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CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guideline for the management of immune-related adverse events in patients treated with immune checkpoint inhibitors (2019)

M. Majem[1,13] · E. García-Martínez[2,13] · M. Martinez[3] · E. Muñoz-Couselo[4] · D. Rodriguez-Abreu[5,13] · R. Alvarez[6] · A. Arance[7,13] · A. Berrocal[8] · L. de la Cruz-Merino[9,10,13] · J. A. Lopez-Martin[11,12,13]

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Abstract

The use of immune checkpoint inhibitors has emerged as an effective treatment option for patients with several tumor types. By increasing the activity of the immune system, they can induce inflammatory side effects, which are often termed immune-related adverse events. These are pathophysiologically unique toxicities, compared with those from other anticancer therapies. In addition, the spectrum of the target organs is very broad. Immune-inflammatory adverse events can be life threatening. Prompt diagnosis and pharmacological intervention are instrumental to avoid progression to severe manifestations. Consequently, clinicians require new skills to successfully diagnose and manage these events. These SEOM guidelines have been developed with the consensus of ten medical oncologists. Relevant studies published in peer-review journals were used for the guideline elaboration. The Infectious Diseases Society of America grading system was used to assign levels of evidence and grades of recommendation.

Keywords Immunotherapy · irAEs · Toxicity

✉ M. Majem
mmajem@santpau.cat

E. García-Martínez
helenagarciam@gmail.com

M. Martinez
MariaMartinezGarcia@parcdesalutmar.cat

E. Muñoz-Couselo
evamuco@hotmail.com

D. Rodriguez-Abreu
drodabr@gobiernodecanarias.org

R. Alvarez
ruthalvarez21@gmail.com

A. Arance
amarance@clinic.cat

A. Berrocal
berrocal.alf@gmail.com

L. de la Cruz-Merino
lucme12@yahoo.es

J. A. Lopez-Martin
jalopezmartin@gmail.com

[1] Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, c/Sant Antoni Maria Claret 167, 08025 Barcelona, Spain

[2] Department of Medical Oncology and Hematology, Hospital Universitario Morales Meseguer, Murcia, Spain

[3] Department of Medical Oncology, Hospital del Mar, Barcelona, Spain

[4] Department of Medical Oncology, Melanoma and Other Skin Tumors Unit, Vall d'Hebron Hospita, Vall d'Hebron Institute of Oncology VHIO, Barcelona, Spain

[5] Department of Medical Oncology, C.H.U. Insular-Materno Infantil de Gran Canaria, Las Palmas, Spain

[6] Department of Medical Oncology, Hospital Virgen de la Salud, Toledo, Spain

[7] Department of Medical Oncology, Hospital Clínic, Barcelona, Spain

[8] Department of Medical Oncology, Consorcio Hospital General Universitario de Valencia, Valencia, Spain

[9] Clinical Oncology Department, Hospital Universitario Virgen Macarena, Seville, Spain

[10] Medicine Department, Universidad de Sevilla, Sevilla, Spain

[11] Department of Medical Oncology, Hospital Universitario, 12 de Octubre, Madrid, Spain

[12] Clinical and Translational Oncology, Instituto de Investigación Sanitaria Hospital, 12 de Octubre, Madrid, Spain

[13] Spanish Group for Cancer Immuno-Biotherapy, GÉTICA, Madrid, Spain

Introduction: landscape of adverse events induced by cancer immunotherapies

The use of immune checkpoint inhibitors (ICI), such as inhibitors of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1), has emerged as effective treatment options for patients with several tumor types. By increasing the activity of the immune system, ICI can induce inflammatory side effects, which are often termed immune-related adverse events (irAEs). These are pathophysiologically unique toxicities compared with those from other anticancer therapies. The severity of irAEs is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [1, 2].

The frequency of irAEs varies according to the specific class of compounds and patient population. Grade 3–4 toxicities have been reported in 10–27% of patients receiving anti-CTLA-4, and in 7–20% of patients receiving anti-PD-1/anti-PD-L1 agents [3]. Fatigue is a commonly reported toxicity, with a frequency of 12–37% of patients receiving an anti-PD-1/anti-PD-L1, and most of the times is not associated with a treatable reason [3]. These frequencies can increase significantly when these drugs are given in combination with another ICI or with chemotherapy [3, 4]. Not only the spectrum of target organs is very broad (Table 1) [5, 6], but also the timing and temporal evolution of the irAEs. The latter also depends on the class of ICI, but, in general, skin toxicity can appear after 2 weeks, endocrine events can have a delayed onset and liver and gastrointestinal toxicities may arise at intermediate time points. All these toxicities can become accelerated when ICIs are combined. Consequently, clinicians require new skills to successfully diagnose and manage these events properly.

