Immunotherapy in Cancer: Review of Adverse Events with Immune Checkpoints Inhibitors

Imunoterapia no Cancro: Revisão de Efeitos Adversos com Inibidores de Checkpoints Imunitários

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Abstract

Over the past few years, remarkable results have been achieved with the availability of Immune-checkpoint inhibitors, including anti-cytotoxic T lymphocyte antigen 4 (CTLA-4), anti-programmed cell death 1 (PD-1) and anti-programmed cell death 1 ligand 1 (PD-L1) antibodies. These therapies have the potential to induce durable responses in multiple solid and hematologic malignancies and thus have reshaped treatment algorithms for numerous tumor types and revolutionized the field of oncology. Immunotherapy, although targeting cancer cells, by the profile of its unique mechanism of action with activation of the immune system can also affect various tissues and organ systems, often leading to immune-related adverse events. With the increasing use of immune-therapeutic agents, clinicians will increasingly be confronted with common but also rare immune-related adverse events which are often distinctly different from the classical chemotherapy-related toxicities. In this review, we provide an overview of potential adverse effects associated with different classes of immunotherapeutic agents organized by organ systems, including pathophysiology, epidemiology and kinetics, screening, surveillance strategies, diagnosis, and management.

Keywords: Immune Checkpoint Inhibitors/adverse effects; Immunologic Factors/therapeutic use; Neoplasms/drug therapy

Resumo

Nos últimos anos, foram obtidos avanços notáveis com os inibidores de *checkpoint* imunitário, incluindo antigénio 4 dos linfócitos T citotóxicos (CTLA-4), o *anti-programmed cell death 1* (PD-1) e *anti-programmed cell death 1 ligand 1* (PD-L1). Estas terapêuticas têm o potencial de induzir respostas clínicas duradouras em múltiplas neoplasias sólidas e hematológicas, reformularam os algoritmos de tratamento de numerosos tipos de cancro e revolucionaram a área da oncologia. A imunoterapia apresenta um mecanismo de ação único com ativação do sistema imunitário e pode afetar vários tecidos e sistemas de órgãos, levando frequentemente a eventos adversos relacionados com a autoimunidade. Com o uso crescente de agentes de imunoterapia os clínicos serão cada vez mais confrontados com eventos adversos comuns, mas também raros, relacionados com a imunidade, que são muitas vezes diferentes das toxicidades clássicas relacionadas com a quimioterapia. Nesta revisão, fornecemos uma visão geral dos potenciais efeitos adversos associados a diferentes classes de agentes de imunoterapia, organizados por sistemas de órgãos, incluindo a fisiopatologia, epidemiologia e cinética, estratégias de vigilância, diagnóstico e tratamento.

Palavras-chave: Fatores Imunológicos/uso terapêutico; Inibidores de Checkpoint Imunológico; Neoplasias/tratamento farmacológico

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Introduction

Cancer is a complex disease characterized by uncontrolled growth of abnormal cells with the potential to invade parts of the body and/or spread to other organs. Cancer is the second leading cause of death globally, which caused over a 10.0 million deaths worldwide and 19.3 million new cancer cases in 2020. The cancer-related mortality in the world is expected to reach 22 million by the year 2030.[1]

Over the past few years, remarkable results have been achieved with the availability of new cancer therapies. The immunotherapy has been at the forefront of cutting-edge developments and discoveries for cancer treatments. New and promising treatments for tumors with historically poor prognosis have been approved in an expedited manner compared to traditional therapies, and the landscape of cancer care is constantly and rapidly evolving.

It has long been recognized that the immune system and malignant cells often coexist in a dynamic equilibrium, and the complex interaction between growing tumors and the immune system may determine the course of disease.

History

The idea to use the immune system as a tool to treat neoplastic disease originated in the nineteenth century, being Wilhelm Busch and Friedrich Fehleisen the first's to describe an epidemiological association between immune status and cancer. They noticed spontaneous regression of tumors following the development of erysipelas.[2] Later, William Coley, often called the 'Father of Cancer Immunotherapy', retrospectively demonstrated that erysipelas was associated with a better outcome in patients with sarcoma.[3]

The next breakthrough was discovering that T cells were key effectors of a tumor-specific immune response and that a T-cell growth factor, known as interleukin 2 (IL-2), could further propagate these responses.[4] During this same era, a number of approaches to prime and direct tumor antigen-specific immunity were designed through vaccines given with a variety of adjuvants.

In the late 20th century, the work led by Steven Rosenberg in the Surgical Branch of the National Cancer Center (MD, USA), established standard procedures to isolate tumor-infiltrating lymphocytes, activate and expand these lymphocytes *ex vivo*, and infuse.[5] These efforts have inspired the development of T cell products with modified T cell receptors (TCRs) or chimeric antigen receptors (CARs), which activate specific antigens expressed on tumor cells and target a potent antigen-specific T cell and specific mediated immunity.

Another important discovery was the identification of immune regulatory elements and agents to disrupt these so-called immune checkpoints changed the history of immunotherapy.[6] Several negative regulators of T cell activation act as 'checkpoint molecules' to adjust the immune response. Cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1) are T cell immune checkpoint molecules. They ensure that T cell preserve self-tolerance while protect the body from pathogens and neoplasia. CTLA4 and PD1 have been successfully targeted by several research groups as treatments for a wide variety of cancers, research that ultimately earned James Allison and Tasuku Honjo the 2018 Nobel Prize in Physiology or Medicine.

Monoclonal antibodies against PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab, durvalumab) were approved in a number of diseases, including melanoma, non-small-cell lung cancer (NSCLC), bladder cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, Merkel cell carcinoma, and many others. There is also data about combination therapy with anti-PD-1/PD-L1 and anti-CTLA4 agents, such as ipilimumab and tremelimumab, being associated with higher response rates in several diseases.

There are numerous ongoing clinical trials with immune checkpoint inhibitors (ICI) and combinations with other targeted therapies.

