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Narrative Review

# New oncologic emergencies: What is there to know about inmunotherapy and its potential side effects?

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ABSTRACT

Over the last decade anticancer treatment has experienced encouraging changes. One of the latest developments is immunotherapy, which is increasingly becoming a mainstay for the treatment of these malignancies. Unlike conventional chemotherapy, immunotherapy enhances anti-tumor immune response by blocking inhibitory immune checkpoints, and allowing our own immune system to fight against the tumor cells, arising as a new and innovative mechanism of action. Therefore, although well tolerated, these drugs have a unique side effect profile and are known to cause immune-related adverse events (irAEs). Adverse effects of immunotherapy are most commonly observed in the skin, gastrointestinal tract, liver, lung and endocrine systems. Less common toxicities may include neurological, haematological, cardiac, ocular or rheumatologic involvement. As far as we know, cancer patients are frequently seen in the Emergency Department due to treatment related toxicities, thus there is an increasing necessity to learn about this particular side effect profile

given that they entail a different and unique management than that of classic chemotherapy drugs.

## 1. Introduction

The relationship between the immune system and cancer is complex. Up to date we know that the immune system is not only able to control infectious diseases, but also plays a major part in the evolution of cancer. Initial proof of this concept was found in patients with immunodeficiency conditions which, when compared to the general population, were found to develop more malignant diseases [1].

Tumor cells are able to use a variety of resources in order to escape from the immune system. This brings us to a three stage process called Immunoediting. In the first phase, called Elimination, transformed malignant cells are destroyed by a competent immune system. However, sporadic tumor cells that manage to survive immune destruction may then enter an Equilibrium phase where editing occurs, where these cells may adopt a new phenotype. Finally the Escape phase represents the third phase of the process, where immunologically sculpted tumor cells begin to grow progressively, become clinically apparent and establish an immunosuppressive tumor microenvironment [2]. Tumor cell escape can occur through many different mechanisms including: reduced immune recognition, increased resistance or survival, or development of an immunosuppressive tumor microenvironment. Each day we learn more about these mechanisms, bringing us the opportunity to block them in order to make the immune system active again.

Immunotherapy is increasingly becoming a mainstay for anti-cancer treatment. Many new drugs are under investigation and many other have been already approved for the treatment of numerous tumors. Currently, the immune checkpoint inhibitors are by far the most developed, including successful therapies that inhibit the cytotoxic T lymphocyte associated protein 4 (CTLA-4) pathway and the programmable cell death protein 1 (PD-1)/PD-L1 pathway. Other drugs under investigation include OX-40, LAG-3 and TIM-3 inhibitors.

Unlike conventional chemotherapy, immunotherapy enhances anti-tumor immune response by blocking inhibitory immune checkpoints, and allowing our own immune system to fight back against the tumor cells. Optimal cytotoxic T-cell (TCD8+) activation requires two distinct signals: binding of the T-cell receptor (TCR) to the cognate antigen presented by the antigen-presenting cells (APCs), followed by binding of CD80 and CD86 ligands on the APCs with the CD28 co-stimulatory receptor on the T cells. However, our immune system must have a deactivating mechanism in order to create tolerance and avoid autoimmune reactions. Once the TCD8+ is activated, expression of CTLA-4 is up-regulated. This protein is a homologue of CD28 that counteracts the activity of CD28 by binding to both CD80 and CD86 with a much

