Asia-Pacific Journal of Oncology Nursing 9 (2022) 7–11

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.ajon.org

Perspective

Development of management strategies for immune-related adverse effects of immunotherapies used in oncological treatment

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ARTICLE INFO

Keywords:
Immune-related adverse effects (irAEs)
Oncology nurses
Immunotherapy
Immune checkpoints inhibitors
Cancer

ABSTRACT

Development of immunotherapy agents has changed the cancer treatment paradigm with better outcomes and lesser side effects. Yet, there are adverse events associated with them. Owing to the increased stimulation of the immune system, the normal homeostatic mechanisms protecting the body from its own immune response can become disrupted, leading to a variety of side effects termed immune-related adverse effects (irAEs). irAEs can have significant associated morbidity and in many cases lead to discontinuation of therapies with unpredictable impact on the course of patients' disease. Few key articles laying out guidelines for the management of irAEs provide general treatment algorithms for the majority of the common irAEs. Nurses should have knowledge of the mechanism and adverse events associated with such therapies. Oncology nurses have a crucial role in identification of irAEs. irAEs may involve multiple systems, and thus, it is necessary to identify and manage these adverse events according to the case these at soon as possible.

Introduction

Incidence and mortality related to malignant neoplasms are increasing in developed and developing world. Decades of research and advancement in medical field and treatment modalities such as radiation therapy, chemotherapy, targeted therapy, and immunotherapy have successfully helped in managing the cancer cases and improved survival outcome.[1,2] However, side effects and adverse events related to such therapies are always a matter of concern as it is important for patients' compliance and for better quality of life.[1–3] Development of immunotherapy agents has changed the cancer treatment paradigm with better outcomes and lesser side effects. Immune-targeted therapies have been a major breakthrough in cancer treatment over recent decades.[4]

Immune checkpoint inhibitors (ICPis) are an example of an immune-targeted therapy which works by stimulating the supressed immune system to attack tumor cells itself. Examples of ICPis include anti-cytotoxic T lymphocyte antigen 4 (CTLA-4), anti–programmed cell death 1 (PD-1), and anti–programmed cell death ligand 1 (PD-L1) antibodies.[5] Owing to the increased stimulation of the immune system, the normal homeostatic mechanisms protecting the body from its own immune response can become disrupted, leading to a variety of side effects termed immune-related adverse effects (irAEs).[5]

Table 1 describes irAEs in relation to the affected organ or system of the human body.[6] irAEs can have significant associated morbidity and in many cases lead to discontinuation of therapies with an unpredictable impact on the course of patients' disease.[6] Severe irAEs lead to more frequent and prolonged hospital stays, requiring the input of multidisciplinary team (MDT) management, leading to increased health care costs.[7]

Current management

The key articles laying out guidelines for the management of irAEs are those published by the European Society of Medical Oncology (ESMO),[8]

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https://doi.org/10.1016/j.apjon.2021.12.007
Received 4 July 2021; Accepted 14 August 2021

Table 1
Common immune-related adverse effects.

Affected organ or system of the human body	Immune-related adverse effects
Skin	Bullous dermatosis
	Skin rash/inflammatory dermatitis
	Severe skin reactions
Gastrointestinal	Colitis
	Hepatitis
Lung	Pneumonitis
Endocrine	Diabetes
	Hyperthyroidism (primary)
	Hypophysitis
	Primary adrenal insufficiency
Musculoskeletal	Inflammatory arthritis
	Myositis
	Polymyalgia rheumatica
Renal	Nephritis
Nervous System	Myasthenia gravis
	Guillain–Barré syndrome
	Peripheral neuropathy
	Autonomic neuropathy
	Aseptic meningitis
	Encephalitis
	Transverse myelitis
Hematological	Autoimmune hemolytic anemia
	Acquired thrombotic thrombocytopenic purpura
	Uremic hemolytic syndrome
	Aplastic anemia
	Lymphopenia
	Immune thrombocytopenia
	Acquired hemophilia
Cardiovascular	Myocarditis
	Pericarditis
	Arrhythmias, heart failure associated with ventricular failure
	Vasculitis
	Venous thromboembolism
Ocular	Uveitis/iritis
	Episcleritis
	Blepharitis

the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group,[9] and the National Comprehensive Cancer Network (NCCN) (*National Comprehensive Cancer Network*, 2018). These guidelines provide general treatment algorithms for the majority of the common irAEs, detailing the immunosuppressive drugs and duration of treatment based on their severity.[5] However, these are not evidence-based approaches, instead being algorithms, suggestions, and recommendations by panels of experts.[6,9,10] Table 2 describes different IrAEs and the recommended management along with the degree of toxicity.[6,12]

