Immune-related toxicities: coming soon to an AMU near you

Dr Tim Cooksley
Consultant in Acute Medicine
The Christie & Manchester University NHS Foundation Trusts
Honorary Senior Lecturer, University of Manchester
Treasurer, Society for Acute Medicine
Editor-in-Chief, Acute Medicine

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@acutemed2
Overview

• Impact of checkpoint inhibitors
• Description of immune-related toxicities
• Current guidelines
• Approach to an unwell patient on checkpoint inhibition
Learning from neutropenic sepsis

For better, for worse?

A review of the care of patients who died within 30 days of receiving systemic anti-cancer therapy
Mechanism of checkpoint inhibitors

- PD-1 inhibitors:
  - Nivolumab
  - Pembrolizumab

- CTLA-4 inhibitors:
  - Ipilimumab
  - Tremelimumab

- PD-L1 inhibitors:
  - Atezolizumab
  - Durvalumab
Evidence for checkpoint inhibitors

Overall Survival Rates: Nivolumab vs. Dacarbazine

- OS at 1 year: 72.9% in nivolumab group vs. 42.1% in dacarbazine group
- Median progression free survival was 5.1 months vs. 2.2 months

Combination Checkpoint Inhibition

A Progression-free Survival

B Overall Survival
Immune-related toxicities

- Encephalopathy, aseptic meningitis, paraesthesias, weakness
- Sicca syndrome
- Myocarditis
- Diarrhea, colitis, perforation, megacolon
- Vasculitis
- Hypophysitis
- Thyroiditis
- Pneumonitis
- Lupus nephritis, acute interstitial nephritis
- Hepatitis
- Myositis
- Inflammatory arthritis

Dirzeno et al. The Rheumatologist
Timing of IR toxicities
Frequency of IR Toxicities

Brahmer et al 2018. ASCO
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen1, F. Carbonnel2, C. Robert3, K. M. Ker4, S. Peters5, J. Larkin6 & K. Jordan7, on behalf of the ESMO Guidelines Committee

1 Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; 2 Department of Gastroenterology, Kremsmünster Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; 3 Department of Medicine, Dermatology Unit, Guise Stewart Cancer Campus, Vittel, France; 4 Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; 5 Oncology Department, Centre Hospitalier Universitaire Vaudois, CHUV, Lausanne, Switzerland; 6 Royal Marsden Hospital NHS Foundation Trust, London, UK; 7 Department of Medicine, Kantonsspital, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddel 4, CH-6920 Vigano-Fiesso, Switzerland. E-mail: clinicalguidelines@esmo.org
†Approved by the ESMO Guidelines Committee May 2017.
UKONS Guidelines

Pneumonitis

Guideline 34: Immune-Related Event

Pulmonary AEs have been observed following treatment with immunotherapy and these occurred after a single dose and after as many as 40 treatments. The frequency of pulmonary AEs may be greater with immunotherapy than with monoclonal antibodies. The majority of cases reported were Grades 1 or Grade 2 and subjects presented with either asymptomatic radiographic changes (e.g., interlobular septal thickening, parahilar nodules) or with symptoms such as cough, shortness of breath, or fever. Subjects with reported Grade 3 or Grade 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia.

Mild (Grade 1)
Clinically asymptomatic or radiographic changes only (e.g., ground glass opacities, parahilar nodules)

Management Plan:
- Clinical Assessment & OS SATS investigations:
  - Spinal screen for MG and SLE
  - Baseline troponin (PCR, U & E, LFTs, CRP, C-reactive protein; CRP)
  - Consider review of chest X-ray
  - Monitor symptoms weekly and reimage if worsening
  - Consider delay of immunotherapy

Moderate (Grade 2)
Mild to moderate new onset of symptoms or limiting instrumental ADLs (e.g., dyspnea, cough, fever, chest pain)

Management Plan:
- Clinical assessment & OS SATS investigations:
  - Spinal screen for MG and SLE
  - Baseline troponin (PCR, U & E, LFTs, CRP, C-reactive protein; CRP)
  - C7 imaging (MRI C7)
  - Pulmonary function test
  - Consider bronchoscopy, biopsy & SAI

To exclude atypical infections:
- Beta-D-glucan
- Luminas antibodies and pneumococcal antigen
- Mycoplasma serology

Treatment:
- Prednisolone 0.5 - 1 mg/kg/day (max. 60 mg/day in pediatric patients) or MP
- If evidence of infection consider ARS
- Consider local protocol
  - Antibiotics
  - Pulmonary function test
  - Consider hospitalization
  - Refer to a chest physician
  - Monitor symptoms daily with clinical examination review if symptoms worsening (first repeat imaging)

