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Review

Immune-related adverse events with immune checkpoint blockade: a comprehensive review

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Abstract Cancer immunotherapy is coming of age; it has prompted a paradigm shift in oncology, in which therapeutic agents are used to target immune cells rather than cancer cells. The first generation of new immunotherapies corresponds to antagonistic antibodies that block specific immune checkpoint molecules cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein (PD-1) and its ligand PD-L1. Targeting these checkpoints in patients living with cancer had led to long-lasting tumour responses. By unbalancing the immune system, these new immunotherapies also generate dysimmune toxicities, called immune-related adverse events (IRAEs) that mainly involve the gut, skin, endocrine glands, liver, and lung but can potentially affect any tissue. In view of their undisputed clinical efficacy, anti-CTLA-4 and anti-PD-1 antibodies are entering in the routine oncological

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practice, and the number of patients exposed to these drugs will increase dramatically in the near future. Although steroids can be used to treat these IRAEs, the associated immunosuppression may compromise the antitumour response. Oncologists must be ready to detect and manage these new types of adverse events. This review focuses on the mechanisms of IRAE generation, putative relationship between dysimmune toxicity and antitumour efficacy, as a basis for management guidelines.

1. Introduction

For over 50 years now, surgery, radiotherapy and chemotherapy have been the physician's main weapons against cancer. However, cancer mortality rates remain high. Recently, immunotherapy has become a new way of overcoming cancer [1]. Cancer cells are able to turn immunosuppressive molecules to their advantage by inhibiting antitumour lymphocytes and thus escaping destruction by the immune system. In the tumour microenvironment, immunosuppressive molecules such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein (PD-1) and its ligand PD-L1 are markedly overexpressed [1]. Targeting these molecules, the immune checkpoint blockade agents reactivate cytotoxic T cells to destroy tumour cells. The first immune checkpoint blockade to display high antitumour activity was the anti-CTLA-4 monoclonal antibody ipilimumab [2]. Since then, the anti-PD-1 antibodies nivolumab and pembrolizumab have demonstrated high activity in melanoma [3,4] and subsequently many other types of cancer – prompting a 'PDLoma' of activity (Fig. 1).

By unbalancing the immune system, immune checkpoint blockade favours the development of autoimmune manifestations [5,6] also referred to as immune-related adverse events (IRAEs). Most of these adverse events can be managed by counteracting lymphocyte activation with steroids [7]. Although the use of steroids causes the IRAEs to regress, the associated immunosuppression may compromise the antitumour response [7]. Understanding IRAEs is critical for their early detection and appropriate management.

2. The physiological roles of CTLA-4 and PD-1/PD-L1.

Self-tolerance in humans is partly maintained by the inhibition of auto-reactive T-cells through the CTLA-4 and PD-1/PD-L1 axes [8,9]. Polymorphisms of *PD-1* and *CTLA-4* are associated with various autoimmune conditions summarised in Table 1. Interestingly, some of these autoimmune diseases share clinical features with the IRAEs that emerge with immune checkpoint blockade agents.

3. Terminology used to report toxicity in clinical trials

The use of harmonised terminologies to report and describe IRAEs is a major issue. Several verbatim (reported) terms for IRAE are used, such as 'drug-related adverse event' or 'event of special interest'. As much as possible, a single terminology as IRAE would enable more understandable, accurate interpretation of the safety data.