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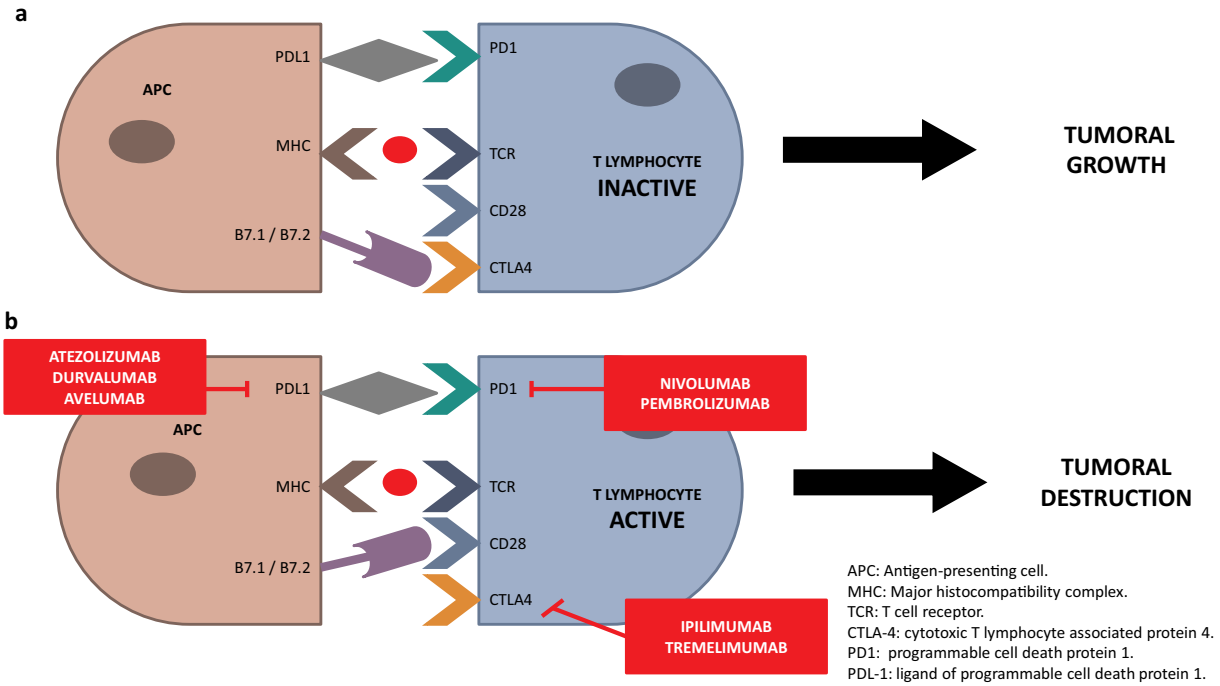


**Fig. 1.** Anti-CTLA4 and anti-PD1/PDL1 mechanism of action. a) Interactions between CTLA4 and B7, as well as PD1 with its ligand, PDL1, block lymphocyte activation in order to create tolerance. This mechanism is used by tumor cells as a means of disguise, to prevent tumor destruction. b) Immune checkpoint inhibitors block CTLA4 and PD1/PDL1 axis, allowing lymphocyte activation once again to enhance anti-tumor immune response.

higher affinity than that of CD28, and subsequently down-regulates T-cell activation [3,4]. In this context, ipilimumab was the first CTLA-4 checkpoint inhibitor to be developed (Fig. 1).

Subsequently, other immune checkpoints responsible for T cell activation/inactivation have been identified. PD-1 is a negative regulator of T-cell activity within the peripheral tissues and the tumor microenvironment. When PD-1 interacts with its ligands, PD-L1 or PD-L2, it down-regulates the effector response of these cells in peripheral tissues. Cancer cells are able to use this mechanism in order to create immune resistance in the tumor microenvironment [5,6]. New drugs have been developed which block PD-1/PDL-1, creating an enhanced anti-tumor immune response (Fig. 1).

Monoclonal antibodies (mAbs) have been designed in order to block these molecules: ipilimumab and tremelimumab are mAbs that inhibit CTLA-4, nivolumab and pembrolizumab block PD-1; and atezolizumab, avelumab and durvalumab are anti-PDL-1 (Table 1). Currently, these drugs have been approved for the treatment of multiple cancers. Ipilimumab was the first drug to prove efficacy in a phase III randomized trial for the treatment of metastatic melanoma patients [7]. Subsequently, other randomized controlled trials involving ipilimumab and other immune checkpoint inhibitors demonstrated substantial anti-tumor activity, not only for the treatment of metastatic melanoma [8,9] but also for other cancer subtypes such as: non-small cell lung cancer (nivolumab, pembrolizumab, atezolizumab) [10–13], kidney cancer (nivolumab) [14], head and neck cancer (nivolumab) [15] and urothelial carcinoma (pembrolizumab, atezolizumab) [16,17]. Furthermore, combination therapy (nivolumab + ipilimumab) has also been approved for the treatment of metastatic melanoma [18] and kidney cancer [19], and treatment trends are moving towards the increased use of combination therapy.

Although well tolerated, immune checkpoint inhibitors have an adverse event profile distinct from that of conventional chemotherapy. These drugs result in toxicities known as immune-related adverse events (irAEs), which occur secondary to the enhanced immune-response that the drugs elicit. As far as we know, cancer patients are frequently seen in the Emergency Department due to treatment related toxicities, thus there is an increasing necessity to learn about this particular side effect profile

given that they entail a different and unique management than that of classic chemotherapy drugs.