Assess response to treatment within 72 hours

Severe/Life-Threatening (Grade 3 & 4)
Severe new onset of symptoms limiting daily activities or hypoxia (new or worsening) or ARDS

Management Plan:
- Clinical assessment & OS SATS investigations:
  - Spinal screen for MG and SLE
  - Baseline troponin (PCR, U & E, LFTs, CRP, C-reactive protein; CRP)
  - C7 imaging (MRI C7)
  - Pulmonary function test
  - Consider bronchoscopy, biopsy & SAI

To exclude atypical infections:
- Beta-D-glucan
- Luminas antibodies and pneumococcal antigen
- Mycoplasma serology

Treatment:
- Prednisolone 0.5 - 1 mg/kg/day (max. 60 mg/day in pediatric patients) or MP
- Consider increasing to 4 mg/kg/day if clinical improvement is unsatisfactory
- If evidence of infection consider ARS
  - As per local protocol
  - Consider the use of ARS with local respiratory team
  - Antibiotics
  - Discontinue immunotherapy
  - Admit patient
  - Refer to a chest physician
  - Monitor symptoms daily with clinical examination and repeat imaging as indicated
  - If symptoms worsening, repeat imaging is required

Persist of worsening > 3 days IV/IM corticosteroids

If symptoms persist after 5 days of IV corticosteroids, reverse MUF
- Under guidance of chest physician

Symptoms: Mucous or chronic cough or Sputum or Fever or Severe shortness of breath

Always make sure that the Acute Oncology Team are informed of patients’ assessment and/or admission as soon as possible.

Immediate advice is available from the Acute Oncology on call rota.

SACT, including oral therapy until, you have discussed the patient with the Acute Oncology Team.
### General approach to IR toxicities

<table>
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<tr>
<th>CTCAE Grade</th>
<th>Management</th>
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| 1           | Supportive treatment  
               Close monitoring  
               Investigations to exclude other cause of symptoms  
               Patient advice and education |
| 2           | As per grade 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 |
Case Study

- 54 year old male
- Metastatic melanoma
- Completed 3 cycles of Ipilimumab
- 4 day history of generalized headache, extreme fatigue and nausea
- Seen 2 days earlier at local Uni hospital
  - CT brain – NAD
  - Diagnosed migraine and discharged
Case Study (Examination)

- Drowsy but easily rousable
- BP = 100/60mmHg. Pulse = 90bpm
- Chest clear
- No focal neurology
- BM = 2.1mmols
Case Study (Pituitary Profile)

- Cortisol < 50
- TSH = 0.03
- LH < 1
- FSH < 2
- ACTH = 10
- Prolactin = 150
Guidelines

ACUTE MANAGEMENT OF CKI ENDOCRINOLOGICAL COMPLICATIONS

EMERGENCY GUIDANCE

SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE

Acute management of the endocrine complications of checkpoint inhibitor therapy

C E Higham1, A Olsson-Brown2,3, P Carroll4, T Cooksley5, J Larkin6, P Lorigan7, D Morganstein8 and P J Trainer1

1Department of Endocrinology, Christie Hospital NHS Foundation Trust, Manchester, Centre for Endocrinology and Diabetes, Institute of Human Development, Faculty of Medical and Human Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
2The Clatterbridge Cancer Centre, Bebington, Wirral, UK
3The University of Liverpool, Brownlow Hill, Liverpool, UK
4Department of Endocrinology, Guy’s & St. Thomas’ NHS Foundation Trust, London, UK
5Department of Acute Medicine, UHSM and Christie Hospital NHS Foundation Trust, Manchester, UK
6Skin Unit, Royal Marsden Hospital, London, UK
7Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester, UK
8Department of Endocrinology, Chelsea and Westminster Hospital, London, UK
9The Society for Endocrinology, Woodlands, Bradley Stoke, Bristol, UK
### Guidance for life-threatening immune-related endocrinopathy

#### Management of a life-threateningly unwell (CTCAE grade 3–4) patient

**Assess** for the following signs/symptoms:
- hypotension (systolic BP <90 mmHg)
- postural hypotension (>20 mmHg drop in BP from standing to sitting)
- dizziness / collapse
- hypovolemic shock
- abdominal pain, tenderness and guarding
- nausea and vomiting

**Severe, potentially life threatening and possibility of hypoadrenalism: needs urgent management**
- tachycardia +/- cardiac arrhythmias
- fever
- confusion/delirium
- coma
- hypernatraemia/hyperkalaemia/hypoglycaemia
- pre-renal/renal failure