Several guidelines have been published [3, 7–9]; for this reason, we will emphasize on key general points regarding the management of irAEs, including severe and/or treatment refractory irAEs.

Methodology

These SEOM guideline have been developed with the consensus of ten medical oncologists from Spanish Society of Medical Oncology (SEOM) and Spanish Group for Cancer Immune-Biotherapy (GÉTICA). Relevant studies published in peer-review journals were used for the elaboration of the guideline. The Infectious Diseases Society of America grading system was used to assign levels of evidence and grades of recommendation [10].

General principles for the management of immune-related adverse events

Immune-inflammatory adverse events can be life threatening [11]. Prompt diagnosis and pharmacological intervention are instrumental to avoid progression to severe manifestations [V, A] [1, 7, 12]. For such purposes, sharing adequate information with patients and their families, other treating physicians (including primary care and emergency room),

Table 1 Immune-related adverse events of affected organs

Organ system	Types of irAEs	
	Frequent	Rare or infrequent
Cutaneous	Rash, pruritus, vitiligo	Acneiform rash, alopecia, bullous pemphigoid, papulopustular rosacea, psoriasis, Stevens–Johnson syndrome, toxic epidermal necrosis, Sweet syndrome
Gastrointestinal	Diarrhea, colitis, lichenoid mucositis	Enteritis, gastritis, pancreatitis
Endocrine	Hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis	Autoimmune type 1 diabetes, primary adrenal insufficiency
Hepatic	Transaminitis, hepatitis	–
Respiratory	Pneumonitis	Pleuritis, sarcoidosis
Rheumatologic	Arthralgia, inflammatory arthritis, myalgia	Dermatomyositis, myositis, polymyalgia-like syndrome, Sjörgren syndrome, vasculitis
Renal	Increase in serum creatinine, nephritis	–
Ocular	–	Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis
Neurological	Sensorimotor neuropathy	Aseptic meningitis, autonomic neuropathy, encephalitis, facial nerve palsy, Guillain–Barré syndrome, myasthenia gravis, posterior reversible leukoencephalopathy, transverse myelitis
Hematological	–	Aplastic anemia, hemolytic anemia, idiopathic thrombocytopenic purpura, lymphopenia, hemophilia
Cardiac	–	Cardiomyopathy, myocarditis, pericarditis

Table 2 General recommendations for the management of IO toxicities (3, 8)

irAE CTCAE grade	Recommendation	Comments
1	Symptom management, usually without systemic glucocorticoids	Usually can continue ICI
2	Consider systemic glucocorticoid (Table 3) (oral prednisone, iv methylprednisolone 1–2 mg/Kg/day) If no improvement in 2–3 days, escalate glucocorticoid dose to 2 mg/Kg/day Once improved to at least grade 1, taper slowly (4–6 weeks)	Withhold immunotherapy until grade 1 and prednisone dose ≤ 10 mg Consider PJP prophylaxis, calcium/vitamin D. Check blood glucose
3–4	Systemic glucocorticoid (Table 3) (oral prednisone, iv methylprednisolone 1–2 mg/Kg/day) If no improvement in 2–3 days, add another immune suppressant (Table 3), according to specific toxicity recommendations Once improved to at least G1, taper slowly (4–6 weeks)	Withhold immunotherapy until G1 without corticosteroids Consider PJP prophylaxis, calcium/vitamin D. Check blood glucose Grade 3—consider discontinuation of immunotherapy, depending on duration and target organ (see specific guidelines) Grade 4—discontinue immunotherapy

irAEs immune-related adverse event, *CTCAE* National Cancer Institute Common Toxicity Criteria for Adverse Events, *ICI* immune-checkpoint Inhibitor, *PJP Pneumocystis jiroveci* pneumonia

Table 3 Main characteristics of immunosuppressive agents recommended in IO toxicity management

Therapy	Common schedules	irAE
Corticosteroids	Oral/IV prednisone 0,5—2 mg/kg/day IV methylprednisolone 1–2 mg/kg/day	From grade ≥ 2 irAEs, in any toxicity
Anti-TNFα	Infliximab 5 mg/kg once every 2 weeks	CRT, especially in colitis, pneumonitis, myocarditis
Anti-IL6	Tocilizumab 8 mg/kg iv once per month	CRT, alternative to anti-TNFα, especially in myocarditis
Anti-IL1	Anakinra 100 mg once per day or canakizumab 300–600 mg once every 8 weeks	CRT, alternative to anti-TNFα, especially in myocarditis
Mycophenolate mofetil	500 mg orally twice a day	CRT, especially in hepatitis, and myocarditis
Anti-CD20	Rituximab 375 mg/m2 iv once weekly for 4 weeks	Multirefractory toxicity, especially in SLE, Sjögren syndrome, nephritis, encephalitis and others
Immunoglobulins	Immunoglobulins iv 400 mg/kg per day, 5 days	GBS, MG, encephalitis and other neurological irAEs
Plasmapheresis	Several courses as needed	GBS, other neurological irAEs