Oral or intravenous (IV) corticosteroids are the mainstay of current irAE treatment, depending on the grade of the toxicity. Most of the irAEs can be managed with early detection and the use of high-dose steroids, which are then stepped down over 2–4 weeks as the patients' symptoms improve. Before resuming ICPi therapy, the severity should have reduced to grade 1 at least, or resolved entirely. Other immunosuppressive medications are indicated in more severe or refractory cases.[11,12]

Future developments

Autoimmune disease

In the past, patients with autoimmune diseases or their associated symptoms have been excluded from clinical trials involving ICPis beause of a higher risk of developing irAEs; however, retrospective studies have suggested that they can be relatively safe and tolerable in these circumstances,[13] with research suggesting that active autoimmune disease can be controlled in patients with anti-PD1 antibodies with concomitant use of immunosuppression.[5] There is a need to further research into the efficacy of using ICPi treatments for patients with autoimmune conditions.

Table 2
Summary of irAE treatment.[6,12]

Common adverse reactions	Research of alternative/ noninflammatory etiologies	Degree of toxicity	Recommended management of irAEs
Gastrointestinal diarrhea/colitis	Exclude infectious etiology (*Clostridium difficile*)	Grade 1 (Mild)	Symptomatic treatment Consider budesonide 9 mg/day Continue immunotherapy
		Grade 2 (Moderate)	Delay immunotherapy Methylprednisolone IV 0.5–1 mg/kg/day (or oral equivalent) Consider gastroenterology and colonoscopy consultation When improving to ≤ grade 1, reduce the dose for at least 4 weeks
		Grades 3–4 (Severe)	Stop immunotherapy Methylprednisolone IV 1–2 mg/kg/day When improving to ≤ grade 1, reduce the dose for at least 4 weeks If no improvement in symptoms within 48–72 h, consider 2nd-line immunosuppression (infliximab)
Hepatitis	Evaluate for - Alcohol intake - Concomitant drugs with hepatotoxic potential - Exclude biliary disease/biliary obstruction	Grade 1 (Mild)	Continue immunotherapy Repeat LFTs within 1 week
		Grade 2 (Moderate)	Delay immunotherapy Repeat LFTs every 3–5 days Methylprednisolone IV 0.5–1 mg/kg/day (or oral equivalent) When improving to mild or baseline, reduce the dose of steroids for at least 4 weeks
		Grades 3–4 (Severe)	Stop immunotherapy Increase the frequency of LFTs to 1–2 days Methylprednisolone IV 1–2 mg/kg/day Gastroenterology consultation If no improvement in symptoms within 48–72 h, consider 2nd-line immunosuppression (infliximab)
Pneumonitis	Evaluate for - Pulmonary embolism - Cardiac causes - Infectious etiology - COPD - Seasonal allergies/ cough post-nasal drip	Grade 1 (Mild)	Delay immunotherapy Monitor symptoms Repeat chest X-ray in 2–4 weeks
		Grade 2 (Moderate)	Delay immunotherapy Monitor symptoms closely, consider hospitalization Reimage every 1–3 days Pneumology and infectious disease consultations, consider bronchoscopy Methylprednisolone IV 1–2 mg/kg/day (or oral equivalent) When symptoms improve, reduce the dose of steroids for at least 4 weeks

Table 2 (*continued*)

Common adverse reactions	Research of alternative/ noninflammatory etiologies	Degree of toxicity	Recommended management of irAEs
		Grades 3–4 (Severe)	Stop immunotherapy Methylprednisolone IV 2–4 mg/kg/day, discontinue steroids for a period of at least 6 weeks If no improvement in symptoms within 48–72 h, consider 2nd-line immunosuppression (infliximab, mycophenolate mofetil, IVIG)
Dermatological adverse reactions	Exclude noninflammatory causes (allergic reaction to other drugs, photosensitivity, etc.)	Grade 1 (Mild)	Continue immunotherapy Supportive therapy emollients, low-potency topical steroids, antihistamines
		Grade 2 (Moderate)	Continue immunotherapy Topical steroids of moderate-high potency If persistent, despite optimized topical treatment, consider methylprednisolone 0.5–1 mg/kg/day (or oral equivalent) If it improves slightly or resolves, reduce the dose of steroids for at least 4 weeks Consider dermatological evaluation and skin biopsy
		Grades 3–4 (Severe)	Delay immunotherapy Methylprednisolone IV 1–2 mg/kg/day (or oral equivalent) If it improves to mild or resolves, reduce the dose of steroids for at least 4 weeks. Consider skin biopsy
Endocrinopathies	Exclude noninflammatory etiology of symptoms	Grade 1 (Mild)	Continue immunotherapy If TSH is abnormal, add free T4 and T3 Consider morning cortisol and ACTH
		Grade 2 (Moderate)	TSH, free T4, morning cortisol and ACTH Consider pituitary MRI Methylprednisolone IV 1–2 mg/kg/day (or oral equivalent) If it improves, reduce the dose of steroids for at least 4 weeks Hormone replacement therapy if indicated Endocrinology consultation
		Grades 3–4 (Severe)	Delay or discontinue immunotherapy If adrenal crisis is suspected, exclude infection/sepsis, BP support Stress doses of mineralocorticosteroid