**Table 1**
Immunotherapy drugs and approved therapeutic indications

| Therapeutic target | Drug | Trade name | Approved therapeutic indications | |
|---|---|---|---|---|
| | | | EMA | FDA |
| CTLA4 | Ipilimumab | Yervoy | Melanoma | Melanoma, kidney |
| | Tremelimumab | - | - | - |
| PD1 | Nivolumab | Opdivo | Melanoma, lung, kidney, LH, head and neck, urothelial. | Melanoma, lung, kidney, LH, head and neck, urothelial, colorrectal (MSI), hepatocarcinoma. |
| | Pembrolizumab | Keytruda | Melanoma, lung, LH, urothelial. | Melanoma, lung, LH, urothelial, head and neck, MSI tumors, gastric, cervix. |
| PDL1 | Atezolizumab | Tecentriq | Lung, urothelial. | Lung, urothelial. |
| | Durvalumab | Imfinzi | Lung. | Lung, urothelial. |
| | Avelumab | Bavencio | Merkel carcinoma. | Merkel carcinoma, urothelial. |

CTLA-4: cytotoxic T lymphocyte associated protein 4. PD1: programmable cell death protein 1. PDL-1: ligand of programmable cell death protein 1. LH: Hodgkin's Linfoma. MSI: Microsatellite instability. EMA: European Medicines Agency. FDA: US Food and Drug Administration.

## 2. Methods

For this review, relevant literature was searched in PubMed database published between the years 2010 and 2018 (march inclusive), using the combination of the terms "adverse events", as well as each of the immunotherapy drugs approved for anti-cancer treatment: "pembrolizumab", "nivolumab", "ipilimumab", "atezolizumab". Phase I, II and III trials were reviewed in order to determine which irAEs were more commonly reported. Additionally, case reports which included more than 10 patients were reviewed for the most common irAEs (skin, gastrointestinal, hepatic, pulmonary and endocrine irAEs), which provide a better understanding of the diagnostic and treatment workup for routine clinical practice of unselected patients attending the Emergency Department. Due to the fact that robust evidence is lacking for the management of less common irAEs (< 1%), series of cases with fewer patients had to be included, to create awareness of these potentially fatal irAEs. Finally, significant clinical practice guidelines from internationally endorsed oncologic agencies were also reviewed: SEOM (Spanish Society of Medical Oncology), ESMO (European Society of Medical Oncology), ASCO (American Society of Clinical Oncology), NCCN (National Comprehensive Cancer Network); which could provide a global view for the management of irAEs.

## 3. Results

### 3.1. Initial management of irAEs

These irAEs are classified depending on their severity according to the Common Terminology Criteria for Adverse Events (CTCAE), were grade 1 is a mild toxicity, whereas grade 4 could be a life-threatening toxicity (Table 2) [20]. The irAE profile is similar between the different checkpoint inhibitors. However, CTLA-4 inhibitors, and furthermore the combination therapy, have shown to cause irAEs more frequently than PD-1 inhibitor monotherapy [21]. The phase III Checkmate 067 trial assessed the use of combination therapy versus monotherapy for the treatment of melanoma. IrAEs grade 3 - 4 were reported in 21% of patients treated with nivolumab, 28% with ipilimumab and 59% with the combination [22]. They most commonly affect the skin, gastrointestinal, liver, endocrine, and pulmonary systems (Table 3). Although less common, neurological, hematological, cardiac, ophthalmological or rheumatologic toxicities must be acknowledged because of their potential severity [23].

In general, irAEs occur quite early, mostly within weeks to 3 months after initiation of immune checkpoint blockers. However, it is important for physicians to be aware that irAEs can occur at any time, from the outset of treatment, during treatment, or after treatment has been discontinued. Skin irAEs usually are the first ones to develop, followed by gastrointestinal toxicities. Hepatitis and hypophysitis may develop later in time [24] (Fig. 2).

