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INVITED REVIEW ARTICLE

Optimal management of immune-related adverse events resulting from treatment with immune checkpoint inhibitors: a review and update

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Abstract
Over the last two decades, molecular-targeted agents have become mainstream treatment for many types of malignancies and have improved the overall survival of patients. However, most patients eventually develop resistance to these targeted therapies. Recently, immunotherapies such as immune checkpoint inhibitors have revolutionized the treatment paradigm for many types of malignancies. Immune checkpoint inhibitors have been approved for treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck squamous cell carcinoma, Hodgkin's lymphoma, bladder cancer and gastric cancer. However, oncologists have been faced with immune-related adverse events caused by immune checkpoint inhibitors; these are generally mild but can be fatal in some cases. Because immune checkpoint inhibitors have distinct toxicity profiles from those of chemotherapy or targeted therapy, many oncologists are not familiar with the principles for optimal management of immune-related adverse events, which require early recognition and appropriate treatment without delay. To achieve this, oncologists must educate patients and health-care workers, develop checklists of appropriate tests for immune-related adverse events and collaborate closely with organ specialists. Clinical questions that remain include whether immune checkpoint inhibitors should be administered to patients with autoimmune disease and whether patients for whom immune-related adverse events lead to delays in immunotherapy should be retreated. In addition, the predicted use of combination immunotherapies in the near future means that oncologists will face a higher incidence and severity of immune-related adverse events. This review provides an overview of the optimal management of immune-related adverse events attributed to immune checkpoint inhibitors.

Keywords Immune-related adverse events · Immune checkpoint inhibitor · Organ specialists · Corticosteroid · Immunomodulatory/immunosuppressive agents

Introduction

Over several decades, surgery, radiotherapy and chemotherapy including cytotoxic agents and targeted therapies have improved the outcomes for patients with cancer. However, despite these advances in cancer treatment, the improvement in outcomes has been disappointing. Recently, immunotherapy has emerged as a new method of overcoming cancer [1]. Immune checkpoint inhibitors (ICPIs), which block cytotoxic T lymphocyte antigen 4 (CTLA-4) (ipilimumab) or the programmed death protein 1 (PD-1)/PD-1 ligand 1 (PD-L1) axis (nivolumab, pembrolizumab, atezolizumab and durvalumab) and thereby reactivate T cell activity against cancer cells, are a major oncological breakthrough. Impressive long-lasting responses (as the result of antitumor immune memory) and significant benefits in clinical outcomes have been reported for many types of cancer, including melanoma [2–4], non-small cell lung cancer (NSCLC) [5–9], renal cell carcinoma (RCC) [10], Hodgkin's lymphoma [11], bladder cancer [12, 13], head and neck squamous cell carcinoma (HNSCC) [14] and gastric cancer (GC) [15]. Additional immunotherapies, such as inhibitors of indoleamine 2,3-dioxygenase 1 (IDO1) and lymphocyte activation gene 3 (LAG3), are undergoing clinical investigation.

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Despite the effective antitumor immune response induced by these inhibitors, they block the negative regulators of immunity that are normally important for balancing the immune system, meaning that treatment can be associated with distinctive inflammatory adverse effects known as immune-related adverse events (irAEs), which can potentially involve every organ system. These side effects are generally manageable but can be fatal in some cases [2–15]. Because irAEs have toxicity profiles that differ from those of chemotherapy or targeted therapy, many oncologists are not familiar with the clinical management of irAEs. Both medical oncologists and doctors in other specialties such as internal medicine, general practice and emergency medicine should be aware of the possibility of irAEs to allow for early diagnosis and treatment. Therefore, it is important to educate health-care providers on the safe and appropriate use of these important new treatments and to develop specific treatment algorithms for mitigating these autoimmune toxicities.

This article provides a general overview of the safety profile of ICPIs, followed by a suggested approach to management of the principal irAEs.

General safety profile associated with ICPIs

Immune toxicity spectrum

The spectrum and mechanism of irAEs are autoimmune in nature and distinct from those of other cancer therapies [16]. It has been reported that irAEs can involve the skin (rash, vitiligo, psoriasis, toxic epidermal necrolysis, drug-induced hypersensitivity syndrome) [17, 18], the gastrointestinal tract (colitis, gastritis, pancreatitis, celiac disease) [19–21], the endocrine systems (dysthyroidism, hypophysitis, adrenal insufficiency, diabetes) [22–24], the lungs (pneumonitis, pleural effusion, sarcoidosis) [25, 26], the nervous system (peripheral neuropathy, aseptic meningitis, Guillain–Barré syndrome, encephalopathy, myelitis, meningoradiculoneuritis, myasthenia) [27–29], the liver (hepatitis) [30, 31], the kidney (granulomatous interstitial nephritis, lupus-like glomerulonephritis) [32–34], hematological cells (hemolytic anemia, thrombocytopenia, neutropenia, pancytopenia) [35–37], the musculoskeletal system (arthritis, myopathies) [38, 39], the heart (pericarditis, cardiomyopathy) [40, 41] or the eyes (uveitis, conjunctivitis, blepharitis, retinitis, choroiditis, orbital myositis) [32, 42]. In a pooled analysis of patients treated with nivolumab, 54% of whom had prior treatment with ipilimumab, the median time of onset of skin irAEs was at 5 weeks, gastrointestinal irAEs at 7.3 weeks, hepatic irAEs at 7.7 weeks, pulmonary irAEs at 8.9 weeks, endocrine irAEs at 10.4 weeks and renal irAEs at 15.1 weeks [43]. However, clinicians should be mindful that all these toxicities can develop at any time because the confidence intervals for different organs can vary widely; e.g., 0.1–57 weeks for skin and 0.1–37.6 weeks for the gastrointestinal tract [43].

