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SPECIAL ARTICLE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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GENERAL ASPECTS OF IMMUNE-RELATED ADVERSE EVENT MANAGEMENT

Overview

Adverse events (AEs) related to the use of immune checkpoint inhibitor (ICI) therapy are defined as immune-related (IR) AEs (irAEs). irAEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.001).[1] The aim of this European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) is to provide specific guidance on irAE management. Recommendations provided are based on evidence from the scientific literature, clinical experience and analogy to the treatment of autoimmune diseases (ADs), where appropriate. Consensus for the recommendations was obtained by direct communication, scientific debate and agreement.

Further information regarding the provision of patient information, routine baseline screening before ICI initiation, monitoring during ICI therapy, management of outpatients versus inpatients and that of corticosteroid (CS)-refractory patients and patients with specific conditions can be found in Section 1 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

General guidance for immunosuppression

irAE management generally consists of four sequential steps: (i) diagnosis and grading of irAEs, (ii) ruling out differential diagnoses and pre-immunosuppression work-up, (iii) selecting the appropriate immunosuppression strategy for grade $\geq$2 events and (iv) active evaluation at 72 h to adapt treatment. See Supplementary Table S2 and Section 1 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

To minimise the occurrence of CS-induced AEs, the following general guidance is proposed[2]:

- The lowest effective CS dose should be prescribed for the shortest possible duration, which, in general will be several weeks for grade $\geq$3 irAEs, including tapering
- CS therapy tapering or discontinuation only on medical advice
- Lifestyle adaptations to minimise the risk of CS-induced AEs

Immunosuppressive drugs

Optimising the choice of immunosuppressive agents. Prospective studies evaluating the safety and efficacy of immunosuppressant agents in irAE management are

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lacking. Several CS-sparing immune-modulating agents have been used in severe or CS-refractory irAEs, including:

- Biologic disease-modifying anti-rheumatic drugs (bDMARDs):
  - Tumour necrosis factor (TNF)-α inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab)
  - Gut-specific immunosuppressants (vedolizumab)
  - Anti-B-cell cluster of differentiation (CD)20 monoclonal antibodies (rituximab, obinutuzumab, ocrelizumab)
  - Anti-interleukin (IL) 6 receptor (IL-6R) therapies (tocilizumab, sarilumab)
  - Anti-IL-4Rα therapy (dupilumab)
  - Anti-IL-17A therapies (secukinumab, ixekizumab, brodalumab)[3,4]
  - Anti-IL-23α antibody (guselkumab)[5]
  - Anti-IL-12 and IL-23 therapy (ustekinumab)[5]
  - Anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept)[6]
  - Anti-CD52 (alemtuzumab)[7]
  - Anti-thymocyte globulin therapy[8]
- Conventional synthetic (cs)DMARDs, including mycophenolate mofetil (MMF), calcineurin inhibitors, cyclophosphamide, methotrexate, azathioprine, sulfasalazine and hydroxychloroquine
- Targeted synthetic DMARDs, including Janus kinase inhibitors such as tofacitinib and baricitinib
- Other immunomodulators such as intravenous immunoglobulin (IVIG)

As the use of these agents has been extrapolated based on their application in ADs, their safety and efficacy in irAE management and impact on response to ICI therapy should be prospectively evaluated.

Personalised anti-cytokine strategies. Specific cytokines have been targeted to reduce irAEs without compromising antitumour immunity in preclinical mouse models and some cancer patients.[9] Some cancer patients with CS-refractory irAEs may benefit from cytokine inhibitors. Unlike CSs, cytokine inhibitors provide a more targeted approach to reducing ICI-induced inflammation.[10] The advantages of cytokine-targeted therapies are numerous. They may[9]:

- Reduce symptom duration and hospitalisation
- Be efficacious in CS-refractory irAEs
- Enable rapid resumption of ICI treatment, and in some cases, promote or maintain antitumour immunity
- Decrease the recurrence of irAEs and prevent pre-existing AD flares when used in combination with ICI therapy
- Uncouple toxicity and antitumour efficacy

Some disadvantages exist and should be considered on an individual basis:

- Unclear impact on antitumour immunity and survival benefit
- Costs and accessibility for irAE treatment

Resuming ICI or rechallenge strategy

Patients who have previously developed grade 3 or 4 irAEs are at risk of redeveloping severe toxicities on ICI rechallenge. Consequently, physicians are hesitant to retreat, even though patients may derive clinical benefit. Thus, balancing clinical benefit and treatment-related toxicities for each patient is challenging.[11] Three scenarios of ICI resumption are possible (Section 1 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001); this decision depends on multiple factors and needs to be discussed in multidisciplinary teams (MDTs) and on a case-by-case basis.[11]

IR-SKIN TOXICITY

Clinical presentation and incidence rates

IR cutaneous AEs (ircAEs) are the most common side-effects of ICI therapy (>50% for all grades) but are rarely severe and usually do not impair treatment continuation.[12-15] Clinical presentation is highly variable with non-specific maculopapular rashes being the most common. More specific autoimmune-like presentations, such as lichenoid reactions, psoriasis and bullous dermatoses, are also reported.

Non-specific maculopapular rashes usually occur in the first 6 weeks of therapy. These rashes can be preceded by or associated with pruritus. Pruritus can also be the sole manifestation of a skin AE, including bullous pemphigoid (BP). Maculopapular rashes usually involve <30% of body surface area and are considered severe (grade >3) in <5% of cases (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.001).[16]

Lichenoid eruptions appear as erythematous papules or plaques more frequently (≤30%) under treatment with anti-programmed cell death protein 1 (PD-1) than anti-CTLA-4 therapy.[17] Lichenoid reactions can also involve mucosal areas and result in painful ulcerative mucosal disease.

Erythrodermic papulosquamous eruptions, including psoriasis or pityriasis rubra pilaris-like eruptions, are frequently reported ircAEs. Psoriasis is a skin inflammatory disease affecting ∼3% of the population. Exacerbation or a new occurrence of *de novo* psoriasis has been reported in association with ICI therapy, appearing as well-delimited erythematous and scaly plaques, which can involve the mucous areas and the nails (subungual hyperkeratosis).

Sarcoidosis or granulomatous reactions frequently involve mediastinal lymph nodes. They can also occur in the skin with a wide spectrum of presentations (papules, nodules and erythematous lesions) and can also be misdiagnosed as skin metastases.

Immunobullous disorders such as BP or cicatricial pemphigoid have been described. They present as bullous or erosive lesions and can involve mucous membranes. They are usually accompanied or preceded by pruritus and can thus be associated with non-specific skin lesions resulting from skin scratching.

Skin and hair vitiligoid depigmentation are mostly seen in melanoma patients treated with ICI therapy where it is observed in 5%-25% of patients.[16,18] Photo-exposed skin areas are usually affected: face, extremities, scalp and facial hair.

There are also rare, isolated reports of lethal or potentially lethal AEs, such as toxic necrolysis (Lyell syndrome), severe Stevens—Johnson syndrome, drug reactions with eosinophilia and systemic syndrome (DRESS), neutrophilic drug eruptions including acute generalised exanthematous pustulosis, cutaneous small-vessel vasculitis and neutrophilic dermatoses (Sweet syndrome and pyoderma gangrenosum-like ulcers).

Diagnosis and biology

The diagnosis of ircAEs is usually based on clinical evaluation when a simple, non-complicated rash is observed; this can be facilitated by skin biopsy and more specific tests, depending on the clinical presentation. Pathological examination of maculopapular rashes shows lymphocytic CD4+ infiltrates with eosinophils and papillary oedema. Lichenoid reactions are associated with a characteristic band of dense dermal lymphocytic infiltrate with degeneration and vacuolisation of the basal membrane.

In BP, direct immunofluorescence shows C3 and immunoglobulin (Ig) G deposits on the basal membrane, and serological testing for anti-basal membrane antibodies may show autoantibodies. Biopsies from vitiligo-like eruptions have shown CD4+ and CD8+ lymphocytes in close vicinity to apoptotic melanocytes. Psoriatic lesions present characteristic signs of a thickened and parakeratotic stratum corneum, elongated rete ridges and perivascular lymphocytic infiltration.

Management

An algorithm for the management of IR-maculopapular rash is shown in Figure 1.

Although the vast majority of ircAEs are of mild or moderate severity, early (and repeated, if needed) evaluation of the disease severity should be carried out to eliminate rare severe irAEs such as Stevens—Johnson syndrome, toxic epidermal necrolysis, bullous lesions and DRESS syndrome that necessitate immediate interruption of ICI therapy, specialist treatment and monitoring.

Details regarding ircAE grading and IR-maculopapular rash management can be found in Section 2 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

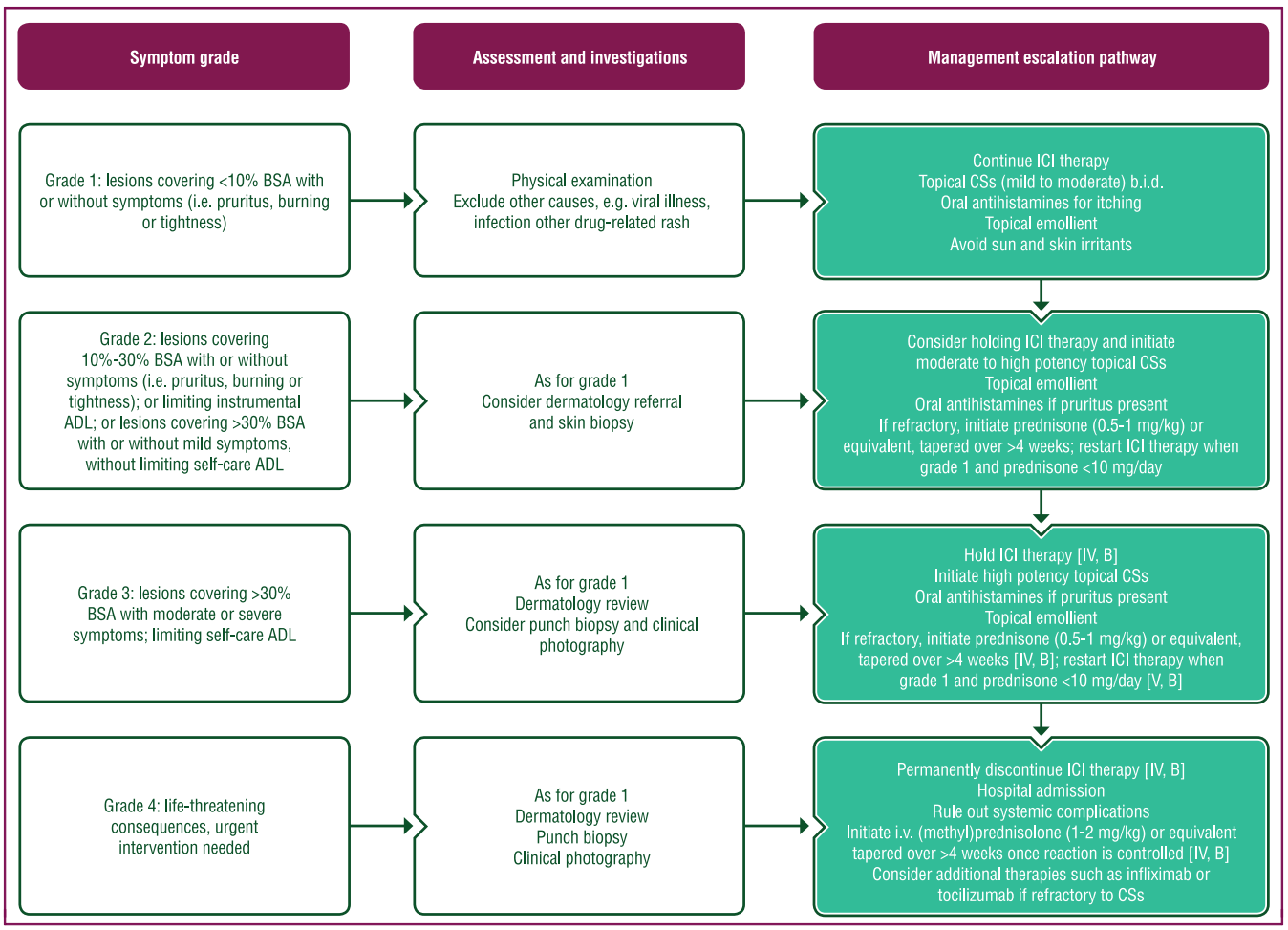

Figure 1. Management of IR-maculopapular rash.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ADL, activities of daily living; b.i.d., twice daily; BSA, body surface area; CS, corticosteroid; ICI, immune checkpoint inhibitor; IR, immune-related; i.v., intravenous.