Mechanism of action

The immune system consists of innate and adaptive immune components. The innate arm is the first defense mechanism against the antigen and responses with monocytes, macrophages, dendritic cells, and natural killer cells. Innate system cells oversee recognition of non-host cells and the presenting of cells of antigenic nature to adaptive system cells. Innate immune system cells have receptors to recognize microorganisms, damaged cells and transformed cells, like tumor cells. The adaptive arm produces long-lasting responses using T cells and B cells, eventually generating immune memory. Adaptive immunity is based on T and B-lymphocytes that proliferate after recognition and destroy antigenic structures by stimulating various mechanisms (Fig. 1).[7]

Cancer growth and metastasis can exert immunosuppression mechanisms that prevent cancer from being recognized by immune system. Thus, immunotherapy aims to activate the immune system against these malignant cells. The immune system tries to detect the cancer cells and it is called "immune surveillance of cancer". The detection and destruction of damaged or cancer cells by the immune system is a complex pathway that develops as a result of the coordination of many cells.[8]

Immune checkpoints engage when proteins on the surface of T cells recognize and bind to partner proteins on other cells, such as tumor cells. These proteins are called immune checkpoint proteins. When the checkpoint and partner pro-

teins bind together, they send an "off" signal to the T cells. This can prevent the immune system from destroying the cancer. Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to recognize and kill cancer cells.[9] Some drugs act against the checkpoint protein CTLA-4, or against a checkpoint protein PD-1, or its partner protein PD-L1. For example, ipilimumab and tremelimumab were developed to inhibit CTLA-4 expressed on T cells and atezolizumab, avelumab and durvalumab inhibit PD-L1 (Fig. 2).[10]

Immunotherapy has now revolutionized the field of oncology by prolonging survival. Novel treatment combinations and newly identified druggable targets will expand the role of immunotherapy in the treatment of cancer in the decades to come. With this treatment becoming the standard of care for an increasing number of cancers, there are an increasing number of patients being exposed to these drugs with a chance of developing toxicities from these treatments.

In this review will we discuss the management of the most frequent immune adverse events associated with ICI.

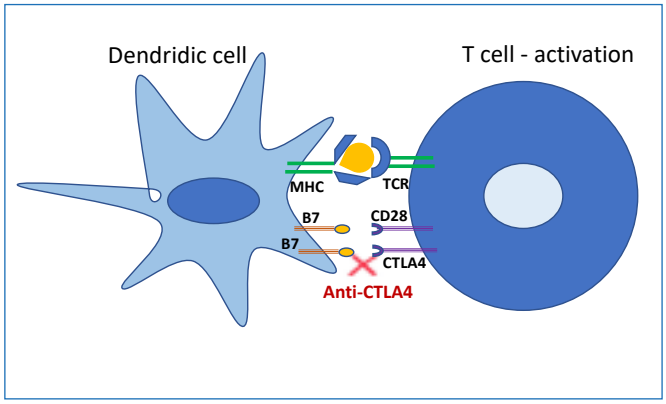

Figure 1. Mechanism of action anti-CTLA4.

MHC major histocompatibility complex; **TCR** T-cell receptor; **B7** superfamily ligand; **CD28** and **CTLA4** T-cell receptor of immune response regulation

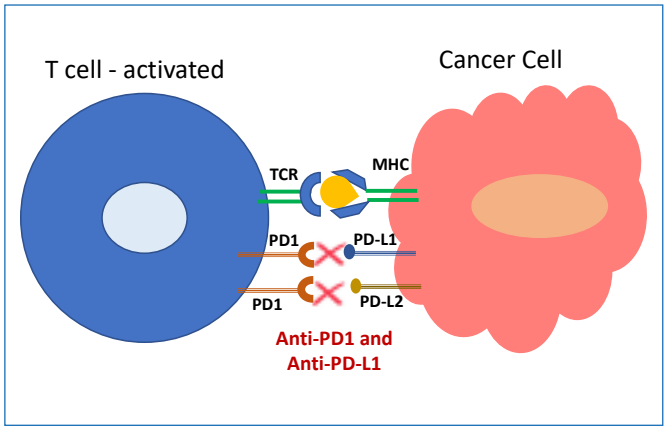

Figure 2. Mechanism of action anti-PD1 and anti-PD-L1.

MHC major histocompatibility complex; **TCR** T-cell receptor; **PD1** immunological tolerance receptor; **PD-L1** and **PD-L2** cancer-cell ligand of immune response regulation

Immune checkpoint inhibitors (ICI) toxicity

Cancer immunotherapies manipulate the immune system to reactivate the antitumor immune response and overcome the pathways leading to escape. Each class of immunotherapy drugs is associated with different types of toxicity. In the case of ICI, after the treatment there is an increase of the tumour specific T cells (CD8 cells), followed by an increase in memory T cells after several months. In addition to an anti-tumour effect, ICI can cause an auto-immune response by expanding an autoreactive clone of CD8 cells.[11] This can result in a wide spectrum of toxicities that have not been seen with previous types of cancer therapies. These adverse reactions of autoimmune origin can occur anywhere in our body, being more frequent in organs with a greater distribution of immune cells, such as skin, gastrointestinal tract, glands, lung.[11]

The frequency and effect organs are different according to the type of ICI.[11] Immune-related events are much more frequent with CTLA-4 inhibitors than with PD-1 and PD-L1 inhibitors. Skin reactions can occur with CTLA-4 inhibitors, but grade 3-5 gastrointestinal adverse events, including colitis, are a particular concern with this type of immunotherapy.[11] The pattern of immunotoxicity is quite different with anti-PD1 agents, with pneumonitis, thyroiditis and arthralgias being the most frequent adverse events, while immune-related adverse events are less frequent with anti-PD-L1 agents.[12] The type of cancer influences too the frequency of some adverse events like for example patients treated with melanoma have higher rates of vitiligo (around 10%), while patients with non-small-cell lung cancer (NSCLC) and renal carcinomas, are more likely to experience pneumonitis, and those treated for thymic carcinoma may have myocarditis, which affects less than 0.5% of patients in general treated with ICI.[12] Furthermore, as expected patients treated with combinations of ICI the immune-related events are more frequent like the grade of these events (higher toxicity).[13] Adverse events with combination immunotherapy can be quite difficult to manage, and combined immunotherapies should be used with caution.