The initial management of irAEs is common regardless of the drug producing the adverse event (Fig. 3). Early recognition and initiation of the adequate treatment remains the key factor in order to reduce severity of these toxicities. Currently, official guidelines have been developed, which include straightforward therapeutic algorithms for the management of the most frequent irAEs [25–27]. Referral to an expert and/or specialist (oncologist, gastroenterologist, pulmonologist, hepatologist, endocrinologist, neurologist or dermatologist) for management of specific adverse events during emergency evaluation should also be considered. In general, grade 1–2 adverse events not interfering with activities of daily living are managed symptomatically and usually do not require dose omission or discontinuation. However, patients who experiment persistent grade 2 adverse events may require dose skipping as well as initiation of oral corticosteroids, such as 0.5 – 1 mg/kg/day of methylprednisolone (or equivalent corticosteroid dosing). For more severe adverse events, grade 3 – 4, treatment discontinuation is recommended and multidisciplinary consultation might be necessary. Additionally, intravenous corticosteroid treatment must me initiated promptly at high dose (1 – 2 mg/kg/day of methylprednisolone or equivalent). There is sparse evidence regarding the use of higher doses of corticosteroids (> 4 mg/kg/day – 1 gr/kg/day). Although these higher doses seem to have no additional effect for the treatment of the most common irAEs according to significant clinical practice guidelines, some less common irAEs such as rheumatologic, neurological or haematological adverse events may benefit during the initial period of treatment, nonetheless upon specialist consultation. If there is no improvement after 48 hours, additional immunosuppressive treatment should be considered, such as infliximab, mycophenolate, azathioprine, cyclophsphamide or cyclosporine, always taking into account the need for a multidisciplinary approach and what type of irAE is taking place. The use of intravenous gammaglobulin (IVIG) is not considered a routine approach and may only be considered for the onset of very rare and severe adverse events such as rheumatologic, neurological or haematological irAEs, exclusively upon specialist recommendation. Commonly, corticosteroids should be continued until symptoms resolve, become mild, or return to baseline levels, whereupon the doses given can be tapered over at least 1 month until cessation of treatment [28,29]. Furthermore, long-term (> 6 weeks) treatment with immunosuppressive drugs increases the chance of opportunistic infections; therefore, pneumocystis prophylaxis (e.g. trimethoprim-sulfamethoxazole one double-strength tablet 3 times per week) should be considered, as well as, calcium (1000 – 1500 mg/day) and vitamin D (800 – 2000 UI/day) supplements for the prevention of corticosteroid-induced osteoporosis [30].

### 3.2. Skin toxicity

#### 3.2.1. Incidence and diagnosis

Skin toxicity is the most frequent irAE and the one with the earliest onset (first weeks), occurring in 35% of patients treated with an anti-PD1 [31] and almost 44% of patients with the use of anti-CTLA4 [32]. Skin irAEs frequently present as pruritus or maculopapular rash, involving limbs and torso, with exception of palmar-plantar areas. Other skin affections include vitiligo, rosacea or alopecia [33]. More severe and potentially fatal skin toxicities can also occur, such as, Sweet syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), therefore a multidisciplinary approach is crucial. It is important to rule out non-inflammatory or infectious causes of these skin conditions, or

**Table 2**
General principles of CTCAE classification.

| Common Terminology Criteria for Adverse Events (CTCAE) | | | | |
|---|---|---|---|---|
| Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| Mild symptoms. | Moderate symptoms. | Severe symptoms but not immediately life-threatening. | Severe symptoms, life-threatening consequences. | Death related to adverse event. |
| Symptomatic treatment. | Symptomatic, non-invasive treatment. | Agressive treatment, hospitalization. | Urgent intervention, agressive treatment, hospitalization. | - |

**Table 3**
CTCAE classification of most frequent irAEs.

| irAEs | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Skin | Covering < 10% BSA, with or without symptoms. | Covering 10% - 30% BSA, with or without symptoms | Covering > 30% BSA, limiting self care. | Covering > 30% BSA, life-threatening symptoms. |
| Diarrhea | Increase of < 4 stools per day over baseline. | Increase of 4 – 6 stools per day over baseline or abdominal pain or bleeding. | Increase of > 6 stools per day over baseline; incontinence; need for i.v fluids for > 24 h. Hospitalization. | Life-threatening or potentially fatal consequences. |
| Lung | Asymptomatic, radiographic observations. | Moderate symptoms: cough, dyspnoea, thoracic pain. | Severe symptoms, hypoxia, ARDS. | Life-threatening or potentially fatal consequences. |
| Liver | AST o ALT ULN – 3.0 x ULN | AST o ALT > 3.0 – 5.0 x ULN | AST o ALT 5.0 – 20.0 x ULN | AST o ALT > 20.0 x ULN |
| Endocrine | Asymptomatic elevation of TSH or endocrinopathy with non-specific symptoms. | Symptomatic endocrinopathy (ej. fatigue, headache) | Severe symptoms, mass effect (hypophysitis), adrenal crisis or myxedema coma. | - |

BSA: Body Surface Area, ARDS: Acute Respiratory Distress Symdrome, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ULN: Upper Limit of Normal.

progression of the patient's underlying malignancy before diagnosing and treating them as an irAE. In some cases biopsy may be needed, for an optimal approach.