Recommendations

- The relationship between ICI therapy and the skin AE (since the patient is usually on several medications) should be evaluated and confirmed, if possible [IV, A].
- The severity of the skin AE should be evaluated and the need for specialist advice or a referral should be assessed. Physicians should be capable of diagnosing early signs of DRESS, Lyell disease and Stevens–Johnson syndrome [IV, A].
- The entire skin and mucosae of the patient should be examined before initiation of ICI therapy [IV, A].
- The history of skin disorders such as psoriasis or ADs with a skin manifestation should be queried [IV, A].

IR-ENDOCRINOPATHIES

IR-endocrinopathies are relatively frequent. Their management differs from other irAEs in three key ways: ICI therapy can be continued in most cases, high-dose CSs are rarely required and endocrine deficiency usually persists, necessitating lifelong replacement. Algorithms for the management of IR-thyroid disorders and IR-hypophysitis are shown in Figures 2 and 3, respectively.

Thyroid disorders

IR-primary hypothyroidism. Primary hypothyroidism is the most common IR-endocrinopathy and occurs in ∼6%-9% of patients treated with anti-PD-1 and/or anti-programmed death-ligand 1 (PD-L1) therapy, in 4% treated with anti-CTLA-4 therapy and in ≤16% treated with anti-PD(L)1–anti-CTLA-4 combination therapy.[19] It may be preceded by a hyperthyroid state, which may be subclinical. While the majority of cases occur within 3 months of therapy initiation, onset may occur at any time during treatment.[20]

IR-hyperthyroidism. IR-hyperthyroidism occurs less frequently; it is reported in ≤2%-5% of patients treated with ICI monotherapy and in 10% treated with anti-PD(L)1–anti-CTLA-4 combination therapy.[19] Transient thyroiditis is the most common cause, with ∼40% presenting as symptomatic thyrotoxicosis and 60% as subclinical followed by hypothyroidism.[21] Primary hyperthyroidism due to Graves-

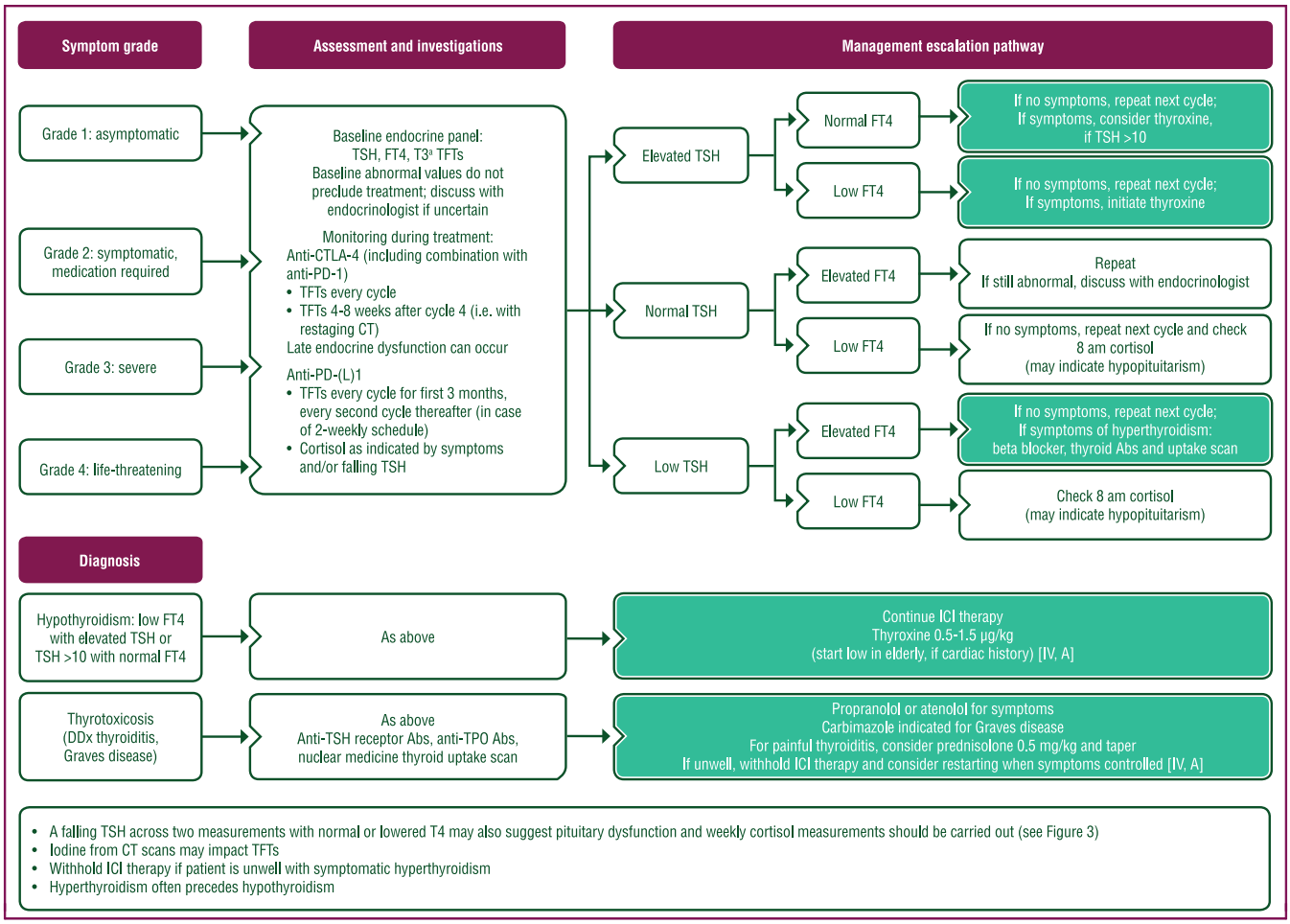

Figure 2. Management of IR-thyroid disorders.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
Ab, antibody; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DDx, differential diagnosis; FT4, free thyroxine; ICI, immune checkpoint inhibitor; IR, immune-related; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; T3, triiodothyronine; T4, thyroxine; TFT, thyroid function test; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.
[a]When indicated.

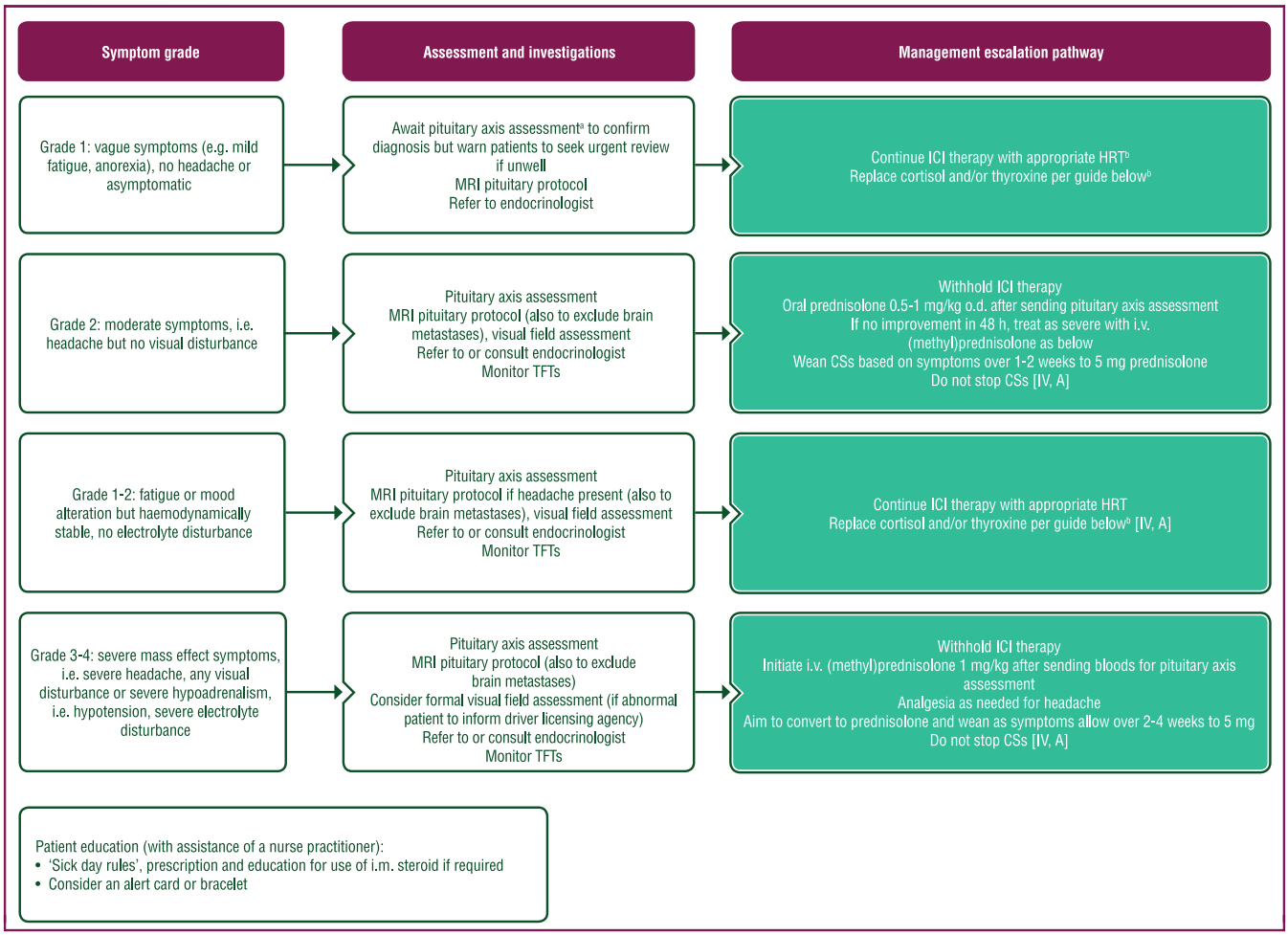

Figure 3. Management of IR-hypophysitis.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ACTH, adrenocorticotropic hormone; CS, corticosteroid; FSH, follicle-stimulating hormone; FT4, free thyroxine; HRT, hormone replacement therapy; ICI, immune checkpoint inhibitor; IGF-1, insulin-like growth factor-1; i.m., intramuscular; IR, immune-related; i.v. intravenous; LH, luteinizing hormone; MRI, magnetic resonance imaging; o.d., once a day; T4, thyroxine; TSH, thyroid-stimulating hormone; TFT, thyroid function test.
[a]Pituitary axis bloods: 9 am cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH or FT4, LH, FSH, estradiol if premenopausal, testosterone in men, IGF-1, prolactin. Mineralocorticoids replacement is rarely necessary in hypopituitarism.
[b]Initial replacement advice for cortisol and thyroid hormones:
- If 9 am cortisol is low (according to institutional reference range):
  - o Replace with hydrocortisone 20/10 mg.
  - o If TFTs are normal, 1-2-weekly monitoring initially (always replace cortisol for 1 week before T4 initiation)
- If falling TSH ± low FT4:
  - o Consider the need for T4 replacement (guide is 0.5-1.5 μg/kg) based on symptoms ± check 9 am weekly cortisol
- See thyroid guidelines for further information regarding interpretation of an abnormal TSH or T4[114]
- Testosterone or estrogen replacement to be considered if low (in men and premenopausal women)
- In case of diabetes insipidus symptoms, refer for specialist advice.

like disease is rarely reported. Persistent hyperthyroidism, diffuse goitre and ophthalmopathy may suggest this diagnosis. Euthyroid ophthalmopathy consequent to IR-Graves' disease has also been noted.[22]

Diagnosis and management. See Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Pituitary disorders

IR-hypophysitis. The incidence of IR-hypophysitis is highest with anti-PD(L)1—anti-CTLA-4 combination therapy (9%-10%), followed by anti-CTLA-4 (2%-6%) and anti-PD-1 therapy (1%).[19] Patients treated with regimens containing anti-CTLA-4 antibodies develop IR-hypophysitis within the first 3-4 months of therapy, whereas cases related to anti-PD-1 monotherapy typically occur later (median 6 months).[23]

Diagnosis and management. See Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

IR-diabetes mellitus

IR-diabetes mellitus (IR-DM) results in a permanent insulin-dependent state consequent to autoimmune destruction of

pancreatic islet cells. The incidence is 1%-2% across ICI regimens.[19] Median onset is after 4.5 cycles, but with anti-PD(L)1—anti-CTLA-4 combination therapy, it occurs earlier (median 2.7 cycles). Islet autoantibodies are positive in ~50% of cases, with low C-peptide levels seen in the majority.[24] Susceptible human leukocyte antigen (HLA) genotypes (mostly HLA-DR4) may increase vulnerability to this irAE.[24]

Diagnosis and management. See Supplementary Figure S1 and Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

IR-primary adrenal insufficiency

IR-primary adrenal insufficiency is an increasingly recognised irAE that can present acutely. It has been associated with fatal outcomes stemming from life-threatening adrenal crisis due to vasodilatory shock.[25] Its incidence ranges from 1%-2% with ICI monotherapy to 5%-8% with anti-PD(L)1—anti-CTLA-4 combination regimens.[19] Onset varies widely from a few days to >12 months (median 4 months).[25] Presenting symptoms may be non-specific or similar to secondary adrenal insufficiency (see above and Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001).

