Immunotherapy for cancer and immune-related adverse events

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Immune checkpoint inhibitors that remove the 'brakes' on the body's immune system, enhancing its attack on cancer cells, have revolutionised the treatment of many cancers. However, these medications can cause a wide range of immune-related adverse events that GPs need to be aware of.

Immunotherapy with checkpoint inhibitors has revolutionised the treatment of many cancers. These medications have provided durable responses and excellent long-term outcomes in a substantial subset of patients with a range of cancer types, including melanoma, renal cell carcinoma and non-small cell lung cancer.[1] Immune checkpoints are regulators that modulate physiological immune responses and maintain self-tolerance.[2] Checkpoint inhibitors can disrupt this interaction and enhance the activity of the immune system against cancer cells. However, they can also induce inflammatory and other immune-related adverse events (AEs).[3]

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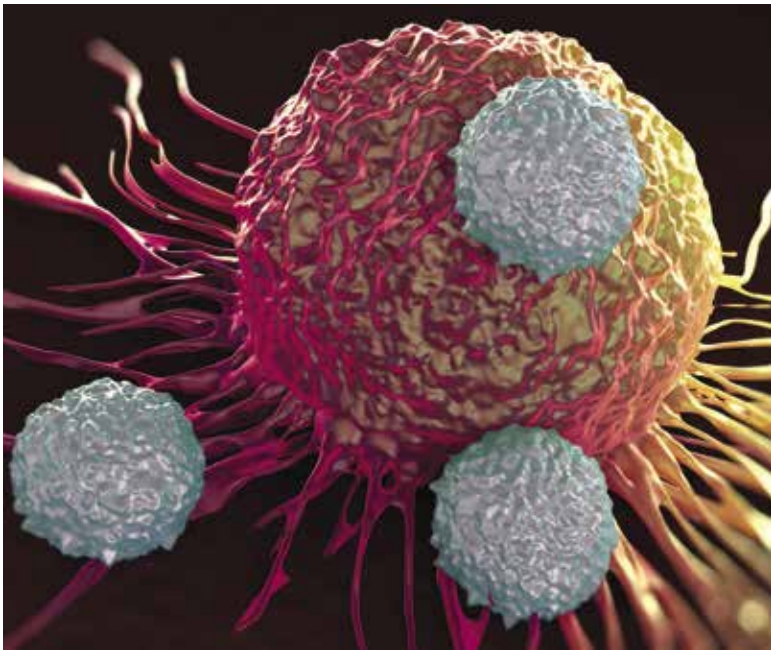

With the increasing use of checkpoint inhibitors and improving patient survival, GPs will have growing numbers of patients receiving these medications and need to be aware of the potential AEs. In this article, we review the checkpoint inhibitors currently in use in Australia and the possible immune-related AEs they can induce. We aim to increase awareness of these AEs and how to approach management of patients receiving checkpoint inhibitors in general practice.

What is immunotherapy?

Self-tolerance, or the ability of the immune system to recognise and avoid attacking self, is maintained via a plethora of checkpoints within the immune cascade that modulate immune responses.[4] Tumour cells can 'take advantage' of these normal immune checkpoints to reduce the effectiveness of antitumour immunity (Figure 1a).[1-3] Molecules involved in these checkpoint pathways include T-cell receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and the PD-1 ligand (PD-L1).

Blocking the immune checkpoints with monoclonal antibodies (checkpoint inhibitors) can release the so-called 'brakes' on the immune system, potentially enhancing antitumour immunity (Figure 1b). Monoclonal antibodies to PD-1, PD-L1 and CTLA-4 have been shown to produce durable antitumour responses.[1,2,5]

Immunotherapy with checkpoint inhibitors differs from traditional cancer therapy with cytotoxic agents that target the cell cycle. The latter lead to numerous side effects, including alopecia, bone marrow suppression (with possible febrile neutropenia), nausea and vomiting, peripheral neuropathies