Severity

Although most irAEs remain mild, in contrast to adverse events caused by cytotoxic agents or targeted therapies, life-threatening, grade 3/4 immune toxicities are sometimes seen during treatment with ICPIs. In terms of the type of ICPI, PD-1/PD-L1 axis inhibitors such as nivolumab, pembrolizumab, atezolizumab and durvalumab have a lower incidence of irAEs than CTLA-4 inhibitors such as ipilimumab, whereas the combination of a PD-1 inhibitor and a CTLA-4 inhibitor has a much higher rate of irAEs (Grade 3/4, approximately 30–50%) than either monotherapy (approximately 10–20%) [2–15]. The incidence and details of irAEs attributed to ICPIs in clinical trials of their effect in many kinds of malignancy are shown in Table 1. Recently, it was reported that PD-1 inhibitors had a significantly higher incidence of any grade of pneumonitis than PD-L1 inhibitors [44, 45]. In a systematic review involving 5744 patients with NSCLC, including 3284 patients treated with PD-1 inhibitor and 2460 patients treated with PD-L1 inhibitor, Pillai et al. reported that compared with patients who received PD-L1 inhibitors, patients treated with PD-1 inhibitors had a slightly higher rate of irAEs [16% (95% confidence limit (CI), 14–17%) vs. 11% (95% CI, 10–13%); $p = 0.07$] and pneumonitis [4% (95% CI, 3–5%) vs. 2% (95% CI, 1–3%); $p = 0.01$] [45].

Features of irAEs

There are three important features of irAEs. First, irAEs are "simultaneous and heterochronous", which means that several kinds of irAE can occur in a patient at the same time or can emerge one after another at different intervals. Second, irAEs are "persistent", which means that they can occur even after cessation of treatment with ICPIs. For example, with ipilimumab, irAEs have been reported to occur up to 2 years after the initial treatment [2, 46]. Third, there is a possible association between irAEs attributed to ICPIs and the clinical benefits of this treatment. In one trial, in which 56 patients with stage IV melanoma were treated with ipilimumab and a peptide vaccine, 36% of patients with a grade 3 or 4 irAE achieved a clinical response, whereas only 5% of patients without an irAE responded [47]. In a retrospective analysis of patients with advanced melanoma who were treated with nivolumab, a significant difference in overall survival was observed between patients who experienced irAEs of any grade versus those who did not [48]. In addition, patients who had a grade ≥ 3 irAE derived greater benefits in terms of overall survival [48].

Table 1 Frequency of immune-related adverse events caused by immune checkpoint inhibitors (%)

Drug	Type of cancer	Sequence	CTCAE grade	Any adverse events	Pruritus	Rash	Diarrhea	Colitis	Elevated AST	Elevated ALT	Hypothyroidism	Hypophysitis	Pneumonitis
Nivolumab [4]	Melanoma	1st line	Any grade	82.1	18.8	25.9	19.2	1.3	3.8	3.8	8.6	0.0	1.3
			Grade 3/4	16.3	0.0	0.6	2.2	0.6	1.0	1.3	0.0	0.0	0.3
Ipilimumab [4]			Any grade	86.2	35.4	32.8	33.1	11.6	3.5	3.9	4.2	0.0	1.6
			Grade 3/4	27.3	0.3	1.9	6.1	8.7	0.6	1.6	0.0	0.0	0.3
Ipilimumab/ Nivolumab [4]			Any grade	95.5	33.2	40.3	44.1	11.8	15.3	17.6	15.0	0.3	6.4
			Grade 3/4	55.0	1.9	4.8	9.3	7.7	6.1	8.3	0.3	0.0	1.0
Nivolumab [7]	NSCLC	1st line	Any grade	71.2	8.2	9.7	13.9	NR	8.6	7.1	6.4	NR	2.6
			Grade 3/4	17.6	0.0	0.7	1.1	NR	2.6	2.6	0.0	NR	1.5
Pembrolizumab [8]			Any grade	73.4	7.8	7.1	14.3	1.9	5.2	6.5	9.1	0.6	5.8
			Grade 3/4	26.6	0.0	0.6	3.9	1.3	1.3	0.0	0.0	0.6	2.6
Atezolizumab [9]		2nd line	Any grade	64.0	NR	NR	15.4	0.3	NR	NR	3.9	< 1%	1.5
			Grade 3/4	14.8	NR	NR	0.7	0	NR	NR	NR	NR	0.7
Nivolumab [10]	RCC	2nd or 3rd line	Any grade	79.0	14.0	10.0	12.0	1.7	3.9	4.7	5.9	0.5	4.0
			Grade 3/4	19.0	0.0	0.5	1.0	0.7	1.7	1.5	0.2	0.2	1.0
Nivolumab [14]	HNSCC	≥ 2nd line	Any grade	58.9	7.2	7.6	6.8	0.0	0.8	0.8	3.8	0.4	2.1
			Grade 3/4	13.1	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.4	0.8
Nivolumab [11]	Hodgkin's lymphoma	≥ 4th line	Any grade	88.8	10.0	16.3	10.0	0.8	5.0	3.8	5.8	NR	2.6
			Grade 3/4	25.0	0.0	1.3	0.0	0.4	2.5	2.5	0.0	NR	1.3
Atezolizumab [12]	Urothelial carcinoma	≥ 2nd line	Any grade	69.4	10.0	7.4	7.7	1.0	3.2	4.0	6.0	NR	2.3
			Grade 3/4	16.1	0.0	0.0	0.0	1.0	1.0	3.0	0.0	NR	1.0
Pembrolizumab [13]		2nd line	Any grade	60.9	19.5	10.9	9.0	2.3	5.3	5.3	6.4	0.0	4.1
			Grade 3/4	15.0	0.0	0.4	1.1	1.1	2.3	1.1	0.0	0.0	2.3
Nivolumab [15]	Gastric cancer	≥ 3rd line	Any grade	42.7	9.1	5.8	7.0	1.0	3.3	2.1	3.0	0.0	0.0
			Grade 3/4	10.3	0.0	0.0	1.0	0.0	1.0	0.0	0.0	0.0	0.0