Diagnosis and management. See Supplementary Figure S2 and Section 3 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Other IR-endocrinopathies

The incidence of IR-hypogonadism is likely underreported. Moreover, IR-hypogonadism is an increasingly important consideration with adjuvant treatment and durable survival. While it occurs secondary to hypophysitis in most cases, primary orchitis has been described.[26] IR-hypoparathyroidism, adrenocorticotrophic hormone-dependent Cushing syndrome and diabetes insipidus have also been reported.[27]

Recommendations

- In grade >2 IR-hypothyroidism, hormone replacement therapy (levothyroxine 50-100 μg/day) should be started in symptomatic cases, and the dose should be increased over several weeks until thyroid-stimulating hormone levels normalise. ICI therapy should be interrupted only if symptoms are severe (grade ≥3) [IV, A].
- In symptomatic IR-hyperthyroidism (grade ≥2), ICI therapy should be interrupted and beta blocker therapy should be started. Oral prednisolone 0.5-1 mg/kg may be required short-term for gland inflammation or if symptoms are severe. ICI therapy should be restarted in asymptomatic cases [IV, A].
- For IR-hypophysitis, if severe headache, diplopia or other neurological symptoms are present (grade 3), (methyl) prednisolone 1 mg/kg is indicated. Secondary adrenal crisis (grade 3 insufficiency) should be managed with stress-dose CS replacement. In asymptomatic and symptomatic cases without severe features (grade 1-2), replacement doses of deficient hormones (adrenal, thyroid and gonadal axes) should be initiated [IV, A].
- For IR-primary adrenal insufficiency, in asymptomatic or minimally symptomatic cases (grade 1-2), replacement CSs are indicated. In severe cases (grade ≥3), stress replacement doses are required [IV, A].
- For new-onset IR-DM, prompt insulin initiation is warranted. Patients presenting with ketoacidosis should be admitted to the hospital. Diabetic ketoacidosis should be managed according to the institutional guidelines, including intravenous (i.v.) insulin, correction of fluid loss and close monitoring of serum potassium, hourly glucose and anion gap. High-dose CSs are not indicated [IV, E].

IR-HEPATOTOXICITY

Incidence

Hepatitis occurs in 5%-10% (1%-2% grade 3) of patients during ICI monotherapy and in 25%-30% (15% grade 3) during anti-PD(L)1—anti-CTLA-4 combination therapy.[28-30] Liver toxicity associated with the combination of ICI and non-ICI agents has also been increasingly recognised.[31]

Diagnosis

All patients undergoing ICI therapy should be routinely assessed with serum transaminases, alkaline phosphatase (ALP) and bilirubin before every treatment cycle. Hepatitis can be asymptomatic or present with fever, malaise, abdominal discomfort, jaundice and anorexia. Serum bilirubin, prothrombin time and factor V add prognostic information. Alternative causes of liver injury should be excluded (e.g. medication, alcohol, viruses, metabolic disorders, ADs if suspected, vascular disease, tumoural involvement). Liver biopsy may assist in the differential diagnosis of more severe hepatitis and guide management. The most common pathological feature of IR-hepatitis is lobular hepatitis with necrosis, either spotty or confluent. Patients who receive anti-PD-(L)1 therapy have heterogeneous liver damage involving lobular and periportal activity,[32-35] whereas sinusoidal histiocytosis, fibrin deposition and central vein endothelitis are more commonly associated with anti-CTLA-4 use.[32,33]

Management

Recommendations for IR-hepatotoxicity management are provided in Figure 4 and Section 4 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

IR-hepatitis usually resolves within 4-6 weeks with appropriate treatment. If it remains unresolved, other contributory causes should be reconsidered and the initial diagnostic work-up repeated.

Recommendations

- Assessment of serum transaminases, ALP and bilirubin before every cycle of ICI therapy is recommended [IV, A].
- For grade 1 IR-liver injury, monitoring of liver enzymes every 1-2 weeks is recommended, with no need to hold ICI therapy [IV, A].
- For grade 2 IR-liver injury, temporarily withholding ICI therapy is suggested, with monitoring of transaminases and bilirubin twice weekly. CS 0.5-1 mg/kg/day should be considered [V, B].
- For patients with grade 3 or 4 IR-liver injury, hospitalisation and initiation of CS 1-2 mg/kg/day should be considered. If there is no response to CS within 2-3 days, alternative immunosuppressive therapy should be considered, such as MMF (1000 mg twice daily), tocilizumab (8 mg/kg), tacrolimus, azathioprine, cyclosporine or anti-thymocyte globulin [IV, B].

IR-CHOLANGITIS

IR-cholangitis is a rare AE which may affect large bile ducts, small ducts or both. Elevations of γ-glutamyltransferase and ALP are more prominent than transaminases. Pathological findings include portal inflammation, bile duct injury or loss, cholestasis and lobular injury. Most patients receive ursodeoxycholic acid and prednisone or budesonide, although other immunosuppressive agents, e.g. MMF, azathioprine, tacrolimus, tocilizumab and plasmapheresis, have also been used. With medical treatment, biliary enzymes decrease in the majority of patients but reach normal values in only a minority of cases after 6-12 weeks.[36]

Recommendation

- Patients with IR-cholangitis should be treated with ursodeoxycholic acid and prednisone/budesonide [V, B].

IR-PANCREATIC TOXICITY

Incidence

The incidence of IR-pancreatic toxicity (IR-PT) is ∼4%; it is more frequent with anti-PD(L)1—anti-CTLA-4 combination therapy than with monotherapy.[37] Knowledge regarding

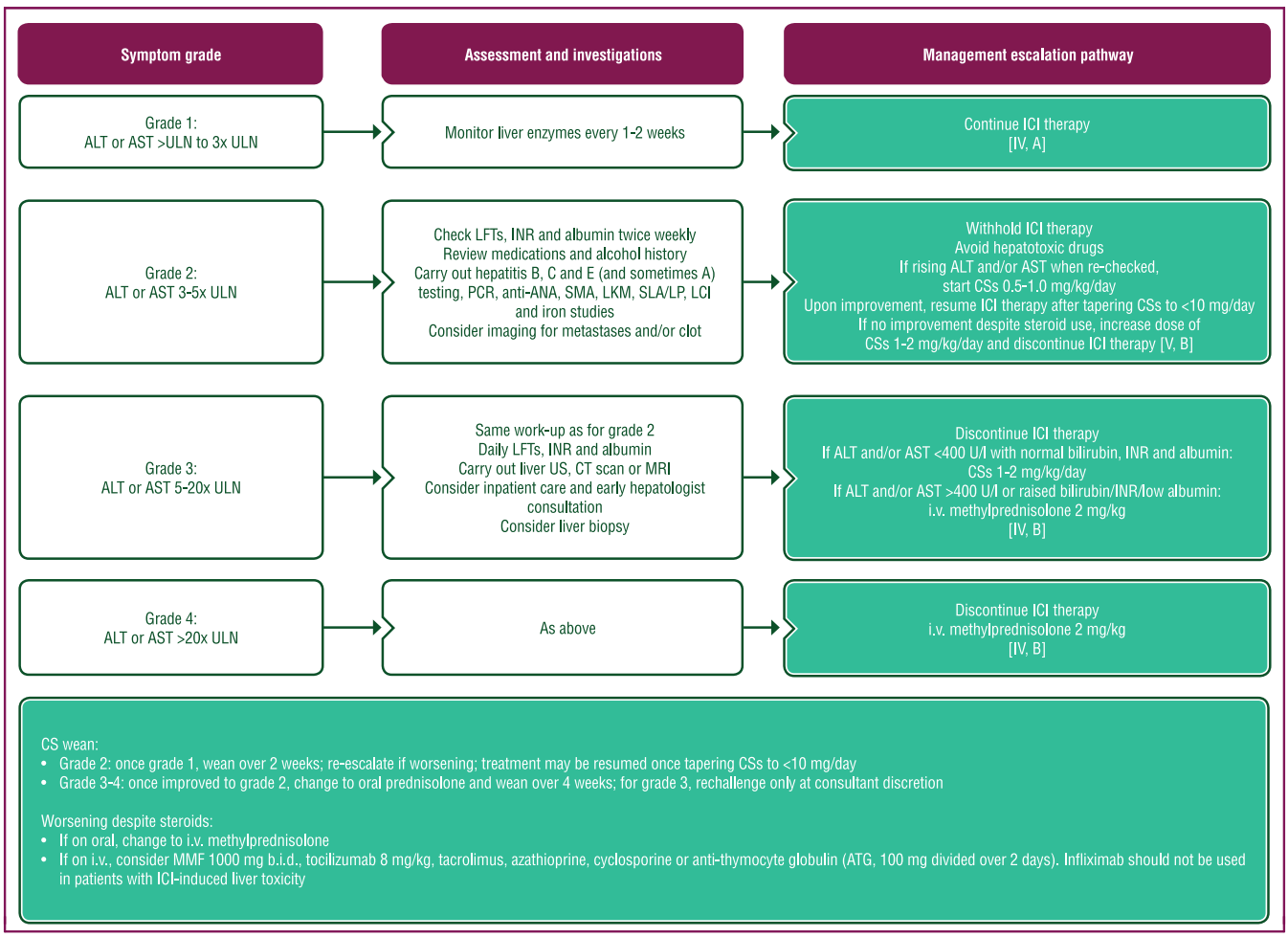

Figure 4. Management of IR-hepatotoxicity.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ALT, alanine transaminase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; ATG, anti-thymocyte globulin; b.i.d., twice daily; CS, corticosteroid; CT, computed tomography; ICI, immune checkpoint inhibitor; INR, international normalised ratio of prothrombin time; IR, immune-related; i.v., intravenous; LCI, lung clearance index; LFT, liver function test; LKM, liver kidney microsomal; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; SLA/LP, soluble liver antigen/liver-pancreas antibody; SMA, smooth muscle autoantibody; ULN, upper limit of normal; US, ultrasound.

IR-PT is very limited. IR-PT is often associated with other irAEs, particularly enterocolitis (33%) and hepatitis (21%).[37]

Diagnosis

The diagnosis of IR-PT is a diagnosis of exclusion. Differential diagnoses include pancreatic metastases (13% of patients referred for IR-PT) and pancreatic injury due to other causes (e.g. alcohol, hypertriglyceridemia, bile stones or sludge, autoimmune pancreatitis, pancreatic parenchyma neoplastic lesions, drugs other than ICIs). The differential diagnosis is based on medical history, biochemical analyses and imaging [ultrasonography, computed tomography (CT) scan, magnetic resonance imaging (MRI) and, if needed, endosonography with biopsies].

Management

See Section 4 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Recommendations

- Elimination of differential diagnoses of IR-PT is recommended, including pancreatic metastases and pancreatic injury due to other causes (e.g. alcohol, hypertriglyceridemia, bile stones or sludge, drugs other than ICIs). The differential diagnosis should be based on medical history, biochemical analyses and imaging (ultrasonography, CT scan, MRI and, if needed, endosonography with biopsies) [V, A].

IR-GASTROINTESTINAL TOXICITY

IR-enterocolitis

Incidence. IR-enterocolitis is the most common form of IR-gastrointestinal (GI) toxicity. It may develop after weeks or months of ICI treatment. The median onset time is shorter with anti-CTLA-4 (1 month after first infusion) than with anti-PD-1 (2-4 months after first infusion). The maximum delay between ICI discontinuation and IR-enterocolitis is 2 months with anti-CTLA-4 and 1 year with anti-PD-1.