ACTH, adrenocorticotrophin; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; IVIG, intravenous immunoglobulin; IV, intravenous; MRI, magnetic resonance image; BP, blood pressure; T3, triiodothyronine; T4, thyroxine; LFTs, liver function tests; TSH, thyroid-stimulating hormone; irAEs, immune-related adverse effects.

Personalized surveillance strategies

Another suggested future development would be the identification of biomarkers which could be used to monitor for the development of specific irAEs, allowing for earlier identification and treatment of these events, as well as the safety of ICPi administration.[14] The proposed method would involve continuous observations of nonspecific biological markers (such as creatinine kinase, liver enzymes, inflammatory markers, isolated autoantibodies).[5] Morgado et al. proposed a method for surveillance of irAEs which is shown in Box 1.[15]

Optimizing the choice of the immunosuppressive agent

Current treatment of irAEs relies heavily on the use of steroids. However, long-term steroid use can be associated with a variety of adverse effects that can affect multiple system, such as gastritis, hypertension, insomnia, hyperglycaemia, and increased risk of opportunistic infections.[16] There has been growing interest in the use of steroid-sparing immune-modulating agents in the management of irAEs.[4] For example, tocilizumab (interleukin-6 receptor monoclonal antibody) has been used in the management of patients with immunotherapy-related pneumonitis and arthritis.[17,18] They have been shown to be both effective and important in treating irAEs that are not steroid sensitive (failing to resolve withing six to 12 weeks of adequate corticosteroid treatment) and are used once other potential causes have been excluded.[19] Considering the promise of using this class of drugs in the management of refractory irAEs, further prospective studies are needed to evaluate the dosing and effectiveness of such treatments.[4]

Improving clinical characterization

The current Common Terminology Criteria for Adverse Events (CTCAE) can be difficult to apply and do not allow for accurate reporting of severity and effect of some irAEs (such as systemic/rheumatic irAEs).[9] It has therefore been suggested that adding more terms into the CTCAE would be beneficial and allow for a standardized capture of all irAEs, and there is a taskforce currently in place which is developing a module to include more irAEs.[4]

Box 1
Proposed surveillance strategy for immune-related adverse events (irAEs).[6]

General pretreatment assessments

- Performance status: including weight, height, and body mass index (BMI)
- Cardiovascular function: including heart rate, blood pressure, electrocardiography, serum cardiac troponin and creatine kinase levels, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), blood electrolytes, and chest radiography
- Kidney function: including estimated glomerular filtration rate, urine spot analysis for proteinuria, creatininuria, calciuria, natriuria, and protein-to-creatinine ratio
- Liver function: including total serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT), and alkaline phosphatase (ALP) levels
- Immune function and/or infection status: including serum C-reactive protein (CRP), erythrocyte sedimentation rate and complete blood counts, screening for antinuclear antibodies[a], complement C3 and/or C4[a], HIV-1 or HIV-2, hepatitis B virus, hepatitis C virus, and/or hepatitis E virus[a], human T lymphotropic virus (HTLV-1) and/or HTLV-2[a] (if endemic), dosage and immunosubtraction or immunofixation of immunoglobulin G (IgG), IgA and IgM[a]
- Endocrine function: including serum levels of cortisol and adrenocorticotropic hormone (ACTH) (at 8 am)[a], luteinizing hormone (LH)[a], follicle-stimulating hormone (FSH)[a], oestradiol[a], testosterone[a], thyroid-stimulating hormone (TSH), and free T4
- Gastrointestinal function: monitoring of pretreatment bowel movements, fecal lactoferrin, and calprotectin
- Storage of pretreatment serum samples

