Problem-based review: Immune-mediated complications of 'Checkpoint Inhibitors' for the Acute Physician

P Webb, TW Rice & T Cooksley

Abstract

Immunotherapy with 'checkpoint-inhibitors' has significantly improved outcomes for patients with a range of malignancies. However, significant immune-mediated toxicities of these therapies are well-described. These immune-mediated toxicities can affect virtually all organ systems and are potentially fatal. The timing of onset of the adverse effects is dependent on the organ system affected and can occur after completion of the treatment. The increasing utilisation of 'checkpoint-inhibitors' means that Acute Physicians are likely to see a number of immune-mediated complications presenting to the AMU.

The fundamental principles of management of immune-mediated toxicities are early recognition, supportive treatment, escalating steroid therapy (dependent on the severity of the toxicity), close liaison with Oncology and specialist organ team input. Research into the optimal strategies and pathways for the management of immune-mediated toxicity, as well as increased collaboration between Acute Physicians and Oncologists, will be necessary.

Keywords

Immune-mediated toxicities, Checkpoint Inhibitors, Immunotherapy, Colitis, Hypophysitis.

Key points

- Immunotherapy with 'checkpoint inhibitors' has significantly improved outcomes for patients with a range of malignancies but significant immune-mediated toxicities of these therapies are well-described.
- The key first step in the management of immune-mediated toxicities of checkpoint inhibitors is their recognition.
- Immune-mediated checkpoint inhibition toxicities can affect virtually all organ systems and are potentially fatal.
- The increasing utilisation of checkpoint inhibitors means that Acute Physicians are likely to see an increasing number of immune-mediated complications presenting to the AMU.
- The fundamental principles of management of immune-mediated toxicities are early recognition, supportive treatment, escalating steroid therapy (dependent on the severity of toxicity), close liaison with Oncology colleagues and specialist organ team input.

Introduction

Immunotherapy with 'checkpoint inhibitors' has significantly improved outcomes for patients with metastatic melanoma and evidence of benefit in a wider range of malignancies is rapidly developing.[1-3] Alongside the clinical benefits of these therapies, well-described immune mediated adverse effects have been identified.[3-5]

The fundamental basis of cancer immunotherapy is that tumour cells (which would normally be recognized and destroyed by T-cells) have developed the ability to evade the immune system through the utilisation of 'peripheral tolerance'.[6] Peripheral tolerance is the process by which numerous 'checkpoint' pathways regulate activation of T-cells during an immune response in order to prevent autoimmunity. These 'checkpoints', such as Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1 (PD-1), act at varying stages of an immune response. Inhibition of the 'checkpoint' pathways prevents peripheral tolerance and has led to the development of cancer immunotherapy agents, such as Ipilimumab (CTLA-4 inhibitor), Nivolumab (PD-1 inhibitor) and Pembrolizumab (PD-1 inhibitor).[1,3,6]

Although the benefits and adverse events associated with 'checkpoint inhibitors' are well-described, experience of their immune-mediated complications in the UK is mainly limited to specialist cancer centres who administer these novel immunotherapies in closely-monitored clinical trial settings. The increasing utilisation of these drugs, reflected by more UK licences being granted and broader indications for their usage, means that Acute Physicians are likely to see a number of immune-mediated complications presenting to the AMU. It is thus important that Acute Physicians have an awareness and understanding of these unique toxicities and have clear pathways with access to specialist Oncological advice and support. This

Philip Webb[1]

Terry W Rice[2]

Tim Cooksley[3]

1 Core Medical Trainee, The Christie, Manchester, UK
2 Associate Professor and Medical Director, Department of Emergency Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
3 Honorary Consultant, Department of Acute Medicine, The Christie, Manchester, UK

Correspondence
Tim Cooksley
Honorary Consultant, Department of Acute Medicine, The Christie, Manchester, UK
Email: cooks199@hotmail.com

© 2017 Rila Publications Ltd.

Table 1. Frequency and time of onset of key immune-mediated toxicities of checkpoint inhibitors.