Incidence rates of all-grade diarrhoea and colitis are ~35% and ~10% with anti-CTLA-4, ~10% and ~1% with anti-PD-1 and ~32% and ~15% with the combination, respectively.[38] Approximately 40% of patients with pre-existing inflammatory bowel disease have a flare-up while undergoing ICI treatment, half of whom experience a moderate to severe grade based on CTCAE version 5.0 criteria (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.001).[39]

Diagnosis

Clinical presentation. The hallmark symptoms of IR-enterocolitis are diarrhoea and abdominal pain; haematochezia and fever are less frequent. Severe acute colitis can lead to dehydration, toxic megacolon, colonic perforation (seen in 1%-6.6% of patients) and death, especially in cases of diagnostic delay.

Endoscopic findings. Early flexible rectosigmoidoscopy or ileocolonoscopy with biopsies in patients with suspected IR-enterocolitis of grade >1 is strongly recommended.[40,41] Endoscopic features include erythema, erosion, ulceration and luminal bleeding, although normal colon mucosa can be present in ≤40% of patients despite grade ≥2 symptoms of colitis.[38,42,43] Deep ulcerations and extensive inflammation above the left colon are predictive of CS-refractory disease and requirement for immunosuppressant treatment.[40,44]

Further details regarding the diagnosis of IR-enterocolitis can be found in Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

IR-microscopic colitis

IR-microscopic colitis is a separate entity. It causes chronic watery diarrhoea in patients treated with anti-PD-1 or anti-CTLA-4 therapy. The endoscopic appearance of IR-microscopic colitis is either normal or shows mild erythema or oedema. There are two main forms: lymphocytic colitis (intraepithelial lymphocytosis and infiltration of the lamina propria) and the less common collagenous colitis (thickening of the collagen subepithelial layer).

Management of IR-enterocolitis

See Figure 5 and Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Management of grade 3-4 diarrhoea and colitis

See Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Upper GI tract inflammation

IR-upper GI tract injury is not as common as IR-enterocolitis and may involve the oral cavity (stomatitis), oesophagus, stomach and duodenum.[45-47] The predominant upper GI symptoms are nausea, vomiting, dysphagia, odynophagia, haematemesis and abdominal pain.[47] Upper GI inflammation can be isolated or associated with enterocolitis. Endoscopic findings include erythema, erosions and ulcerations.[45-48] Histological inflammation of the stomach and the duodenum, with or without clinical symptoms, has been reported in 50%-75% of patients with GI irAEs.[43,48] Gastric biopsies show intraepithelial lymphocytosis and inflammatory infiltrate with neutrophils. Duodenal biopsies show partial (rarely total) villous blunting, crypt distortion, intraepithelial lymphocytosis and eosinophilic, lymphocytic and plasma-cell infiltration of the lamina propria. Upper GI inflammation is often patchy and mild; in most cases, it can be managed effectively with proton-pump inhibitors (PPIs). Severe forms with deep gastric ulcerations, however, may require CSs or biologics.[45,47]

Other presentations

Fissuring or fistulising anal lesions like those observed in Crohn disease have been reported. Two case reports

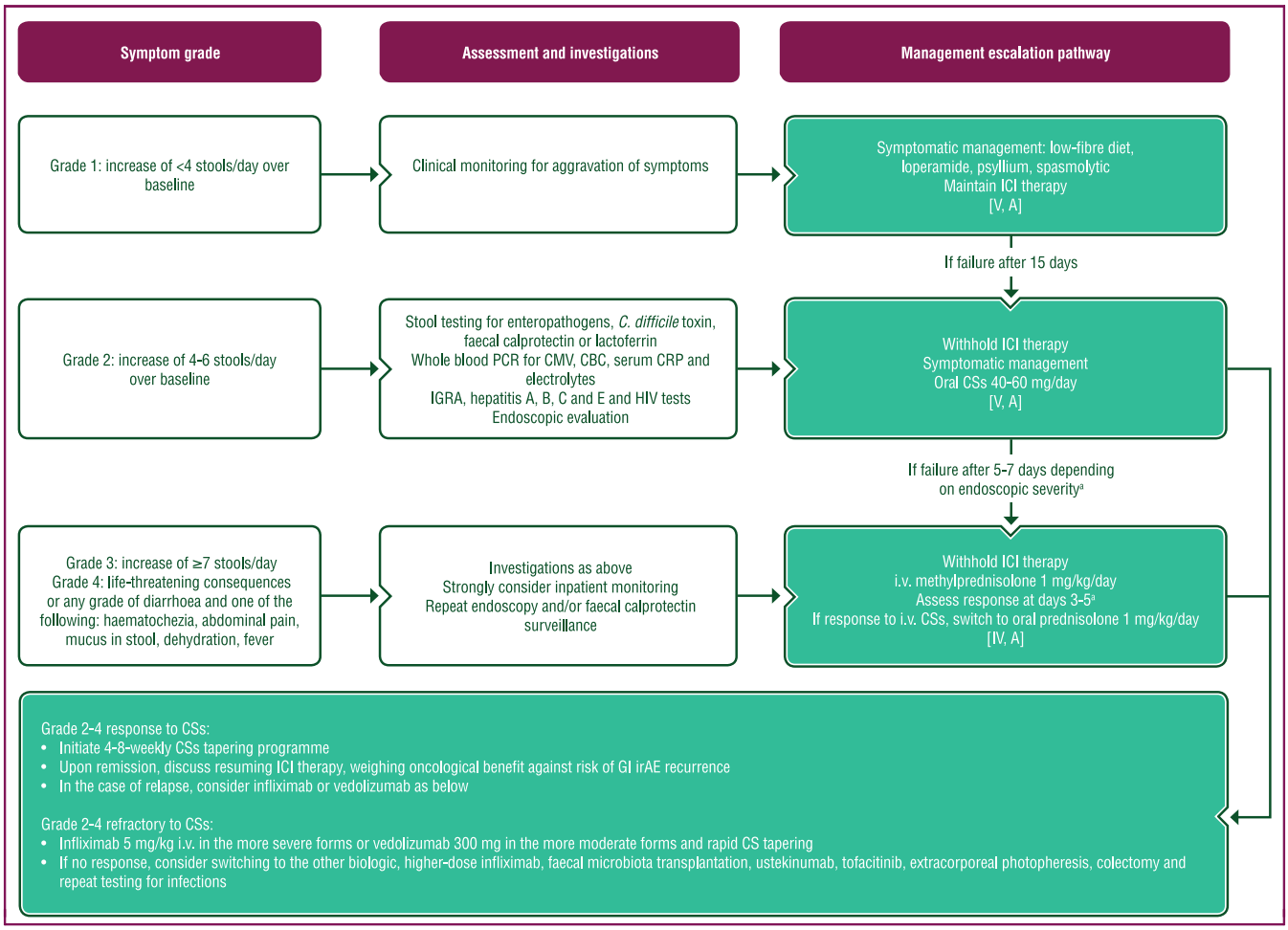

Figure 5. Management of IR-diarrhoea and enterocolitis.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
C. difficile, Clostridioides difficile; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CS, corticosteroid; GI, gastrointestinal; HIV, human immunodeficiency virus; ICI, immune checkpoint inhibitor; IGRA, interferon-gamma release assay; IR, immune-related; irAE, immune-related adverse event; i.v., intravenous.
[a]In cases of extensive colitis and ulcerations or high levels of faecal calprotectin (>400 μg/mg), if colonoscopy is not available.

described enteric neuropathy induced by ipilimumab, revealed by severe constipation.[49,50]

Risk of recurrent GI irAEs after ICI resumption

See Section 5 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Recommendations

- Flexible sigmoidoscopy or colonoscopy and biopsies in patients treated with ICIs experiencing grade >1 diarrhoea should be carried out [IV, A].
- A CT scan to diagnose IR-enterocolitis is not recommended because of insufficient sensitivity [IV, E].
- Grade 1 diarrhoea or colitis should be treated with a low-fibre diet and loperamide; ICI therapy can be continued under close medical supervision [V, A].
- Grade 2 colitis should be treated with oral CSs, with vedolizumab or infliximab used for non-responders [V, A].
- Grade 3-4 colitis should be treated by hospitalisation, with i.v. CSs [IV, A]. Infliximab is the drug of choice for non-responders with acute, severe colitis [IV, A]. Vedolizumab is an option but is associated with a slightly delayed response [IV, B].
- Resuming ICI therapy in patients who have experienced GI irAEs should be discussed on a case-by-case and multidisciplinary basis [IV, A].

IR-PULMONARY TOXICITY

IR-pulmonary toxicities are a group of heterogeneous diseases including different clinical entities such as the frequent IR-interstitial lung disease (IR-ILD) or IR-pneumonitis and other rare entities such as IR-bronchiolitis or IR-lung sarcoidosis.

IR-ILD or IR-pneumonitis

Incidence. IR-ILD or IR-pneumonitis is defined as a focal or diffuse inflammation of the lung parenchyma.[51,52] IR-pneumonitis is relatively rare but can be a serious and potentially life-threatening AE.[53] The incidence of any-grade IR-pneumonitis in clinical studies is ∼4% for anti-PD-1 therapies, 2% for anti-PD-L1 inhibitors[54] and <1% for

anti-CTLA-4 inhibitors; the incidence of high-grade pneumonitis is ~1%. IR-pneumonitis is more frequent with anti-PD(L)1—anti-CTLA-4 combination therapy versus monotherapy (10% versus 1%-5%, respectively).[51]

Diagnosis. Clinical and radiological IR-ILD diagnosis in patients with cancer is frequently challenging due to pre-existing inflammatory lung disease, chronic obstructive pulmonary disease (COPD), infections or concomitant drug-related pneumonitis that may occur with chemotherapy, targeted drugs and radiotherapy (RT).[51]

Risk factors for IR-ILD have not been fully elucidated, but tobacco exposure or pre-existing chronic lung diseases such as COPD in patients with lung cancer could predispose them to more severe pneumonitis.[55] Other factors such as previous RT,[56] smoking history and possibly squamous histology[56] may increase the risk of IR-pneumonitis. Radiological patterns of IR-ILD have been classified into five possible subtypes: cryptogenic organising pneumonia-like, ground-glass opacities, interstitial, hypersensitivity and pneumonitis not otherwise specified. The imaging findings follow the American Thoracic Society and European Respiratory Society classification of interstitial pneumonia.[57]

Several histopathological findings have been reported for IR-ILD, including cellular interstitial pneumonitis, organising pneumonia and diffuse alveolar damage, while sometimes only minimal abnormalities can be identified. Nevertheless, it is important that any pathognomonic radiological or pathological features are clearly identified. Chronic IR-pneumonitis with distinct clinicopathological features requiring long-term immunosuppression (≥12 weeks) was recently reported in ~2% of patients with non-small-cell lung cancer or melanoma.[58]

Information regarding the pathogenic mechanisms of lung injury in IR-ILD is provided in Section 6 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

In general, symptoms include dyspnoea, cough, chest pain, fever and hypoxia. Many cases of grade 1 asymptomatic IR-pneumonitis are radiologically detectable on CT scans. Dyspnoea should prompt a full clinical work-up including the exclusion of infectious pneumonia, tumour progression, pulmonary embolism, cardiac events and pleural carcinomatosis.

The grading of IR-pneumonitis is provided in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Management. An algorithm for the management of IR-ILD is shown in Figure 6. Monitoring of respiratory function before starting immunotherapy is advocated in patients with COPD or pre-existing ILD; high-resolution CT should be used when IR-pneumonitis is suspected. Details regarding the management of patients with IR-pneumonitis are provided in Section 6 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Sarcoidosis-like granulomatous inflammation

A sarcoidosis-like reaction is a rare event, which may be radiologically misinterpreted on imaging as treatment failure and tumour progression.[59] The most affected organs are the lymph nodes, lungs and skin. A lesion biopsy should be strongly considered to differentiate from tumour progression.[60] In general, most reported sarcoidosis-like reactions are sensitive to CS treatment or discontinuation of ICI therapy. In case of observed benefit from ICI, if the patient is asymptomatic, therapy can be continued. If the patient is symptomatic, then lower doses of CS ≤0.5-1 mg/kg can be considered, and ICI therapy can be resumed after resolution of the irAE.[61]

Recommendations

- Dyspnoea should trigger a full clinical work-up, including the exclusion of infectious pneumonia, tumour progression, pulmonary embolism, cardiac events (including heart failure, myocarditis, acute myocardial infarction and arrhythmias) and pleural carcinomatosis or effusion [IV, A].
- Patient cases with pre-existing ILD should be discussed with a specialist before initiation of ICI [IV, A].
- If IR-ILD is suspected, a high-resolution chest CT with contrast should be considered to rule out other aetiologies. If the CT scan is negative, pulmonary function tests should be considered to identify a potential functional deficit [IV, A].
- Bronchoalveolar lavage to rule out infection or tumour infiltration and investigations for infection with sputum, blood and urine culture if clinically indicated should be considered [IV, A].
- In cases of grade 2 IR-pneumonitis, rechallenge with ICI therapy upon complete resolution of symptoms can be considered on an individual basis with close monitoring [V, B].
- In cases of grade 2 IR-ILD, 1 mg/kg/day prednisolone (or equivalent) should be considered. For grade ≥3 IR-ILD, 1-2 mg/kg/day methylprednisolone i.v. or equivalent should be considered. CS tapering should be initiated after improvement to grade <1, over 4-6 weeks for grade 2 and over ≥6-8 weeks for grade ≥3 [V, A].
- If there is no improvement within 72 h of CS use, consultation with or referral to an expert should be arranged and therapeutic escalation should occur. Additional options include tocilizumab (8 mg/kg, one dose and every 2 weeks if needed),[62] infliximab (5 mg/kg, one dose and every 2 weeks if needed)[51,63-65] and IVIG (2 g/kg over 2-5 days).[66] Other options, such as MMF (1 g twice daily)[67] or cyclophosphamide,[51] are possible [V, A].

