REVIEW ARTICLE

Immunotherapy of solid tumors: safety of treatment

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KEY WORDS

immune checkpoint inhibitors, immune--related adverse events, immunotherapy

ABSTRACT

Immunotherapy with immune checkpoint inhibitors (ICIs) was shown to improve survival of patients with solid tumors such as: melanoma, renal carcinoma, non–small cell lung cancer, cutaneous carcinomas, or head and neck carcinoma. However, a special type of ICIs toxicity is observed, namely noninfectious inflammation of different organs associated with autoimmunity known as immune-related adverse events (irAEs). This noninfectious inflammation may affect the endocrine system, gastrointestinal tract, heart, skin, and nervous system. The lungs are also often involved and this condition is referred to as checkpoint inhibitor pneumonitis. The toxicity of ICIs is graded from 1 to 5 depending on the clinical course, 5 being a fatal complication. Corticosteroids are the treatment of choice, generally with good efficacy. In some difficult cases, escalation of immunosuppression is required. Knowledge of irAEs should be promoted among clinicians of all specialties, nurses, patients and their families. The aim of this review is to present the wide spectrum of irAEs: clinical signs and symptoms, differential diagnosis, diagnostic procedures, and treatment. Data are supported by our own clinical observations.

Introduction Immune checkpoint inhibitors (ICIs) that are increasingly successful in oncological patients may lead to immune-related adverse events (irAEs) in all systems of the human body. The highest prevalence of irAEs is observed in combination therapies, anti–CTLA-4, anti–PD-1, and anti–PD--L1 inhibitors with some specificity for individual organs.[1,2] The mechanisms of irAEs are almost the same and related to the hyperactivation of the immune system leading to an autoimmune response to the body tissues. Some of these irAEs may have delayed onset even after withdrawal of ICIs. Infusion-related reactions occur in less than 1% of patients treated with ICIs, slightly more frequently in patients treated with ICIs combined with anti–PD-L1 drugs. However, avelumab is a striking exception because infusion-related reactions were noted in approximately one-fourth of patients and premedication is used before the first infusion.[3] Only few studies specifically evaluated ICIs in patients excluded or underrepresented in clinical trials, who are usually referred to as "special populations," including patients with autoimmune disorders, immunosuppression, major viral infections, and major organ dysfunctions, so uncertainty remains regarding the use of immunotherapy in such populations.[4] This also includes the elderly; however, new data indicate that the ICI therapy is safe and at least as efficient in the older population as in younger patients.[4,5] Effective management depends on early diagnosis and introduction of multidisciplinary immunomodulatory therapies (usually starting with corticosteroids) according to the standardized management algorithms by the European Society of Medical Oncology,[1] Society for Immunotherapy of Cancer,[2] American Society of Clinical Oncology,[6] National Comprehensive Cancer Network,[7] or Polish authors.[8]

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Gastrointestinal toxicities induced by immunotherapy

Diarrhea and liver injury are the most frequent and severe irAEs leading to the discontinuation of immunotherapy.[9] Other gastrointestinal toxicities are mouth ulcers, esophagitis, gastritis, duodenitis, cholangitis, and pancreatitis.[10] Severe constipation related to enteric neuropathy induced by immunotherapy has recently been reported in 2 cases.[11,12]

The frequency of diarrhea ranges from 19% to 54%.[13] Diarrhea usually appears between fifth and tenth week from the treatment initiation, but it may occur at any time after the first dose of ICI or even after 4 months after the end of therapy.[1,14]

The reasons behind diarrhea associated with immunotherapy are not clear. Diarrhea may be related to fungal, bacterial (*Clostridioides difficile*, formerly *Clostridium difficile*), viral (cytomegalovirus), or parasitic infestation and these should be considered during the differential diagnostic workup. The potential cause is colitis, which may be a life-threatening complication leading to perforation (0.7%–1.5%),[9,15] toxic megacolon, and even death (0.6%–1%).[10] The risk of immune-related colitis is described in 5% to 22% of patients receiving ICIs.[1,14,16] Recently, important risk factors for the occurrence of immune-related colitis have been identified: dose, concomitant intake of nonsteroidal anti-inflammatory drugs, coexistent inflammatory bowel diseases, and intestinal microbiota disturbance.[10,17,18] Immune-related colitis seems to be more frequent in patients treated for melanoma in comparison to non–small cell lung cancer (NSCLC) or renal cell cancer.[19,20]

Diarrhea is an indication for the differential diagnostic workup. It should be carried out as soon as possible because early diagnosis allows effective treatment.[21] The infectious causes should be excluded and stool investigation for enteropathogens and *C. difficile* toxin should be performed.[1,2,10]

Immunotherapy should be taken into account when the infectious causes of diarrhea have been excluded.[14] Coexisting symptoms such as mouth ulcers, perianal abnormalities, arthritis, skin lesions, liver damage, or endocrinopathy suggest a relation between diarrhea and adverse effects of immunotherapy. Blood tests may reveal anemia, elevated C-reactive protein, hypoalbuminemia, and increased fecal calprotectin.[22]

A definitive diagnosis of immune-related colitis is based on endoscopic and histopathologic evaluation. In the majority of patients, the rectum and/or left colon are involved, therefore the flexible sigmoidoscopy is sufficient for diagnosis. However, in some patients, colonoscopy is needed.[22-24] Endoscopic lesions include erythema, luminal bleeding, erosions, and ulcerations.[22-24] These changes and the normal appearance of the mucosa are usually not sufficient. The final diagnosis can be made only after histologic (immunohistologic) evaluation of the biopsy, which allows for definitive exclusion of an infectious disease and confirm inflammatory bowel disease (if there are no macroscopic changes and histopathologic features of inflammation, microscopic colitis is diagnosed).