CRT corticosteroid refractory toxicity, *SLE* systemic lupus erythematosus, *GBS* Guillain–Barré syndrome, *irAEs* immune-related adverse events, *ATG* antithymocyte globulin

pharmacists, and nurses is essential. Patients should be instructed on how to act or when to consult, and contact persons should be defined. Managing irAEs frequently involve other specialists, such as dermatologists, gastroenterologists, neurologists, endocrinologists, and others, who should become aware of these toxicities [12].

As shown in Table 2, grade 2 irAEs usually require withholding ICI and close monitoring, and to decide if systemic corticosteroids (prednisone, initial dose of 0.5 to 1 mg/kg/day, or equivalent) should be initiated [V, A] [7]. For most of the grade 1 irAEs, ICIs can be continued, with some exceptions (e.g., neurologic or cardiac toxicities) [7]. Grade 3–4 irAEs must be treated with high-dose corticosteroids (prednisone 1 to 2 mg/kg/day, or methylprednisolone IV 1 to 2 mg/kg/day) [V, A] [7]. Once initiated, corticosteroids should be tapered over 4–6 weeks. If there is no improvement after 48–72 h, consider other immunosuppressors [V, A] [7] (Table 3). Dose adjustments of ICIs are not recommended [7]. No prophylactic role has been demonstrated for steroids [II, D] [13].

Patient selection and baseline assessments

Baseline assessments are recommended before starting treatment to rule out susceptibility to develop irAEs. These include a complete patient and family history, general physical condition, concomitant herbs and medication. Baseline laboratory tests may include complete blood counts, renal, liver and pancreatic functions tests, hormonal axis tests and viral serologies [V, C].

Due to ICI mechanism of action, several groups of patients have been excluded from clinical trials, including patients with chronic infectious diseases (hepatitis B and C, HIV), transplant recipients or patients with autoimmune

diseases. These challenging patients should be managed by multidisciplinary teams and followed up closely [V, A]. ICIs appear to be relatively safe in patients with autoimmune diseases [14] [V, B], as well as in chronic viral hepatitis [III, B]. HIV infection should not be a contraindication for ICI, although patients with low CD4 counts should be monitored closely for efficacy and immune reconstitution [III, B]. ICIs have very high risk of causing post-transplant complications and organ rejection [V, A]. Ipilimumab appears to have superior safety in this setting [V, B]. Anti-PD-1/PD-L1 therapy can result in spontaneous abortion in pregnant women and should be avoided [15] [V, A].

Specific recommendations

Management of frequent toxicities

Management of gastrointestinal toxicity

Epidemiology Gastrointestinal toxicities are among the leading causes of immune-related adverse effects of ICIs. The frequency with anti-CTLA-4 of diarrhea is 23–33% and 3–6% for grade 3–4 colitis, [16, 17] and with anti-PD-1/PD-L1 the frequency of diarrhea is 11–19% and 1–4% for grade 3–4 colitis [18]; the frequency of the combination anti–CTLA-4 and anti-PD-1/PDL1is up to 45%, grade 3/4, 9–11% [19].

Clinical presentation The median onset of diarrhea is approximately 6–8 weeks after initiation of therapy and 1/3 of patients have concurrent enteritis [12, 20].

Diagnosis Diagnosis is based on duration, severity, and presence of alarm features that may require hospital admission [21]. Patients should undergo a complete blood count, serum electrolyte profile, serum albumin and serum C-reactive protein. Stool analyses for enteropathogens and *Clostridium difficile* toxin analysis should be carried out [20, 21]. Abdominal imaging is not routinely required in patients with grade 1–2 diarrhea. In severe cases, abdominal CT may be indicated to rule out complications [22]. Flexible sigmoidoscopy or colonoscopy should be performed in patients with bloody diarrhea or those with persistent ≥ grade 2 diarrhea [23] [IV, D].

Management See Fig. 1 [3, 24–28] [V, B].

Management of hepatic toxicity [29–32]

Epidemiology It has been described in 5–10% (1–2% grade 3) of patients receiving monotherapy and in 25–30% (15% grade 3) of patients receiving combination of ICIs.