The management of toxicities with immunotherapies used to treat cancer is relatively new, as these therapies have been used in clinical practice for only the last ten years. Overall, immunotherapy is better tolerated than chemotherapy. For example, a study comparing the PD-1 inhibitor nivolumab with docetaxel showed a lower rate of treatment-related adverse events with nivolumab (69%) than with docetaxel (88%).[14] The rate of severe adverse events (grade 3-4) was also lower with immunotherapy (10% *vs* 54%) and, importantly, fewer patients stopped treatment due to adverse events (5% *vs* 15%).[14] The diversity of adverse events with immunotherapy is perhaps more important than the frequency when managing toxicity. Patients treated with ICI experience a wide range of adverse events

not previously seen with other types of cancer treatments.[11] The identification of the timing of the onset of immune-related adverse events and their potential resolution is very important for the patients' outcomes. A pooled analysis of patients with advanced melanoma treated with nivolumab showed that most adverse events occurred at around 10 weeks.[15] However adverse events can occur at any time during treatment with immunotherapy and even after stopping it.[16] The Fig. 3 shows us the predicted time of occurrence of some events that were detected during treatment with anti-CTLA 4 (ipilimumab) as like the grade of severity of them. Usually, the first adverse events occur in skin with mild-moderate grade, then in gastrointestinal tract, like colitis that can be severe with this treatment, and endocrinopathies that can be persistent in time.[11]

Immunotoxicity can be correlated with the applicated doses of ICI, especially in anti-CTLA4 agents. Sometimes it may be helpful to reduce the frequency of dosing in patients with immune adverse events, even in patients treated with anti-PD1 and anti-PD-L1.[12] In some clinicals trials there have been suggestions that immunotoxicity may be associated with improved tumor control. A pooled analysis of studies in patients with advanced melanoma treated with nivolumab showed that the occurrence of immune-related adverse events (like vitiligo) was associated with a higher overall response rate (48.6% *vs* 17.8%, $p<0.001$).[15] This information suggests that patients showing immunotoxicity will also show response to immunotherapy. However, is not a condition for to get tumoral response and better patient outcomes.

It is important to explain to the patients that adverse events with immunotherapy are unpredictable and can happen at any time during treatment, and sometimes even afterwards. Adequate patient information about adverse events is one of the crucial points in their management. For physicians there are patient information that are relevant too. Some models

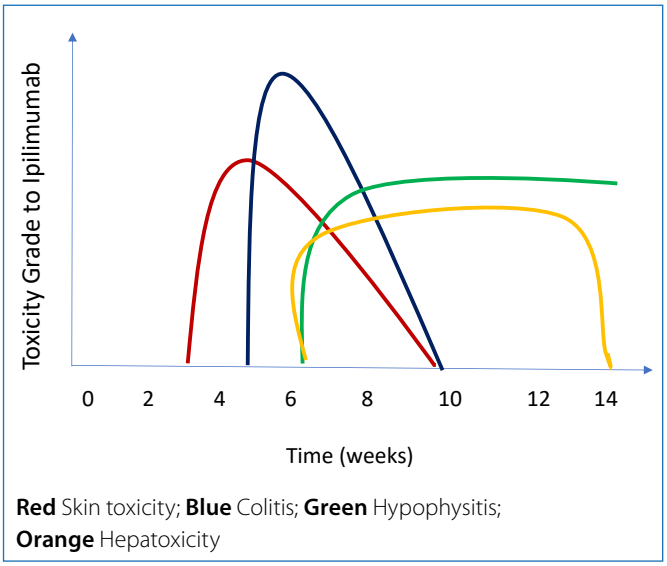

Figure 3. Time and grade of the toxicity with anti-CTLA4 (ipilimumab).

about immune adverse events have been implicates several factors, including local inflammation, genetic background, immunotherapy exposure, environment, and co-medication, which have direct or indirect effects on the immune system, and possibility to develop immune-related events. It is important to check a patient's medical history for these factors like: underlying autoimmune disease, chronic organ dysfunction (renal failure/dialysis, respiratory failure, COPD, heart failure), chronic viral infection (HIV, viral hepatitis), organ transplant… These are not contraindications for immunotherapy, but it is important to check with the specialist managing these pre-existing conditions that they are well controlled.[11]

Dermatologic toxicity

The dermatologic toxicity is one of the most frequent immune-related adverse events. The incidence depends on the type of immunotherapy, being most frequent with anti-CTLA4 (ipilimumab), compared to antiPD1/PDL1.[17-20] Although is one of most frequent, in the majority of cases is a low-grade toxicity (grade 1 or 2).[17,19,20] The most common adverse event is maculo-papular rash associated or not to pruritus, which can also occur alone and vitiligo. Other adverse events associated with immunotherapy are alopecia areata, stomatitis, xerosis cutis and photosensitivity. More rarely, serious adverse events can occur as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or DRESS.[17-19] A skin biopsy can be performed to confirm the adverse event. Specifically, vitiligo can be associated with a clinical response. This phenomenon is very well described in melanoma patients, but not with lung and renal patients.[21-26] Normally cutaneous toxicity is one of the first to appear, usually in a few weeks after the treatment was initiated. It is essential to classify the toxicity according to Common Terminology Criteria for Adverse Events (CTCAE). The management of the toxicity depends on this classification. The low-grade symptoms can be treated with topical emollients, oral antihistamines and in some cases with topical corticosteroids. Normally is not necessary to stop immunotherapy. Grade 3 or 4 toxicity usually requires to resume immunotherapy until resolution to grade 1 toxicity and systemic steroids may be necessary. The tapering of steroids should be made with caution. Grade 4 life threating toxicity requires a permanent discontinuation of treatment.[23]

Gastrointestinal toxicity

Gastrointestinal toxicity from immunotherapy is well described for anti-CTLA4, and less frequent for anti-PD-1 and anti- PDL1 drugs.