CTCAE common terminology criteria for adverse events, *AST* aspartate transaminase, *ALT* alanine transaminase, *NSCLC* non-small cell lung cancer, RCC *renal* cell carcinoma, *HNSCC* head and neck squamous cell carcinoma

Optimal management of irAEs in clinical practice

The optimal management of irAEs is based on clinical experience because no prospective trials have been performed to evaluate the best treatment strategy for irAEs. There is evidence that early intervention for irAEs reduces both their severity and duration [2]. Therefore, the general principles for the optimal management of irAEs mainly consist of early recognition and judicious use of immunosuppressive agents. To achieve both of these aims requires implementation of several important elements of clinical practice, including education of patients and health-care professionals, the development of checklists of laboratory tests to detect signs of irAEs, close collaboration with organ specialists and the inclusion of irAEs in differential diagnoses [49].

Education

Patient education is vital for early recognition and successful management of irAEs. Patients should be educated using patient-specific educational materials about the symptoms and signs of irAEs, precautions to be taken in daily life and they should have a hotline available for consultation in an emergency. In addition, patients must also be informed that irAEs may occur at any time: at the beginning of immunotherapy, during immunotherapy and after immunotherapy. Such education prompts patients to contact their primary physicians immediately when they have any new symptoms related to irAEs.

For health-care workers, education about irAEs is also crucial. An essential first step in managing irAEs is awareness of the symptom profile of irAEs, which requires education of all members of the multidisciplinary team. To avoid delays in the diagnosis and treatment of irAEs, not only the medical oncologist or primary responsible physician but also other potentially involved clinicians, such as general practitioners or physicians in internal medicine or emergency medicine, should be aware of the profile of irAEs.

Oncologists are also less familiar with irAEs than with the adverse events associated with other treatments, which may lead to a risk of misdiagnosis. Therefore, when treating patients with ICPIs, it is important to remain open-minded to the possibility of irAEs, both rare and common, and develop a careful approach to their assessment.

Checklists of laboratory tests and symptoms for irAEs

Physical examination, laboratory tests and imaging performed at baseline before starting immunotherapy provide a useful reference for any new symptoms occurring during immunotherapy.

We have defined an “Immunotherapy Baseline Checklist”, which every doctor in our hospital uses. In addition, oncologists should check chest X-rays and the results of routine laboratory tests, including complete blood count, renal function, liver function, creatine phosphokinase, serum electrolytes, glycemia, C-reactive protein and coagulation before each administration of immunotherapy (every 2 or 3 weeks). It is also advisable that thyroid function (thyroid stimulating hormone and free T4), diabetes markers (glycated hemoglobin or glycoalbumin) and proteinuria are evaluated every month. Table 2 outlines our recommendations for a panel of routine laboratory tests required prior to the start of immunotherapy and prior to each administration (every 2 or 3 weeks) of ICPIs. We underline essential items of baseline checklist in Table 2.

In particular, to allow early recognition of one important irAE, fulminant type 1 diabetes mellitus, patients treated with ICPIs in our hospital are requested to check their urine sugar twice per week in the morning using a urine test kit at home as part of their self-management. The method for checking urine sugar levels is simple and involves dipping the test strip in the collected urine sample and comparing the color of the test strip with the color chart to estimate the sugar level.