Clinical presentation Hepatitis induced by ICIs appears approximately 6–8 weeks after initiation of therapy and usually consists of an asymptomatic elevation of transaminases. Severe hepatotoxicity involving liver injury with jaundice, and other signs and symptoms of hepatic failure is not frequent.

Diagnosis Initial workup includes a blood test with serum transaminases, bilirubin and prothrombin time [V, A], as well as the exclusion of other causes of transaminase increase such as infectious disease, liver metastasis, concomitant drugs or alcohol intake [V, A]. Liver biopsy [V, C] may be needed in case of severe or corticosteroid-refractory hepatitis and may help to dismiss other causes of liver toxicity or tumor infiltration.

Management See Fig. 2 [V, A]. A multidisciplinary management is essential in the treatment of hepatic toxicity.

Management of endocrine events

Epidemiology Endocrine AEs occur in 10% of patients receiving ICIs [33]. Hypophysitis is more frequent with anti-CTLA-4 and thyroid dysfunction with anti-PD-1/PD-L1 drugs. Other uncommon irAEs include primary adrenal insufficiency, Graves' disease, Graves' ophthalmopathy and autoimmune diabetes mellitus.

Clinical presentation Endocrine toxicities usually present with nonspecific symptoms that make them difficult to suspect and many of them are irreversible due to the permanent damage of the affected gland [34]. The most common are those affecting the thyroid gland, which are usually grade ≤ 2. These occur due to a transient inflammation of the gland, which can present with overproduction of thyroid hormone (hyperthyroidism) or underproduction (hypothyroidism).

Diagnosis and treatment See Fig. 3 [V, A]. Hyperthyroidism usually does not need active treatment, although it may evolve to hypothyroidism. Hypothyroidism is usually a permanent condition that needs levothyroxine substitution for life. Hypophysitis can affect one or several of the pituitary axes with or without a pathological image in the MRI. The steroid axis is the most frequently affected permanently [35]. In these patients, any additional stress can cause an acute adrenal crisis, seriously threatening patient's life and requiring urgent treatment. For grade ≥ 3 toxicity to seek endocrinology consultation is recommended.