**Measure (alongside other acute assessment measures as indicated e.g. blood cultures):**
- random serum cortisol and plasma ACTH
- U+E/LFTs/CRP/FBC/TSH/FT4/glucose
- Prolactin, testosterone/oestradiol, LH/FSH

**Treat as adrenal insufficiency as per Society for Endocrinology Emergency Endocrine Guidance:**

- Hydrocortisone (immediate bolus injection of 100 mg hydrocortisone i.v. or i.m. followed by continuous intravenous infusion of 200 mg hydrocortisone per 24 h (alternatively 50 mg hydrocortisone per i.v. or i.m. infusion every 6 h)

**Rehydration with rapid intravenous infusion of 1000 mL of isotonic saline infusion within the first hour, followed by further intravenous rehydration as required (usually 4–6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients)**

**random serum cortisol >450 nmol/l**

- stop adrenal insufficiency management
- reassess cause of signs and symptoms

**random serum cortisol <450 nmol/l**

- convert to oral hydrocortisone (initially 20/10/10 mg to reduce to maintenance of 10/5/5 mg or oral prednisolone (maintenance 3–5 mg per day)
- consider primary adrenal failure; assess renin/aldosterone (particularly if ACTH elevated/norma) and hypernatremia present
- continue immunotherapy if no other contraindications

**Once clinically stable:**
- continue i.v.i.m infusion of hydrocortisone until clinically stable (usually 24–48 hrs)
- assess for additional underlying conditions if response is delayed
- review ACTH results
- measure remainder of pituitary function if not already measured (LH/FSH, oestradiol/testosterone, prolactin, IGF-I)
- if suspicion of hypopituitarism arrange (urgent) MRI pituitary with contrast

**Once replaced with glucocorticoids, if develops significant polyuria/polydipsia consider Diabetes Insipidus**
Guidance for possible mild/moderate immune-related endocrinopathy

Management of patient with mild/moderate symptoms (CTCAE grade 1–2) compatible with cortisol deficiency

- tiredness/fatigue
- weight loss
- susceptibility to infection
- normal BP with no postural drop

mid/mild: non life-threatening (may become life-threatening if intermittent illness/physical stress occurs)

measure serum cortisol (ideally at 9 am), and ACTH

(footnote 1)

9 am cortisol <200 nmol/l or random cortisol <100 nmol/l
adrenal insufficiency likely

- start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5mg)
- refer to specialist services (Endocrinology)
- measure remainder of pituitary profile: IGF-1/TSH/T4/LH+FSH/24hr corticosterone
  For TFT abnormalities see Algorithm 3
- if suspicion of primary adrenal failure or ACTH elevated measure plasma renin and aldosterone
- give emergency advice about HIC: https://www.endocrinology.org/adrenal-crisis/
  https://doi.org/10.1530/EC-16-0084
- continue immunotherapy if no other contraindications

9 am cortisol 200–450 nmol/l or random cortisol 100–450 nmol/l
adrenal insufficiency possible

- refer to Endocrinology
- measure remainder of pituitary profile: IGF-1/TSH/T4/LH+FSH/T24hr corticosterone
  For TFT abnormalities see Algorithm 3
- consider SST (but interpret with caution if ACTH low as may be falsely reassuring in recent onset pituitary disease – discuss with Endocrinology)
- continue immunotherapy if no other contraindications
- if delay in Endocrine referral anticipated start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5mg)

9 am or random cortisol >450 nmol/l
adrenal insufficiency unlikely

- consider other causes of symptoms
- continue immunotherapy if no other contraindications

Footnotes:

Footnote 1: Review patient information for evidence of recent steroid use:
- any supraphysiological dose of glucocorticoid can suppress the adrenal axis.
- patients receiving doses of dexamethasone >0.75 mg or prednisolone >3mg daily likely have a suppressed endogenous HPA axis and may have a serum cortisol measurement <50 nmol/l. If the glucocorticoid treatment is ongoing they are not adrenally insufficient but may need higher doses of glucocorticoids when clinically unwell. Seek specialist advice from endocrinology.
Immune-related myocarditis