Furthermore, the quality of IRAE data reporting in clinical trials appears to be suboptimal [10], and important data such as the event's time of onset, reversibility, management, etc. are not systematically reported. Infrequent or unexpected adverse events (even

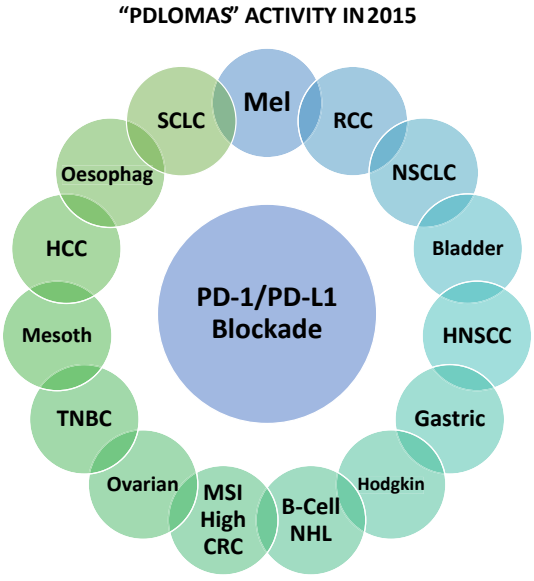

Fig. 1. The spectrum of activity of PD-1 and PD-L1 antibodies in many types of cancer defines the 'PDLoma' concept. PD-1: programmed cell death protein; Mel: melanoma; RCC: renal cell carcinoma; NSCLC: non-small cell lung cancer; HNSCC: head and neck squamous cell carcinoma; NHL: non-Hodgkin lymphoma; MSI high CRC: microsatellite instability colorectal carcinoma; TNBC: triple-negative breast cancer; Mesoth: mesothelioma; HCC: hepatocellular carcinoma; oesophag: oesophageal cancer; SCLC: small cell lung cancer.

Table 1
The *CTLA4*, *PD-1* and *PD-L1* genes are linked to self-tolerance and are involved in autoimmune diseases.

Autoimmune disease	Polymorphism	Ethnic group	Referred studies
Thyroiditis, Graves' disease and Hashimoto's disease	CTLA-4	European	Ueda, Nature 2003 [8] Vaidya, Rheumatology 2002 [72]
Diabetes mellitus	CTLA-4	European Asian	Ueda, Nature 2003 [8] Zhernakova, Hum Genet, 2005 [73] Zalloua PA, Hum Immunol 2004 [10] Jin, P of Endocrinol Investig, 2014 [74]
Celiac disease	CTLA-4	European	Zhernakova, Hum Genet, 2005 [73] Song, Hum Immunol, 2013 [75]
Myasthenia gravis	CTLA-4	South American	Fernández-Mestre, Hum. Immunol. 2009 [76]
Systemic lupus erythematosus	CTLA-4	Asian	Hudson, Hum Genet, 2002 [77]
	PD-1	European and Mexicans	Prokunina, Nat Gene, 2002 [9] Bertsias, Arthritis Rheum. 2009 [78]
Rheumatoid arthritis	CTLA-4	European	Vaidya, rheumatology 2002 [72]
	PD-1	European and Asian	Lee, Z. Rheumatol. 2015 [79]
Addison's disease	CTLA-4	European	Blomhoff, J Clin Endocrinol Metabol 2004 [8]

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; PD-1: programmed cell death protein.

if initially thought not be immune-related) should be accurately reported and explored clinically.

4. Correlations between biomarkers, efficacy, and IRAEs

4.1. Biomarkers-efficacy relationship

The first-reported biomarker for predicting the efficacy of anti-PD-1 therapy was the expression level of PD-L1 on tumour cells [11]. However, there is still no consensus on how a PD-L1-positive tumour should be defined, since each pharmaceutical company has used different antibodies clones for its immunohistochemically staining, different scoring algorithms (cancer cells alone versus cancer cells plus associated infiltrating immune cells), and different positivity thresholds. Other biomarkers said to be predictive of the efficacy of immune checkpoint blockade therapy include peripheral blood cell counts, markers of T-cell activation [12], factors in the tumour's inflammatory microenvironment [13], a high frequency of T-cell receptor clonotypes [14]. Finally, a high mutational burden in the tumour is correlated with efficacy, especially in the tumours with microsatellite instability [15].