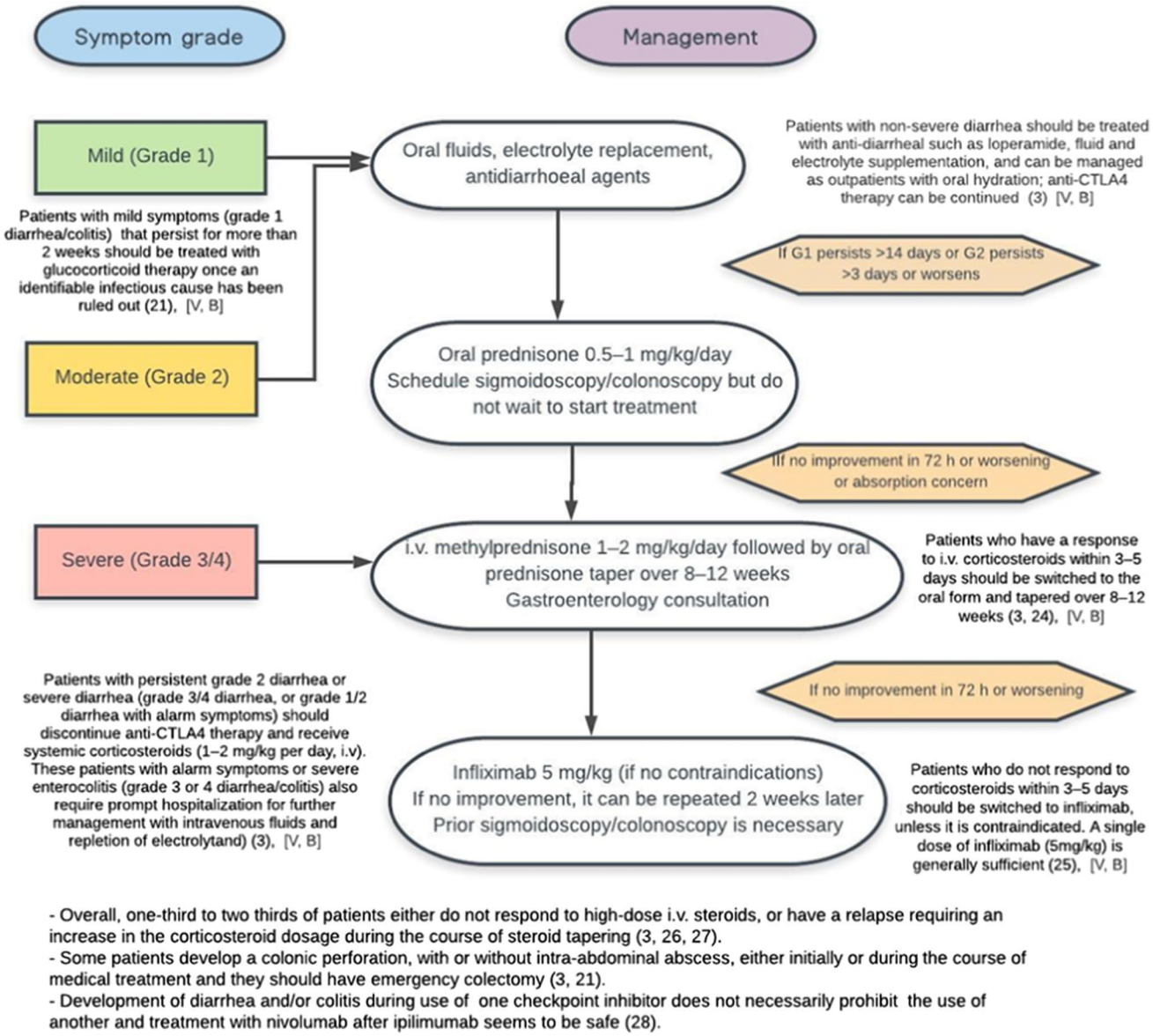

Fig. 1 Management of gastrointestinal toxicity

Management of pneumonitis

Epidemiology Pneumonitis occurs predominantly in patients receiving anti-PD-1/PD-L1 alone or combination with anti-CTLA-4 [36]. The incidence is higher in patients with lung and renal cell cancer, suggesting that chemotherapy-induced lung inflammation, previous radiotherapy, pre-existing lung disease or smoking may contribute to the occurrence of this toxicity [37].

Clinical presentation Pneumonitis can mimic other symptoms encountered in cancer patients including dyspnea and nonproductive cough. Fever and chest pain are less common.

Diagnosis Patients should undergo a chest CT scan as chest X-ray may fail to identify about 25% of cases of pneumonitis [38]. Several patterns of radiological presentation have been reported, being cryptogenetic organizing pneumonia the most frequent [36].

Management Treatment of incidental radiographic changes is controversial, and most guidelines suggest delaying treatment until radiographic improvement or resolution [V, C]. For grade 2 pneumonitis, treatment with oral steroids is indicated (prednisone 1 mg/kg/day) and ICIs should be withheld [V, B]. Grade ≥ 3 pneumonitis requires hospitalization and treatment with I.V. steroids (methyl/prednisolone 2–4 mg/kg/day), and ICIs should be permanently discontin-