Regardless of the cause and severity of the symptoms, the first step should be change of diet to slow down intestinal peristalsis and reduce intestinal secretion.[1,10] In the mild form of diarrhea (grade 1 according to the National Common Terminology Criteria for Adverse Events [CTCAE]), it is not necessary to discontinue immunotherapy. Antidiarrheal drugs such as loperamide and atropine sulphate may be used only after excluding infection.[1,14]

If the above methods are ineffective and there is a diagnosis or strong suspicion of inflammatory bowel disease, immunotherapy should be discontinued and corticosteroids should be introduced (TABLE 1).[14,25,26] Corticotherapy is highly effective and leads to the resolution of symptoms in 87.5% of patients.[24] However, in a small group of patients resistant to corticosteroids, an infusion of a single dose of infliximab should be used. Response to a single dose is usually very good; however, sometimes the dose is repeated.[27,28]

Very rarely, there is a severe damage to the large bowel and colectomy with ileostomy is indicated.[22] In severe colitis, a definitive discontinuation of immunotherapy is recommended. In patients with moderate colitis, it is debatable, but immunotherapy should be discontinued at least temporarily. After resolving, a return to immunotherapy with low-dose corticosteroids may be considered. Alternatively, if the damage occurred after the administration of anti–CTLA-4, the patient may be switched to anti–PD-1 or anti–PD-L1.[29]

Immune-related hepatitis Immune-related hepatitis is the second most frequent gastrointestinal complication of immunotherapy. It usually appears between week 6 and 14 of treatment[9,14,29] and affects 1% to 17% of patients.[30]

The clinical signs of immune-related hepatitis appear late and are usually associated with severe liver damage. Therefore, liver function tests have to be carefully monitored to recognize immune-related hepatitis early (activity of aminotransferases, γ-glutamyl transpeptidase, and alkaline phosphatase).

The results of laboratory indices of liver damage strongly support immune etiology of hepatitis. However, the need for exclusion of other possible causes of liver injury always applies: progression of the neoplasm or its complications (eg, thromboembolism), which can be determined by imaging examinations: ultrasonography or computed tomography. It is also necessary to perform serological tests to exclude acute viral infection[31] and to take history to eliminate other possible causes such as alcohol, drugs, herbs. Liver biopsy is not necessary but may be useful individually in rare cases of doubt or fulminant course.[9]

TABLE 1 Treatment of gastrointestinal adverse events of immunotherapy depending on the severity of symptoms according to the National Common Terminology Criteria for Adverse Events

Immune-related colitis	
Grade 1 (G1)	Increase of <4 stools per day from baseline: continue treatment; diet, antidiarrheals
Grade 2 (G2)	Increase of 4–6 stools per day from baseline, abdominal pain, blood in stool, general symptoms: stop immunotherapy; budesonide 9 mg/day for 8 weeks; if symptoms aggravate, prednisone 0.5–1 mg/kg for 7 days
Grade 3/4 (G3/G4)	Increase of ≥7 stools per day from baseline, severe or persistent abdominal pain, fever, peritoneal signs, blood in stool, deficiencies in blood tests, severe lesions in colon: stop treatment; intravenous methylprednisolone 1–2 mg/kg for 5 days followed by oral steroids or a single dose of infliximab 5 mg/kg
Immune-related hepatitis	
Grade 1 (G1)	AT <3 × ULN: continue immunotherapy; diet plus AT observation once a week
Grade 2 (G2)	AT, 3–5 × ULN: stop immunotherapy; diet plus AT observation twice a week; if no improvement, oral prednisone 0.5–2 mg/kg
Grade 3 (G3)	AT, 5–20 × ULN and/or symptoms of liver failure: discontinuation of immunotherapy; diet plus intravenous methylprednisolone 1–2 mg/kg and 1200 acetylcysteine; if no improvement, mycophenolate mofetil 500–1000 mg or tacrolimus
Grade 4 (G4)	AT >20 × ULN: stop immunotherapy permanently; diet plus intravenous corticosteroids; if no improvement, mycophenolate mofetil

Abbreviations: AT, aminotransferases; ULN, upper limit of normal

The initial finding of liver damage is an indication to repeat laboratory tests at least once a week.[1,31] Mild immune-related hepatitis usually disappears after 4 to 6 weeks of appropriate treatment (TABLE 1) and return to immunotherapy is acceptable.[1] It has recently been shown that azathioprine in a dose of 1 to 2 mg/kg may be effective in patients who do not completely respond to prednisone or who flare during tapering of the corticosteroid.[26,31-33] The administration of infliximab for immune-related hepatitis is contraindicated due to possible immune-mediated hepatitis.[31]

Endocrine immune-related adverse events Activation of the immune system induced by ICIs often leads to endocrine irAEs. Endocrinopathies are usually mild (CTCAE grade ≤2) and severe or life-threatening events (CTCAE grade ≥3) are very rare. Endocrinopathies generally do not require permanent discontinuation of ICIs (even in CTCAE grade ≥3) and rarely require high-dose corticosteroids, although lifelong management may be required when persistent.[34-36] The most frequent endocrinopathies include thyroiditis and hypophysitis and the symptoms are rather nonspecific. Centers using immunotherapy should have access to appropriate hormonal diagnostic procedures and cooperate with endocrinologists.

Immune checkpoint inhibitor–induced hypophysitis ICI-induced hypophysitis has been described as the most frequent endocrine irAEs associated with anti–CTLA-4 administration with the incidence up to 17%.[1] However, in recent meta-analyzes, it is estimated at 3.2% to 5.6%,[35,36] and it occurs least frequently with anti–PD-1 or anti–PD-L1 monotherapy (<1%).[34,36] Risk factors for ICI-induced hypophysitis include male sex and older age. There are observations indicating longer survival of patients who develop ICI-induced hypophysitis.[37]

Nonspecific symptoms include headache, weakness, nausea, loss of appetite and weight, cold intolerance. Infrequently, symptoms of the optic chiasm compression are present. The diagnostic workup of ICI-induced hypophysitis is based on clinical presentation and the results of hormonal tests showing hypopituitarism. Magnetic resonance imaging (MRI) indicates pituitary gland abnormalities with enlargement, stalk thickening, and contrast enhancement. However, a normal image of pituitary MRI does not rule out ICI-induced hypophysitis. The majority of patients (80%) have multiple hormone deficiencies, usually affecting the secretion of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and follicle stimulating hormone/luteinizing hormone, although isolated anterior pituitary hormone deficiency can be present, while diabetes insipidus is extremely rare.[38,39]

When ICI-induced hypophysitis is suspected, the corticotropic axis should be evaluated first. Untreated severe adrenal insufficiency (with hypotension, dehydration, hyponatremia, and hyperkalemia) leads to adrenal crisis which is a life-threatening condition. The diagnosis of secondary adrenal insufficiency is confirmed by low levels of morning cortisol (<5 μg/l) with low/normal ACTH levels. In case of ICI-induced hypophysitis, it is also advisable to determine other hormones assessing pituitary function (TSH, free thyroxine [fT_4], follicle stimulating hormone, luteinizing hormone, estradiol, testosterone).