4.2. The toxicity–efficacy relationship

Similarities between microbial epitopes and tumour neoantigens have been described [15] in patients who respond to anti-CTLA-4 blockade, highlighting the role of gut microbiota in antitumour immunity [16]. Then, higher response rate was observed in patients who have had an IRAE with anti-PD-1 given for an advanced melanoma [7]. Furthermore, the safety profile of immunotherapies is not similar in all tumour types. For example, vitiligo appears to be more frequent in melanoma patients (11%) [3]. Tumour neoantigens and normal tissue antigens could be cross-reactive, leading to the IRAE generation by immunotherapy [15].

5. Detection and global management of IRAEs

5.1. Frequency and timeline of occurrence

IRAEs are frequent; they occur in up to 90% of patients treated with an anti-CTLA-4 antibody [2] and 70% of patients treated with an PD-1/PD-L1 antibody [11,17]. By comparing the various organs involved, grade I–II events mainly affect the skin and the gut, whereas grades III–V are mainly restricted to the digestive tract (Fig. 2). Most IRAEs occur within 3–6 months of the initiation of anti-CTLA-4 [18,19] or anti-PD-1 [7]. While the IRAE risk appears to be dose-dependent with anti-CTLA-4 antibodies [20,21], cumulative toxicities with prolonged exposure to anti-PD1 [19] were not observed. A delayed effect of immune checkpoint antibodies cannot be ruled out, sometimes up to 1 year after the start of the anti-PD-1 treatment [7,22], and physicians must keep this in mind during the follow-up of their patients exposed.

5.2. Biological tools for IRAEs, circulating auto-antibody assays

Most of the time no circulating auto-antibodies are identified [23–25] in context of IRAE, therefore the diagnostic utility of these autoimmune tests is not proven. To better characterise the role of circulating auto-antibodies in IRAE, exploratory studies are needed. A panel of these potential antibodies associated with IRAE is proposed in Table 2.

5.3. Global management

The management of IRAEs is based on the safety reports of pharmaceutics [7,26,27], expert's opinion and on the knowledge of autoimmune diseases. An overall treatment approach and actions to be implemented for IRAEs is summarised in Table 3. Most IRAEs are