#### 3.2.2. Management

Most instances of skin irAE will be less-severe grade 1-2 rashes and can be treated symptomatically with topical corticosteroids and oral antihistamines as needed, without discontinuation of immunotherapy treatment. In addition, some patients might need oral antibiotics such as tetracyclines because of secondary bacterial infection (e.g. oral minocycline 100 mg twice daily for up to 12 weeks). The patient should be aware that, if their symptoms worsen or persist for more than 1-2 weeks after treatment, a close follow-up is warranted. For persistent symptoms or grade 3-4 rashes, immune checkpoint therapy should be delayed, 1-2 mg/kg/day IV methylprednisolone (or oral equivalent) should be administered and a dermatology consult should be scheduled to assess the need of additional immunosuppressive treatment which may include the use of cyclosporine (e.g. 5 mg/kg/day for a 3 – 7 days short course) or IVIG (e.g. 0.4 g/kg/day for 5 days for a total dose of 2 g/kg) in the case of severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS. Finally, patients may need to be admitted to the hospital depending on the severity of the irAE.

### 3.3. Gastrointestinal toxicity

#### 3.3.1. Incidence and diagnosis

Gastrointestinal toxicity is most frequently associated with anti-CTLA4 treatment and is an often cause of permanent discontinuation. It occurs approximately in 35% of patients, being severe in 11% of cases, including reports of 1.5% of colon perforations, in melanoma patients receiving ipilimumab [34]. On the other hand, gastrointestinal toxicity is less common when using anti-PD1 agents, with grade 3 - 4 toxicity described in 1 - 3% of patients [35]. It mostly appears in the form of diarrhea (95%) or as colitis, which includes abdominal pain (38%), rectal bleeding (24%) and fever in some occasions. It is always important to rule out other causes of diarrhea, such as an infectious cause. Complete blood work and stool testing (including Clostridium difficile `toxin testing) should be performed. Other examinations such as imaging (in order to rule out perforation) or colonoscopy may be considered.

#### 3.3.2. Management

Grade 1 diarrhea should be managed symptomatically with dietary measures, rehydration and anti-motility agents. Grade 2 diarrhea or colitis can also be managed symptomatically, but it requires discontinuation of immune checkpoint treatment. Patients should be re-examined if grade 2 symptoms persist for 3 days after symptomatic treatment has been established, as they may benefit from oral corticosteroids. For more severe cases, grade 3 - 4, immune checkpoint therapy should be discontinued, and 1-2 mg/kg/day intravenous methylprednisolone (or equivalent) should be given without further delay. The administration of antibiotics should be considered for the prophylactic treatment of opportunistic infections that might arise. If after de first 3-5 days symptoms persist and are refractory to corticosteroid therapy, a multidisciplinary approach is vital and additional immunosuppressive such as infliximab should be administered, provided that there are no contraindications. A first dose of infliximab 5 mg/kg will be administered in these cases. If symptoms persist after the first infliximab dose, a second dose of infliximab 5 mg/kg can be repeated two weeks after the initial dose. Specialist consultation and follow up is required for such cases.