The use of high doses of corticosteroids is not necessary because it does not reverse hypopituitarism.[35] It is recommended (eg, prednisone in a dose of 1 mg/kg/day) when the symptoms of the so-called mass effect are present, that is, severe headaches or visual disturbances. In our

experience, in adrenal insufficiency, replacement with hydrocortisone (10–30 mg/day orally) leads to a rapid clinical improvement. Patients in adrenal crisis require intravenous administration of high-doses of hydrocortisone, hydration, and monitoring. Levothyroxine (LT_4) replacement for secondary hypothyroidism should be implemented if fT_4 levels are below the normal range. Hydrocortisone replacement is important before starting LT_4 to avoid precipitating adrenal crisis. Secondary hypothyroidism may be transient, whereas adrenal insufficiency is permanent and requires lifelong hydrocortisone replacement. Hypogonadism can be corrected if the gonadal axis did not recover after 3 months and no contraindications are present.[40]

Thyroid dysfunction Thyroid dysfunction is one of the most common organ-specific irAEs. The lowest incidence of thyroid dysfunction can be observed with anti–CTLA-4 (7%), higher with anti–PD-1 or anti–PD-L1 (19%), and the highest with a combination of anti–PD-1 and anti–CTLA-4 (28%–50%).[41,42] Thyroid dysfunction is typically caused by a destructive (silent) thyroiditis, which is manifested initially by transient thyrotoxicosis, appearing in the first weeks after starting immunotherapy.[43] Thyrotoxicosis may be asymptomatic or cause mild symptoms of hyperthyroidism. Extremely rarely, thyroiditis is the cause of life-threatening disorders (0.1%).[38] The phase of hyperthyroidism resolves spontaneously within 4 to 6 weeks or in the majority of cases (80%) progresses to permanent hypothyroidism. The antithyroid antibodies (anti-TPO, anti-Tg) can be detected in some patients. ICI-induced Graves disease is very rare.[38] The destructive thyroiditis and Graves disease may also coexist in some patients.

The acute phase of thyroiditis with asymptomatic and transient thyrotoxicosis does not require treatment, only monitoring of TSH, fT_4, free triiodothyronine at intervals of 2 to 3 weeks. In symptomatic patients (with tachycardia), β-blockers are recommended. In severe hyperthyroidism, corticosteroids should be introduced (eg, prednisone 1 mg/kg). Antithyroid drugs should be considered in patients with Graves hyperthyroidism. LT_4 replacement for symptomatic hypothyroidism should be started with a dose of 25 to 50 μg in the morning and adjusted (after 4–6 weeks) to achieve normal TSH levels. Immunotherapy may be continued in most cases of thyroid dysfunction. In our opinion, TSH level should be also regularly monitored in patients treated for hypothyroidism before using ICIs, as TSH may increase or transient thyrotoxicosis may occur after starting immunotherapy.

Autoimmune diabetes mellitus Autoimmune diabetes mellitus (DM) is a rare complication (<1%).[30,44] The time to onset of hyperglycemia varies from the first weeks to 12 months after initiating ICIs.[45,46] A characteristic feature is a very rapid increase in glycemia with complete lack of insulin secretion, confirmed by undetectable C-peptide levels at the time of diagnosis. Patients often present with signs and symptoms of hyperglycemia or ketoacidosis.[44] Glucose levels should be routinely checked during the course of immunotherapy. ICI-induced DM resembles the so-called fulminant DM, a form of type 1 DM first described in Japan.[47] ICI-induced diabetes is a life-threatening condition, patients often require admission to intensive care units. ICI-related DM results in a long-term need for insulin; restarting ICIs can be considered when adequate glucose control has been achieved.

Primary adrenal insufficiency Primary adrenal insufficiency is a very rare complication of immunotherapy[38,48] but can lead to life-threatening adrenal crisis. Laboratory tests show hyponatremia with hyperkaliemia, and may include hypoglycemia and hypercalcemia. Elevated ACTH in the presence of low morning cortisol levels indicate primary adrenal insufficiency.

Skin toxicity Skin toxicity is among the most prevalent irAEs reported with ICIs. It occurs in 30% to 40% of patients receiving PD-1 or PD-L1 inhibitors and in approximately 50% of patients treated with ipilimumab.[2] The mechanism of formation of dermatological irAEs is not fully understood. However, their close association with T-cell activation bound by checkpoint blockers is noteworthy. Dermal toxicity is the first to occur during treatment with ICIs and it appears to be independent of the drug dose used.[49] In addition, some of the irAEs such as maculopapular rash and vitiligo may be correlated with a better therapeutic response.[50-52] The overall incidence of dermatological irAEs is higher with ipilimumab compared to anti–PD-1 or anti–PD-L1 agents and occur more frequently, appear earlier, last longer, and are more severe when anti–CTLA-4 and anti–PD-1 antibodies are used in combination.[49,53] Most of irAEs are mild (grade 1–2) and their nature is very similar. A pruritic maculopapular rash is the most common irAEs (FIGURE 1A–1C) (with an incidence of 24.3% for ipilimumab, 16.7% for pembrolizumab, and 14.3% for nivolumab)[49,54,55]. Rash occurs mainly on the trunk, less frequently on the upper limbs, next it spreads peripherally to the extremities. Most often it appears after a couple of treatment cycles, and the severity of the changes may increase during subsequent cycles. The average time to onset of maculopapular rash is 3 to 4 weeks from the start of anti–CTLA-4, 5 weeks from the start of anti–PD-1, and 2 weeks from the start of a combination of ipilimumab and nivolumab.[49] Changes may also appear many months after the introduction of treatment.[53] The extent of the lesions and the negative impact on health-related quality of life is taken into account in assessing the severity of the lesions (CTCAE). Grade 1 includes lesions occupying less than 10% of the skin's surface, grade 2, 10% to 30%, and grade 3, more than 30%. Grade