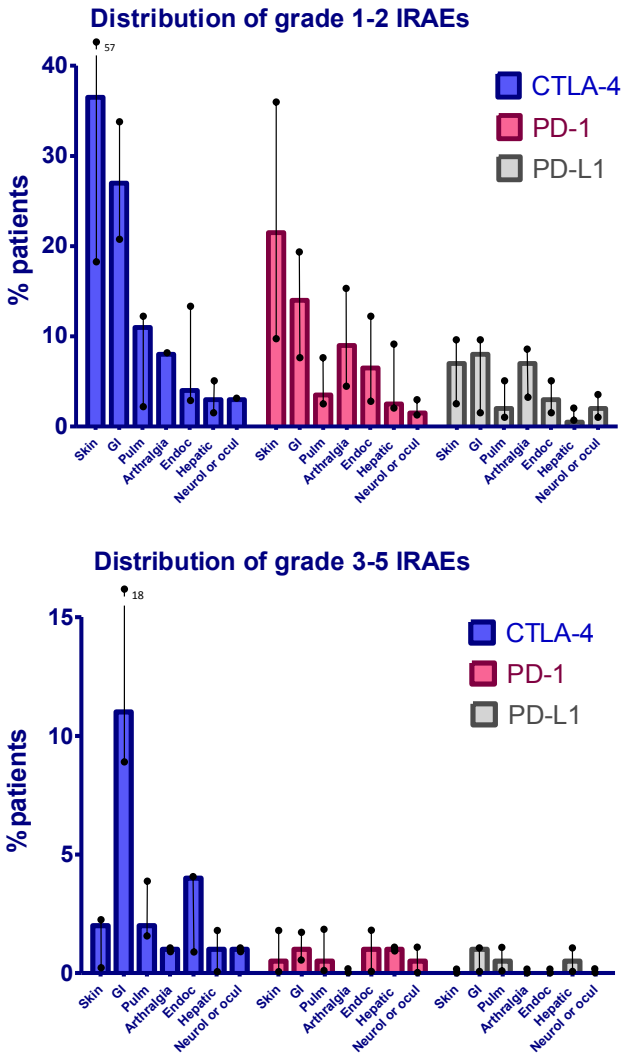

Fig. 2. Distribution of grade I–II and grade III–V IRAEs for all tumour types in the main clinical trials with anti-CTLA4 [2,51,67,68], anti-PD-1 [3,11,19,33,59,69,70] or anti-PD-L1 [17,31,71] antibodies as single therapies. The values quoted are the median (range) IRAE rates for the set of clinical trials as a whole. IRAEs: immune-related adverse events; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; PD-1: programmed cell death protein; GI: Gastro-Intestinal.

steroid-sensitive and resolve within 6–12 weeks [18]. When the IRAE is steroid-refractory, immunomodulatory or immunosuppressive agents such as tumour necrosis factor (TNF)-alpha antagonists, azathioprine and mycophenolate mofetil (MMF) may be effective [26,27]. While the anti-TNF alpha has an immediate therapeutic effect [28], the other immunosuppressive drugs such as azathioprine and MMF only become effective after several weeks. For all severe IRAEs, a close collaboration with organ specialists is critical for improving both our knowledge and management of IRAEs.

Steroids should be employed at initial doses used to treat autoimmune diseases (Table 3), but for a shorter period of time in order to avoid compromising anti-tumour immunity. After a full steroid dose treatment course of generally 2–4 weeks, steroids must be reduced gradually over a period of at least 1 month to avoid that the IRAE recur. For a steroid equivalent dose of 1 mg/kg or more, the prophylactic use of sulfamethoxazole trimethoprim prevents opportunistic infections [29]. Skipping a dose of immunotherapy or discontinuing the immunotherapy can be considered, depending on the benefit/risk ratio of each given situation (Table 3).

6. Understand IRAEs organ by organ

The clinical spectrum of IRAEs is portrayed in the Fig. 3.

6.1. Skin and mucosal

6.1.1. Skin

Dermatologic immune-related event – especially vitiligo – is the most frequent IRAE for both anti-CTLA-4 and anti-PD-1 blockade therapies in patients with melanoma [4,20]. Other dermatological lesions included rash/erythema [42]. Cases of Stevens-Johnson syndrome and toxic epidermal necrosis have been only sporadically reported [18]. For the management of grade I–II events, combination treatment with topical corticosteroids and an oral antipruritic is useful. Skin infections must be ruled out before applying steroids. For grade III–IV events, a skin biopsy is necessary for histological classification of dermatological damage and a systemic steroid course is appropriate.

6.1.2. Mucosae

Around 5% of patients receiving immune checkpoint blockade antibodies have symptoms of dry mouth [19]. An oral candidiasis must be firstly ruled out in this context. Further serum antibodies tests as antinuclear antibodies (ANA) and Sjögren's syndrome A / Sjögren's syndrome B (SSA / SSB) screen an associated autoimmune disorder as Gougerot-Sjögren syndrome. In addition to the use of lubricating eye drops, oral corticosteroid rinses or pilocarpine chlorhydrate [43] can be helpful in problem cases.

6.2. Gastro-intestinal disorders

It is important to distinguish between diarrhoea (an increase in the frequency of stools) from colitis (abdominal pain or imaging and/or endoscopic evidence of colonic inflammation). Diarrhoea is more common during CTLA-4 blockade than during PD-1/PD-L1 blockade (Fig. 2) [3,4,31]. In patients receiving anti-CTLA-4 agents, around 30% develop diarrhoea of any grade and around 10% have severe (grade III–IV) diarrhoea.