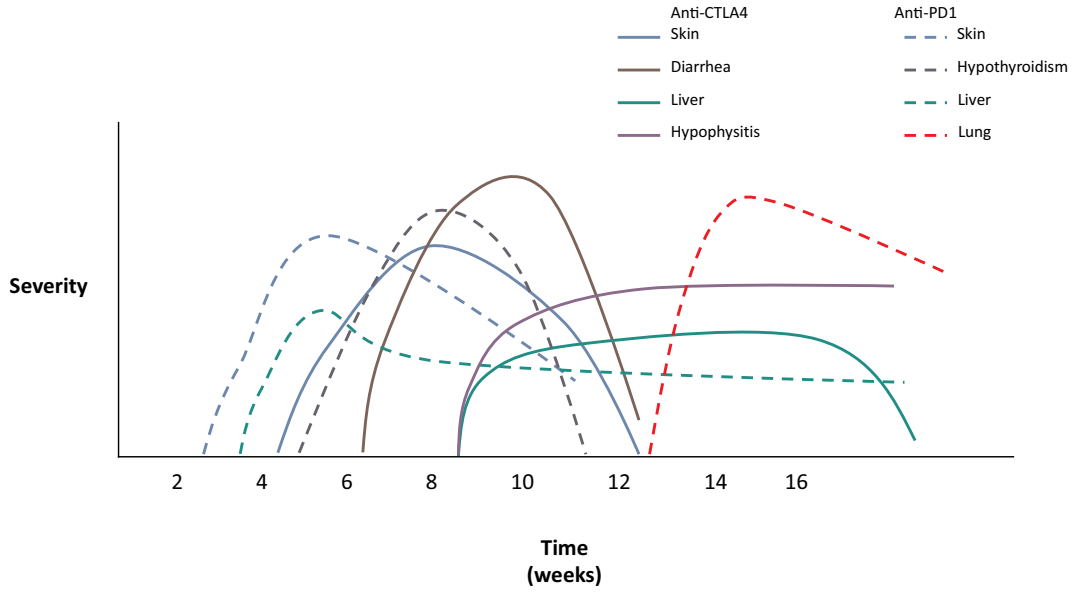


**Figure 2.** Kinetics of irAEs.

### 3.4. Pulmonary toxicity

#### 3.4.1. Incidence and diagnosis

The main pulmonary irAE of interest is pneumonitis. It is more frequent in patients treated with anti-PD1/PDL1 drugs (10%), and even more frequent with combined therapy (up to three times more), where several cases of life-threatening respiratory events have been reported [36]. Although no predisposing factors have been established, patients with lung or renal cancer tend to experiment more cases of pneumonitis [37]. On the contrary, other factors such as smoking habit or previous radiotherapy do not increase the risk of immune-related pneumonitis [38]. Moreover, even though it may be observed at any time, pneumonitis tends to occur later than other irAEs. Cases of pneumonitis have been reported 24 months after treatment initiation. Clinical manifestations include dyspnoea, cough, fever and thoracic pain. Radiographic appearance may seem as a non-specific interstitial pneumonitis [39]. Differential diagnosis should rule out infectious causes or malignant progression. Imaging techniques and bronchoscopy with the need of pulmonary biopsy may be warranted.