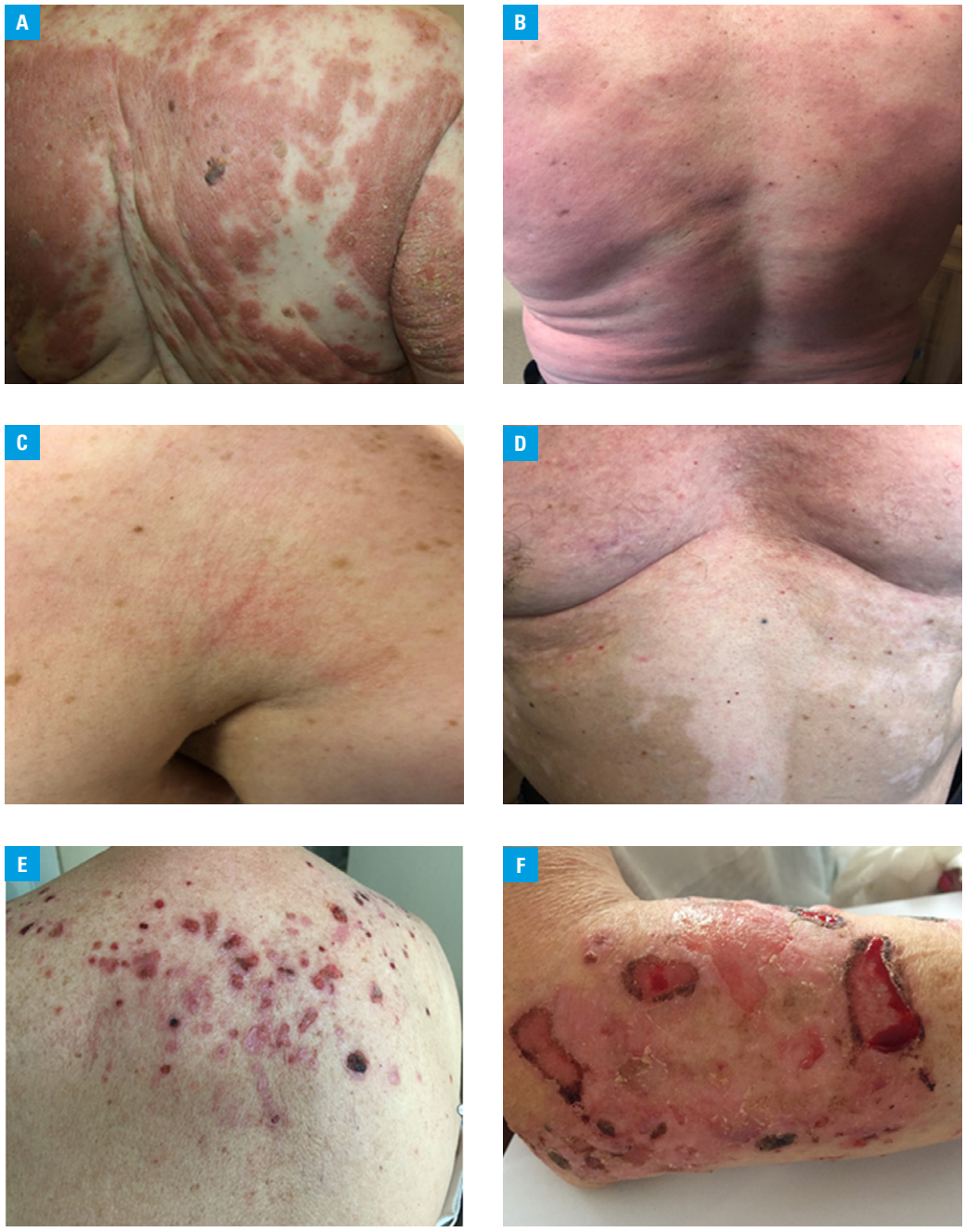

FIGURE 1 Skin toxicity in patients treated with immune checkpoint inhibitors. **A**–**C** – maculopapular rash (**A** – grade 4; **B** – grade 3; **C** – grade 1); **D** – vitiligo; **E**, **F** – bullous pemphigoid. Written informed consent was obtained from the patient for publication of this report and any accompanying images.

4/5 is rare. In patients treated for advanced melanoma, changes equal to or higher than grade 3 were observed in 2% or less of patients on monotherapy, and in 3% to 5% of patients on combination therapy.[2,49] The rash may also be the first clinical manifestation of a severe cutaneous drug reaction. During ICIs therapies, the occurrence of Stevens–Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, or drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported.[49,56] Itching is a common and troublesome symptom. It typically develops concomitantly with maculopapular rash, albeit it can also be associated with a normal-appearing skin. The frequency in patients during treatment for advanced melanoma ranges between 14% to 47% and is the lowest in anti–PD-1 therapies and the highest in the combination therapy with anti–CTLA-4 and anti–PD-1. Pruritus with severity of grade 3 or higher occurred in 2% or less of treated patients.[2,49,53] Vitiligo-induced ICIs occurs during melanoma therapy (7.5%–11%) (FIGURE 1D). The mechanism of its formation is probably related to a cross-reaction against antigens shared by melanoma cells and normal melanocytes.[49] PD-1 or PD-L1 blockers can activate pre-existing immune disorders and/or induce the development of de novo autoimmune skin diseases. Bullous pemphigoid (FIGURE 1E and 1F), dermatitis herpetiformis, psoriasis, vasculitis, Sjögren syndrome, dermatomyositis have been reported. These immune disorders may overlap in some patients. Individual cases of Grover disease, sarcoidosis, Sweet syndrome, and pyoderma gangrenosum have also been recorded. In addition, hair and nail changes (most often alopecia in 1%–2% of patients), as well as

changes in the texture of the hair and nail dystrophy with onychomadesis or proximal onychoschizia were found. Diffuse onycholysis and paronychia involving whole fingers or toenails can develop. Other irAEs are oral symptoms: xerostomy and oral lichenoid reactions.[2,49]

Treatment of skin complications of ICI therapy depends on the severity of the symptoms. It should be remembered that symptoms that are initially mild might suddenly become much worse and severe. Therefore, it is very important to diagnose irAEs correctly, define their severity, and introduce an appropriate treatment as soon as possible. In the case of mild lesions, the procedure includes proper skin care and protection against UV radiation. In more severe lesions, topical corticosteroids are recommended. If the changes improve, systemic corticosteroids are used. For grade 4 cutaneous toxicity, it is strongly advised to discontinue immune therapy.[2,53] Algorithms for the prevention and treatment of skin toxicity are useful in the management. In some cases, dermatological consultation and skin biopsy should be considered for histopathologic and immunopathologic evaluation.[2,53,57] If autoimmune skin disorders are found, treatment should be adequate to the diagnosed disease. Thus, early recognition and management of the lesions are critical in controlling their severity.