IR-RHEUMATOLOGICAL TOXICITY

Rheumatic and musculoskeletal irAEs occur in ~10% of patients with cancer receiving ICI therapy. An algorithm for the management of IR-rheumatological toxicity is shown in Figure 7.

Arthralgia and myalgia

Arthralgia and myalgia are the most frequent IR-rheumatic manifestations (incidence rates: 1%-43% and 2%-20%, respectively).[68] Since they can also occur secondary to

paraneoplastic manifestations or other cancer therapy, it is challenging to define whether symptoms are IR or if they relate to other irAEs, such as endocrine irAEs. Myalgia secondary to myositis should be ruled out. After evaluation and exclusion of differential diagnoses, symptomatic treatment [analgesics ± nonsteroidal anti-inflammatory drugs (NSAIDs)] should be initiated.

IR-inflammatory arthritis and IR-polymyalgia rheumatica

IR-inflammatory arthritis and IR-polymyalgia rheumatica (PMR) syndrome are the two major clinical presentations encountered (5%-10%) in ICI-treated patients.[69] Arthritis is defined as joint stiffness and swelling and can present as mono-, oligo- or polyarthritis with frequent tenosynovitis. Initial evaluation should include joint count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), antinuclear antibodies (ANAs), analysis of synovial fluid whenever possible, X-rays and ultrasound (US) of affected joints. NSAIDs should be considered in patients with mild forms of arthritis and intra-articular CS should be used in cases of mono- or oligoarthritis. Most patients, however, will require systemic CSs, which should be initiated at a moderate dose of 10-20 mg prednisone. Some patients will require long-term, low- to moderate-dose CS to enable ICI treatment continuation. Early referral to a rheumatologist should be considered (grade ≥2 symptoms) before starting CSs, in cases of insufficient response to acceptable doses of CS and in cases requiring CS-sparing regimens. In these patients, csDMARDs should be considered such as methotrexate, hydroxychloroquine or sulfasalazine. For severe inflammatory arthritis or insufficient response to a csDMARD, IL-6R inhibitors (preferred) or TNF-α inhibitors may be considered. ICI treatment continuation should be evaluated on an individual basis.[70]

PMR presents as an acute, predominantly bilateral shoulder and/or hip pain with morning stiffness and possible swelling of the hands and knees.[71] Diagnostic evaluation should include ESR, CRP (which may be normal), RF, anti-CCP, creatine kinase (CK) level (to rule out myositis owing to a similar clinical presentation), X-rays and US of affected joints. Giant cell arteritis should be ruled out. Management of IR-PMR is based on prednisone 10-20 mg/day for grade ≥2

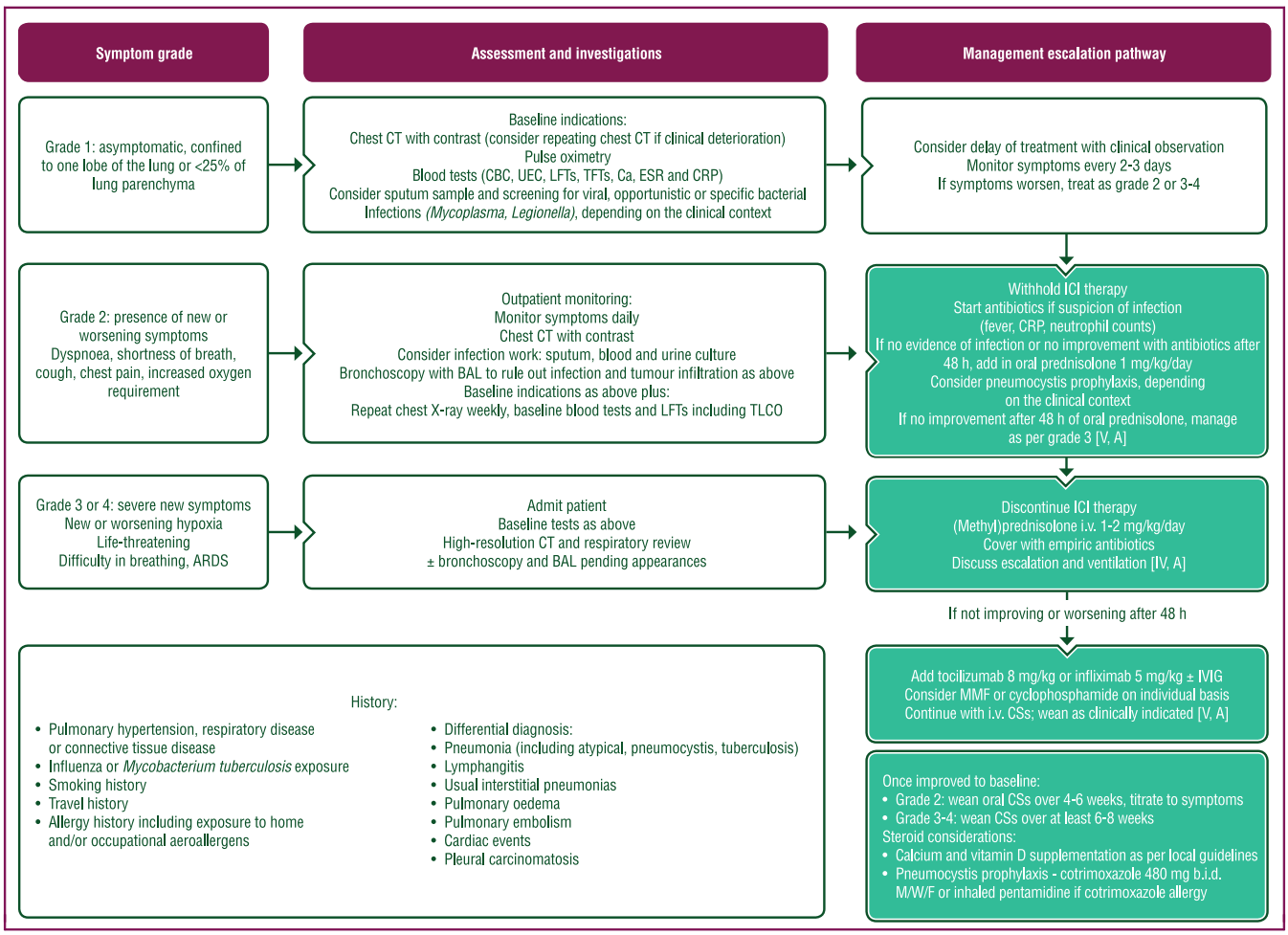

Figure 6. Management of IR-ILD.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; b.i.d., twice daily; Ca, calcium; CBC, complete blood count; CRP, C-reactive protein; CS, corticosteroid; CT, computed tomography; ESR, erythrocyte sedimentation rate; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; IR, immune-related; i.v., intravenous; IVIG, intravenous immunoglobulin; LFT, liver function test; MMF, mycophenolate mofetil; M/W/F, Monday, Wednesday and Friday; TLCO, transfer capacity of the lung for carbon monoxide; TFT, thyroid function test; UEC, urea and electrolytes.

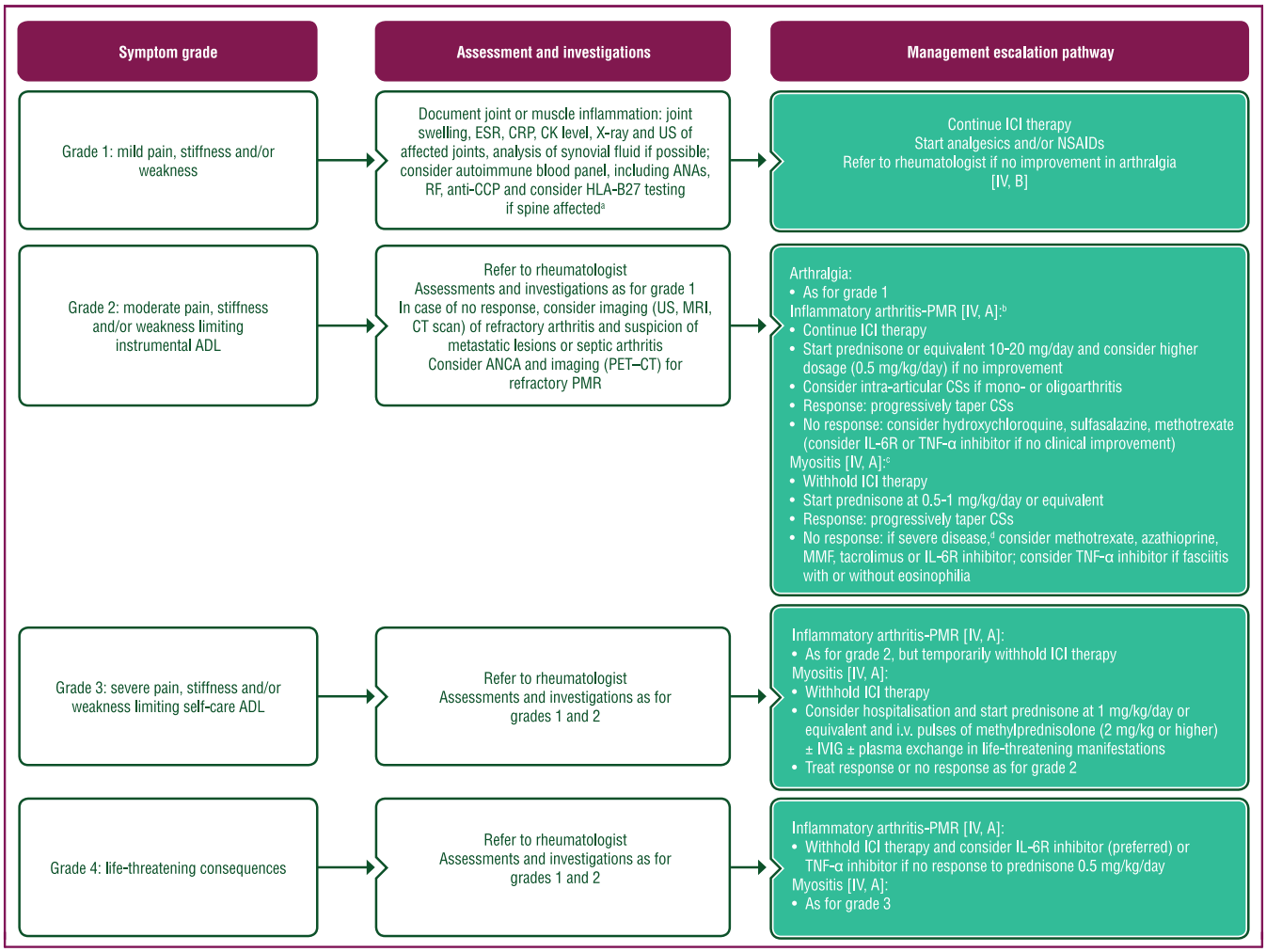

Figure 7. Management of IR-rheumatological toxicity.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

Ab, antibody; AChR, acetylcholine receptor; ADL, activities of daily living; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; AST, aspartate aminotransferase; CCP, cyclic citrullinated peptide; CK, creatine kinase; CRP, C-reactive protein; CS, corticosteroid; CT, computed tomography; EMG, electromyogram; ESR, erythrocyte sedimentation rate; HLA, human leukocyte; ICI, immune checkpoint inhibitor; IL-6R, interleukin 6 receptor; IR, immune-related; i.v., intravenous; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase; MG, myasthenia gravis; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PET, positron emission tomography; PMR, polymyalgia rheumatica; RF, rheumatoid factor; RS3PE, remitting seronegative symmetrical synovitis with pitting oedema; TNF, tumour necrosis factor; US, ultrasound.