Colitis after administration of anti-CTLA-4 agents shares some features with Crohn's disease [28,32], such as mucosal erythema and ulcerations in a colonoscopic assessment. Histologic patterns include lymphocytic and

Table 2
Serum auto-antibody assays with potential value for identifying IRAEs.

Immune-related organ involved		Antibodies
Gastro-intestinal		None
Liver		Antinuclear antibodies (ANAs)
		Anti-smooth muscle, anti-liver kidney microsomal antibody type 1, anti-liver cytosol type 1
Lung		Antinuclear antibodies (ANAs)
		Rheumatoid factor
		Anti-centromere
		Extractable nuclear antigens (ENA): anti-Sm, anti-RNP; anti-Ro (SSA), anti-La (SSB); anti-Scl70, anti-Jo
Endocrine	Thyroid	Anti-thyroglobulin and anti-TPO
	Diabetes mellitus	Anti-GAD, anti-insulin, anti-carbonic anhydrase
	Addison's disease	Anti-21 hydroxylase
	Hypophysitis	Anti-pituitary
Skin		None
Polyarthritis		Antinuclear antibodies (ANAs)
		Anti-ENA: Anti-SSA, SSB, Sm
		Anti-CCP, complement fractions C3 C4 CH50
Renal		Antinuclear antibodies (ANAs)
		Complement fractions C3 C4 CH50
		Anti-neutrophil cytoplasmic (ANCA)
Haematologic syndromes		Antinuclear antibodies (ANAs)
		Coombs' erythrocyte test

IRAEs = immune-related adverse events; CCP = cyclic citrullinated peptide; GAD = Glutamate decarboxylase; RNP = ribonucleoprotein; Sm = Small nuclear ribonucleoprotein; SSA = Sjogren's syndrome-related antigen A; Scl = Sclerosis systemic; SSB = Sjogren's syndrome-related antigen B; TPO = Thyroid peroxidase.

Table 3
The overall management approach and actions to be implemented for IRAEs associated with immune checkpoint blockade, according to the Common Terminology Criteria for Adverse Events (CTCAE) severity grade.

Severity CTCAE grade	Type of patient care	Steroids	Other immunosuppressive drugs	Immunotherapy and subsequent approach
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or systemic steroids oral 0.5–1 mg/kg/d	Not recommended	Suspend** temporarily
3	Hospitalisation	Systemic steroids oral or IV 1–2 mg/kg/d for 3 d then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3–5 d of steroid course Organ specialist advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalisation consider the intensive care unit	Systemic steroids IV methylprednisolone 1–2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d	To be considered for patients with unresolved symptoms after 3–5 d of steroid course Organ specialist advised	Discontinue permanently

** Outside skin or endocrine disorders, where immunotherapy can be maintained.

neutrophil inflammation with cryptitis and, in some cases crypt abscesses and granuloma [28]. Management of colitis is first based on ruling out infectious diarrhoea by screening stool samples for bacterial/viral pathogens, parasites and *Clostridium difficile* toxin, and cytomegalovirus reactivation. An abdominal computed tomography (CT) scan is mandatory for establishing the severity and extent of any digestive lesions. A faecal calprotectin assay may be useful for distinguishing between immune-related inflammatory diarrhoea and other causes. Rectosigmoidoscopy or ileocolonoscopy with biopsies should be considered for confirmation of the diagnosis. Treatment is based on corticosteroids, with budesonide for grade I–II colitis, and systemic steroids for more severe cases [32]. In cases of severe and steroid refractory colitis after 3 d of full-dose steroids, a short course (one to two infusions) of the anti-TNF alpha antibody infliximab [32] is required.

6.3. Endocrine disorders

Around 5–10% of patients receiving anti CTLA-4 and anti PD-1/PD-L1 antibodies are likely to develop an endocrine IRAEs of any grade [11,40].