	Approximate frequency with CTLA-4 inhibitor (%)	Approximate frequency with Anti-PD-1 inhibitor (%)	Median time of onset with CTLA-4 inhibitor (weeks)	Median time of onset with PD-1 inhibitor (weeks)
Colitis	10	3	6	10
Dermatitis	20	10	3	4
Hepatitis	2	2	10	13
Hypophysitis	2	1	11	10
Pneumonitis	<1	2	10	8

review describes the key complications and strategies for their management.

Immune-mediated toxicity

Traditionally, systemic anti-cancer treatment (SACT) toxicities have occurred largely as a direct result of immune suppression. In checkpoint inhibition immunotherapy, toxicities stem from increased activity within the T-cell lineage, similar to that observed in autoimmune diseases. These immune-mediated toxicities can affect virtually all organ systems and are potentially fatal. The most common adverse effects are gastrointestinal and dermatological (see Table 1). The timing of onset of the adverse effects is dependent on the organ system affected and may be delayed until after completion of the treatment course.[4]

Recognising and managing immune-mediated toxicity

The key first step in the management of immune-mediated toxicities of checkpoint inhibitors is their recognition. This necessitates education of general physicians, members of the MDT and crucially, patients. Early recognition and intervention reduces the duration and severity of complications. There are no prospective trials into the management of immune-mediated toxicities and so current management and guidelines are predominantly based on clinical experience and expert opinion.

The principles of treatment are to withhold the immunotherapy drug, provide supportive treatment of the organ system affected and consider the use of corticosteroid therapy.[3,4] The severity of toxicity should be graded using the Common Terminology Criteria for Adverse Events (CTCAE)[7] and treatment based on this assessment (see table 2). Patients experiencing grade 2 toxicities or less can be managed expectantly with supportive care, close monitoring and by withholding the checkpoint inhibitor. If symptoms persist for 7 days, the use of corticosteroids should be considered.[4]

In patients experiencing grade 3 or 4 toxicities (severe or life-threatening), urgent administration of high-dose intravenous methylprednisolone (1-2mg/kg daily), supportive treatment and input from a specialist in the affected organ system.[3-5]

Case Vignette 1

A 68 year old lady with metastatic adenocarcinoma of the lung presents to AMU with profuse diarrhoea (>10 episodes per day) and abdominal pain. She feels fatigued but has no other systemic symptoms such as fever or vomiting.

Other than her malignancy she has no other medical history. She has completed 2 cycles of nivolumab (anti PD-1) treatment. She is not on any other medications and has not had any recent antibiotic treatment.

On examination, she is dry, hypotensive and tachycardic. Abdominal examination reveals a soft abdomen with generalized tenderness and hyperactive bowel sounds.

Table 2. General approach to the management of immune-mediated toxicities of checkpoint inhibitors.

CTCAE Grade	Management
1	Supportive treatment Close monitoring Investigations to exclude other cause of symptoms Patient advice and education
2	As per grade 1 with the addition of:-Withhold checkpoint inhibitor until symptoms settle/resolve If symptoms persist for >5 days consider oral prednisolone Liaison with Oncology and Organ-related specialist
3/4	Supportive treatment Commence high dose steroids (1-2mg/kg OD IV Methylprednisolone) Withhold checkpoint inhibitor Investigations to exclude other cause of symptoms and assess severity Liaison with Oncology and organ-related specialist If symptoms persist despite steroids consider additional immunosuppressive agent

© 2017 Rila Publications Ltd.

Her FBC is normal. U&Es demonstrate a stage 1 acute kidney injury with mild hypokalaemia. Her CRP is 30 and albumin is 32. Her abdominal x-ray is featureless. Stool culture is sent.

Diarrhoea is a common presentation in patients on checkpoint inhibitors. Typically the diarrhoea occurs 6 weeks after treatment.[8] It is more common in patients on CTLA-4 inhibitors, such as Ipilimumab. It is important to exclude other causes of diarrhoea, especially infective causes, and bloody diarrhoea is an uncommon presentation of immune-mediated colitis.