[a]For myositis, search for life-threatening manifestations (bulbar symptoms, dyspnoea, myocarditis)[d] and carry out complete diagnostic work-up: CK, AST, ALT, LDH, ferritin, troponin I or T,[e] myositis-associated Abs, paraneoplastic Abs, MRI, EMG ± biopsy on an individual basis, anti-AChR Abs if myasthenia gravis. Rule out dermatomyositis if skin involvement.

[b]Inflammatory arthritis (either mono-, oligo- or polyarthritis, psoriatic arthritis, RS3PE syndrome) and polymyalgia rheumatica-like syndrome are the two major clinical presentations encountered.

[c]Increased CK level reported in most patients with myositis while usually within the normal range in patients presenting with myalgia.

[d]In case of associated MG or myocarditis, refer to specific section.

[e]High-sensitivity troponin T is expressed by skeletal muscle, including regenerating skeletal muscle tissue, whereas high-sensitivity troponin I is specific to the myocardium. In case of myositis, troponin T could be increased without myocardium involvement.

symptoms, progressively tapered when improvement is achieved. For CS-dependent or -refractory cases, referral to a rheumatologist is recommended and methotrexate or IL-6R inhibitors should be considered. For both IR-inflammatory arthritis and IR-PMR, holding ICI treatment in cases of grade $\geq$3 symptoms should be considered.

IR-sicca syndrome

IR-sicca syndrome includes mostly dry mouth and, less frequently, dry eyes and arthralgia; neurological manifestations are rare.[72,73] Importantly, dry mouth may be related to the use of other drugs (i.e. morphine), RT or infection (candidiasis). Patients with suspected IR-sicca syndrome should be tested for ANAs, anti-Sjögren-syndrome-related antigen A autoantibodies, anti-Sjögren syndrome type B antigen, RF and C3 and C4 complement; ideally, a minor salivary gland biopsy should be carried out. Symptomatic treatment, pilocarpine and hydroxychloroquine may be considered for any grade of IR-sicca syndrome. Systemic CSs are advocated only for extra-glandular manifestations or grade $\geq$3 symptoms.

Withdrawal of ICI should be discussed in cases of grade ≥3 symptoms.

IR-myositis

Myositis is a rare (1%) but potentially life-threatening irAE. For cases of IR-myositis, the median exposure to ICI therapy is 4 weeks. Clinical presentation includes myalgia with axial, limb-girdle, bulbar and oculomotor weakness.[74] The pathological mechanism of rhabdomyolysis leads to a CK increase, spontaneous activity in electromyography of the affected muscles and a myogenic recruitment pattern of muscle fibres. IR-myositis can be a fatal complication of ICIs due to both the involvement of bulbar muscle and secondary myocardial inflammation [see sections on overlapping syndromes and cardiovascular (CV) toxicities].[75] Diagnostic evaluation should include myositis-associated autoantibodies, MRI and electromyogram (EMG) ± biopsy. Fasciitis is frequently reported on MRI. Over 80% of patients with IR-myositis experience a favourable clinical outcome within several months after ICI discontinuation and immunomodulatory treatment.[76,77] For grade 2 symptoms, CSs represent the first therapeutic choice and should be initiated at 0.5-1 mg/kg/day prednisone. In the presence of bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and/or myocarditis, high-dose CS (pulses then 1-2 mg/kg) and additional treatment options such as IVIG and/or plasma exchange or selective separation may be necessary (40% of patients).[76,78] In patients with moderate symptoms (grade 2), improvement is often noted within days after ICI discontinuation.[74,76]

In refractory cases, IL-6R inhibitors may be considered,[79] as well as TNF-α inhibitors if there is associated fasciitis. ICI treatment withdrawal is necessary for grade ≥2 symptoms.

Other IR-systemic rheumatological conditions

All vessel-sized vasculitis, scleroderma-like reaction and lupus have been reported with ICI treatment, but they remain rare.[80] Referral to a rheumatologist or internist-immunologist is recommended for appropriate clinical, biological, immunological and imaging evaluations. Whenever possible, biopsy (i.e. skin, temporal artery) should be carried out since histology is a contributory factor in most cases. Management includes CSs, with dose and route of administration depending on the clinical entity and severity; additional immunomodulatory or immunosuppressive drugs may be considered, such as hydroxychloroquine, MMF, methotrexate, cyclophosphamide, rituximab or IVIG.

Recommendations

- Early referral to a rheumatologist should be considered (grade ≥2 symptoms) before starting CSs, in cases of insufficient response to acceptable doses of CSs and in cases requiring CS-sparing regimens [V, B].
- Initial evaluation of possible IR-inflammatory arthritis or IR-PMR should include joint count, analysis of synovial fluid whenever possible, ESR, CRP, RF, CCP, ANAs (for inflammatory arthritis), X-rays and US of affected joints [IV, A].
- CK level must be assessed in patients experiencing myalgia or PMR to rule out myositis. If elevated, myositis-associated autoantibodies, MRI and EMG ± biopsy should be considered [IV, A].
- Following a definitive diagnosis, symptomatic treatment (analgesics ± NSAIDs) should be initiated for arthralgia and myalgia [IV, B].
- In patients with mild forms of arthritis or with mono- or oligoarthritis, NSAIDs and/or intra-articular CSs should be considered [IV, B].
- Prednisone 10-20 mg/day should be initiated in grade ≥2 IR-inflammatory arthritis and IR-PMR, and then progressively tapered following improvement. A higher dosage (0.5 mg/kg) may be considered if no improvement, as well as csDMARDs (methotrexate, hydroxychloroquine or sulfasalazine) or bDMARDs [anti-IL-6R (preferred), TNF-α inhibitor] for severe or persistent symptoms. ICI treatment continuation should be evaluated on an individual basis [IV, A].
- Prednisone 0.5-1 mg/kg should be initiated in grade ≥2 IR-myositis. In the presence of life-threatening manifestations, high-dose CSs, IVIG and/or plasma exchange/selective separation should be considered; ICI withdrawal is always necessary [IV, A].
- Symptomatic treatment, pilocarpine and hydroxychloroquine may be considered for any grade of IR-sicca syndrome, after testing for specific autoantibodies and, if possible, minor salivary gland biopsy. Systemic CSs are advocated only in cases of extra-glandular manifestations or grade ≥3 symptoms [IV, B].

IR-NEUROLOGICAL TOXICITY

Incidence

The estimated incidence of neurological irAEs is ∼1%-5%.[81] The time to onset varies from 6 to 13 weeks. A range of neurological irAEs have been described, including irAEs involving the central nervous system (CNS; encephalitis and aseptic meningitis) and those involving the peripheral nervous system (acute immune demyelinating polyneuropathy, chronic immune demyelinating polyneuropathy, cranial nerve neuropathies, myasthenic syndromes and myositis). Neuromuscular disorders account for ∼50% of neurological irAEs, which primarily include myositis, myasthenia gravis (MG), demyelinating polyradiculoneuropathy and overlapping syndromes.[77] It is important to recognise IR-myositis and monitor for myocardial involvement, as well as bulbar involvement that may rapidly lead to cardiac or respiratory failure, persisting disability or even death. An algorithm for the management of IR-neuro(muscular) toxicity is shown in Figure 8.

IR-MG-like syndrome

IR-MG-like syndrome is an increasingly recognised and feared ICI-related complication. Typical symptoms include exercise-dependent fluctuating weakness of the proximal

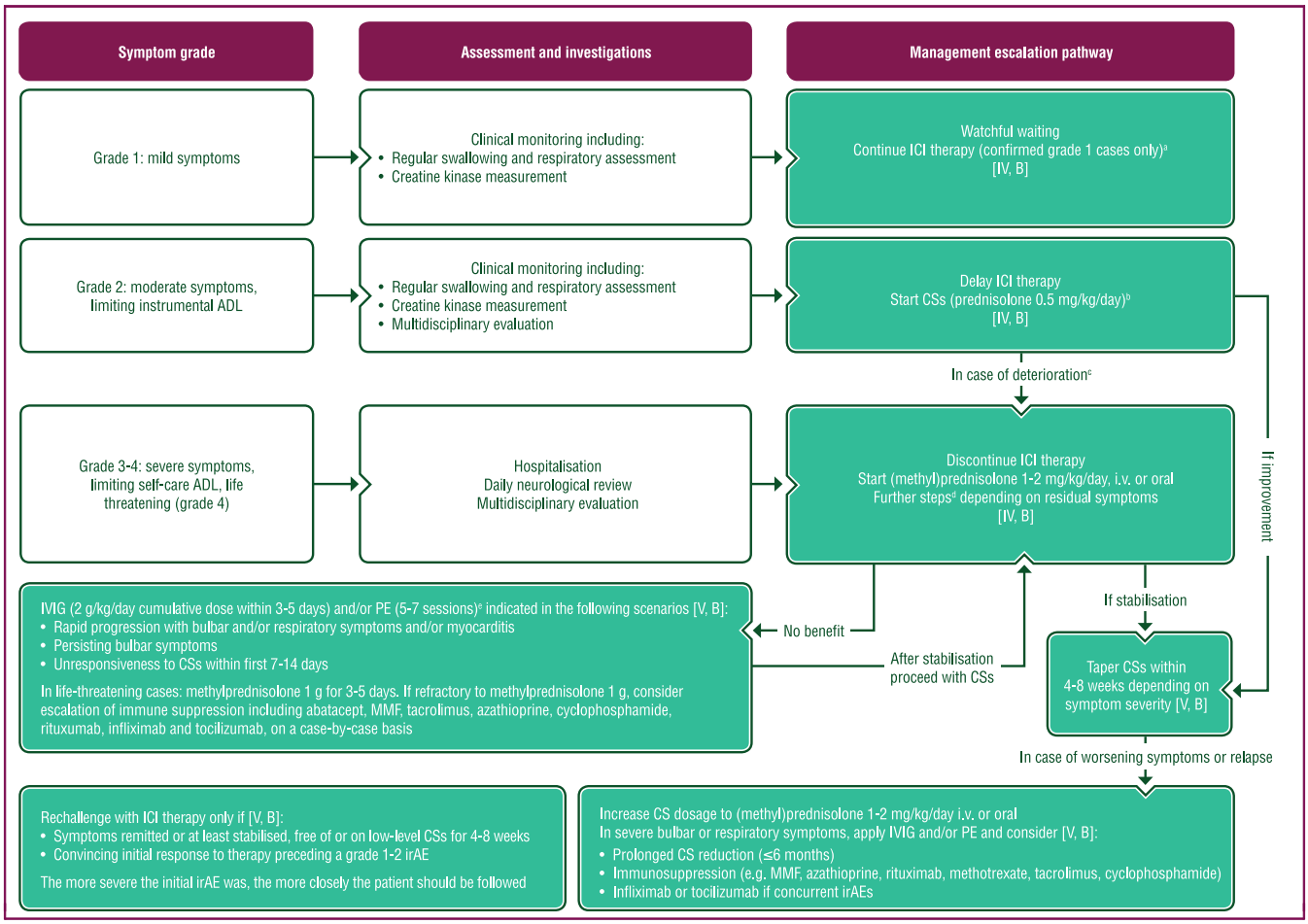

Figure 8. Management of IR-neuro(muscular) toxicity.[115]
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. ADL, activities of daily living; CS, corticosteroid; GBS, Guillain—Barré syndrome; ICI, immune checkpoint inhibitor; IR, immune-related; irAE, immune-related adverse event; i.v., intravenous; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; PE, plasma exchange.
[a]Patients presenting with any neurological symptoms should be referred to a neurologist and ICI should be held until the grade of symptoms is confirmed.
[b]In all scenarios, pyridostigmine starting from 3 × 30 mg orally up to 600 mg daily may be used in case of myasthenic symptoms; in i.v. application, 30 mg oral pyridostigmine corresponds to 1 mg i.v. or 0.75 mg neostigmine i.m. In case of intubation, pyridostigmine may be discontinued or withheld.
[c]Timely consultation of a neurologist.
[d]CSs are not usually recommended for idiopathic GBS; in mild ICI-related forms, however, a trial is reasonable (methylprednisolone 2-4 mg/kg/day) followed by slow CS taper. Pulse CS dosing (methylprednisolone 1 g/day for 5 days) may also be considered for grade 3-4 events along with IVIG or plasmapheresis.
[e]For life-threatening symptoms, PE might be the favourable option; consider contraindications: renal failure, hypercoagulable states, sepsis, haemodynamic instability.

extremities or bulbar muscle groups and ocular symptoms such as ptosis and diplopia. Generally, IR-MG-like syndrome occurs *de novo*[81] and two-thirds of patients are positive for anti-acetylcholine receptor antibodies. Early involvement of neurological expertise is mandatory. In addition to ICI discontinuation, CSs and pyridostigmine are the first-line management approach. Similar to IR-myositis, severe initial presentation, including respiratory and bulbar symptoms, often requires the immediate use of IVIG and/or plasma exchange or selective separation. Importantly, remission without long-term use of immunosuppression has been noted in only a few patients with mild symptoms limited to the ocular or facial muscles.[76]

Myasthenia—myositis—myocarditis overlap

As both myasthenia and myositis may involve weakness of ocular, facial and bulbar muscles as well as proximal tetraparesis, it is essential to recognise clinical signs for potential myositis and myocarditis (e.g. CK elevation, troponin T or I elevation, pain). See sections on IR-rheumatological and IR-CV toxicities.