Diarrhea is a common complication of ICI therapy, with a higher incidence in patients treated with anti-CTLA-4. A systematic review of 10 clinical trials reported diarrhea in 27%-54% and colitis in 8%-22% of patients treated with anti-CTLA-4 therapy.[24] The highest incidence of colitis occurs in patients treated

with combination of anti-CTLA-4/PD-1 agents, and the risk of grade 3-4 colitis is also increased with combination therapy compared with monotherapy. A randomized phase 3 trial of 945 patients with advanced melanoma reported any-grade colitis in 2.2% of patients treated with nivolumab, 11.3% of patients treated with ipilimumab, and 12.8% of patients treated with ipilimumab and nivolumab.[25] Grade 3 and 4 colitis was described in 1% of patients treated with nivolumab, 7.7% of patients treated with ipilimumab, and 8.3% of patients treated with combination ipilimumab-nivolumab. Diarrhea or colitis may recur after discontinuation of therapy, and patients may have a presentation similar to that of chronic inflammatory bowel disease, especially with anti-CTLA4 agents.[26]

The main differential diagnoses of anti-CTLA4 enterocolitis are GI infections and tumour-related symptoms. Patients with diarrhea on anti-CTLA4 therapy should undergo a workup including complete blood count, serum electrolyte profile, stool analyses for enteropathogens and Clostridium difficile toxin. Anti-CTLA4-induced enterocolitis should be confirmed by flexible sigmoidoscopy or colonoscopy with biopsies. Endoscopic lesions of anti-CTLA4 colitis are erythema/loss of vascular pattern, erosions and ulcerations. The sigmoid colon and the rectum are involved in most cases. However, endoscopic lesions of the colon are often extensive and may extend proximal to the sigmoid colon in two thirds of cases. The histological picture generally differs from that observed in inflammatory bowel disease. In most cases, it is that of an acute colitis (infiltration with neutrophils, eosinophils), either diffuse or focal with patchy crypt abscesses.[23]

Patients with non-severe diarrhea should be treated with anti-diarrheal, fluid and electrolyte supplementation, if needed. The ICI therapy can be continued. In patients presenting with persistent grade 2 or higher diarrhea/colitis, ICI should be stopped and systemic corticosteroids started (1-2 mg/kg per day, i.v.).[23,27] Patients who have a response to i.v. corticosteroids within 3-5 days should be switched to the oral form and tapered over 8-12 weeks.[23] If there is no response within 3 to 5 days, infliximab should be considered; a single 5 mg/kg dose is usually sufficient.[23,28] Patients who do not respond to corticosteroids within 3-5 days should be switched to infliximab, unless it is contraindicated.[29] Overall, one-third to two-thirds of patients either do not respond to high-dose i.v. steroids, or have a relapse requiring an increase in the corticosteroid dosage during the course of steroid tapering.[30,31] These patients require infliximab and usually have an excellent response. A single dose of infliximab (5 mg/kg) is generally sufficient.[23,27] Some patients may need a second dose of infliximab 2 weeks after the first administration.[27] Vedolizumab, an anti-integrin α4β7 antibody with gut-specific effects, has been investigated for patients with steroid-dependent or refractory ICI-induced colitis. For instance, a retrospective series of 28 patients who were treated with vedolizumab for immune-related enterocolitis that was refractory to steroids and/or infliximab described sustained clinical remission in 24 of 28 patients after a median of 3 doses of vedolizumab.[32] Retrospective studies have examined outcomes in patients who received earlier treatment with biologic agents. A series that included 1479 patients treated with ICI, of whom 179 developed immune-related enterocolitis, found that patients who received infliximab or vedolizumab ≤ 10 days after colitis onset had improved clinical outcomes, including decreased hospitalization, a shorter duration of steroid treatment and reduced rates of steroid failure, and shorter symptom duration.[33] Further studies are needed to confirm the efficacy and safety of vedolizumab in patients with ipilimumab-induced enterocolitis. Recently, a colitis, possibly due to cytomegalovirus reactivation, has been reported in a patient with medically refractory anti-CTLA4 colitis.[23] Further studies are needed to determine whether CMV plays a significant role in this setting.

Some patients develop a colonic perforation, with or without intra-abdominal abscess, either initially or during medical treatment. They should have emergency colectomy. In international guidelines are recommend subtotal colectomy with ileostomy and sigmoidostomy because colonic lesions are generally extensive and segmental colonic resection is generally followed by a severe inflammation of the remaining colon in the postoperative phase.[23,27]

Hepatoxicity

The hepatitis is an immune-related event frequent during treatment with ICI. The estimated incidence of hepatotoxicity is 5%-10% in patients treated with ICI agents in monotherapy and 25%-30% in those treated with the combination therapy of ipilimumab 3 mg/kg and nivolumab 1 mg/kg.[34,35] Different dosing regimens of ipilimumab-nivolumab have been investigated with variable toxicity profiles observed given the dose-dependence of ipilimumab-induced hepatitis. In a pooled retrospective safety review, which included 448 patients treated with Nivolumab 1 mg/Kg plus Ipilimumab 3 mg/Kg followed by maintenance nivolumab for advanced melanoma, hepatic adverse events were the most frequently observed grade ≥ 3 toxicity, with 17% incidence.[36]