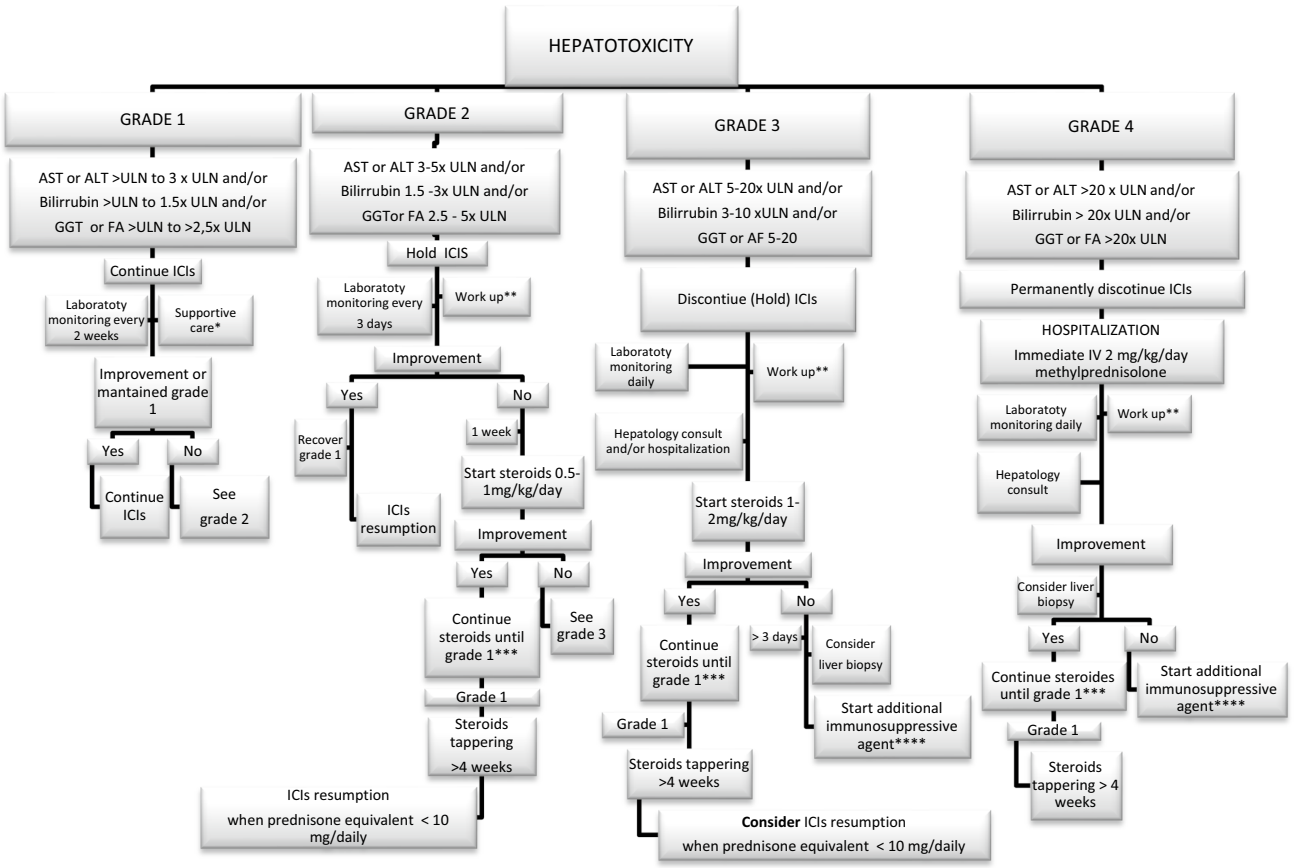

Fig. 2 Management of hepatic toxicity. *Supportive care: avoid alcohol and hepatotoxic drugs. Supportive treatment in case of symptoms. **Workup: review concomitant medications, herbs, dietary supplements, homeopathic. Liver function test, prothrombin time, albumin, serology hepatitis, autoimmune and iron studies, investigate new metastasis. ***If steroids therapy if required > 2 weeks consider prophylactic antibiotic. ****Additional immunosuppressive medications include mycophenolate mofetil, tacrolimus, antithymocyte globulin, or cyclosporine

ued [V, B]. A bronchoscopy should be performed to exclude infectious etiologies before starting immunosuppression. Infliximab and/or cyclophosphamide should be considered for refractory pneumonitis [3, 7–9].

Management of cutaneous adverse events [39, 40]

Epidemiology Cutaneous side effects are common under ICIs (anti-CTLA-4: 43–45%, anti-PD-1/PD-L1: 35%), and may be serious and dose limiting. Cutaneous adverse events appear later with anti-PD-1/PD-L1 than with anti-CTLA-4 or combination.

Clinical presentation The most frequently reported cutaneous adverse events are maculo-papular rash, pruritus and vitiligo. Exacerbation of psoriasis or psoriasiform and lichenoid reactions has also been reported.

Diagnosis Careful physical examination of the skin and mucosal areas is required. Blood tests may be helpful if life-threatening syndromes are suspected. Skin biopsy and a review by dermatologist may also be indicated.

Management ICIs can be maintained in grade 1–2 toxicities, interrupted in grade 3 and permanently discontinued in grade 4 [V, A]. Symptomatic treatment with systemic antihistamines, high to very high strength topical steroids, and topical moisturizers is indicated in all grades [V, A]. High-dose steroids are indicated in grade ≥ 3. Other immunosuppressive drugs may be needed in steroid-refractory cases [V, A].

Management of less frequent toxicities

Management of neurological toxicity

Epidemiology and clinical presentation The incidence of neurological complications varies from 2–4% [1, 41, 42]. Moderate AEs have been reported in 6–12% (dizziness, headaches, sensory neuropathies, etc.), whereas severe