Patients’ test results should always be compared with baseline values to detect any gradual change in these values over time. Patients should also be closely monitored because an irAE may occur at any time: at the beginning, during or after the end of immunotherapy. Therefore, oncologists should be vigilant for the occurrence or worsening of any symptoms that may be related to irAEs. In cases of suspected irAEs occurring during or following treatment with ICPIs, additional diagnostic testing should be considered on an individual basis, taking into account the type of event and its severity. In our hospital, we have developed an “Examination Checklist for irAEs” (Table 3). These checklist examinations are performed prior to referral of the patient to an organ specialist, who may order additional examinations. When oncologists are faced with irAEs during treatment with ICPIs, they can immediately follow through the “Examination Checklists for irAEs” and then consult closely with the relevant organ specialist or internist.

Table 2 Immunotherapy baseline checklist

1. Examination before starting immunotherapy
Blood examination
Complete CBC
Serum electrolytes: Na, K, Cl, Ca
CRP, CK, total protein, albumin
Liver function: total bilirubin, AST, ALT, ALP, γ-GTP, LDH
Renal function: creatinine with estimated GFR, blood urea nitrogen
Pancreas function: amylase
Cardiac function: BNP
Diabetes: blood glucose, HbA1c, glycoalbumin, C-peptide, anti-GAD antibody
KL-6, SP-D
Endocrinological tests: ACTH, cortisol, TSH, T3, T4
Immunoglobulin: IgG, IgA, IgM
Virology: HBs-Ag, HBs-Ab, HBc-Ab, HCV-Ab
Autoimmune tests: ANA, RF
Coagulation tests: PT, APTT, D-dimer
Urine examination
Urinary qualitative/semiqualitative examination, urinary sediment, urinary sugar, proteinuria
Urinary N-acetylglucosamine, urinary creatinine, urea nitrogen, urinary β2-microglobulin
Imaging
Chest X-ray
CT scan before starting immunotherapy
Plasma biobanking
2. Routine laboratory tests before each administration
Blood examination
Complete CBC
Serum electrolytes: Na, K, Cl, Ca
CRP, CK, total protein, albumin
Liver function: total bilirubin, AST, ALT, ALP, γ-GTP, LDH
Renal function: creatinine with estimated GFR, BUN
Diabetes tests: blood glucose, HbA1c[a], glycoalbumin[a]
Triglyceride, total cholesterol
Endocrinological tests: cortisol[a], TSH[a], T4[a]
Coagulation tests: PT[a], APTT[a], D-dimer[a]
Urine examination
Urinary qualitative/semiqualitative examination, urinary sediment
Proteinuria[a], urinary creatinine[a]
Imaging
Chest X-ray

CBC complete blood count, *CRP* C reactive protein, *CK* creatine kinase, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *γ-GTP* γ-glutamyl trans peptidase, *LDH* lactate dehydrogenase, *GFR* glomerular filtration rate, *BUN* blood urea nitrogen, *BNP* brain natriuretic peptide, *HbA1c* hemoglobin A1C, *GAD* glutamic acid decarboxylase, *SP-D* surfactant protein D, *ACTH* adrenocorticotropic hormone, *TSH* thyroid stimulating hormone, *Ag* antigen, *Ab* antibody, *ANA* antinuclear antibodies, *RF* rheumatoid factor, *PT* prothrombin, *APTT* activated partial thromboplastin time

[a] Once per month

Close collaboration with organ specialists

The current experience of managing immunotherapy toxicities is limited and requires expertise. Moreover, the diversity and relatively low frequency of most irAEs reduce the ability of clinicians to gain sufficient experience in this field. Indeed, the clinical management of irAEs is new to many oncologists.

For all irAEs, a close collaboration with organ specialists (such as respirologists, gastroenterologists, hepatologists,

Table 3 Examination checklists for irAEs

- Pneumonitis
  - Blood test
    - Blood gas analysis
    - KL-6, SP-D, BNP
    - Cytomegalovirus antigenemia, quantiferon
    - Serology: chlamydia pneumoniae-IgG, chlamydia pneumoniae-IgA, mycoplasma antibody (PA)
  - Thoracic CT
  - Bacteriological culture
    - Blood culture
    - Sputum culture
  - Urinary antigen
    - *Streptococcus pneumoniae*
    - Legionella
  - Pulmonary function tests
  - Bronchoscopy
- Colitis
  - Blood test
    - Cytomegalovirus antigenemia
  - Bacteriological culture
    - Stool culture
  - Abdominal CT (contrast enhanced, if possible)
  - Colonoscopy
- Hepatitis
  - Abdominal ultrasound
- Thyroid disorder
  - Blood test
    - Thyroglobulin
    - Anti-TPO antibody
    - Anti-thyroglobulin antibody
    - Anti-TSH receptor antibody
- Adrenal insufficiency
  - MRI of pituitary gland
- Diabetes mellitus (including fulminant type 1 diabetes mellitus)
  - Blood examination
    - Diabetes tests: blood glucose, HbA1c, glycoalbumin, C-peptide, anti-GAD antibody
    - Subtype of ketone body
    - Blood gas analysis
- Myasthenia gravis
  - Blood examination
    - Aldolase
    - Anti-AchR antibody
    - Anti-MuSK antibody
  - Pulmonary function test
  - Muscle MRI
  - Needle electromyography test
  - Muscle biopsy
- Renal insufficiency
  - Urine examination
    - Urinary qualitative/semiqualitative examination, urinary sediment, urinary sugar, proteinuria
    - Urinary N-acetylglucosamine, urinary creatinine, urea nitrogen, urinary β2-microglobulin
    - Urinary electrolytes (Na, K, Cl)

