, myocarditis or accompanying myasthenia-like features. Comprehensive myositis evaluation containing muscle biopsy, laboratory studies including CK levels and myositis antibody panel (PM-Scl, Ku, RNP, synthetase, SRP, Mi-2, p-155/140, MDA5) and electromyography (EMG) should be performed [104, 113], and treatment with corticosteroids (prednisone 0.5–1 mg/kg) should be started [16]. In severe situations, immunosuppressors such as methotrexate, azathioprine or calcineurin inhibitors, and biological agents such as rituximab, may also be considered [17].

2.9.4 Other Rheumatological Disturbances

A few cases of drug-induced lupus erythematosus following anti-PD-1/PD-L1 therapy, with positive direct immunofluorescence for IgG and C3, lymphocytic dermal infiltration around adnexal sites, and positive ANA and SSA in serum, have also been described [114, 115]. Sicca syndrome with negative Ro/SSA antibodies and positive ANA has also been noted in patients treated with anti-PD-1 immunotherapy [110].

2.10 Neurological Disorders

The incidence of immune-related neurotoxicity is rare (<1%) and only a few cases of neurotoxicity have been reported with anti-PD-1/PD-L1 agents (peripheral neuropathy, encephalitis, myasthenia gravis, acute and chronic demyelinating polyradiculoneuropathy, and a case of multifocal central nervous system demyelination) [116]. The underlying mechanism of immune-mediated neurotoxicity could be the development of immune responses against neuronal antigens by hidden autoimmunity and/or molecular mimicry [117]. Neurological impairment can also be caused by disease progression, seizure activity, infection and metabolic alteration [63]. Imaging of the central nervous system, lumbar puncture for cerebrospinal fluid (CSF) analysis and EMG for nerve conduction study are helpful for diagnosis, and consultation with a neurologist is usually preferred as a complex differential diagnosis might emerge.

2.10.1 Acute/Chronic Demyelinating Polyradiculoneuropathy

Acute and chronic demyelinating polyradiculoneuropathy mimicking Guillain-Barré syndrome under anti-PD-1 treatment has been reported [118, 119]. The median time from drug initiation to symptom onset was 4 weeks and clinical presentation was usually paresthesia, sensory loss, weakness, loss of taste, diplopia, decreased visual acuity and dysarthria. On spine MRI, contrast medium uptake of the nerve fibres was observed, and, on EMG nerve, conduction velocity was reduced. Cerebral MRI must be performed to rule out brain metastases and CSF, usually showing albumin-cytologic dissociation, and an anti-ganglioside antibody test must be considered. Since this entity may endanger a patient's life, an aggressive approach, including intravenous immunoglobulins and/or high-dose corticosteroids (methylprednisolone 1 g), may be considered upfront in addition to readiness for intensive care support of ventilator functions [16].

2.10.2 Encephalitis

Encephalitis associated with anti-PD-1/PD-L1 agents and in combination therapy is a rare adverse event and is characterized by confusion, fatigue, spastic tremors, fever and vomiting [120–122]. Diffuse dural enhancement without parenchymal abnormalities is reported on brain MRI. CSF analysis shows mononuclear pleocytosis, normal glucose and increased protein level, and electroencephalography reveals diffuse non-specific slowing. Anti-NMDA receptor antibodies have been reported to be positive in some cases. Dominance of cerebellar symptoms may occur, including gait disturbance, tremor and altered movements. Treatment with empirical broad spectrum antibiotics and antiviral therapy may be started until microbiological results become available. Corticosteroids (methylprednisolone 1–2 mg) should be administered if immune-related encephalitis is highly suspected [17]. In some severe cases, intravenous immunoglobulins may be a valid option. A spectrum of antibodies associated with neurological paraneoplastic syndrome should be performed [16, 17, 123].

2.10.3 Myasthenia Gravis and Myasthenia-Like Syndromes

In anti-PD-1/PD-L1-induced myasthenia gravis, no leptomeningeal or cranial nerve enhancement or parenchymal alterations were observed on brain MRI, but single-fibre EMG usually showed pathologic jitter [117, 124, 125]. Serum anti-acetylcholine receptor and anti-muscle-specific kinase antibodies must be studied, as well as the possible concomitant presence of a thymoma. Exacerbation of pre-existing myasthenia gravis has also been described [126, 127]. Due

Fig. 2 Main adverse events related to antiPD-1/antiPD-L1 agents

to myasthenia gravis potential to affect respiratory musculature, patient transfer to the intensive care unit should be considered. Treatment with a high dose of corticosteroids (methylprednisolone 1–2 mg) and/or other suppressors (azathioprine, mycophenolate or cyclosporine) should be started; in some refractory cases, intravenous immunoglobulins or plasmapheresis may be considered [16, 17].

3 Conclusions

Anti-PD-1/PD-L1 agents have dramatically changed the prognosis of malignancies such as metastatic melanoma or metastatic non-small cell lung cancer, previously considered as lethal. During the past 5 years, many oncological indications have been approved by both American and European regulatory agencies. The number of patients who benefit from immune checkpoint inhibitors is increasing exponentially, leading not only to new scenarios in terms of disease control and overall survival but also the emergence of new toxicity patterns. Although these immune-related symptoms are usually easy manageable, they sometimes constitute a real threat to patients, endangering not only their continuity of treatment but also their own survival. An efficient and precise diagnosis and therapeutic approach should be pursued in order to decrease the severity of complications (Fig. 2). Fluid communications within different medical specialties

are key to accomplishing this task and minimizing the risk of immune-related toxicity.

Compliance with Ethical Standards

Conflict of interest Iosune Baraibar, Mariano Ponz-Sarvisé and Eduardo Castanon have no conflicts of interest to declare that are directly relevant to the contents of this study. Ignacio Melero has received grants from Roche, BMS, Alligator and Bioncotech, as well as consulting fees from BMS, Roche, Bioncotech, Genmab, Cytomx, F-Star, Alligator and EMD.

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