Management of immune-mediated colitis is a stepwise approach dependent on the CTCAE grading:[4,8,9]

Grade 1 (Mild) – less than 4 stools a day – Supportive treatment with oral and intravenous fluids and electrolyte correction. Anti-motility agents, such as loperamide, may be used to control symptoms.[3,8]

Grade 2 (Moderate) – 4-6 stools a day – Supportive treatment with intravenous fluids and electrolyte correction. If symptoms persist for more than 5 days, oral prednisolone (0.5mg/kg a day) at a tapering dose should be commenced. Colonoscopy should be considered if the diagnosis is unclear and may be useful in determining the need for longer-term immunosuppression.

Grade 3/4 (Severe/Life-threatening) – 7 or more stools a day – Supportive treatment with intravenous fluids and electrolyte correction. Urgent administration of high dose methylprednisolone (1-2mg/kg a day) should be given for 3 days.[8] It is important to discontinue the checkpoint inhibitor permanently in patients with this severity of toxicity.[8]

Case vignette 1 continued

The patient receives supportive treatment with intravenous fluids and potassium correction. Her physiology improves and her U&Es normalize. Her stool culture is negative.

She receives 1mg/kg a day of intravenous methylprednisolone from admission. Despite 3 days of supportive treatment and high dose steroids, she continues to have 10 loose stools a day. A CT scan of her abdomen demonstrates severe colitis but no evidence of perforation.

If patients continue to experience severe diarrhoea following 3 days of high dose steroid therapy, then infliximab (anti-TNF) therapy should be initiated.[10] This is typically dosed in a similar regimen to patients undergoing rescue therapy for inflammatory bowel disease. The use of other immunosuppressive agents, such as Mycophenolate Mofetil or Tacrolimus, may be considered in cases refractory to steroids and infliximab.[3] These patients require urgent Gastroenterology input.

Perforation as a result of immune-mediated colitis is well described and associated with significant mortality.[11] Patients require urgent surgical opinion for assessment for colectomy, intravenous antibiotics and discontinuation of the steroids.

Case vignette 2

A 50-yea- old male with metastatic melanoma presents to the AMU with a 4 day history of headache, nausea and extreme fatigue. He has no visual symptoms. He has no limb weakness. He has no infective symptoms.

Other than his malignancy he has no significant medical history. He is not known to have metastatic brain disease and does not have a history of migraine. He has completed 3 cycles of ipilimumab (CTLA-4 inhibitor).

On examination he is alert. His blood pressure is 100/50mmHg with a pulse rate of 90bpm. His blood glucose is 2.1mmol/L. He has no focal neurology.

An urgent CT brain shows no abnormality. An urgent pituitary screen is sent.

The diagnosis of ipilimumab-related hypophysitis is suspected.

A range of endocrinopathies may be seen with checkpoint-inhibition including hypophysitis, hypothyroidism and adrenalitis.[12,13] They often present non-specifically and are only diagnosed with routine blood monitoring.

Typically, hypophysitis presents with headache, fatigue and visual loss. It is more common in patients treated with CTLA-4 inhibitors and occurs in around 2% of these patients.[1] The diagnosis is made by biochemical demonstration of panhypopituitarism (low levels of cortisol, TSH, FH, LSH, ACTH and prolactin). The diagnosis can be supported by an MRI scan demonstrating enhancement and swelling of the pituitary gland.[14]

Patients with suspected immune-mediated hypophysitis need urgent inpatient management with supportive treatment and 3 days of high dose intravenous methylprednisolone (1mg/kg a day).[3,12] Early administration of high dose steroids may reduce the need for long term hormone replacement.[13]

Case Vignette 2 continued

The patient is treated with high dose methylprednisolone and within 24 hours his symptoms of headache, fatigue and nausea resolve.

His pituitary screen shows cortisol of <50nmol/L, TSH = 0.03, FSH + LH levels <1 IU/L, ACTH = 10ng/L and Prolactin =150mU/L. His MRI pituitary demonstrates swelling of the gland.

The diagnosis of ipilimumab-related hypophysitis is made. He completes 3 days of intravenous methylprednisolone and feels entirely well.

© 2017 Rila Publications Ltd.

He is discharged with levothyroxine 100mcg OD and hydrocortisone 10mg TDS. His ipilimumab is discontinued and follow up is arranged in 1 week with his Oncologist to discuss further treatment options and with the Endocrinologist for ongoing monitoring and management of his hypopituitarism.