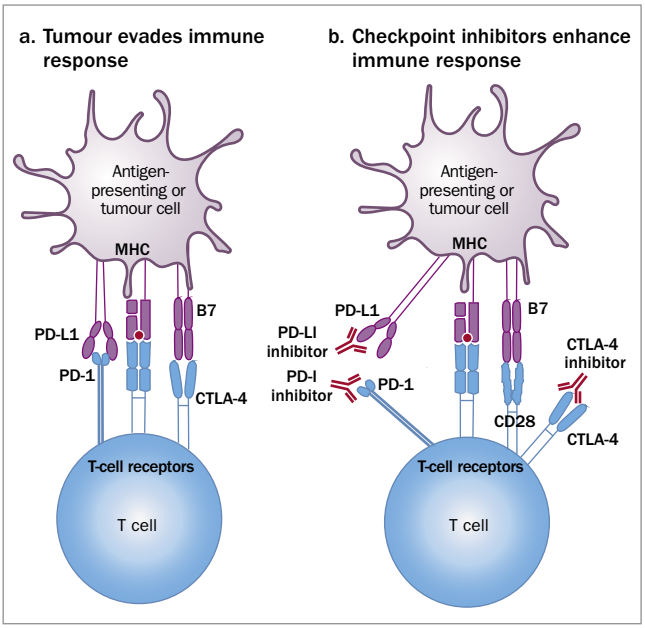

Figure 1a and b. Mechanism of action of immune checkpoint inhibitors. a (left). Tumour and antigen-presenting cells present tumour antigens via the major histocompatibility complex (MHC), which interacts with receptors on T cells, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Costimulatory signals at these receptors create checkpoints that modulate the immune response. For example, binding of PD-1 ligand (PD-L1) to PD-1 and B7 to CTLA-4 leads to immune tolerance or tumour evasion of the immune response. b (right). Monoclonal antibodies to PD-1, PD-L1 and CTLA-4 block these checkpoints, increasing T cell activation and thereby enhancing the antitumour response.

and infertility.[6] In contrast, immunotherapy can result in inflammatory and other immune-related AEs that have not traditionally been seen with cytotoxic therapies.

What are the indications for immunotherapy?

The indications for checkpoint inhibitors are expanding across malignancies.[7] Checkpoint inhibitors registered for use in Australia comprise:

- two PD-1 inhibitors (nivolumab and pembrolizumab)
- two PD-L1 inhibitors (atezolizumab and avelumab)
- a CTLA-4 inhibitor (ipilimumab).[8]

The indications for these medications are listed in Box 1.[9,10] Many more checkpoint inhibitors are available via expanded access programs and are being investigated in clinical trials.

Why do immune-related adverse events occur?

The therapeutic benefits of checkpoint inhibitors can be complicated by immune-related AEs caused by the unleashing of the brakes on immune tolerance. As well as increasing immune system activity directed against tumour cells, this can lead to autoimmunity. It is plausible for any autoimmune or autoinflammatory manifestation to occur as an AE, although the nature and treatment can differ from 'classic' autoimmune diseases.

1. CHECKPOINT INHIBITORS AVAILABLE IN AUSTRALIA AND THEIR INDICATIONS*

Programmed cell death protein 1 (PD-1) inhibitors

Nivolumab

- Melanoma
- Non-small cell lung cancer
- Renal cell carcinoma
- Squamous cell cancer of head and neck
- Classic Hodgkin lymphoma
- Urothelial carcinoma
- Hepatocellular carcinoma
- Oesophageal squamous cell carcinoma

Pembrolizumab

- Melanoma
- Non-small cell lung cancer
- Renal cell carcinoma
- Squamous cell cancer of head and neck
- Classic Hodgkin lymphoma
- Urothelial carcinoma
- Primary mediastinal B-cell lymphoma
- Mismatch repair deficient cancer (e.g. colorectal, non-colorectal)
- Endometrial cancer

PD-1 ligand (PD-L1) inhibitors

Atezolizumab

- Non-small cell lung cancer
- Small cell lung cancer
- Urothelial carcinoma
- Hepatocellular carcinoma
- Triple-negative breast cancer

Avelumab

- Merkel cell carcinoma
- Renal cell carcinoma
- Urothelial carcinoma

Cytotoxic T-lymphocyte associated protein-4 (CTLA-4) inhibitor

Ipilimumab

- Melanoma
- Non-small cell lung cancer
- Renal cell carcinoma

* Depending on the indication, immune checkpoint blockade can be indicated for metastatic or unresectable tumours, either as first-line treatment or after previous systemic therapies.[9] These treatments have also become available in certain adjuvant settings.[10]