SP-D surfactant protein D, *BNP* brain natriuretic peptide, *CT* Computed Tomography, *TPO* thyroid peroxidase, *TSH* thyroid stimulating hormone, *MRI* magnetic resonance imaging, *HbA1c* hemoglobin A1C, *GAD* glutamic acid decarboxylase, *AchR* acetylcholine receptor, *MuSK* muscle-specific tyrosine kinase

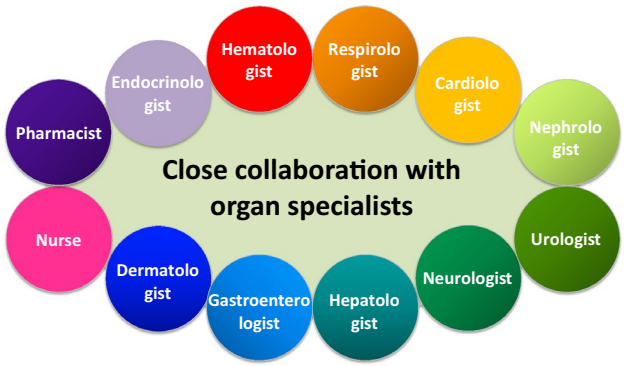

Fig. 1 The consultation with organ specialists or internists is needed for optimal management of irAEs. By way of consultation and discussion, oncologists can learn the appropriate management of specific immune toxicities and also organ specialists can increase their knowledge about these new drug-mediated toxicities. Oncologists should form a multidisciplinary team including oncologists, specialized nurses and pharmacists, and organ specialists or internists

endocrinologists, neurologists or dermatologists) is critical for improving knowledge about and management of irAEs (Fig. 1). Therefore, the organ specialists should be informed of the contents of the product label and be made aware of any other educational materials relating to the management of irAEs. In our hospital, the "Immunotherapy Baseline Checklist", "Examination Checklists for irAEs" and the recommended treatment for irAEs have been developed by consultation with organ specialists or internists.

The consultation with organ specialists or internists is needed for two main reasons: for oncologists to learn the appropriate management of specific immune toxicities and also for organ specialists to increase their knowledge about these new drug-mediated toxicities. Oncologists should form a multidisciplinary team including oncologists, specialized nurses and pharmacists, and organ specialists or internists.

Differential diagnosis

When an adverse event is observed during treatment with ICPIs, three potential etiologies should be considered: disease progression, a fortuitous event including infection or a treatment-related immune toxicity, i.e., an irAE. Oncologists should always be clear that the most frequent adverse events are related to disease progression. However, partly because the immune infiltrates induced by ICPIs may enhance peritumoral inflammation and be responsible for different patterns of toxicity depending on the tumor location, and partly because oncologists are less familiar with immune toxicities, oncologists should recognize that there is a high risk that patients suffering from an irAE might be misdiagnosed with disease progression and their prognosis worsened by a delay in initiating adequate care of the irAE. Differentiating irAEs from disease progression is often difficult if there are no other lesions that are simultaneously progressing. Only cytological or histological evaluation can assist in these situations.

Thus, any new symptoms should first prompt evaluation of the tumor to identify any disease progression. However, the possibility of irAEs should always be considered, particularly when the work-up suggests that the underlying disease is stable.

Treatment

General overview of treatment

Because irAEs are most likely caused by general immunologic enhancement, temporary immunosuppression is often necessary. The mainstay of irAE treatment consists of immunosuppression with corticosteroids or other immunomodulatory agents [50]. Most irAEs resolve with appropriate management and treatment [2–15], and temporary immunosuppression to treat an irAE does not seem to impair the efficacy of ICPIs [43, 51]. Oncologists should refer to the FDA Risk Evaluation and Mitigation Strategy concerning the treatment of irAEs [50]. However, because no prospective trials have been performed to evaluate the best irAE treatment strategy, oncologists should decide the strategy for treating irAEs in consultation with the relevant organ specialists.

Corticosteroids

The route of administration and choice of corticosteroid depends on the severity of the irAE. After a full-dose steroid treatment course, generally 2–4 weeks, the dose of steroids should be reduced gradually over a period of at least one month to avoid recurrence or worsening of the irAEs [52]. In general, the starting dose of corticosteroids and the schedule for tapering corticosteroid dose will differ according to the type of irAE. Therefore, oncologists should consult closely with the organ specialists about the administration of corticosteroids.

Immunomodulatory/immunosuppressive agents

Most irAEs are steroid-sensitive and resolve within 6–12 weeks [53]. If irAEs worsen or show insufficient improvement despite the use of adequate corticosteroid treatment, oncologists should discuss the possibility of additional immunomodulatory medications with the organ specialists. Representative immunomodulatory or immunosuppressive agents that may be considered include tumor necrosis factor-α

antagonists, azathioprine, mycophenolate mofetil and the calcineurin inhibitors tacrolimus and cyclosporine [50].