Pulmonary toxicity Pulmonary complications of immunotherapy are frequently observed IrAEs, but are not restricted to the treatment of lung cancer. IrAEs of the respiratory system are referred to as checkpoint inhibitors pneumonitis (CIP).[58] The term pneumonitis shows the importance of involvement of lung parenchyma rather than of airways. The definition of CIP includes the new respiratory signs and symptoms: dyspnea, cough, fever, chest pains with desaturation on effort in the presence of new infiltrations visible on chest imaging. The recognition of ICIs pneumonitis needs confirmation of ICIs use and exclusion of other adverse events, especially infections.[58,59] Grading the severity of this complication is similar to other irAEs and depends on the development of respiratory failure (TABLE 2).[1,2,6]

The incidence of CIP in clinical trials was as follows: 0.5% to 10% for all grades, 0.5% to 3% in grades 3 or higher, and was higher when ICIs were combined with chemotherapy, up to 6.5% and with anti–CTLA-4 agents, up to 7%. CIP is the leading cause of death by irAEs: 35% to 42% of all fatal irAEs. The mean time from ICIs introduction to CIP was 7 to 15 weeks. Case reports present the prevalence of CIP of 3.5% to 19%, including patients with NSCLC in whom the onset of CIP is shorter than in other malignancies.[60,61]

To date, there are no defined risk factors for the development of CIP. The influence of smoking is uncertain and histologic type of NSCLC as well as PD-L1 expression do not predict CIP. Also, pre-existing autoimmune diseases seem not to predict complications.[62,63] The analysis of observations showed that lung fibrosis does not exclude immunotherapy[60]; however, the course of pulmonary complications may be exacerbated by comorbidities. Many patients have chronic obstructive lung disease and interstitial lung diseases. The diagnosis of CIP is complicated due to the unspecificity of symptoms, and the course is unfavorable, especially in the elderly.[58-60,64] Among pulmonary complications, tuberculosis and opportunistic infections need to be considered. Thus, the knowledge of patient history is essential for a differential diagnosis. Furthermore, the signs in patient examination are also unspecific and these are mainly crackles in auscultation. The analysis of blood gases and pulmonary function tests with the diffusion capacity is necessary to assess the severity of restriction or hyperinflation as well as gas exchange disturbances

The key modality of CIP recognition is chest imaging with high-resolution computed tomography as the best method. Different patterns in high-resolution computed tomography could be visible and the most frequent ones are: ground glass opacities, consolidations, reticular opacities, and micronodules.[60,64] The overlap of abnormalities is frequently observed.[58] Interstitial inflammation is dynamic and the high-resolution computed tomography pattern may show more or less active or more or less irreversible (fibrotic) changes. There have been some attempts to incorporate the classification of interstitial lung diseases to the CIP classification and the nonspecific interstitial pneumonia pattern seems to be leading followed by the organizing pneumonia–like pattern.[60,64] Bilateral distribution and localization away from the lung tumor are often observed.[58] Pleural effusion and mediastinal lymph nodes involvement are rare.

The issue of CIP is noninfectious parenchymal inflammation and cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), or nonspecific interstitial pneumonia pattern was confirmed by histologic examination, however the data are scarce.[59] Sarcoid granulomatosis is a special, yet rare, type of possible toxicity. It may, however, involve extrapulmonary organs.[60] The differential diagnosis of new lung infiltrations in patients treated with ICIs include tumor progression or pseudoprogression, pneumonia, or pneumonitis. Thus, full microbiological tests and histopathologic examination of sputum or material obtained during bronchoscopy is often needed and decisive. The course of CIP is often rapid and the decision about the therapy is urgent, hence, the application of bronchoalveolar lavage (BAL) fluid examination might be suggested[60,65] (acute pneumonitis may be a contraindication to bronchoscopy with BAL). BAL fluid analysis allows the recognition of infection (also opportunistic), malignant cells, and, by total and differential immune cell count, the character of interstitial lung disorder.[66] The predominance of lymphocytes is suggestive for active noninfectious inflammation.[65] According to our experience, the

TABLE 2 Management and treatment of pulmonary adverse events of immunotherapy according to severity

Grade	Description	Investigation, monitoring	ICI		Treatment
			Administration	Drug rechallenge	
G1	Asymptomatic radiological abnormalities	Monitor clinically HRCT Pulse oximetry Microbial assessment Bronchoscopy and BAL Hospitalization	Hold therapy		Nonspecific
G2	Mild symptoms Medical intervention indicated		Withold therapy	Yes if resolution to G1	Prednisone 1–2 mg/kg Taper over 4–6 weeks
G3	Severe symptoms interfering with ADL Supplementation of oxygen required		Discontinuation	No	Empirical antibiotics, prophylactic antimicrobials Methylprednisolone intravenously 1–2 mg/kg Taper corticosteroids 6–8 weeks If no improvement after 48 hours, infliximab or mycophenolate mofetil
G4	Life-threatening respiratory failure Invasive support required				
G5	Death	–	–	–	–

Abbreviations: ADL, activities on daily living; BAL, bronchoalveolar lavage; HRCT, high-resolution computed tomography; ICI, immune checkpoint inhibitors; others, see TABLE 1

complex BAL fluid evaluation could be ensured by a microscopic examination of slides assessed using hematologic and histologic staining, combined with flow cytometry analysis for immune cell subtyping.[66,67]

The treatment and management of CIP include the modification of ICIs therapy with or without immunosuppression and depends on the clinical course.[68] The summary of current recommendations is shown in TABLE 2.[1,2,6] In general, in stages 1 and 2, improvement is possible. However, a relapse could occur and if corticosteroids are ineffective, another immunosuppressant is indicated: mycophenolate mofetil, infliximab, cyclophosphamide. The prognosis is worse in patients with symptomatic pneumonitis, other coexisting lung diseases, combined therapies, and previous chemoradiotherapy.[69] Interestingly, better efficacy of ICIs was reported in patients with associated irAEs.[70,71]