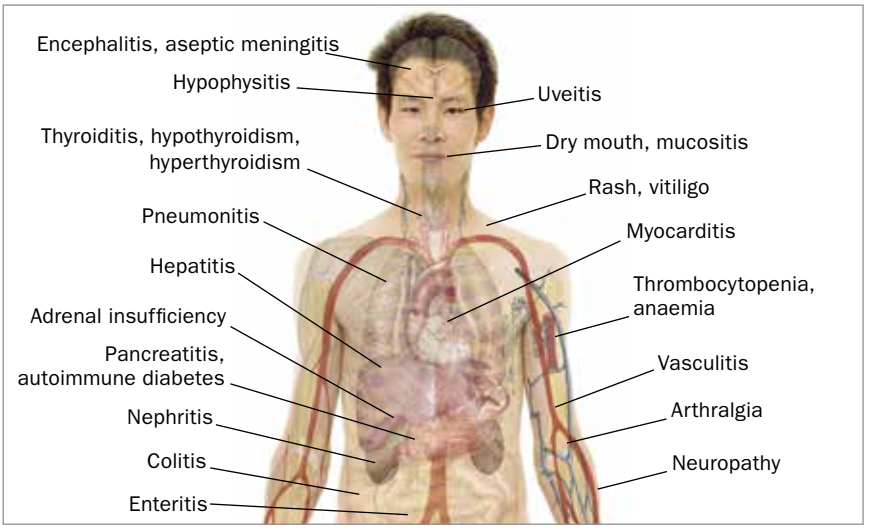

Figure 2. Organs that can be affected by checkpoint inhibitors and organ-specific immune-related adverse events.[11]

What are the potential adverse events?

The spectrum of immune-related AEs is wide. Symptoms can range from mild, where immunotherapy can be continued or resumed after a brief interruption, to severe or even life-threatening, necessitating permanent discontinuation of immunotherapy.[11] Although any tissue or organ can be involved, immune-related AEs most commonly affect the skin, colon, endocrine organs, liver and lungs.[3,11] Cardiac and neurological immune-related AEs are less common but can be dangerous and even life-threatening.[3] The organs that can be affected by checkpoint inhibitors and organ-specific immune-related AEs are shown in Figure 2 and the Table.[7,11-20]

This wide array of AEs can be graded for severity on a scale of 1 to 5 using the Common Terminology Criteria for Adverse Events (CTCAE).[21] This classification system is used by oncologists for clinical trials; management also often depends on the severity or grade of the AE.

Immune-related AEs can occur at any time, even months after discontinuing treatment. However, the median onset is within two to 16 weeks of commencement of therapy.[22]

Can we predict adverse events?

Studies have indicated that a history of autoimmune disease and the use of combination immunotherapy with both PD-1 or PD-L1 plus CTLA-4 inhibitors increase the risk for developing immune-related AEs.[22] Patients with pre-existing autoimmune disease have been excluded from clinical trials. However, retrospective data have been encouraging for the use of checkpoint inhibitors in these patients.[23] Other likely factors include genetics, previous infections and treatments, the microbiome and environmental factors.[24]

Ultimately, the balance between the cancer versus the risk of an immune-related AE needs to be discussed between the patient and doctor.[25] The incidence of severe (grade 3 to 4) AEs is about 20 to 25% for anti-PD-1 therapy alone, and about 55 to 60% for combination immunotherapy.[26]

What are the organ-specific adverse events?

The immune-related AEs of greatest clinical importance and their incidence are listed in the Table.[7,12-20] A more extensive list of organ-specific manifestations appears in Box 2.[7,12-20] Further information and guidance can be obtained from the European Society for Medical Oncology and American Society of Clinical Oncology guidelines.[3,27]

TABLE. INCIDENCE OF IMMUNE-RELATED ADVERSE EFFECTS OF CHECKPOINT INHIBITORS WITH MOST CLINICAL RELEVANCE[7,12-20]

Adverse event	Incidence	
	PD-1 + CTLA-4 blockade	PD-1 blockade
Rash, dermatitis	40%	10%
Hypothyroidism	25%*	10%
Colitis	25%	5%
Arthralgia	20%†	20%
Hepatitis	15%	5%
Hypophysitis	10%	<1%
Pneumonitis	5%‡	3%
Nephritis	2%	1%
Uveitis	1%	1%
Autoimmune diabetes	1%	<1%
Myocarditis	<1%	<1%
Encephalitis	<1%	<1%

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1 = programmed cell death protein 1.
* Hypothyroidism can be preceded by thyroiditis or hyperthyroidism.
† Incidence varies with the definition of arthralgia.
‡ Risk of pneumonitis can be higher for patients treated for lung cancer compared with other malignancies.

How are patients with AEs treated?

Treatment depends on which organ system is affected and the severity (grade) of the toxicity based on the CTCAE classification.[3,21] Many therapeutic algorithms have been suggested to assist in the diagnosis and management of immune-related AEs.