6.3.1. Thyroid dysfunction

In this context, hypothyroidism is thought to occur more commonly than hyperthyroidism [4,11]. In patients who

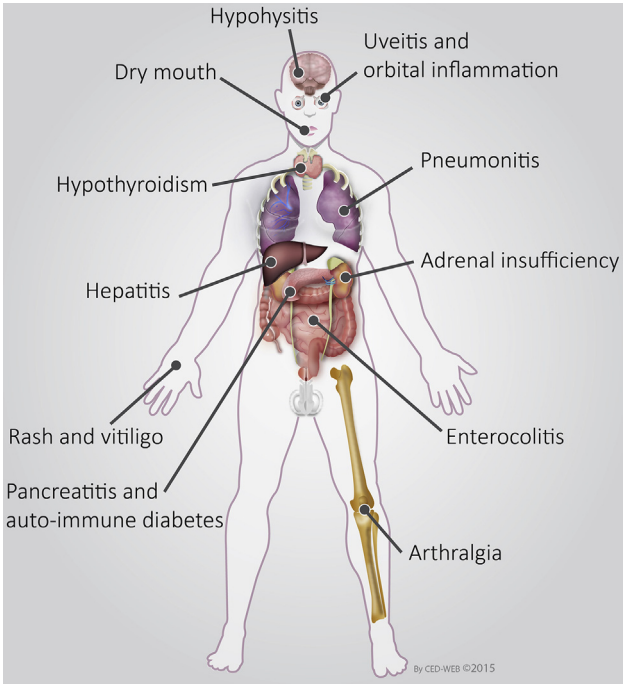

Fig. 3. The clinical spectrum of IRAEs. IRAEs: immune-related adverse events.

display elevated (>10 mIU/l) thyroid-stimulating hormone (TSH) levels, an additional assay for free T4 and T3 is required, and hormone replacement therapy (e.g. levothyroxine) should be initiated [26,27]. A few cases of hyperthyroidism have been reported; in this setting, non-selective beta-blockers (e.g. propranolol) are suggested as the initial treatment. Hyperthyroidism resolves spontaneously in almost all cases, with the subsequent appearance of hypothyroidism [24].

6.3.2. Hypophysitis

Hypophysitis is mainly observed with anti-CTLA-4 therapy and can affect up to 10% of patients [41]. Hypophysitis results in low release of all or some of the following pituitary gland hormones: adrenocorticotropic hormone (ACTH), TSH, follicle-stimulating hormone (FSH), luteinising hormone (LH), growth hormone or prolactin. Hypophysitis is difficult to diagnose because its symptoms are non-specific: headaches, fatigue and muscle weakness, paleness or constipation, weight loss, anorexia, nausea. Additional symptoms reflecting specific hormonal deficiency could be helpful for the diagnosis: weight gain, constipation, bradycardia, attention or cognitive difficulties for the thyrotropin axis; erectile dysfunction or amenorrhoea for the gonadotropin axis defect (LH/FSH); orthostatic hypotension and hypoglycaemia/hyponatraemia for the corticotrophin deficiency (ACTH) [41]. The central hypothyroidism appears to be the most frequent hormone deficiency [41]. Serum pituitary auto-antibodies could be present [25]. Pituitary magnetic resonance imaging imaging with gadolinium and selective slides should be considered, searching enlargement or heterogeneity of the gland [40]. Treatment is based on the replacement of appropriate hormones deficiency (e.g. levothyroxine and hydrocortisone) is required [25,41].