Risk of opportunistic infections

Although not directly related to irAEs, it is important to note that if a requirement for prolonged immunosuppressive treatment is expected, patients must receive appropriate antibiotic prophylaxis to prevent opportunistic infections; e.g., sulfamethoxazole/trimethoprim against pneumocystic pneumonia [50, 52, 54]. We also recommend that patients are tested for tuberculosis (Quantiferon), without delaying treatment in cases of severe toxicity requiring additional immunosuppressive drugs, and that antituberculosis prophylaxis is introduced if the result is positive.

Oncologists must be very careful regarding the development of opportunistic infections during immunosuppressive therapy because early detection, diagnosis and treatment remain critical for a favorable outcome.

Discontinuation/resumption

Skipping a dose of immunotherapy or discontinuing the immunotherapy should be considered based on the severity of the irAEs and the clinical benefits such as response rate.

The criteria for definitive discontinuation of immunotherapy are as follows [49]:

- Life-threatening irAE (grade 4) or,
- Recurrence of severe irAE (grade 3) or,
- Moderate irAE (grade 2) that does not improve despite appropriate treatment.

However, endocrinologic irAEs are the exception to these criteria. Even if endocrinologic irAEs are grade 4, oncologists need not discontinue the immunotherapy but should provide appropriate hormone replacement therapy.

The criteria for resumption of immunotherapy are as follows [49]:

- The irAE is stable at $\leq$ grade 1 (or returns to baseline) and,
- The corticosteroid dose is less than 10 mg/day prednisone or equivalent and,
- The patient is not receiving other immunosuppressive drugs.

Ongoing clinical questions

Use of ICPIs in patients with autoimmune disease (AID)

Most patients with AID have been excluded from clinical trials of immunotherapy [2–15]. Thus, there are few data other than case reports describing immunotherapy use in patients with a history of AID [55–57]. Weinstock et al. collected safety data on patients with a history of AID who were treated with PD-1/PD-L1 immunotherapy agents in a clinical trial setting [58], reporting that six of 522 patients enrolled in 22 clinical trials showed worsening of their underlying AID to grade 3 or 4 [58]. Leonardi et al. performed a multicenter, retrospective analysis of 46 patients with advanced NSCLC and a history of AID who received treatment with PD-1 inhibitor monotherapy [59], reporting that exacerbation of the underlying AID occurred in eight patients (17%), two of whom required steroid treatment and three of whom required temporary interruption of treatment because of a flare of their AID [59]. These may indicate that symptomatic flares of the underlying AID are uncommon during the use of PD-1/PD-L1 immunotherapy agents in patients with a history of AID. However, the frequency and severity of such flares might depend on the type of AID: rheumatologic, dermatologic, endocrinologic, gastrointestinal or neurologic.

Meanwhile, it was reported from the data of the REISAMIC registry that overall survival time and objective response rate were similar between AID patients and Non-AID patients and that anti-PD-1 antibodies were just as effective in AID patients as Non-AID patients [60]. In administering ICPI to patients with metastatic cancer and AID, multidisciplinary team can help to improve the care of these patients.

The mechanism for the development of irAEs remains unclear. Therefore, further investigation of this clinical question is required. And in the future, we will need a biomarker to anticipate severe irAEs before the administration of ICPIs.

Retreatment with ICPIs after interruption because of irAEs

An important clinical question is whether it is better to resume or discontinue treatment with ICPIs in patients in whom treatment is delayed because of irAEs that improve to $\leq$ grade 1 or return to baseline.

Santini et al. performed a retrospective analysis of 71 patients with advanced NSCLC in whom treatment with PD-1 or PD-L1 inhibitor monotherapy was delayed

because of irAEs [predominantly pneumonitis (21%), colitis (17%), rash (14%), or hepatitis (13%)]. Of these patients, treatment was permanently discontinued in 32 and 39 were retreated with PD-1 or PD-L1 inhibitor monotherapy [60]. The authors reported that the same irAE recurred in 10/39 (26%) and a new irAE occurred in 9/39 (23%) of the patients who were retreated and that although most of the recurrent/new irAEs were successfully controlled, two patients died [61].

There is another retrospective analysis of 80 patients with advanced melanoma in whom treatment with combined CTLA-4 and PD-1 blockade was discontinued because of irAEs [including colitis (41%), hepatitis (36%), pneumonitis (4%)] [62]. All patients were rechallenged with anti-PD-1, and the same irAE recurred in 14/80 (18%) including 1 patient with grade 5 of Steven-Johnson Syndrome and distinct irAE occurred in additional 17/80 (21%) of the patients. Interestingly, it was reported that a tendency to recur with anti-PD-1 resumption after discontinuation of combined CTLA-4 and PD-1 blockade differed depending on the type of irAE. In this retrospective analysis, colitis seemed unlikely to recur (6%, 2/33 patients), but conversely hepatitis (17%, 5/29 patients), pancreatitis (100%, 2/2 patients), pneumonitis (33%, 1/3 patients) and nephritis (50%, 1/2 patients) appeared to recur more often. The authors suggested that many patients, particularly with colitis, tolerated anti-PD-1 rechallenge well.