Workup for suspicion of specific irAEs and/or autoimmune diseases

- Suspected connective tissue diseases: presence of anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-nRNP/U1-RNP, anti-Scl-70/anti-topoisomerase, anti-double-stranded DNA (dsDNA), anti-Jo1, anti-histone, anti-gp210, anti-p62, anti-sp100, anti-centromere, and/or anti-PM-Scl autoantibodies
- Suspected vasculitis: presence of antineutrophil cytoplasmic antibodies (ANCAs) with c-ANCA proteinase, p-ANCA myeloperoxidase, and atypical ANCA (x-ANCA or a-ANCA) and cryoglobulinaemia
- Suspected inflammatory bowel disease: presence of anti–transglutaminase autoantibodies (anti-tTG and anti-eTG) and anti–*Saccharomyces cerevisiae* antibody
- Suspected autoimmune hepatitis: antimitochondrial, anti–liver kidney microsomal type 1, anti-actin, and anti–smooth muscle autoantibodies
- Suspected thyroiditis with antithyroid antibodies: antithyroglobulin, antimicrosomal, and/or antithyroid peroxidase and anti-TSH receptor autoantibodies
- Suspected rheumatoid arthritis: presence of rheumatoid factor and anti–cyclic citrullinated peptides
- Suspected diabetes mellitus: presence of circulating islet cell autoantibodies
- Suspected myasthenia gravis: anti-acetylcholine receptor, anti-MUSK, and anti-ganglioside antibodies
- Suspected antisynthetase syndrome: presence of antiphospholipid antibodies
- Suspected sarcoidosis: angiotensin-converting enzyme, corrected calcium, and 24-h calciuria measurements

All patients

- The emergence of new autoimmune disease symptoms such as arthralgia, myalgia, dyspnoea, cardiac pain or palpitation, diarrhea, abdominal pain, sicca syndrome, cutaneous rash, conjunctivitis, scleroderma, headache, and nausea and vomiting should prompt investigations for the signs of the suspected autoimmune disease

[a] Test is considered advisable but not mandatory

Education

Patient education is key for early recognition and effective management of irAEs.[20] They should be informed of the presentation of some of the most common of these side effects and given hotline numbers to call if they are developing symptoms. It is also important to educate members of the MDTs caring for these patients on the irAEs and their management, avoiding delays in treatment.[10,13] This extends to education of General Practitioners (GP) and emergency department practitioners who may be the first to see these patients presenting with irAEs from immune checkpoint inhibitor (ICI) treatment. Prompts such as medical alert cards or electronic alerts on patients notes may be needed to prompt practitioners who are not experienced in oncology to consider irAEs as a differential diagnosis in these patients.[12,21]

Further our understanding of mechanism of irAEs

The exact pathophysiology by which the adverse events are related to the immune system is unknown, although it is thought to be related to the role of ICPis in immune homeostasis.[22] Translational studies have shown that the T-cell, antibody, and cytokine responses may be involved. Studies are needed to understand the mechanisms of irAEs to allow for development of more precise treatments of irAEs.[22]

Role of oncology nurses in managing irAEs

Oncology nurses have a crucial role in identification of irAEs of therapeutic agents such as ipilimumab. Nurses have an important role in communications related to identification of irAE signs and symptoms to the patients and caregivers and advised to make a call, in case of any adverse events. It should be noted that these adverse events may happen even within 2 years of treatment.[23,24] Nurses should have knowledge of the mechanism and adverse events associated with such therapies.[25] irAEs may involve multiple systems, and thus, it is necessary to identify and manage these adverse events according to the case as soon as possible.[24,26]

The Clatterbridge Cancer Centre formulated guidelines for nurses to manage irAEs. With a dedicated nursing team for irAEs, it categorized the adverse events or toxicity into four grades, that is, mild (grade 1) to severe or life-threatening (grade 4) with specific management of each type

of graded events. They adopted widely used color coding, that is, red, amber, green (RAG), to make these guidelines easy to implement.[26] Updated version of these guidelines is available online (www.clatterbridgecc.nhs.uk).

The American Society of Clinical Oncology recommends educating the patients as an initial step in managing irAEs. Use of wallet card can be arranged to identify the patients who are receiving immunotherapy. Nurses should be familiar in identifying any adverse signs or symptoms, benign or advance stage, and triage accordingly.[27]

The Oncology Nursing Society collaborated with the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology to formulate guidelines to manage irAEs. These guidelines include information related to adverse events and education to patients and caregivers during therapies and afterward.[25]

Conclusions

ICIs are clearly an important development in the treatment of cancer. Despite this, irAEs requiring specialist MDT management can occur as a result of treatment. Many of these are reversible through the use of high-dose corticosteroids. Patient and practitioner education is vital however to ensure early detection and therefore management of these events. However, further research is needed to create internationally accepted evidence-based guidance on management of irAEs.

Further research is also needed to understand the pathophysiology of these events to improve both management and allow for the use of personalized surveillance strategies, adjusted to monitor for biochemical markers of developing irAEs.