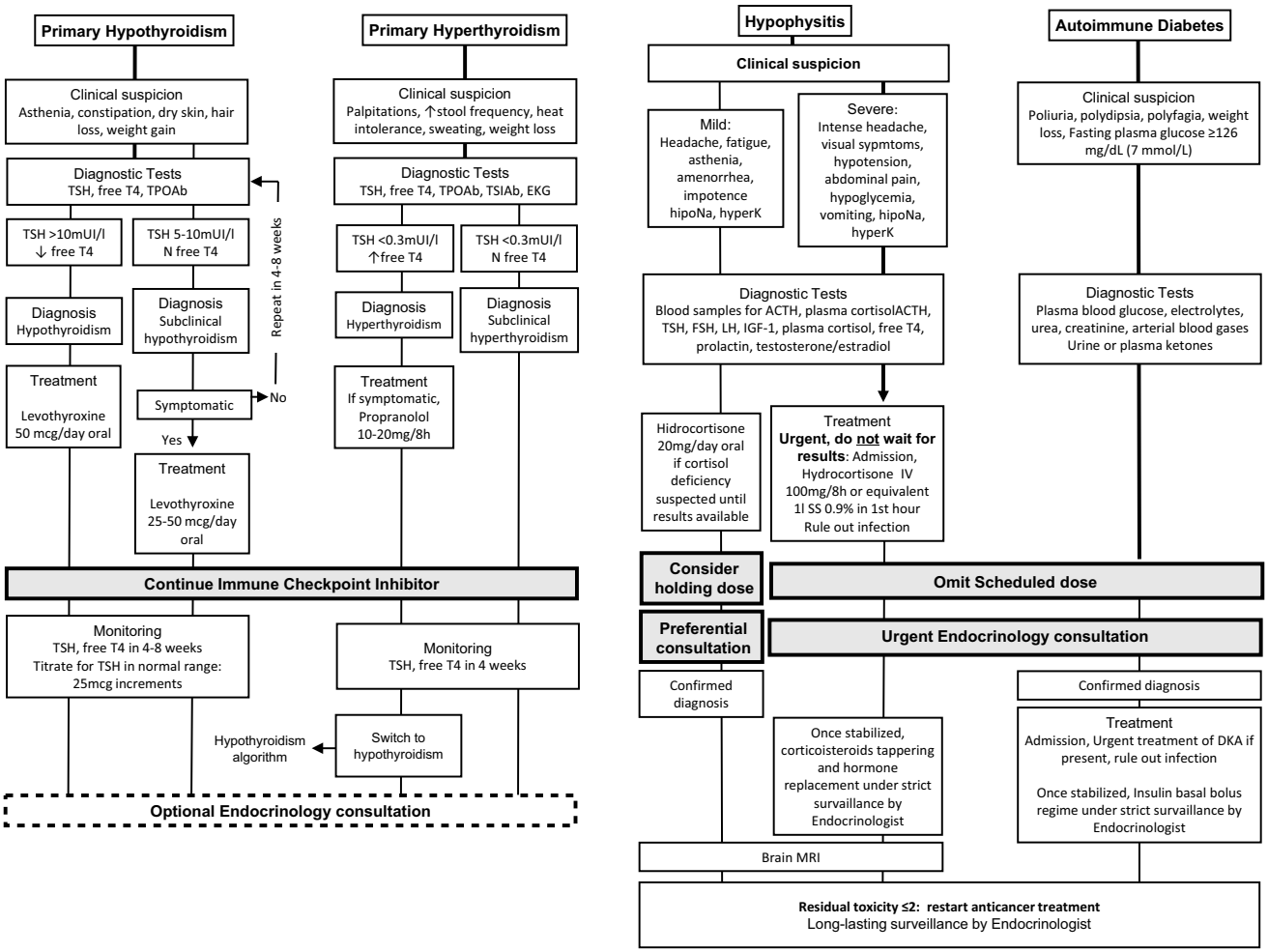

Fig. 3 Management of endocrine toxicity. *TSH* thyrotropin-stimulating hormone, *TPOAb* anti-peroxidase antibodies, *TSIAb* anti-TSH receptor antibodies, *SS* saline solution 0.9%

events (encephalitis, aseptic meningitis, inflammatory myopathies, *myasthenia gravis*, Guillain–Barre syndrome, multiple sclerosis, etc.) are present in < 1% of patients. This incidence can be higher when ICIs are given in combination (14%), or if there is preexisting autoimmune disease (27–38%) [1, 41, 43–45].

Management A neurologic consult is indicated. There is no standard therapy and treatment is decided according to the type and severity of the neurological event. Improvements have been described after discontinuation of ICIs and with systemic high-dose steroids [V, B]. Other treatments such as intravenous immunoglobulin, plasmapheresis or immunosuppressive agents have shown non-consistent results [V, B]. After neurological toxicity recovery, resumption of ICIs is controversial, and risk/benefit ratio should be carefully taken into consideration [46].

Management of cardiovascular toxicity

Epidemiology and clinical presentation The incidence of cardiac toxicity is < 1%, although it might have been underreported and/or underestimated. The incidence is higher with the combination of anti-CTLA-4 and anti-PD-1/PD-L1 (0.27%) compared with anti-PD-1/PD-L1 alone (0.06%). A wide range of toxicities, including myocarditis, pericarditis, arrhythmias, cardiomyopathy and decrease in ventricular function, have been reported [47].