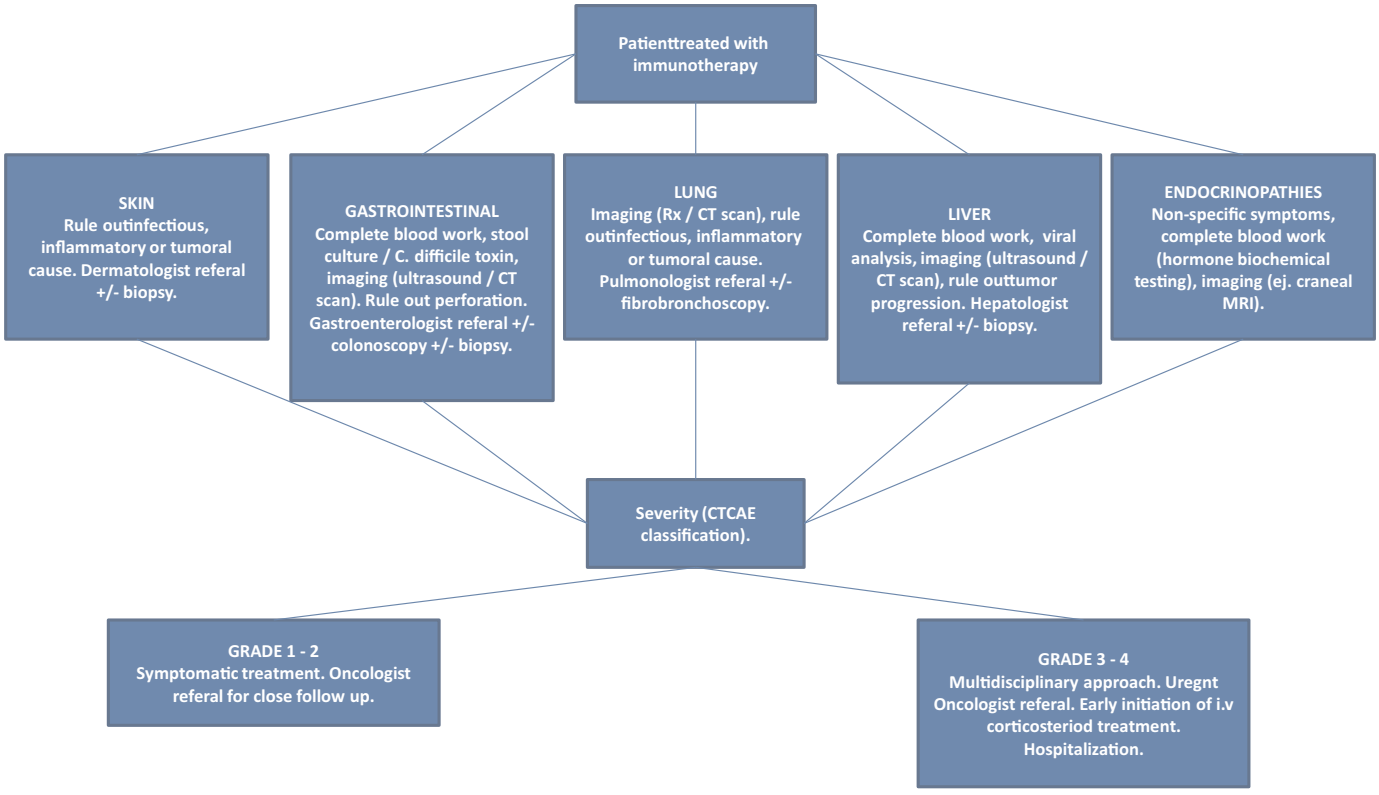


**Figure 3.** General approach for the management of the most frequent irAEs in the Emergency Department.

#### 3.4.2. Management

For individuals with grade 1 - 2 pneumonitis, immune checkpoint therapy must be delayed, 1 mg/kg/day oral methylprednisolone (or oral equivalent) should be administered, and a close clinical and radiographic follow up is strongly recommended (every 3 days at least). For patients with grade 3 - 4 pneumonitis, hospitalization should be considered and high dose intravenous corticosteroid therapy (1-2 mg/kg/day) should be initiated promptly, along with supportive care measures such as oxygen and bronchodilator therapy, as well as prophylactic antibiotics. If the patient does not respond after 48 hours, multidisciplinary approach is vital and additional immunosuppressive drugs should be considered, including the use of a single course of Infliximab 5 mg/kg, mycophenolate 1 g twice daily or even IVIG 2 g/kg over a 5 day course. Once symptoms have resolved, tapering of steroids should be done very slow and carefully, preferably over 6 weeks or more; as relapses of pneumonitis during steroid tapering have been reported [40].

### 3.5. Liver toxicity

#### 3.5.1. Incidence and diagnosis

Hepatitis occurs in 5% of patients treated with anti-PD1 agents and 10% of patients treated with anti-CTLA4 agents, with grade 3 - 4 cases reported in 1 - 2% of them [41]. Hepatitis is usually asymptomatic or associates non-specific manifestations such as fatigue or abdominal pain, and is typically detected on routine blood monitoring. Transaminase elevation may be accompanied by hyperbilirrubinemia or cholestatic enzyme elevation. If hepatitis develops, disease-related causes, concomitant drug administration (including alcohol or herbal products) and infectious causes, particularly viral hepatitis, should be ruled out. The use of imaging techniques (CT scan or abdominal ultrasound) and hepatic biopsy may be needed, especially in patients with more severe hepatic reactions.

#### 3.5.2. Management

Patients with maintained grade 2 liver toxicity for more than 1-2 weeks should initiate oral corticosteroids at dose of 0.5-1 mg/kg/day, and close blood work monitoring should be established. Once more, if such toxicity is maintained or worsens to grade 3 - 4 hepatitis, high dose intravenous corticosteroids should be initiated rapidly. Moreover, if after 48-72 hours of corticosteroid therapy there is still not a favorable response, multidisciplinary approach should be taken into account and additional immunosuppressive treatment should be considered with mycophenolate therapy 1 g twice daily for example. In this case, infliximab is not recommended for the treatment of immune-related hepatitis as it can produce additional hepatic damage [42].

### 3.6. Endocrinopathies

#### 3.6.1. Incidence and diagnosis

Endocrinopathies are considered a late event, since median time of onset is approximately 11 weeks. Endocrine irAEs are likely the most difficult to diagnose, therefore it is important to keep these complications in mind when a patient on an immune checkpoint inhibitor presents at the Emergency Department with non-specific symptoms. Common symptoms associated with endocrine irAEs include fatigue, headache, and nausea. Autoimmune hypophysitis is frequently associated with the use of anti-CTLA4 drugs, occurring in 13% of the patients [43]. Clinical features of hypophysitis may include headache and visual disturbances. For these patients magnetic resonance imaging showing enlargement and enhancement of the pituitary gland, and biochemical testing demonstrating pituitary dysfunction is needed. Furthermore, thyroid disorders seem to be more frequent with the use of anti-PD1 drugs, appearing in 10% of the patients [44]. Both, hyper- and hypothyroidism, have been reported, although hypothyroidism is more frequent. Other less common endocrinopathies associated with immune checkpoint inhibitors include thyroiditis, insulin-dependent diabetes mellitus and adrenal insufficiency [45].