Cardiotoxicity associated with immune checkpoint inhibitors In real-life practice, true incidence of ICIs cardiotoxicity is unknown and it seems that the issue is underestimated. This is particularly important as not only the range of ICI-sensitive cancers but also treatment strategies that include ICIs are increasing rapidly. Clinical observations have shown that immune involvement of the cardiovascular system, particularly of the heart, leads to the highest case fatality rate among the IrAEs.[72]

The ICIs block inhibitory molecules expressed on T lymphocytes, which causes the activation of a systemic T-cell response as well as a response of T cells in the cardiovascular system, especially the myocardium. T lymphocytes contribute not only to the induction of inflammation but also myocardial damage in the experimental autoimmune myocarditis. In experimental studies, for example, CTLA-4– or PD-1–deficient animals displayed increased inflammation and myocardial damage.[73,74] PD-L1 is also expressed on the cardiomyocytes. It is postulated that PD-L1 exerts dual cardioprotective effect by transmitting direct cardioprotective signaling. This seems particularly important in patients with pre-existing cardiovascular dysfunction such as cardiac stress, ischemia, hypertrophy upregulated PD-L1 expression.[75] Thus, in the cardiovascular system, ICIs can result not only in autoimmune T-cell–related injury, but also PD-L1 inhibition, which might accelerate pre-existing heart disease.

Cardiac antigens, being tumor-related factors, stimulate tumor / cardiac T-cell clones and can increase ICIs toxicity. The concurrent ICI--related toxic effects, for example, myositis, are common in patients with myocarditis and may reflect a shared antigen profile between cardiac and skeletal muscle. Pre-existing cardiovascular diseases as well as autoimmune diseases are potential risk factors for irAEs.

Risk factors of cardiotoxicity vary between patients, and due to diverse presentation, the strategy for personalizing surveillance should be incorporated based on the initial assessment.[76,77]

The incidence of myocarditis is higher during ICIs combination therapy, and usually occurs early after the exposure. Around 50% of cases are fatal. Myocarditis may have an acute manifestation, that is, acute heart failure with cardiogenic shock, multiorgan failure, pulmonary edema (mimicking pneumonitis), new event of left ventricular failure, malignant ventricular arrhythmia, or advanced conduction disorders.[78] ICI-associated cardiotoxic effects can extend beyond myocarditis; however the first approach is to exclude myocarditis; if confirmed, it is crucial to urgently follow a myocarditis management protocol.

Cardiotoxicity is also manifested as arrhythmias including atrial fibrillation, atrioventricular conduction diseases, pericarditis with or without pericardial effusion.[76,79] A possible complication is myocardial infarction related to coronary vasculitis or vasospasm. Different forms of left

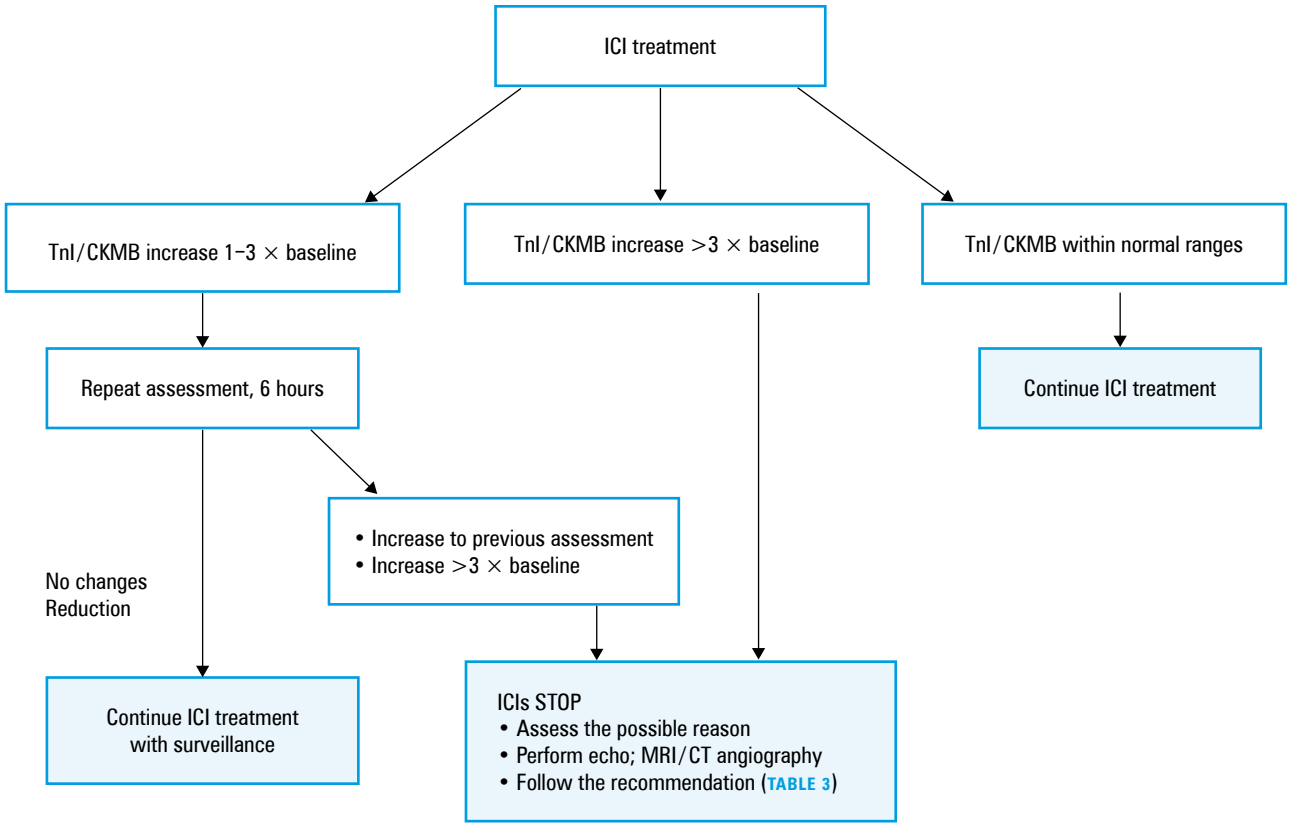

FIGURE 2 Management in the case of myocardial infarction related to immune checkpoint inhibitors
Abbreviations: CKMB, creatine kinase myocardial band; CT, computed tomography; echo, echocardiography; MRI, magnetic resonance imaging; TnI, troponin level; others, see TABLE 2

ventricular dysfunction without evidence of myocarditis are observed including a new episode of ventricular impairment or Takotsubo syndrome.