Funding

Nil.

Declaration of competing interest

None declared.

References

1. Devlin EJ, Denson LA, Whitford HS. Cancer treatment side effects: a meta-analysis of the relationship between response expectancies and experience. *J Pain Symptom Manag*. 2017;54:245–258.e2.
2. Shankar A, Roy S, Malik A, Julka PK, Rath GK. Prevention of chemotherapy-induced nausea and vomiting in cancer patients. *APJCP*. 2015;16:6207–6213.
3. Shankar A, Roy S, Bhandari M, Rath GK, Biswas AS, Kanodia R, et al. Current trends in management of oral mucositis in cancer treatment. *APJCP*. 2017;18:2019–2026.
4. Naing A, Hajjar J, Gulley JL, Atkins MB, Ciliberto G, Meric-Bernstam F, et al. Strategies for improving the management of immune-related adverse events. *J Immunother Cancer*. 2020;8:e001754.
5. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16:563–580.
6. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1714–1768.
7. Balaji A, Zhang J, Wills B, Marrone KA, Elmariah H, Yarchoan M, et al. Immune-related adverse events requiring hospitalization: spectrum of toxicity, treatment, and outcomes. *J Oncology Practice*. 2019;15:e825–e834.
8. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv119–i142.
9. Puzanov I, Diab A, Abdallah K, Bingham 3rd CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the society for immunotherapy of cancer (SITC) toxicity management working Group. *J Immunother Cancer*. 2017;5:95.
10. Barquín-García A, Molina-Cerrillo J, Garrido P, Garcia-Palos D, Carrato A, Alonso-Gordoa T. New oncologic emergencies: what is there to know about inmunotherapy and its potential side effects? *Eur J Intern Med*. 2019;66:1–8.
11. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51–60.
12. Bourke JM, O'Sullivan M, Khattak MA. Management of adverse events related to new cancer immunotherapy (immune checkpoint inhibitors). *Med J Aust*. 2016;205:418–424.
13. Nagai H, Muto M. Optimal management of immune-related adverse events resulting from treatment with immune checkpoint inhibitors: a review and update. *Int J Clin Oncol*. 2018;23:410–420.
14. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. *Lancet Oncol*. 2019;20:e54–e64.
15. Morgado M, Plácido A, Morgado S, Roque F. Management of the adverse effects of immune checkpoint inhibitors. *Vaccines (Basel)*. 2020;8:575.
16. Wang H, Zhou J, Guo X, Li Y, Duan L, Si X, et al. Use of glucocorticoids in the management of immunotherapy-related adverse effects. *Thorac Cancer*. 2020;11:3047–3052.
17. Naqash AR, Yang LV, Sanderlin EJ, Atwell DC, Walker PR. Interleukin-6 as one of the potential mediators of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint blockade: evidence from a case report. *Acta Oncologica (Stockholm, Sweden)*. 2018;57:705–708.
18. Kim ST, Tayar J, Trinh VA, Suarez-Almazor M, Garcia S, Hwu P, et al. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. *Ann Rheumatic Dis*. 2017;76:2061–2064.
19. Si X, Song P, Ni J, Di M, He C, Zhang L, et al. Management of immune checkpoint inhibitor-related adverse events: a review of case reports. *Thorac Cancer*. 2020;11:498–504.
20. Elder CT, Davis EC, Jaipal S, Wight CE. Immune-checkpoint inhibitor toxicity during a pandemic: overcoming patient fears to provide care. A case report. *J Oncol Pharm Pract*. 2021;27:2035–2040.
21. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol*. 2016;27:559–574.
22. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158–168.
23. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13:473–486.
24. Rubin KM. Managing immune-related adverse events to ipilimumab: a nurse's guide. *Clin J Oncol Nurs*. 2012;16:E69–E75.
25. Brassil K. ONS role in new guideline for irAE management. In: *Oncology nursing society's annual meeting | conference*. CancerNetwork; 2018 [updated May 16; cited Aug 9, 2021]. Available from: https://www.cancernetwork.com/view/ons-role-new-guideline-irae-management.
26. Upton J. *Creating guidelines for managing the side-effects of immunotherapy: nursing Times*; 2017 [online]; [cited July 2, 2021]. Available from: https://www.nursingtimes.net/clinical-archive/cancer-clinical-archive/creating-guidelines-for-managing-the-side-effects-of-immunotherapy-27-11-2017/.
27. Cole S, Zibelman M, Bertino E, Yucebay F, Reynolds K. Managing immuno-oncology toxicity: top 10 innovative institutional solutions. *Am Soc Clin Oncol Educ Book*. 2019:96–104.