Patients have often shown long-lasting responses even after immunotherapy treatment has been terminated because of irAEs. When a good response (complete or partial) is observed prior to the onset of irAEs that require a treatment delay, it may be better to suspend retreatment with ICPIs.

Conclusion and perspectives

Oncologists are not familiar with irAEs because they differ from the adverse events associated with cytotoxic agents and targeted therapies. While irAEs are not frequent in clinical practice, the optimal management of irAEs is based on clinical experience because no prospective trials have been conducted to evaluate the best irAE treatment strategy. Therefore, oncologists should be encouraged to share their experiences of irAEs.

Recently, the use of ICPI therapy has expanded across several types of malignancy, including melanoma, NSCLC, RCC, HNSCC, Hodgkin's lymphoma, urothelial carcinoma and GC. The frequency of typical irAEs in patients with these malignancies is shown in Table 1 and this review provides an overview of the optimal management of the irAEs.

It is predicted that implementation of combination immunotherapy based on PD-1 or PD-L1 inhibitors is imminent. Because oncologists are likely to face a higher incidence and severity of irAEs during combination immunotherapy, they should become familiar with the principles of optimal management of irAEs.

Complaince with ethical standards

Conflict of interest None of the authors of this study declared conflict of interest.

References

1. Mellman I, Coukos G, Dranoff G (2011) Cancer immunotherapy comes of age. Nature 480:480–489
2. Hodi FS, O'Day SJ, McDermott DF et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363(8):711–723
3. Robert C, Long GV, Brady B et al (2015) Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372(4):320–330
4. Larkin J, Chiarion-Sileni V, Gonzalez R et al (2015) Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373(1):23–34
5. Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373(2):123–135
6. Borghaei H, Paz-Ares L, Horn L et al (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373(17):1627–1639
7. Carbone DP, Reck M, Paz-Ares L et al (2017) First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376(25):2415–2426
8. Reck M, Rodríguez-Abreu D, Robinson AG et al (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375(19):1823–1833
9. Rittmeyer A, Barlesi F, Waterkamp D et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265
10. Motzer RJ, Escudier B, McDermott DF et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373(19):1803–1813
11. Younes A, Santoro A, Shipp M et al (2016) Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 17:1283–1294
12. Rosenberg JE, Hoffman-Censits J, Powles T et al (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 387:1909–1920
13. Bellmunt J, de Wit R, Vaughn DJ et al (2017) Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 376(11):1015–1026
14. Ferris RL, Blumenschein G Jr, Fayette J et al (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 375(19):1856–1867
15. Kang YK, Boku N, Satoh T et al (2017) Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390(10111):2461–2471