6.4. Liver disorders

Immune-related hepatitis must be considered whenever the physician is confronted with an unexplained elevation of serum levels of hepatic alanine aminotransferase or aspartate aminotransferase enzymes, which occurs in less than 5% of patients [4,31,33]. Most patients are asymptomatic and present with abnormal laboratory test results [34]. Viral infection with hepatitis A (primary infection), B or C (primary or chronic infection) and emergent hepatitis E should be ruled out. A CT scan or an ultrasound of the liver and biliary tract may help to rule out liver metastases or cholelithiasis. Some patients with IRAE hepatitis may have mild hepatomegaly, periportal oedema or lymphadenomegaly [34]. Serum assays for ANAs, anti-smooth muscle antibodies, anti-liver kidney microsomal antibody type 1 and anti-liver cytosol type 1 are often negative [23]. The formal diagnosis of autoimmune hepatitis requires a liver biopsy showing a diffuse T-cell infiltrate in all lobes, prominent sinusoidal histiocytic infiltrates and central vein damage with endothelialitis [23]. Patients should be treated with corticosteroids [23], and in steroid-refractory cases, adding the azathioprine or MMF is in accordance with the management of autoimmune hepatitis [35].

6.5. Lung disorders

Immune-related pneumonitis (including sarcoidosis [36,37] and organising inflammatory pneumonitis [38]) occurs in around 1% of patients taking anti-PD-1/PDL-1 or CTLA-4 antibodies [11,33,39]. This condition can be severe and life threatening, and thus requires the physician to pay particular attention to respiratory symptoms [22]. Alerting symptoms are dry cough, progressive shortness of breath and fine inspiratory crackles. In cases of suspected immune-related pneumonitis, a chest CT scan and spirometry (with measurement of the carbon monoxide diffusing capacity) are useful. Immune-related pneumonitis shows ground-glass lesions and/or disseminated nodular infiltrates, predominantly in the lower lobes [22,38]. Cardiac abnormalities with left ventricular dysfunction must be ruled out in this setting. A bronchoscopy with bronchoalveolar lavage should be considered to search infectious agents such as *Pneumocystis jirovecii* and respiratory virus as *influenza*, *metapneumovirus* or the *syncytial virus*. Other atypical infectious agents, such as *Legionella pneumophilia*, *Chlamydia* and *Mycoplasma pneumoniae*, should be also screened. The treatment of immune-related pneumonitis is based on the systemic steroids [26,27]. If a course of steroids does not reduce the severity of the initial symptoms, additional immunosuppression with infliximab could be considered [22].

Other rare endocrine disorders: immune-related adrenal insufficiency and diabetes mellitus. Hormonal tests can distinguish hypophysitis from the primary adrenal insufficiency with low cortisol and high ACTH. Acute adrenal insufficiency (adrenal crisis) is an urgent diagnosis leading to dehydration, hypotension and electrolyte imbalances. In this case, immediate hospitalisation and intravenous hydrocortisone is required. To manage immune-related diabetes, insulin replacement therapy is recommended, and steroid in this setting is not recommended because possibly worsening the metabolic dysfunction.

6.6. Eye and neurologic syndromes

A few series of ophthalmological IRAEs have been reported in patients taking anti-CTLA-4 antibodies [44]. These events include episcleritis, conjunctivitis, uveitis and orbital inflammation [44,45]. Mild-to-moderate uveitis can be treated with topical steroids, whereas oral corticosteroids are indicated in more severe inflammation (including cases with orbital involvement). Cases of neurological IRAEs with Guillain Barré syndrome [46,47], aseptic or lymphocytic meningitis [47], posterior reversible encephalopathy syndrome [48], inflammatory enteric neuropathy [49] or transverse myelitis [50] have been reported in patients with anti-CTLA-4 blockade.

6.7. Polyarthritis

Polyarthritis or arthralgia has been reported in around 5% of patients with immune checkpoint blockade [19,31,33,51]. A few cases of erythematous lupus or polymyalgia rheumatica/giant cell arteritis have been described in CTLA-4 blockade [52–55]. In this setting, the auto-antibodies ANAs and anti-cyclic citrullinated peptide could detect auto-immune condition such as lupus or for dysimmune polyarthritis. Low-dose oral steroids (0.5 mg/kg) should be sufficient to clinically control joint manifestations.