Diagnostic tests including electrocardiography, Holter electrocardiography, cardiac biomarkers, and different cardiac imagining (eg, echocardiography, MRI, computed tomography, angiography) are appropriate. Optimal diagnostic tools should be selected depending on the kind of ICI-related toxicity and its clinical manifestation (FIGURE 2, TABLE 3).[79]

The first and most urgent step is to consider ICI discontinuation. The final decision should be taken jointly by an oncologist and cardio-oncologist. The second step is the implementation of typical conventional cardiac treatment to alleviate complications. In the most severe cases, intensive monitoring and adequate invasive management is recommended. The third approach is the introduction of immunosuppression. High-intensity immunosuppression followed by oral corticosteroids is recommended in the most serious events, for example, myocarditis, severe heart failure, effusion pericarditis, advanced conduction disturbance, serious arrhythmia with confirmed (or highly probable) ICIs relation.

Finally, starting ICI again after the interruption is very difficult. It is crucial to define the clinical certainty that the event is an ICI-related cardiac complication. The restart in myocarditis is not recommended because of the potential risk for fatal relapse. In cases of less severe cardiotoxic ICI-related complications (eg, subclinical myocardial dysfunction or pericarditis), it may be possible to restart immunotherapy with close surveillance for recurrence. A close cooperation between an oncologist and a cardiologist is crucial to make a decision.[76-79]

Other rare immune-related toxicities Rheumatologic (musculoskeletal), renal, neurologic, ophthalmologic, and hematologic irAEs are relatively less frequent. Most of these irAEs are rather mild in severity but occasionally may be life-threatening.

Rheumatologic immune-related adverse events Rheumatologic irAEs are the most common rare ICI-related toxicities (2%–15% of all patients on immunotherapy, most frequently on anti–PD-1). The differential diagnostic workup of myalgia and arthralgia is the most challenging.[1,2,80] Generally, rheumatic or musculoskeletal adverse events are mild in severity, reversible, varying in the timing of presentation, and are usually treated with nonsteroidal anti-inflammatory drugs. Inflammatory oligo- or polyarthritis is rarely the sole irAEs with 3 phenotypes: 1) large-joint reactive arthritis (the most frequent), sometimes developing in association with uveitis and conjunctivitis; 2) polyarthritis similar to rheumatoid-like arthritis,

TABLE 3 Immune checkpoint inhibitors: proposed management of the associated cardiotoxicity (modified and based on Lyon et al[76])

Event description	Immunosuppression	Cardiac management
Stop ICI		
Confirmed myocarditis	First line: intravenous methylprednisolone 500–1000 mg daily until clinically stable, followed by oral prednisolone 1 mg/kg once Second line: mycophenolate mofetil or infliximab Third line: antithymocyte globulin or intravenous immunoglobulin	Follow ESC/PSC guidelines for HF management
New severe conduction disorders	If evidence of myocarditis, intravenous methylprednisolone	Emergency pacing
Ventricular tachycardia/fibrillation	If myocarditis confirmed: as above	Emergency cardioversion/defibrillation; followed by adequate anti arrhythmic management
Acute myocardial infarction	If coronary vasculitis on angiography Consider intravenous methylprednisolone Rechallenge only when clinically stable and >30 days post myocardial infarction, if there was no evidence of vasculitis on initial angiography.	Follow ESC/PSC guidelines for STEMI/NSTEMI If atherosclerosis is absent on coronary angiography, consider vasculitis.
Pericarditis with cardiac tamponade	First line: as above	Urgent pericardiocentesis; followed by colchicine and/or NSAID
Interrupt ICI		
New left ventricular systolic dysfunction without inflammation	Exclude myocarditis Follow myocarditis protocol if myocarditis confirmed	Follow ESC/PSC guidelines for HF management
Takotsubo syndrome	Rechallenge only after myocarditis excluded; once left ventricular function stabilized or recovered, with surveillance	Follow ESC/PSC guidelines for HF management and avoid QT-prolonging drugs
Frequent ventricular ectopics (>1% of heart beats)		Adequate anti arrhythmic management
New atrial fibrillation		Follow ESC/PSC guidelines for atrial fibrillation;
New asymptomatic increase in cardiac troponin		Check baseline (before ICI introduction – if available) and repeat measurements
Acute pericarditis without cardiac tamponade (with/without effusion)	Interrupt ICI exclude myocarditis Consider prednisolone 1 mg/kg	Consider oral colchicine and/or a NSAID
Continue ICI		
New early conduction abnormality on ECG	Continue ICI once Holter ECG excludes advanced heart block	Assess Holter ECG for advanced conduced disease; if absent, continue ICI increase surveillance with ECG before each cycle
New asymptomatic increase in BNP/NT- proBNP	Continue ICI, unless myocarditis/new left ventricular systolic dysfunction is detected	Check baseline (before ICI introduction, if available) and repeat measurements

Abbreviations: BNP, brain natriuretic peptide; ECG, electrocardiography; ESC, European Society of Cardiology; HF, heart failure; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non–ST-segment elevation myocardial infarction; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; PCS, Polish Cardiac Society; STEMI, ST-segment elevation myocardial infarction; others, see TABLES 1 and 2

affecting the small joints of the hand, very rarely seropositive, potentially erosive; 3) seronegative, oligo- and polyarthritis, which typically starts in the medium or large joints and is characterized by synovitis or involvement of tendons and entheses, with or without joint erosions.[2] When limited joints are affected, intra-articular corticosteroid injections may be considered. The management of more severe symptoms (at least grade 2) requires corticosteroids, sometimes in conjunction with immunomodulators and disease-modifying antirheumatic drugs including antitumor necrosis factor drugs, methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine.[2,81]

The prevalence of other manifestations of rheumatic irAEs such as inflammatory myositis, vasculitis, and sicca syndrome (with severe eye and mouth syndrome, parotitis), polymyalgia rheumatica, or systemic lupus erythematosus is less clear.

Current CTCAE terms for musculoskeletal symptoms (eg, arthritis and myositis) are not easily converted to clinically relevant descriptors.[1] All patients with CTCAE grade 2 or higher should be referred to a rheumatologist and discontinuation of ICIs may be required. Persistence of rheumatic AEs may occur after stopping immunotherapy.[1,6] The use of ICIs may exacerbate the disease in patients with rheumatologic disorders.