Patients require Endocrinology support to direct long-term hormone replacement therapy which includes levothyroxine, hydrocortisone and potentially replacement of sex hormones dependent on symptoms.[13] Hypophysitis is usually irreversible and the checkpoint inhibitor should be discontinued.[1,14]

Other immune-mediated toxicities

Skin manifestations are the most common immune-mediated complication of checkpoint inhibitors, occurring to some degree in approximately 40% of patients.[15] Pneumonitis (more common in patients undergoing anti-PD-1 treatment[16]), hepatitis, pancreatitis, myositis, arthralgias, uveitis and nephritis are also well-described in this population.[3,4] A recent case series described 2 fatalities from fulminant myocarditis in patients undergoing combination checkpoint inhibition with anti-CTLA-4 and anti-PD-1 agents.[17]

Irrespective of the organ involved, the fundamental principles of management are early recognition, supportive treatment, escalating steroid therapy (dependent on the severity of the toxicity), close liaison with Oncology colleagues and specialist organ doctor input.

Conclusion

Targeted and specialist cancer treatments are likely to continue to improve outcomes for patients but alongside this, challenging immune-mediated toxicities will become more prevalent on the AMU.[18] Recognition of these complications and knowledge of their management will become increasingly important for Acute Physicians. Research into the optimal strategies and pathways for their management as well as increased collaboration between Acute Physicians and Oncologists will be necessary.

Conflicts of interest

None

References

1. Hodi FS, O'Day S, McDermott D *et al.* Improved survival with ipilumumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711-23.
2. Ansell S, Lesokhin A, Borrello I *et al.* PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015; **372**: 311-9.
3. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev.* 2016; **44**: 51-60.
4. Champiat S, Lambotte O, Barreau E *et al.* Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol* 2016; **27**: 559-74.
5. Naidoo J, Page D, Li B *et al.* Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015; **26**: 2375-91.
6. Buchbinder E, Desai. CTLA-4 and PD-1 pathways: Similarities, Differences and Implications of their inhibition. *Am J Clin Oncol* 2016; **39**: 98-106.
7. U.S.D.o.H.a.H. Services. Common Terminology Criteria for Adverse Events; Version 4.0: 2009.
8. Weber J, Kahler K, Hauschild A. Management of immune-mediated adverse events and kinetics of response with ipilimumab. *J Clin Onc* 2012; **30**: 2691-7.
9. Di Giacomo A, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol* 2010; **37**: 499-507.
10. Minor D, Chin K, Kashani-Sabet M. Infliximab in the treatment of anti-CTLA-4 antibody (ipilimumab) induced immune-mediated colitis. *Cancer Biother Radiopharm* 2009; **24**: 321-5.
11. Eggermont A, Chiarion-Sileni V, Grob J *et al.* Adjuvant ipilumumab versus placebo after complete resection of high risk stage III melanoma: a randomised controlled trial. *Lancet Oncol* 2015; **16**: 522-30.
12. Corsello S, Barnabei A, Marchetti P *et al.* Endocrine side effects induced by immune checkpoint inhibitors. *J Clin Endocrinol Metab* 2013; **169**: 1361-75.
13. Torino F, Baranbei A, Paragliola R *et al.* Endocrine side effects of anti-cancer drugs: mAbs and pituitary dysfunction. *Eur J Endocrinol* 2015; **172**: 195-204.
14. Dillard T, Yedinak C, Alumkal J *et al.* Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a range of cancer subtypes. *Pituitary* 2010; **13**: 29-38.
15. Lacouture M, Wolchok J, Yosipovitch G et al. Ipilimumab in patients with cancer and management of dermatologic adverse events. *J Am Acad Dermatol* 2014; **71**: 161-9.
16. Nishino M, Giobbie-Hurder A, Hatabu H *et al.* Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol* 2016; **2**: 1607-16.
17. Johnson D, Balko J, Compton M *et al.* Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016; **375**: 1749-55.
18. Cooksley T, Rice T. Emergency Oncology: Development, Current Position and Future Direction in the US and UK. *Support Care Cancer* 2017; **25**:3-7.

© 2017 Rila Publications Ltd.