#### 3.6.2. Management

Grade 1 endocrinopathies are managed with close follow up every 2 – 3 weeks with hormone monitoring, except for adrenal insufficiency and hypophysitis, for which immediate hormone replacement may be considered. For grade 2 or more, permanent hormone replacement is the fundamental basis of immune-related endocrinopathies. For patients with hypothyroidism and without risk factors, full replacement with levothyroxine can be estimated with an ideal body weight–based dose of approximately 1.6 μg/kg/day. For elderly or fragile patients with multiple comorbidities, consider titrating up from low dose, starting at 25-50 μg/day. Patients with hyperthyroidism should be offered a β-blocker for symptom relief (e.g. atenolol 25 – 50 mg/day), as well as methimazole (15 – 40 mg divided into 3 doses at 8-hour intervals initially depending on severity, with a subsequent maintenance dosage which ranges from 5 to 15 mg daily); and close monitoring of thyroid function every 2-3 weeks after diagnosis is recommended to catch a possible transition to hypothyroidism. Moreover, those patients with severe symptoms, grade 3 – 4, may require additional corticosteroid therapy and endocrinology consultation is strongly recommended. If the patient presents at the Emergency Department with low blood pressure or severely dehydrated, an adrenal crisis should be suspected and appropriate supportive therapy should be established. It is important to ensure that sepsis is ruled out as a possible cause of these symptoms.

### 3.7. Rare irAEs

Treatment with checkpoint inhibitors has also been associated with less common side effects in other organs. Even though the incidence may be low (< 1%), in some instances, these irAEs have been severe or fatal [46]. Neuro-related AEs may include polineuropathies, myasthenia gravis, Guillain-Barre syndrome or even autoimmune encephalitis. Moreover, a wide range of cardiovascular toxicities including myocarditis, pericarditis, arrhythmias, cardiomyopathy and impaired ventricular function have been reported [47]. Clinicians should be vigilant for immune-mediated myocarditis, particularly due to its early onset, non-specific symptoms and fulminant progression; therefore diagnostic workup should include troponin and brain natriuretic peptide (BNP) analysis, ECG, echocardiogram or even cardiac catherization for the more severe cases [48]. Furthermore, recent data strongly suggest that PD-1 blockade may induce accelerated atherosclerotic plaque development and inflammation, as well as, increasing the risk for arterial and/or venous thromboembolism, although further studies are required to identify pathophysiology, risk factors and benefit of thromboprophylaxis in this setting [49,50]. Kidney injury may also occur, with reported cases of nephritis [51]. Ocular toxicities have also been described and can be divided into ocular inflammation (keratitis, uveitis), retinal and choroidal disease [52]. Case reports have been documented with rheumatologic (vasculitis, polymyositis, myositis and temporal arteritis) and hematological irAEs (lethal aplastic anaemia, autoimmune haemolytic anaemia and immune thrombocytopenic purpura) [53–55]. Due to the low incidence, treatment recommendations are based on anecdotal evidence and the life-threatening nature of theses complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. In spite of the diversity of clinical presentations, treatment approach with corticosteroid therapy and multidisciplinary handling with specialist consultation, remain the essential cornerstones for the management of these patients.

## 4. Discussion

Immune checkpoint blockade with monoclonal antibodies directed

against CTLA-4 and/or PD-1, used either alone or in combination, have changed the landscape of treatment and prognosis for numerous tumor types. With the approval of these drugs and investigational trends towards the development of new agents for T lymphocyte activation, such as OX-40 agonists, LAG-3 and TIM-3 inhibitors, common and unusual autoimmune toxicities will arise. Because of the relatively new and complex mechanism of action, these drugs elicit a different type of adverse event which can mimic the symptoms of other, more common diseases, becoming a diagnostic challenge. Furthermore, solid evidence for the management of these irAEs is still too sparse as we can only rely on the communication of these irAEs during clinical trials, as well as clinical practice guidelines and case reports with few patients. Therefore, limitations of this review stem from the heterogeneity of the included studies, investigator-dependent communication of irAES and short follow-up of some studies.

Although the most common and serious irAEs affect the skin, gastrointestinal, liver, respiratory and endocrine systems, irAEs from immune checkpoint inhibitors can affect almost any organ system and become potentially fatal. Consequently, the ability to consider if an acute presentation is due to autoimmune toxicity is essential, provided that other causes, as could be tumor progression, have been ruled out. As a result, patient education and physician awareness of irAEs is key to reducing the severity of these events. Timely intervention with corticosteroids is crucial to limit the severity of these events, even though multidisciplinary approach and referral to the oncologist, as well as other specialists, must be taken into account.

## Conflict of interests

ABG declares no conflict of interests. JMC declares no conflict of interests. PG has acted as a consultant for BMS, AstraZeneca, MSD and Roche. DGP declares no conflict of interests. AC has acted as a consultant for BMS, AstraZeneca, MSD and Roche. TAG has acted as a consultant for BMS, AstraZeneca, MSD and Roche.

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