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

Douglas B. Johnson, M.D., Justin M. Balko, Pharm.D., Ph.D.,
Margaret L. Compton, M.D., Spyridon Chalkias, M.D., Joshua Gorham, B.A.,
Yaoxin Xu, Ph.D., Melissa Hicks, Ph.D., Igor Puzanov, M.D.,
Matthew R. Alexander, M.D., Ph.D., Tyler L. Bloomer, M.D.,
Jason R. Becker, M.D., David A. Slosky, M.D., Elizabeth J. Phillips, M.D.,
Mark A. Pilkington, M.D., Ph.D., Laura Craig-Owens, M.D., Nina Kola, M.D.,
Gregory Plautz, M.D., Daniel S. Reshef, M.D., M.P.H., Ph.D.,
Jonathan S. Deutsch, M.D., Raquel P. Deering, Ph.D.,
Benjamin A. Olenchock, M.D., Ph.D., Andrew H. Lichtman, M.D.,
Dan M. Roden, M.D., Christine E. Seidman, M.D., Igor J. Koralnik, M.D.,
Jonathan G. Seidman, Ph.D., Robert D. Hoffman, M.D., Ph.D.,
Janis T. Taube, M.D., Luis A. Diaz, Jr., M.D., Robert A. Anders, M.D.,
Jeffrey A. Sosman, M.D., and Javid J. Moslehi, M.D.

SUMMARY

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations in infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell–driven drug reaction. (Funded by Vanderbilt-Ingram Cancer Center Ambassadors and others.)
Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

• 1.14% prevalence of myocarditis
• Median onset of 34 days
• More common in patients on combination checkpoint inhibition
• More common in diabetic patients
• 54% had no other IR toxicities
• 38% of major adverse cardiac events had normal LV
• Lower steroid doses were associated with
  Higher residual troponin rates
  Higher major adverse cardiac events
CENTRAL ILLUSTRATION: Algorithm for Work-Up and Management of Immune-Mediated Myocarditis

- Patient on immune checkpoint inhibitors (ICI) or prior ICI use

- Patient presenting with new cardiovascular (CV) symptoms
  - Electrocardiogram (ECG) and troponin test
    - Normal results
    - Elevated results
      - New ventricular arrhythmia or conduction system disease?
        - N
        - Outpatient echo and NT-proBNP testing
      - Y
      - Elevated troponin/abnormal EKG
        - If indeterminate troponin, retest to eliminate false result

- Patient with acute CV symptoms

Possible myocarditis: Admit patient
Stop ICI therapy; Urgent Cardiology/Cardio-Oncology consult;
Determine whether patient is stable or unstable to dictate treatment

Case Study

- 62 year old male
- Melanoma
- Completed 3 cycles of adjuvant combination checkpoint inhibition
- History of Type 2 Diabetes and Hypertension
- Presents with dyspnoea
- ECG – Atrial flutter with 2:1 block
- High-Sensitive Troponin – 3,549 ng/L
Case Study

- Urgent Cardiac MRI
- Demonstrates reversible ischaemia in LAD
- No features of IR myocarditis
- Treated for NSTEMI

- Not an immune-related myocarditis
  - Could checkpoint inhibitors activate inflammation in pre-existing atherosclerotic coronary artery disease?
Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center


Imad El Majzoub, MD, Aitham Odajat, MD, Kyaw Z. Thein, MD, Myint A. Win, MD, Myel M. Han, MD, Kellen Jacobson, MD, Patrick S. Chaffari, MD, Michael Prejean, RN, Ciclito Reyes-Gilby, PhD, Sai-Ching J. Yeung, MD, PhD
Emergency Workup

- Low threshold for considering IR toxicities
- Need thorough clinical work up
- Need to exclude important non-IR related diagnoses

- Early initiation of high dose steroids in those with high clinical suspicion
- Role for early infliximab (anti-TNF) to minimize long-term steroid exposure?

- Urgently need more “real world” data regarding IR and non-IR events presenting as emergencies
• Biomarkers for prediction of those at risk
• Biomarkers for detection
• Antibiotic therapy and risk of infection
  • GI microbiome may affect risk of IR colitis
  • May affect effectiveness of treatment
• RCTs into the optimal management
  • Timing of infliximab/immunosuppression
• Ambulatory management?
  • Is it possible to identify cohort at low risk of complications with Grade 3 toxicity?
Disseminating knowledge

- IR toxicities will become more prevalent in AMUs
- Recognition of these complications and knowledge of their management will be increasingly important for Acute Physicians
- Research is needed into the optimal strategies and pathways for their management
- Education of patient and physicians
Conclusions

- Emergency presentations in patients on checkpoint inhibition are a challenge
- Need to distinguish IR and non-IR presentations
- Research needed into management and pathways of IR toxicities
- Real world data required
- Education of patients and health care professionals
- Significant opportunity and need for Acute Medicine involvement