All patients undergoing ICI therapy should be assessed for signs and symptoms of hepatitis with serum transaminases and bilirubin measured before every cycle of treatment.[23,27] Hepatitis is usually asymptomatic and detected on such routine blood monitoring. Transaminase elevation is observed between 6 and 14 weeks after the initiation of treatment.[28] Although most cases resolve with treatment discontinuation, multiple reports of acute liver failure secondary to nivolumab, pembrolizumab, and ipilimumab have been published.[37] A series of 16 patients who developed grade ≥ 3 hepatitis during ICI therapy iden-

tified different histologic patterns of liver injury in patients treated who received anti-CTLA-4 compared with anti-PD-1/anti-PD-L1 therapies.[38] If hepatitis develops, disease-related causes, concomitant drug administration (including alcohol) and infectious causes, particularly viral hepatitis, should be ruled out. However, initiation of therapy, if needed, should not be delayed while awaiting serological results if there is no other apparent cause.[23,27] Liver biopsy may be considered in assisting in the differential diagnosis of more severe hepatic reactions.[39] Lobular hepatitis indistinguishable from autoimmune hepatitis is most reported.[40,41] Most cases are panlobular but inflammation may be confined to zone 3.[40,41] Additional sinusoidal histiocytosis and central vein endothelitis may help identify ipilimumab-associated inflammation. Rare cases show portal tract inflammation and cholangitis or changes indistinguishable from non-alcoholic steatohepatitis (NASH).[27]

In cases of grade 2 toxicity, ICI should be held and liver function tests monitored; therapy can be resumed when there is resolution to grade 1, and corticosteroids should be started if there is no improvement.[23] Rare cases are refractory to high-dose steroids, and then mycophenolate mofetil should be considered. Infliximab is contraindicated according to some guidelines given concerns about hepatotoxicity.[23,41,42] However, a case report describing the use of infliximab in a case of life-threatening hepatitis refractory to high-dose steroids and mycophenolate mofetil in a patient who received ipilimumab-nivolumab for metastatic melanoma has been published.[43] Additional studies are needed to clarify the safety of infliximab for this indication. The successful use of antithymocyte globulin has been reported for a case of steroid-refractory hepatitis and can be considered in cases of acute clinical deterioration.[44] Hepatitis usually resolves within 4-6 weeks with appropriate treatment but in the event that it does not resolve, other contributory causes should be reconsidered and the initial diagnostic work repeated as necessary, particularly bearing in mind the concomitant administration of other hepatotoxic drugs (including herbal medications and those purchased over the counter) and cytomegalovirus reactivation.[23,27]

Endocrinopathies

Endocrine dysfunction is one type of toxicity associated with immunotherapy, being most common with anti-CTLA4 in comparation with antiPD1, occurring even more frequently with combination of both. Specifically, this toxicity usually is permanent, even after cessation of the treatment and can occur even after the treatment was stopped. Characteristically occurs a few months after the treatment was started and most of the times is non-reversible.[23,27]

In most cases the diagnosis of thyroid dysfunction is made by alterations in routine blood tests evaluations. The most common is hypothyroidism and the treatment is levothyroxine replacement. Sometimes hypothyroidism can be preceded by thyrotoxicosis or hyperthyroidism. It is important to monitor eventual progression to hypothyroidism. The treatment is based on beta blockers and in rare cases steroids. Normally it is not necessary to withhold checkpoint inhibitors.[23,27]

Hypophysitis is a very rare endocrine immune-related adverse event. The symptoms leading to this diagnosis are very unspecific, more commonly headache and fatigue and rarely visual disturbances. After suspicious symptoms blood tests should be done, with hormonal evaluation of TSH, adrenocorticotropic hormone, follicle-stimulating hormone/luteinizing hormone (FSH/LH), thyroid function and cortisol levels. Brain MRI can also show pituitary enlargement. The treatment with immunotherapy should be stopped and start hormonal replacement therapy and glucocorticoids.[23,27]

Treatment with checkpoint inhibitors can induce in rare cases diabetes. This occurs in < 1% of cases, but glucose levels should be evaluated regularly. As other endocrine adverse events, this toxicity can be permanent, and treatment with insulin substitution is necessary. In most cases, the treatment with checkpoint inhibitors can be re-started.[23,27]

Pneumonitis

Pneumonitis is the most common pulmonary toxicity of ICI therapy.[28] Although the overall incidence of pneumonitis is low, it is potentially life-threatening and should be considered in any patient who develops new respiratory symptoms.[27]

Pneumonitis associated with ICI agents is a toxicity of variable onset and clinical, radiological and pathological appearances, which has been observed with anti-PD-1/PD-L1 monoclonal antibodies and, more rarely, with anti-CTLA4 agents. The frequency is higher in combination immunotherapy.[23,27]

Acute interstitial pneumonitis/diffuse alveolar damage syndrome is the most acute, life-threatening event, but organising inflammatory pneumonia, as well as a sarcoidosis-like pulmonary granulomatosis have been described and may result in difficulties in differential diagnosis with progression of disease.[45-50] Rarely, pneumonitis worsens despite immunosuppression, and may be fatal due to infection or progressive disease.[23,27]

Data documenting pulmonary immune-related toxicities have been progressively reported from retrospective series, from large published prospective trials and subsequent expanded access programs, especially in the treatment of melanoma, NSCLC and renal carcinoma.[23] Pneumonitis secondary to anti-PD-1/anti-PD-L1 therapy is more common and more severe in patients who have NSCLC compared with those who have melanoma. For instance, a meta-analysis that included 20 trials of anti-PD-1 therapy for melanoma, NSCLC, and RCC found that the incidence of all-grade and grade ≥ 3 pneumonitis was

higher in patients who had NSCLC (4.1% and 1.8%, respectively) compared with those who had melanoma (1.6% and 0.2%, respectively). The incidence of all-grade pneumonitis, but not grade ≥ 3 pneumonitis, was higher in patients who had RCC compared with those who had melanoma.[45] Patients with NSCLC may be at higher risk of pneumonitis given underlying lung pathology, including chronic obstructive pulmonary disease and pulmonary fibrosis. Another meta-analysis that included 19 trials of PD-1 and PD-L1 therapy for NSCLC found that the incidence of any grade and grade ≥ 3 pneumonitis was higher with PD-1 inhibitors compared with PD-L1 inhibitors (3.6% *vs* 1.3% and 1.1% *vs* 0.4%, respectively).[49] The incidence of pneumonitis was also higher in treatment-naive patients compared with previously treated patients (4.3% *vs* 2.8%).[49] Larger studies are needed to determine risk factors for pneumonitis, including the relationship between smoking history and the risk and role of the PD-1/PD-L1 pathway in development of pneumonitis.[27]