6.8. Fatigue

Fatigue is one of the most commonly reported side-effects with immune checkpoint blockade [7,19]. However, it remains difficult to establish a causal link between this vague, non-specific symptom and immunotherapy. Endocrine disorder (hypothyroidism, hypophysitis and adrenal dysfunction) and cancer progression must firstly be checked in the fatigue context. Abnormal fatigue could correspond to form of chronic fatigue syndrome, in this setting one possible remedy is exercise therapy [30].

6.9. Renal disorders

Kidney failure has been described with CTLA-4 [54], PD1-blockade [33] or the combined blockade of the CTLA-4 and PD-1 [56]. These renal IRAEs have been rarely reported, with an incidence of 1% [4,52,56], and included interstitial nephritis with inflammatory cortical renal enlargement [57] or granulomatous nephritis [58], and glomerular lupus-like nephropathy [54]. Treatment is based on systemic corticosteroids [52,57].

6.10. Pancreatic disorders

Immune-related elevation of pancreatic enzyme levels has been reported in CTLA-4 and PD-1 blockade [59,60]. However, these cases mostly corresponded to isolated abnormal laboratory tests because the patients did not meet the diagnostic criteria for pancreatitis [61]. Pancreatic imaging must be performed, in order to rule out obstructive causes and screen for true pancreatitis.

6.11. Haematologic syndromes

Cytopenia is rarely associated with immune checkpoint blockade in patients with solid tumours, but appears to occur more frequently in patients with lymphoma [62]. Red cell aplasia [63], autoimmune neutropenia or pancytopenia [64,65] and acquired hemophilia A [66] have been reported in patients receiving anti-CTLA-4 antibodies. Haematological causes of cytopenia (such as bone marrow malignant infiltration) must be comprehensively ruled out. Relevant diagnostic tests include a peripheral blood smear, a reticulocyte count, Coombs' test, haemolysis assays (lactate dehydrogenase, haptoglobin and bilirubin) and bone marrow analysis to determine whether a central or peripheral cause is present.

7. Further discussion

7.1. Further perspectives to explore IRAEs

Although the immune checkpoint blockade is typically described as being well-tolerated, they still generate life-disabling IRAEs that are sometimes severe and/or irreversible. The long-term impact of immune checkpoint blockade on quality of life should be specifically evaluated in future research. Furthermore, the potential detrimental effect of steroid administration (in response to an IRAE) on anticancer efficacy has yet to be investigated. Further biological and ancillary pharmacogenomics studies will also have to establish whether the patient's immunologic profile (e.g. polymorphisms or human leucocyte antigen status) predispose to the occurrence of IRAEs.

7.2. Optimising the management of IRAEs

Most IRAEs are reversible with steroids, provided that the treatment is initiated early at a sufficient dose level, gradually tapered and then withdrawn. However, some IRAEs (such as endocrine disorders) may be permanent

but can be easily managed with hormone replacement treatment. Very importantly, some patients may gain long-term benefit from immune checkpoint blockade or even be cured – implying that they should be carefully monitored for late-onset IRAEs up to several years after the initiation of treatment. Although the long-term safety profile of anti-CTLA-4 and anti-PD-1 antibodies has not yet been established, the close, careful follow-up of surviving patients is essential. Furthermore, the safety of immune checkpoint blockade in patients with an underlying autoimmune disorder is unknown, since these patients have always been excluded from clinical trials. Therefore, the risk of toxicity should always be balanced against the benefits that may be derived from immune checkpoint blockade. The physician and his/her patient should always discuss these issues in detail.

8. Conclusion

Immune checkpoint blockade leads to a new spectrum of dysimmune toxicity in hemato-oncology. From a practical perspective, the management requires a close collaboration between with organ specialists, which could see in return new insights into the pathophysiology of autoimmune diseases such as Crohn's disease and hypophysitis. Dysimmune toxicity may be associated with the antitumour response and the use of steroids must be cautious. Dysimmune toxicity need to be extensively explored in the way that reflecting an effective antitumour response throughout neoantigens generation.

Conflict of interest statement

None declared for all authors.

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