Diagnosis and management Initial workup may include EKG, troponin, BNP and echocardiogram. Early consultation with a cardiologist is highly recommended [V, B] and additional testing with cardiac MRI may be indicated. High-dose steroids have been used successfully and should be given quickly if suspected [V, B]. Other immunosuppressive drugs such as mycophenolate, infliximab, or antithymocyte globulin may be indicated if patient does not respond to ster-

oids [V, B] [3]. Infliximab in contraindicated in the presence of moderate to severe heart failure.

Management of renal toxicity

Epidemiology and clinical presentation Renal toxicity is rare in patients receiving monotherapy (< 1%) but can reach 5% when ICIs are combined together or with a platinum-based chemotherapy. The most common event is acute tubule-interstitial nephritis.

Diagnosis and management Renal function should be measured before every infusion of ICI and nephrotoxic drugs may be stopped in case of renal dysfunction. Presence of infection or urinary tract obstruction must be evaluated. ICI should be interrupted in grade ≥ 2 renal dysfunction and treatment with high-dose steroids is recommended [V, B]. Nephrology evaluation is also recommended and a renal biopsy may be useful [V, B] [3, 48].

Management of rheumatologic toxicity

Epidemiology and clinical presentation Incidence of rheumatologic toxicity is generally underestimated and is more common with anti-PD-1/PD-L1. They can be grouped in inflammatory arthritis, myositis, and polymyalgia rheumatica (PMR)-like syndromes [49].

Diagnosis and management A multidisciplinary approach would be the first measure. Comprehensive anamnesis including joint examination and muscle strength, autoimmune blood panels and inflammatory markers, and radiological assessment with plain-X ray, ultrasound and or MRI is recommended [50] [V, D]. For grade 1 events, common analgesia with paracetamol or NSAIDs is recommended. From ≥ grade 2, referral to rheumatologist, temporary or permanent discontinuation of ICIs, steroids and biologic disease-modifying anti-rheumatic drugs must be considered [51] [V, D].

Management of ocular toxicities

Epidemiology and clinical presentation Ocular toxicities represent < 1% of irAEs [52] and consist of ocular inflammation (uveitis, peripheral keratitis, Vogt–Koyanagi–Harada syndrome), orbital inflammation, as well as retinal and choroidal diseases (retinopathy, neovascularization) [53]. Previous trials have shown that patients who develop ocular toxicities are more likely to present other irAEs. Uveitis has been reported in patients treated with anti-CTLA-4 and anti-PD-1 [54]. Idiopathic orbital inflammation has been described in relation to ipilimumab [52, 55]. Choroidal neovascularization has been reported in a patient treated with ipilimumab [56], requiring intravitreal anti-VEGF injections.

Diagnosis and management Treatment of ocular toxicities depends on the severity and type of toxicity. In case of uveitis, topical steroids can be effective, and for more severe toxicities, systemic steroids are indicated and discontinuation of ICIs should be considered [V, B]. Resumption can be considered in patients with grade 1–2 ocular toxicities but in case of grade ≥ 3, permanent discontinuation should be recommended [V, B].

Management of refractory toxicities (Table 3)

Epidemiology of steroid-refractory high-grade irAEs is currently unknown. Due to the lack of validated biomarkers, a gradual approach is advocated to manage severe irAEs, starting with high-dose steroids. If the latter fails, a more aggressive immunosuppression is recommended, considering the introduction of cytokine-directed mAb against IL-1, IL-6 or TNFα [11, 57]. Anti-TNFα mAb infliximab (single dose of 5 mg/kg) is the upfront recommended treatment for corticosteroid-refractory colitis and pneumonitis, and mycophenolate mofetil with appropriate antibacterial and antiviral prophylaxis for corticosteroid-refractory hepatitis [V, C], although use of anti-IL6 (tocilizumab) and anti-IL1 (anakinra) may represent good alternatives for the previous and many other irAEs in the context of a personalized approach with close monitorization [7] [V, D]. Immunoglobulins and plasmapheresis could be an option in severe and multirefractory irAEs, especially in neurological irAEs [8] [IV, D].

Conclusions

ICIs are an effective treatment option in several tumor types that can induce inflammatory side effects, termed irAES. irAEs can affect multiple organs of the body and its severity can be low to life threatening. As a consequence, clinicians require new skills to successfully diagnose and manage these events, and also a multidisciplinary approach may be indicated.

Author contributions All the authors have contributed equally to the writing of the manuscript.

Compliance with ethical standards

Conflict of interest MMT reports grants and personal fees from BMS; personal fees from Astra Zeneca, Roche, MSD, Boehringer Ingelheim, Takeda, and Bayer; non-financial support and other from Astra Zeneca, MSD, Boehringer Ingelheim, and other from Takeda, outside the

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Ethical approval The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Not applicable.

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