Whereas pulmonary adverse events are most often related to disease progression, particularly in the context of lung cancer or lung metastases, any new respiratory symptom should prompt a dedicated evaluation to formally exclude lung toxicity. All patients presenting with pulmonary symptoms, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by CT. Any respiratory symptom or sign must be carefully monitored, since fatal and life-threatening cases of pneumonitis have been reported.[23]

The presentation of pneumonitis varies in both severity and acuity of onset.[28] Patients may develop cough, chest pain, wheezing, shortness of breath, new hypoxia, or fatigue. Some patients are asymptomatic, with a diagnosis made incidentally on imaging studies; in 1 series, 33% of patients were asymptomatic at diagnosis.[50] In rare cases, hypoxia progresses rapidly, leading to respiratory failure.[51]

Imaging findings are variable and include cryptogenic organizing pneumonia, nonspecific interstitial pneumonitis, hypersensitivity pneumonitis, or usual interstitial pneumonitis/pulmonary fibrosis.[28] Imaging findings consistent with cryptogenic organizing pneumonia are more common in patients with NSCLC and have been associated with an increased likelihood of requiring immunosuppression compared with other imaging subtypes.[50] In addition, pulmonary and extrapulmonary sarcoid have been reported in patients treated with anti-PD-1/anti-PD-L1 and anti-CTLA-4 therapy and should be considered when chest imaging shows mediastinal or hilar lymphadenopathy or reticulonodular opacities.[28]

In general, lung biopsy is not required for subsequent patient management. However, if there is radiological or clinical doubt as to the aetiology of pulmonary infiltrates, then biopsy may provide an answer. While transbronchial lung biopsy may secure a diagnosis of infection or malignancy, and perhaps granulomatous disease or organising pneumonia, a surgical lung biopsy using video-assisted thoracoscopic surgery is more likely to secure a specific diagnosis.[23] If a biopsy is taken, it is vital that the reporting pathologist is informed about the background to, and reason for, the diagnostic procedure.[23,27]

Baseline pulmonary function tests can be considered in patients who are at high risk of developing pulmonary toxicity.[42] Guidelines recommend concurrent broad-spectrum antibiotics and immunosuppression during workup because of the potential for overlapping presentation of pneumonitis and infection.[23,28] In grade 1 to 2 pneumonitis, treatment consists of oral steroids with prednisone 1 mg/kg daily or equivalent.[27] Patients should be clinically assessed every 2-3 days initially and, ideally, also radiologically in grade 2 pneumonitis. Steroids should be tapered over 4-6 weeks after recovery and reintroduction of the checkpoint inhibitor should be delayed until the daily dose of steroids equals 10 mg of oral prednisone per day or less.[27] In patients with grade ≥ 2 pneumonitis, ICI should be withheld, pulmonology should be consulted for bronchoscopy with bronchoalveolar lavage, high-dose steroids should be started[(methyl)prednisolone 2-4 mg/kg/day or equivalent], and hospitalization may be needed.[23,29] The immunotherapy treatment should permanently discontinued. Where the patient's condition does not improve or there is no imaging improvement after 2 days, additional immunosuppressive strategies should be implemented.[23,44] The addition of infliximab, mycophenolate mofetil (MMF) or cyclophosphamide are possible options. Tapering of steroids should be very slow and careful, over 6 weeks or more; relapses of pneumonitis during steroid tapering have been reported, adding considerations about recurrence in patients who rechallenge immunotherapy.[50]

Rare toxicities

There are three 'red alert' categories of toxicity with immunotherapy: cardiovascular, including myocarditis, pericarditis and vasculitis; neurological, including neuropathy and encephalopathy; and haematological, including haemolytic anaemia, thrombocytopenia and aplastic anaemia.[27]

Patients suffering even grade 1 cardiovascular, neurological or haematological adverse events should promptly put treatment on hold and be rapidly and comprehensively investigated for these three organs: heart, brain and nervous system, and the haematopoietic system.[27]

An analysis using a pharmacovigilance database reported an overall incidence of 0.93% of serious neurologic immune-related adverse events in patients who had melanoma who were treated with nivolumab with or without ipilimumab.[52] The median time to onset was 45 days, and the time to resolution was 32 days. Thirty-two of 43 observed neurologic events were grade 3 or 4, and 1 case of encephalitis was fatal. Another anal-

ysis of a pharmacovigilance database identified different patterns of neurologic toxicity, depending on class of immunotherapy.[53] For instance, myasthenia gravis was associated with anti-PD-1/anti-PD-L1 therapy. Noninfectious encephalitis/myelitis was more common with anti-PD-1/anti-PD-L1 therapy than with anti-CTLA-4 therapy and with combination therapy versus monotherapy. Guillain-Barre syndrome and noninfectious meningitis were more common with anti-CTLA-4 compared with anti-PD-1/anti-PD-L1 therapy and with combination therapy compared with monotherapy. Myasthenia gravis had an earlier onset (median, 29 days) compared with other neurologic toxicities (median, 61-80 days), and was often associated with myocarditis and myositis.[27] Furthermore, myasthenia gravis was associated with a higher fatality rate compared with other neurologic toxicities, with the highest fatality rate noted in patients who had myasthenia gravis in addition to myositis and myocarditis.