- Patients with mild immune-related AEs (grade 1) do not always require

2. IMMUNE-RELATED ADVERSE EFFECTS OF CHECKPOINT INHIBITORS[7,12-20]

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Thyroiditis
- Graves disease
- Hypophysitis
- Autoimmune or type 1 diabetes mellitus
- Adrenal insufficiency
- Hypoparathyroidism
- Hyperparathyroidism
- Hypogonadism

Gastrointestinal
- Diarrhoea, colitis
- Hepatitis
- Pancreatitis
- Nausea, gastritis
- Enteritis

Cutaneous
- Vitiligo
- Alopecia areata or universalis
- Morbilliform exanthems
- Pruritis
- Dermatitis
- Sweet syndrome
- Erythema nodosum or sarcoidosis
- Stevens-Johnson syndrome, toxic epidermal necrolysis
- Drug reaction with eosinophilia and systemic symptoms

Rheumatic and systemic
- Arthritis (psoriatic, rheumatoid)
- Tenosynovitis
- Enthesitis
- Polymyalgia rheumatica
- Myositis
- Sicca
- Sarcoid
- Vasculitis

Neurological
- Myasthenia gravis
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Length dependent peripheral polyneuropathies
- Meningoencephalitis
- Neurosarcoidosis
- Neuromyelitis optica spectrum disorder

Cardiac
- Myocarditis
- Pericarditis
- Acute cardiac failure
- Arrhythmias

Respiratory
- Pneumonitis
- Pulmonary fibrosis

Ocular
- Uveitis
- Sicca symptoms
- Inflammatory orbitopathies
- Optic neuritis
- Meibomian gland dysfunction
- Immune retinopathy
- Retinal vascular occlusion

Haematological
- Haemolytic anaemia
- Aplastic anaemia
- Neutropenia
- Immune thrombocytopenia

Renal
- Acute tubulointerstitial nephritis
- Glomerulonephritis

therapy and can often be carefully monitored and continue on the checkpoint inhibitor.
- If immune-related AEs become more severe, treatment discontinuation is essential, and immunosuppressive agents are frequently required alongside referral to the relevant specialist.
- In severe cases, checkpoint inhibitor therapy needs to be discontinued permanently.
- Glucocorticoids are the mainstay of therapy, except for patients with endocrine immune-related AEs, where hormone replacement is usually sufficient. Hormone replacement may be required lifelong as recovery from immunotherapy-induced endocrinopathies is rare.

What is the GP's role?

In this era of increasing use of immunotherapy, GPs will encounter immune-related adverse events more frequently. Immune-related AEs can present in unusual and unpredictable ways, different from classic autoimmune or autoinflammatory diseases. In rare cases, they can be

3. PRACTICE POINTS ON IMMUNOTHERAPY AND IMMUNE-RELATED ADVERSE EVENTS

- Immunotherapy with checkpoint inhibitors such as nivolumab, pembrolizumab, atezolizumab, avelumab and ipilimumab has revolutionised oncology, with excellent clinical outcomes in a substantial proportion of patients with a wide range of cancers.
- Immunotherapy is generally safe but can cause immune-related adverse events (AEs) affecting a wide range of body systems.
- Immune-related AEs are usually manageable but in rare cases can be life-threatening, particularly cardiac and neurological AEs.
- Early recognition of immune-related AEs is crucial.
- If an immune-related AE is suspected in general practice, prompt communication with the treating oncology team is essential to initiate diagnostic work-up and further management.

life-threatening (e.g. neurotoxicity and cardiomyopathy) or permanent (e.g. diabetes mellitus). Although therapeutic algorithms exist, treating immune-related AEs is challenging and requires a highly individualised approach that needs to be initiated and coordinated by an experienced oncology team.

A high index of clinical suspicion and early recognition of immune-related AEs are essential. If an immune-related AE is suspected in general practice, prompt communication with the treating oncology team is essential to initiate diagnostic work-up and further management. Clinical practice points on immunotherapy and immune-related AEs are summarised in Box 3.

Conclusion

Immunotherapy with checkpoint inhibitors has improved the responses to malignancies that have traditionally had poor outcomes. As use of these therapies is expanded, we will increasingly encounter side effects such as immune-related AEs that differ to those seen with traditional cytotoxic agents. The detection and management of these clinically heterogeneous immune-related AEs is complex and requires multidisciplinary input and co-ordination by the oncology team. Early recognition of immune-related AEs is crucial and depends on a high index of clinical suspicion. If an immune-related AE is suspected in general practice, prompt communication with the treating oncology team is essential. MT

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