IR-peripheral neuropathy

IR-neuropathies are mostly demyelinating and may present as an acute polyradiculoneuritis [IR-Guillain—Barré syndrome (GBS)] with an incidence of ∼0.2%-0.4%. Clinical findings resemble classical ascending GBS symptoms, including bilateral proximal weakness, ataxia, distal sensory, autonomic disturbances and cranial nerve involvement. Corresponding swelling of nerve roots impairs cerebrospinal fluid flow leading to cytoalbuminary dissociation. Anti-ganglioside antibodies are negative. Prompt recognition of symptoms is essential to prevent respiratory insufficiency due to affected cervical nerve roots. Unlike non-ICI-

associated GBS, CSs are associated with a favourable outcome in IR-GBS and are recommended as first-line treatment. IVIG is used as an additional or alternative treatment if CSs are not possible.

IR-central neurological toxicity

A proposed algorithm for the management of suspected IR-central neurological toxicity is shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2022.10.001. Details regarding the management of IR-meningitis and IR-encephalitis can be found in Section 7 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Recommendations

- Referral to a neurologist should be considered for mild (or more severe) symptoms of GBS, leukoencephalopathy, MG, myopathy and peripheral neuropathy. The type and frequency of assessments vary according to the grade of symptoms [IV, B].
- Patients presenting with any neurological symptoms should be referred to a neurologist and ICI should be held until the grade of symptoms is confirmed [IV, B].
- For grade 1 symptoms, ICI treatment can be continued and the patient monitored for deterioration [IV, B].
- For grade 2 symptoms, ICI treatment should be interrupted and oral or i.v. (methyl)prednisolone initiated [IV, B].
- For grade 3 or 4 symptoms, more intensive immune modulation may be required in addition to CSs or by exchanging CSs for IVIG (or plasma exchange or selective separation in cases of GBS, leukoencephalopathy, MG or IR-myopathy) [V, B].

IR-CARDIOVASCULAR TOXICITIES

There is a range of CV toxicities caused by ICI therapy, including IR-myocarditis, pericarditis, vasculitis, acute coronary syndrome (ACS), conduction disease (including complete heart block), atrial and ventricular arrhythmias, Takotsubo syndrome, non-inflammatory left ventricular dysfunction and heart failure (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.10.001).[82] IR-myocarditis, pericarditis, vasculitis and cardiac conduction disease usually present in the first four cycles of treatment, although a quarter of cases present after four cycles.[83] IR-non-inflammatory heart failure usually presents after $\geq$3 months of ICI treatment and most commonly after the first 6 months. IR-arrhythmias and ACSs can occur throughout treatment, and atrial tachycardias may be primary or secondary to acute thyrotoxicosis, acute systemic inflammatory syndromes or other irAEs associated with significant electrolyte imbalance. Severe IR-myocarditis occurs in $<$1% of cases, but with increased utilisation of troponin measurement (including high-sensitivity cardiac troponin assays) and cardiac imaging, CV complications can occur in $\leq$5% of patients receiving ICIs.[84] The long-term effects of ICI treatment on CV disease are unknown. A recent study suggests ICI therapy may accelerate atherosclerosis, leading to an increased incidence of ACS in cancer survivors following ICI therapy.[85]

The diagnosis of IR-myocarditis depends on a combination of clinical, electrocardiographic, cardiac biomarker and CV imaging [echocardiogram and cardiac MRI (CMR)] assessments. CMR, including T1 and T2 mapping, T2-weighted short tau inversion recovery (T2STIR) and late gadolinium enhancement (LGE), is recommended given the high sensitivity of T1 and T2 mapping for a diagnosis of IR-myocarditis.[86] Both major and minor diagnostic criteria have been proposed in a recent consensus paper from the International Cardio-Oncology Society,[87] where the diagnosis requires one major or two minor criteria (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.10.001). Once the diagnosis is confirmed, IR-myocarditis can also be divided into categories according to the severity of clinical presentation, response to treatment and degree of recovery (Supplementary Tables S6 and S7, available at https://doi.org/10.1016/j.annonc.2022.10.001).[87] Half of confirmed cases of IR-myocarditis have a normal left ventricular ejection fraction at presentation,[83] and a reduction in global longitudinal strain on echocardiography can predict a worse clinical outcome.[88]

If IR-myocarditis is suspected, but either serum troponin levels or left ventricular function on echocardiography is normal, then CMR is recommended. If CMR is not available, contraindicated or non-diagnostic, then cardiac positron emission tomography (PET)—CT (or PET—MRI, if available) is recommended to evaluate for myocardial inflammation using either [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG)—PET—CT or preferentially Gallium-68-DOTA(0)-Phe(1)-Tyr(3)-octreotide (^{68}Ga-DOTATOC)—PET—CT.[89] In cases where the diagnosis remains uncertain, endomyocardial biopsy should be considered to confirm or refute the diagnosis before restarting ICI treatment.

Treatment of IR-CV toxicities is summarised in Supplementary Table S8 and Section 8 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001, and a proposed algorithm for the management of IR-myocarditis is shown in Figure 9.

Recommendations

- Suspected cases of IR-myocarditis should be admitted to level 2 or 3 care with electrocardiogram monitoring and resuscitation facilities [V, A].
- Other causes of troponin elevation should be ruled out, including ACS if appropriate (patients with CV risk factors or established coronary artery disease) [V, A].
- ICI therapy should be interrupted and, in most cases, if IR-myocarditis is confirmed, permanently discontinued [V, A].
- A diagnostic CMR with inflammatory sequences (T2STIR, T1, LGE) and cardiac troponin are recommended in cases of suspected IR-myocarditis or pericarditis [IV, A].
- If ^{68}Ga-DOTATOC—PET—CT is not available, endomyocardial biopsy should be considered to confirm or refute the

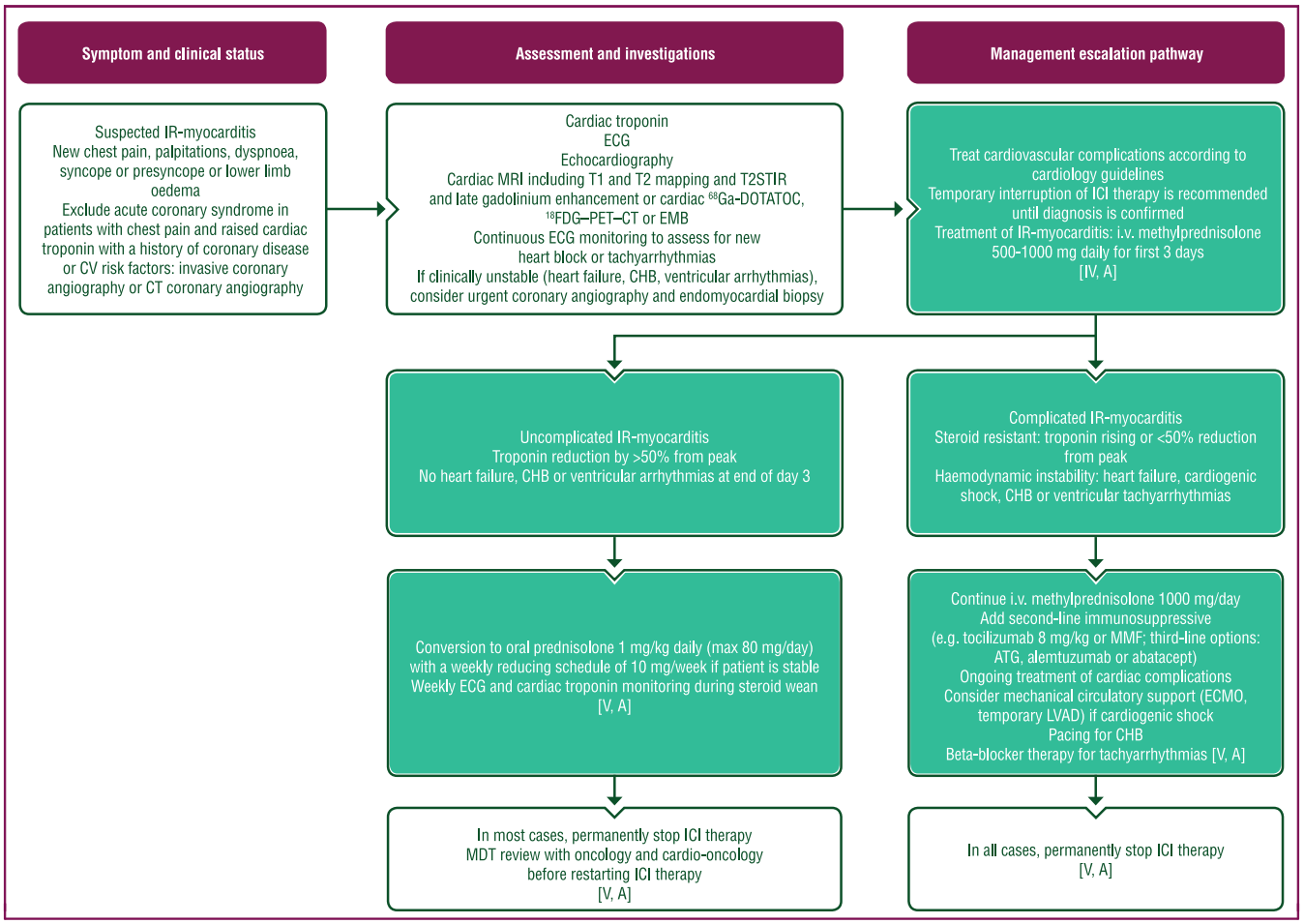

Figure 9. Management of IR-myocarditis.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
^{18}FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; ^{68}Ga-DOTATOC, Gallium-68-DOTA(0)-Phe(1)-Tyr(3)-octreotide; ATG, anti-thymocyte globulin; CHB, complete heart block; CT, computed tomography; CV, cardiovascular; ECG, electrocardiogram; ECMO extracorporeal membrane oxygenation; EMB, endomyocardial biopsy; ICI, immune checkpoint inhibitor; IR, immune-related; i.v., intravenous; LVAD, left ventricular assist device; MDT, multidisciplinary team; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; PET, positron emission tomography; T2STIR, T2-weighted short tau inversion recovery.

diagnosis in suspected cases where CMR and troponin are not diagnostic before restarting ICI [V, A].

- i.v. methylprednisone 500-1000 mg should be initiated daily for 3 days and then reviewed in confirmed cases of IR-myocarditis [V, A].
- If troponin has fallen to <50% of peak level or to normal after 3 days of i.v. methylprednisolone and the patient is clinically stable (no heart failure, ventricular arrhythmias, complete heart block) then conversion to oral prednisolone 1 mg/kg/day (up to a maximum of 80 mg/day) is recommended, reducing by 10 mg/week with troponin monitoring providing CV stability continues [V, A].
- Heart failure or cardiogenic shock should be treated according to the European Society of Cardiology heart failure guidelines [III, A].[90]
- An MDT discussion is recommended before restarting ICI treatment in patients with mild, clinically uncomplicated IR-myocarditis [V, A].
- Treatment of uncomplicated IR-pericarditis with oral prednisolone and colchicine (500 µg twice daily) is recommended [IV, A].
- Treatment of IR-pericarditis complicated by moderate or large pericardial effusion with i.v. methylprednisone 500-1000 mg and colchicine (500 µg twice daily) and temporary interruption of ICI are recommended. Large pericardial effusions with or without tamponade physiology require urgent percutaneous pericardiocentesis [V, A].