The presentation of neurologic events can be diverse, with potential for involvement of any aspect of the central or peripheral nervous system. Most neurologic toxicities are low grade, with a higher incidence of grade 3 and 4 toxicity after anti-CTLA-4 treatment (0.7%) compared with anti-PD-1 treatment.[53,54] The differential diagnosis for patients who develop neurologic symptoms on ICI therapy is broad and includes infection, central nervous system (CNS) metastasis or leptomeningeal spread, paraneoplastic syndromes, vitamin B12 deficiency, and diabetic neuropathy. Because there is potential for variable timing of onset and for rapid clinical deterioration, neurologic events and early neurology consultation should be considered in patients who develop new neurologic symptoms.[55] For patients with grade ≥ 2 neurologic symptoms, ICI should be withheld, and steroids started while diagnostic evaluation is pursued. Patients who require hospitalization should be managed in close collaboration with neurology. In steroid-refractory or rapidly progressive cases, additional lines of immunosuppression can be considered, although data are limited, and current recommendations are drawn from case reports.[55]

A retrospective and prospective multicenter registry of patients with ICI-induced myocarditis estimated an incidence of 1.14% with a median onset at 34 days.[56] An earlier analysis using a pharmacovigilance database for patients receiving nivolumab with or without ipilimumab reported 18 cases of severe drug-related myocarditis among 20,594 patients (0.09%), with a higher incidence in patients who received ipilimumab-nivolumab (0.27%) compared with nivolumab alone (0.06%).[57] Concurrent severe adverse events are common in patients with cardiac immune related adverse events and occurred in 42 of 101 patients with myocarditis, most commonly myositis (25 patients) and myasthenia gravis (11 patients).[58]

The presentation of cardiac immune adverse events varies and can include dyspnea, chest pain, or acute cardiovascular collapse.[29] Cardiac immune adverse events include myocarditis, pericarditis, cardiac fibrosis, arrhythmias, and new-onset heart failure.[28] Myocarditis can be rapidly fatal; in the multicenter registry of patients with ICI-induced myocarditis, 16 of 35 patients with myocarditis experienced a major adverse cardiac event at a median follow-up of 102 days, including 6 cases of cardiovascular death, 3 of cardiogenic shock, 4 of cardiac arrest, and 3 of complete heart block, 94 highlighting the potentially life-threatening nature of this immune adverse events and the importance of vigilant monitoring.[27]

Guidelines recommend baseline electrocardiography and troponin in all patients, although the optimal monitoring frequency for troponin is not known.[23,28] Diagnostic evaluation in patients who have symptoms consistent with cardiac events includes electrocardiogram, troponin, brain natriuretic peptide, echocardiogram, and chest x-ray.[23,28] Patients with suspected myocarditis should be managed by a multidisciplinary team, with early cardiology consultation given the potential for fatal cardiac events. In cases of confirmed myocarditis, ICI should be stopped, and patients should be treated with high-dose corticosteroids. The timing of corticosteroid initiation is made on an individual basis, because there are no data available to establish a threshold (e.g., cutoff troponin) for starting corticosteroids in patients with suspected myocarditis.[28] Therefore, guidelines recommend initial methylprednisolone pulse dosing (1 g/day for 3-5 days).[23] In unstable patients and patients who do not respond to corticosteroids, additional immunosuppression should be considered, although the optimal agent is not known.[59] Infliximab, antithymocyte globulin, intravenous immunoglobulin, mycophenolate mofetil, and tacrolimus can be used.[59]

Hematologic immune-related adverse events are rare; however, diverse manifestations, including hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, myelodysplasia, hemophilia A, aplastic anemia, and hemophagocytic lymphohistocytosis have been described.[23] An analysis of the World Health Organization database identified 168 individual case-safety reports of hematologic toxicity secondary to ICI therapy.[60] The most common hematologic immune events were immune thrombocytopenic purpura (68 cases) and hemolytic anemia (57 cases), including 4 cases of concomitant immune thrombocytopenic purpura and hemolytic anemia. The median onset occurred at 40 days. An observational study that included 35 patients treated with anti-PD-1/anti-PD-L1 who had hematologic events reported an overall incidence of < 1%, although the majority (77%) of hematologic events were grade 4, and there were 2 deaths secondary to febrile neutropenia.[61]

The differential diagnosis for progressive cytopenias includes cancer progression, bone marrow involvement, gastrointestinal bleeding, and drug effect. Guidelines recommend treat-

ment with corticosteroids on an individual basis in addition to hematology consultation.[23,28]

In some hard-to-manage cases, advice from a specialist in general internal medicine could be useful and add value.

Professional and patient education

Being a relatively new modality, the knowledge about immunotherapy is somewhat limited among patients and even in some healthcare providers. An assessment by the Association of Community Cancer Centers (ACCC) in 2014 showed that only 7% of the community of clinicians reported being "extremely familiar" with immuno-oncology therapies.[62]

Thus, one of the key pieces to responsive and coordinated care across healthcare team is to ensure that healthcare providers are familiar with these treatments so that they can address them with patients when appropriate. On the other hand, the patient must also be well informed about toxicities and effectively engaged in shared, informed decision-making. Educating patients and professionals to achieve a better understanding about the immune system and the mechanism of action of these treatments and their particular adverse events is essential to the successful choice of the usage of immunotherapy.[63]

Immune-related adverse events occurred by different mechanisms than adverse events associated with chemotherapy.[64,65] Typically, they are caused by loss of immune self-tolerance, leading to autoimmunity and inflammatory-type reactions. Unlike adverse events seen with other agents, immune-related events do not have a direct dose-response or proportional dose-toxicity relationship, although many immune-related events develop early in treatment, some manifest after treatment completion.[66-68]

On the other hand, they can persist even after immunotherapy has ceased and can be irreversible with long-term treatment based on corticosteroids or hormone replacement, which can also cause their own additional side effects.[69,70]