Nephrotoxicity is considered a rare adverse event. In a large meta-analysis including 3695 patients, ICI-related acute kidney injury was estimated to occur in approximately 2.2% of patients,[82] higher in other studies[83] or isolated cases of interstitial nephritis,[2] granulomatous nephritis, thrombotic microangiopathy, or lupus nephritis.[82-84] Renal involvement is usually asymptomatic. Serum sodium, potassium, creatinine, and urea should be measured before every infusion of ICIs. When renal dysfunction is suspected, it is

TABLE 4 The most common symptoms associated with irAE of rheumatic, renal, neurologic, ocular, or hematologic origin (according to Champiat et al[7])

Origin	Symptoms/laboratory abnormalities	IrAE suspected
Rheumatologic	Arthralgia	Dysimmune arthritis
Renal	Elevated serum creatinine	Dysimmune nephritis
		TTP
		HUS
	Hypokalemia	Dysimmune nephritis
	Hyponatremia	
	Abnormality of the urinary Sediment	
	Oliguria	
Ocular	Red or painful eye	Dysimmune conjunctivitis
		Dysimmune scleritis
		Dysimmune episcleritis
		Dysimmune uveitis
		Dysimmune blepharitis
	Visual impairment	Dysimmune uveitis
		Dysimmune retinitis
		Dysimmune optic neuritis
		Dysimmune encephalitis
		Dysimmune vasculitis
		Dysimmune thyroiditis
		Myasthenia gravis
		Dysimmune neuritis
	Diplopia	–
Neurologic	Motor deficit	Dysimmune mononeuritis
		Dysimmune polyradiculoneuritis/Guillain–Barré syndrome
		Encephalitis
		Myelitis
		Vasculitis
		Myasthenia
		Myositis
	Sensory loss	Dysimmune mononeuritis
		Dysimmune polyradiculoneuritis/Guillain–Barré syndrome
		Encephalitis
		Myelitis
		Vasculitis
	Seizure	Dysimmune encephalitis
Hematologic	Anemia	Dysimmune hemolytic anemia
		Dysimmune hypothyroidism
		Dysimmune pancytopenia
		Immune thrombocytopenic purpura
		Thrombotic microangiopathy: TTP, HUS
		Evans syndrome
	Thrombocytopenia	Immune thrombocytopenic purpura
		Evans syndrome
		Autoimmune pancytopenia
		Thrombotic microangiopathy: TTP, HUS
	Abnormal hemostasis	Immune thrombocytopenic purpura
		Evans syndrome
		Dysimmune pancytopenia
		Thrombotic microangiopathy: TTP, HUS
		Acquired hemophilia A
	Thrombosis	Antiphospholipid syndrome

Abbreviations: HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura

initially necessary to stop nephrotoxic drugs, to perform a differential diagnostic workup to exclude other reasons for renal insufficiency. ICIs therapy should be withheld and the administration of systemic corticosteroids should be considered. Close monitoring of serum creatinine levels should accompany the treatment.

Nephrotoxicity typically resolves and ICIs treatment can be resumed if grade 2 to 3 adverse events resolve promptly, but therapy should be permanently discontinued in case of persistent or recurrent grade 2 to 3 adverse events or grade 4 toxicity with help of a nephrologist.[2]

Neurotoxicity Incidence of neurotoxicity related to ICIs is low but probably underreported. Its incidence is related to the terminology and reporting common symptoms as headache or dysgeusia.[1,85,86] The onset of neurologic irAEs is usually early within the first 2 weeks of therapy; nevertheless, there are reports of neuro-related toxic events occurring late after stopping ICIs. The most common are encephalitis and myopathies; however, there is a diversity of reported events (TABLE 4).[87,88] Although rare, neurologic toxicities may be a fatal complication of immunotherapy.[89] It is always important to rule out the progression of malignant disease in the central nervous system, infection, depression, and metabolic / hormonal disturbances.[1,8] In rare clinical situations, neurotoxicity may be related to a concomitant use of radiation therapy on the central nervous system. According to the clinical presentation, diagnostic investigations should include imaging of the central nervous system, nerve conduction studies, and / or lumbar puncture (characteristic feature is lymphocytic pleocytosis in the cerebrospinal fluid).[90-92] Early consultation with a neurologist should be considered. For all but mild neurologic symptoms (grade 1), ICI therapy should be held until the AE nature is diagnosed. In the case of moderate / severe symptoms, intravenous corticosteroids should be immediately administered since neurotoxicities may be life-threatening. Additionally, an aggressive approach with plasmapheresis or intravenous immunoglobulins may be required in the treatment of myasthenia, Guillain Barre syndrome, and acute or chronic demyelinating polyradiculoneuropathy. Moreover, upfront readiness for intensive care support of ventilator functions should be taken into account.[92] In case of neurotoxicity, early detection and multidisciplinary treatment is critical for reducing the risk of morbidity and mortality.

Ocular irAEs are rare and occur in less than 1% of patients. These AEs are heterogeneous (TABLE 4).[1,2,8,91,93] Patients treated with ICIs should be warned to inform the clinician about the onset of any ocular symptoms. Patient counseling is the basis for early recognition of eye toxicity as uveitis may lead to a decrease in the clearness of vision and potentially cause loss of visual function (in this case, permanent cessation of ICI treatment is required). Early referral to ophthalmologist is crucial and treatment of these rare ICI-related adverse events depends on their severity with the use of topical corticosteroids in patients with episcleritis and anterior uveitis as well as administration of systemic corticosteroids in severe ocular and orbital inflammation. Intravitreal antivascular endothelial growth factor is usually indicated for choroidal neovascularization.[93]

Hematologic immune-related adverse events Hematologic irAEs do not occur commonly but they represent a heterogenous group of events as autoimmune hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia, hemophilia A, myelodysplastic syndrome, lethal aplastic anemia, immune thrombocytopenic purpura.[1,2,61,94,95] They should be distinguished from transient changes in laboratory blood tests at the initiation of immunotherapy, as well as from other etiologies, for example, hemorrhage or progerssive cancer in the blood marrow.[8,96] When diagnosed, high-dose corticosteroids and other immunosuppressive drugs are usually required after consultation with hematologist.

ARTICLE INFORMATION

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