16. Wolchok JD, Saenger Y (2008) The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 13:2–9
17. Minkis K, Garden BC, Wu S et al (2013) The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. J Am Acad Dermatol 69(3):e121–e128
18. Abdel-Rahman O, El Halawani H, Fouad M (2015) Risk of cutaneous toxicities in patients with solid tumors treated with immune checkpoint inhibitors: a meta-analysis. Future Oncol 11:2471–2484
19. Cheng R, Cooper A, Kench J et al (2015) Ipilimumab-induced toxicities and the gastroenterologist. J Gastroenterol Hepatol 30(4):657–666
20. Di Giacomo AM, Danielli R, Guidoboni M et al (2009) Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. Cancer Immunol Immunother 58(8):1297–1306
21. Gentile NM, D'Souza A, Fujii LL et al (2013) Association between ipilimumab and celiac disease. Mayo Clin Proc 88(4):414–417
22. Ryder M, Callahan M, Postow MA et al (2014) Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. Endocr Relat Cancer 21(2):371–381
23. Albarel F, Gaudy C, Castinetti F et al (2015) Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol 172(2):195–204
24. Gaudy C, Clévy C, Monestier S et al (2015) Anti-PD1 pembrolizumab can induce exceptional fulminant type 1 diabetes. Diabetes Care 38(11):e182–e183
25. Barjaktarevic IZ, Qadir N, Suri A et al (2013) Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. Chest 143(3):858–861
26. Berthod G, Lazor R, Letovanec I et al (2012) Pulmonary sarcoid-like granulomatosis induced by ipilimumab. J Clin Oncol 30(17):e156–e159
27. Thaipisuttikul I, Chapman P, Avila EK (2015) Peripheral neuropathy associated with ipilimumab: a report of 2 cases. J Immunother 38(2):77–79
28. Gaudy-Marqueste C, Monestier S, Franques J et al (2013) A severe case of ipilimumab-induced Guillain–Barré syndrome revealed by an occlusive enteric neuropathy: a differential diagnosis for ipilimumab-induced colitis. J Immunother 36(1):77–78
29. Loochtan AI, Nickolich MS, Hobson-Webb LD (2015) Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve 52(2):307–308
30. Bernardo SG, Moskalenko M, Pan M et al (2013) Elevated rates of transaminitis during ipilimumab therapy for metastatic melanoma. Melanoma Res 23(1):47–54
31. Kleiner DE, Berman D (2012) Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 57(8):2233–2240
32. Voskens C, Cavallaro A, Erdmann M et al (2012) Anti-cytotoxic T-cell lymphocyte antigen-4-induced regression of spinal cord metastases in association with renal failure, atypical pneumonia, vision loss, and hearing loss. J Clin Oncol 30(33):e356–e357
33. Fadel F, Karoui EIK, Knebelmann B (2009) Anti-CTLA4 antibody-induced lupus nephritis. N Engl J Med 361(2):211–212
34. Izzedine H, Gueutin V, Gharbi C et al (2014) Kidney injuries related to ipilimumab. Invest New Drugs 32(4):769–773
35. Ahmad S, Lewis M, Corrie P et al (2012) Ipilimumab-induced thrombocytopenia in a patient with metastatic melanoma. J Oncol Pharm Pract 18(2):287–292
36. Akhtari M, Waller EK, Jaye DL et al (2009) Neutropenia in a patient treated with ipilimumab (anti-CTLA-4 antibody). J Immunother 32(3):322–324
37. Du Rusquec P, Saint-Jean M, Brocard A et al (2014) Ipilimumab-induced autoimmune pancytopenia in a case of metastatic melanoma. J Immunother 37(6):348–350
38. Chan MMK, Kefford RF, Carlino M et al (2015) Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. J Immunother 38(1):37–39
39. Hunter G, Voll C, Robinson CA (2009) Autoimmune inflammatory myopathy after treatment with ipilimumab. Can J Neurol Sci 36(4):518–520
40. Läubli H, Balmelli C, Bossard M et al (2015) Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. J Immunother Cancer 3(1):11
41. Geisler BP, Raad RA, Esaian D et al (2015) Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. J Immunother Cancer 3(1):4
42. Miserocchi E, Cimminiello C, Mazzola M et al (2015) New-onset uveitis during CTLA-4 blockade therapy with ipilimumab in metastatic melanoma patient. Can J Ophthalmol 50(1):e2–e4
43. Weber JS, Hodi FS, Wolchok JD et al (2017) Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 35(7):785–792
44. Khunger M, Rakshit S, Pasupuleti V et al (2017) Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. Chest 152(2):271–281
45. Pillai RN, Behera M, Owonikoko TK et al (2018) Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: a systematic analysis of the literature. Cancer 124(2):271–277
46. Wolchok JD, Neyns B, Linette G et al (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 11(2):155–164
47. Phan GQ, Yang JC, Sherry RM et al (2003) Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci USA 100:8372–8377
48. Freeman-Keller M, Kim Y, Cronin H et al (2016) Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 22(4):886–894
49. Champiat S, Lambotte O, Barreau E et al (2016) Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol 27(4):559–574
50. Bristol-Meyers Squibb: Yervoy (ipilimumab): Immune-mediated adverse reaction management guide. http://www.hcp.yervoy.com/servlet/servlet.FileDownload?file=00Pi000000PI1ZVEA1. Accessed 6 Mar 2018
51. Horvat TZ, Adel NG, Dang T-O et al (2015) Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol 33(28):3193–3198
52. Weber JS, Kähler KC, Hauschild A (2012) Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 30(21):2691–2697
53. Weber JS, Dummer R, de Pril V et al (2013) Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 119(9):1675–1682
54. Kronbichler A, Jayne DRW, Mayer G (2015) Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis. Eur J Clin Invest 45(3):346–368

55. Pedersen M, Andersen R, Nørgaard P et al (2014) Successful treatment with ipilimumab and interleukin-2 in two patients with metastatic melanoma and systemic autoimmune disease. Cancer Immunol Immunother 63(12):1341–1346
56. Kyi C, Carvajal RD, Wolchok JD et al (2014) Ipilimumab in patients with melanoma and autoimmune disease. J Immunother Cancer 2(1):35
57. Bostwick AD, Salama AK, Hanks BA (2015) Rapid complete response of metastatic melanoma in a patient undergoing ipilimumab immunotherapy in the setting of active ulcerative colitis. J Immunother Cancer 3:19
58. Weinstock C, Singh H, Maher VE et al (2017) FDA analysis of patients with baseline autoimmune diseases treated with PD-1/PD-L1 immunotherapy agents. J Clin Oncol. https://doi.org/10.1200/JCO.2017.35.15_suppl.3018
59. Leonardi GC, Gainor JF, Azimi RS et al (2017) Use of PD-1 pathway inhibitors among patients with non-small cell lung cancer (NSCLC) and preexisting autoimmune disorders. J Clin Oncol. https://doi.org/10.1200/JCO.2017.35.15_suppl.9081
60. Danlos FX, Voisin AL, Dyevre V et al (2018) Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. Eur J Cancer. 91:21–29
61. Santini FC, Rizvi H, Wilkins O et al (2017) Safety of retreatment with immunotherapy after immune-related toxicity in patients with lung cancers treated with anti-PD(L)-1 therapy. J Clin Oncol. https://doi.org/10.1200/JCO.2017.35.15_suppl.9012
62. Pollack MH, Betof A, Dearden H et al (2018) Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann Oncol 29(1):250–255