Management of immune-related adverse events requires healthcare professionals with experience in dealing with it. There should be a high level of suspicion that new symptoms are related to immunotherapy until proven otherwise. In this field, close collaboration between the patient and the healthcare team in the necessary surveillance is essential. Non-delayed appropriate management, combining withhold or cessation of immunotherapy and the use of corticosteroids may result in resolution of immune events, but it must be kept in mind that long-term sequelae and mortality may still occur.[69,71]

Patient education about their treatment and early recognition of symptoms is a quality criterion as well as it is of utmost importance for the patient to be supported by a dedicated healthcare team that correctly identifies and treats immune related events in a timely manner to prevent severe morbidities and ultimately mortality.[69,72]

Experience based on educating patients conventionally undergoing chemotherapy shows that education is essential for cancer patients to understand how to best care for themselves, managing side effects of treatment, and contacting healthcare providers for their assistance.[73] Effective patient education during initial diagnosis and treatment can improve anxiety and self-care decisions, resilience, decrease the intensity of side effects, and improve quality of life and treatment adherence.[72,74]

Patient education is most effective when practiced prior to the start of treatment, in a quiet environment that supports learning, and provided by members of the oncology team at their healthcare facility.[74] Treatment side effects, management strategies, and infusion center orientation are consistently shown to be the most important topics to help reduce patient anxiety.[74] Educational structure is an important consideration to maximize information retention and must always be based on the awareness of barrier recognition and learning methods.[70] The provision of timely, consistent, relevant and personalized information for patients and caregivers is therefore critical.[72] Educational resources should include a variety of teaching strategies that consider patients individual needs and preferences and that they are geared toward patient empowerment.

While patient education prior to treatment is essential, ongoing support and timely learning needs assessment should also be available. Specific patient education about ICIs must be developed with the input from the healthcare team and regularly revised according to emerging clinical guidelines.[66-68,71]

Key messages for patients receiving ICIs shall also include the expected timing of therapeutic response and corresponding immune-related adverse events, the importance of early identification of these events for effective management, and the unique ability of ICIs to influence the immune response even after discontinuation.

Other patient support materials may include symptom diaries or questionnaires and wallet patient alert cards, so that they can be used to notify healthcare providers of their treatment with ICIs. Standardizing information regarding these immune events in conjunction with information systems could enable practitioners to build a greater knowledge about the usage of immunotherapy and patient responses to treatment.[73]

Table 1 aims to summarize some of the key points that should be the focused in the patient's approach when undergoing immunotherapy treatments with ICIs.

Multiple online resources are increasingly available to support patients and healthcare providers' practice (published and reviewed by reputable bodies, e.g. ASCO, ESMO, NCCN, EVIQ) which are key resources for understanding and well managing ICI treatments.[23]

Treatment	irAEs	Searching Healthcare
• EXPLAIN the difference between chemotherapy and immunotherapy • DESCRIBE the mechanism of action and duration of time to presume tumor response • ELUCIDATE about the various types of response you may experience • ALERT to the potential long-term benefits of completing all treatments • PROVIDE support guides with information about the drug, irAEs surveillance, and preferred contacts (in case of symptoms)	• DESCRIBE the most common irAEs and care for their minimization • CLARIFY the use of supportive medication, if previously prescribed (e.g. loperamide, corticosteroids) • TRANSMIT the importance of patient vigilance in the early detection and reporting of symptoms (record even seemingly unrelated ones) • TRANQUILIZE to reassure the patient about the irAEs, because they can be approached without affecting the clinical results of the treatment • ASSURE that the patient is not reluctant to report symptoms	• INSTRUCT to ALWAYS reach the healthcare team at the numbers provided, in case of irAEs (mild or severe) • RECOMMEND how to proceed when the Oncological Center is closed (e.g. emergency services) • ENCOURAGE preferential recourse in case of IrAEs to the institution where you are undergoing treatment (expertise) • RECOMMEND TO GO, in case of severe IrAEs and/or geographically distant from your center, the nearest emergency service and inform: undergoing treatment with immunotherapy and the supposed availability for articulation of the oncological healthcare team • ADVISE TO SEEK in advance, if planning to travel, other local healthcare facilities that can provide the wright support

Table 1. Key points for the approach of the patient undergoing ICI.

Due to the increased use of immunotherapy therapy in oncology patients may navigate various care settings, including emergency services or inpatient services. The education of healthcare professionals who administer the treatments is fundamental, but it increasingly extends to teams such as those from the services mentioned, which should be supported by practical guidelines to address common scenarios like initial presentation for suspected immunotherapy toxicity, initial management of immune-related events, and management of refractory immune-related events.[74]

It is the responsibility of healthcare professionals to protect patients from the harm that results from a lack of recognition and subsequent failure to institute appropriate therapy when immunotherapy derived immune-adverse events arise. Educational opportunities should be promoted among healthcare professionals in general to contribute to greater awareness of the treatment modality, recognizing and instituting appropriate therapy for immune-related adverse events.

Conclusion

The indications for immunotherapy continue to expand across malignancies and disease settings. It is increasingly a mainstay in the treatment of various oncological diseases, at different stages, alone or in combination with other modalities such as chemotherapy, surgery, radiotherapy and other targeted therapies.

Despite achieving remarkable results in traditional survival goals, these transformative treatments have the potential to impact health-related quality of life through adverse events.

Improving awareness, training physicians with specific skills and extensive knowledge in the diagnosis and management of immune-related adverse events, and developing multidisciplinary collaboration, are crucial for the prompt recognition and treatment of this unique adverse events.

One must be aware that while many of these toxicities are rare, clinicians need to be vigilant in monitoring for this new group of adverse events. In fact, if such adverse events go unrecognized, this can lead to significant morbidity and mortality. Many of these severe toxicities can be reversed with prompt recognition, discontinuation of the immunotherapy agent, and administering steroids.

Additionally, proper patient education on the adverse effects of these agents along with the process of joint decision making between the provider and physician, is essential for the success of treatment.

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