IR-RENAL TOXICITY

Incidence

The incidence of IR-renal dysfunction is 2%-7% and is most prevalent in patients who receive anti-PD(L)1—anti-CTLA-4 combination therapy (5%).[91-94] Four different pathologies have been noted on renal biopsy. The most common is acute interstitial nephritis (AIN), observed in 80%-90% of patients in studies where renal biopsy was evaluated.[95,96] In patients with kidney cancer, development of AIN appears to be a good prognostic factor, possibly due to recognition of a shared antigen by activated T cells.[97] According to data from a single study (N = 63), findings consistent with

glomerular disease are noted in 8%,[95] with reported diagnoses including minimal-change disease, membranous nephropathy, lupus nephritis, pauci-immune glomerulonephritis, IgA nephropathy, complement-related and focal segmental glomerulosclerosis.[98,99] Both glomerular disease and AIN may be present on biopsy.[98] Acute tubular injury was reported in 29% in the same small study,[95] often in combination with other pathologies. Tubular damage is less common but may present with acid or base or electrolyte disturbance without evidence of change in kidney function.[99] Risk factors for acute tubulointerstitial nephritis include concomitant PPI and NSAID use during ICI therapy.[99] Pre-existing chronic kidney disease does not predispose to IR-renal dysfunction.[99] Median onset of IR-renal dysfunction is 3-4 months,[94] and most patients will have a concurrent extra-renal irAE.[91,100]

Diagnosis and management

Acute kidney injury (AKI) secondary to hypovolaemia, medication, obstruction and i.v. contrast should all be excluded. There are no consistent features of IR-AIN that differentiate its presentation from other causes of kidney injury.[91,94] Most studies of IR-renal dysfunction in the literature base their management recommendations on the Kidney Disease: Improving Global Outcomes criteria,[101] which incorporates three stages of progressive dysfunction based on creatinine values or reduced urine output; this differs from the CTCAE version 5.0's 'Acute kidney injury' and 'Creatinine increased' criteria[1] (Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2022.10.001). An algorithm for the management of IR-renal toxicity is shown in Figure 10; further information regarding the management of IR-renal toxicity is provided in Section 9 of the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2022.10.001.

Recommendations

- In cases of suspected IR-nephritis [V, B]:
  - Other causes of renal failure should be ruled out.
  - ICI therapy should be interrupted or permanently discontinued depending on the severity of the renal insufficiency.
  - Other nephrotoxic drugs should be stopped.
  - (Methyl)prednisone 1 mg/kg should be started, or pulse methylprednisolone should be considered in stage 3 AKI.
  - Renal biopsy should be considered on a case-by-case basis to confirm the diagnosis.

IR-OCULAR TOXICITY

IR-ocular toxicity is rare (<1%)[102] but can threaten vision if not diagnosed and treated promptly. Time to onset is variable but can be soon after initiating ICI therapy. Clinical presentation includes dry, itchy or watery eyes, pain and changes in vision, such as blurry or double vision. Initial assessment should rule out other causes of ocular symptoms such as foreign bodies, CNS metastasis, infection and vascular pathologies. Early involvement of an ophthalmologist is necessary for both diagnosis and treatment.[102,103]

IR-ocular toxicity can manifest in multiple ways, including ocular surface disease (conjunctivitis, keratitis), intraocular inflammation (uveitis) and orbital myopathy (orbital myositis).[103,104] Notably, dry eyes can be a manifestation of a systemic Sjögren-like syndrome and orbital myopathies may present as part of a more generalised muscular or neuromuscular toxicity syndrome such as myositis, myocarditis, MG and GBS.

Treatment of IR-ocular toxicity depends on the severity; mild cases of uveitis, for example, often respond to local therapies such as topical CSs.[102] In such cases, the administration of systemic CSs may be avoided and continuation of ICI therapy may be feasible, taking into account individual benefit—risk considerations. In cases of more severe IR-ocular toxicities, particularly orbital myopathies, ICI therapy should be discontinued and systemic CSs administered,[102] with second-line immunosuppressants used, if necessary, in the CS-refractory setting. Subsequent continuation or rechallenge with ICI therapy should be considered cautiously, again considering individual benefit—risk considerations.

Recommendation

- For cases of suspected IR-ocular toxicity, prompt involvement of an ophthalmologist is recommended for both the diagnosis and treatment [IV, B].

IR-HAEMATOLOGICAL TOXICITY

IR-major haematological toxicity is relatively rare (<5%)[105-107] but can be associated with significant mortality. IR-haematological toxicity has been reported after both anti-CTLA-4 and anti-PD-(L)1 agents given as monotherapy and anti-PD(L)1—anti-CTLA-4 combination therapy.[106] Among patients who experience significant haematological toxicity, >90% of those treated with anti-PD(L)1—anti-CTLA-4 combination therapy experience grade ≥3 toxicity compared with ∼70% for those treated with monotherapy. The median time to onset of IR-haematological toxicity with anti-PD(L)1—anti-CTLA-4 combination therapy has been reported as shorter than with monotherapy (∼12 versus ∼25 weeks, respectively). Nevertheless, time to onset is variable. Clear predisposing risk factors have not been reported; most reports to date, however, are from patients with metastatic solid tumours. In patients with underlying haematological disorders such as chronic lymphocytic leukaemia treated with ICIs, a higher rate of haemolytic anaemia has been observed.[108]

IR-haematological toxicity can be severe or even fatal and presents in various ways such as anaemia [including aplastic and autoimmune haemolytic anaemias (AIHAs)], leukopenia, lymphopenia, neutropenia, thrombocytopenia, pancytopenia, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, hemophagocytic lymphohistiocytosis (HLH) and clotting disorders, including acquired haemophilia. In contrast to primary AIHA, a unique aspect

of IR-AIHA is a high incidence of direct antiglobulin test (or the Coombs test) negativity of ~40%.[109]

Early consultation with a haematologist is advised for both diagnosis and management. A relatively low threshold for bone marrow examination should be considered, particularly to rule out other causes of pancytopenia, such as marrow infiltration, secondary myelodysplastic syndrome or aplastic anaemia. Treatment of IR-haematological toxicity is dependent on severity but includes symptomatic management, such as blood transfusion, growth factor support and systemic CSs. In one series, ~70% of IR-haematological toxicities responded to CSs,[106] with second-line immunosuppressants, such as IVIG, rituximab, MMF and cyclosporine, used in refractory cases. Recently, IVIG- and CS-refractory IR-thrombocytopaenia was effectively treated with eltrombopag, an oral thrombopoietin receptor agonist (TPO-RA).[110]

ICI therapy should be discontinued while significant IR-haematological toxicity is investigated and treated. Subsequent continuation of ICI therapy should consider the benefits and risks, noting that 20% of affected patients may have evidence of persistently abnormal blood counts,[106] and continued therapy or rechallenge may carry a significant risk of exacerbating symptoms.

Recommendations

- In cases of suspected IR-haematological toxicity, early involvement of a haematologist is recommended, and ICI

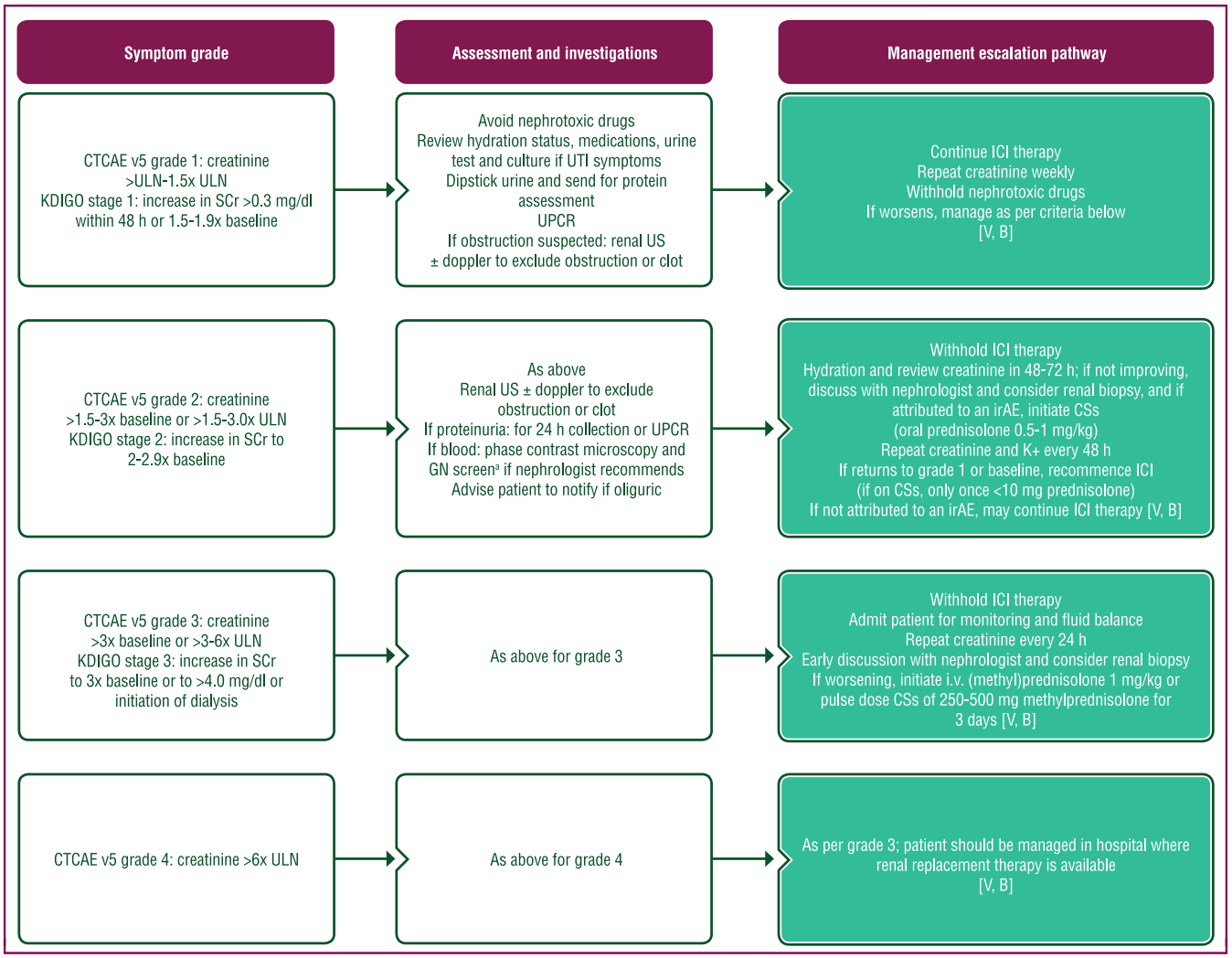

Figure 10. Management of IR-renal toxicity.
Renal injury occurs in ~1%-4% of patients treated with ICIs, usually in a pattern of ATIN with a lymphocytic infiltrate. Attention should be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN. Confounding diagnoses include dehydration, recent i.v. contrast, UTI, medications, hypotension or hypertension. Early consideration of renal biopsy is helpful, as this may negate the need for steroids and determine whether renal deterioration is related to another pathology. Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy. CS wean: begin to wean once creatinine grade 1; grade 2 severity episode, wean CS over 4 weeks; grade 3-4 episode, wean over 4-12 weeks. If on CSs for >4 weeks, initiate PJP prophylaxis, calcium and vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ATIN, acute tubulointerstitial nephritis; CS, corticosteroid; CTCAE, Common Terminology Criteria for Adverse Events; GBM; glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; ICI, immune checkpoint inhibitor; IR, immune-related; irAE, immune-related adverse event; i.v., intravenous; K, potassium; KDIGO, Kidney Disease: Improving Global Outcomes; PJP, *Pneumocystis jiroveci* pneumonia; SCr, serum creatinine; ULN, upper limit of normal; UPCR, urine protein to creatinine ratio; US, ultrasound; UTI, urinary tract infection; v, version.
[a]ANA, complement C3 and C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis.

therapy should be withheld. There should be a low threshold for obtaining a bone marrow aspirate and trephine to assist in the diagnosis [IV, B].
- Blood product and growth factor support in addition to i.v. (methyl)prednisolone 1 mg/kg should be initiated as first-line treatment [V, B].
- Anti-IL-6R therapy may be used for IR-HLH.[111]
- Eltrombopag or other oral TPO-RAs could be considered for IVIG- and CS-refractory IR-thrombocytopaenia, in agreement with a consultant haematologist [V, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S10, available at https://doi.org/10.1016/j.annonc.2022.10.001.[112,113] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/supportive-and-palliative-care/toxicities-from-immunotherapy.

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