Evaluation of immune-related toxicities from an emergency standpoint

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@acutemed2
Faculty Disclosure

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Overview

• Models of delivering care for immune-related toxicities
• Description of immune-related toxicities
• Current guidelines
• Approach to an unwell patient on checkpoint inhibition
‘Every system is perfectly designed to achieve the results it obtains’

• Medicine has 3 key tenets:-
  – Understanding disease biology
  – Discovering effective therapies
  – Ensuring those therapies delivered effectively

• Many factors; system determines performance and need to change its pieces
Emergency oncology: development, current position and future direction in the USA and UK

Tim Cooksley¹ • Terry Rice²
“In what has become a near-weekly ritual, one of us receives an emotionally laden call about the plight of a loved one, colleague or acquaintance with cancer who needs our help to navigate the labyrinth of emergency care. The patient may receive care at our comprehensive cancer center but become “stranded” in an ED outside the often rigid borders between our center and other healthcare systems.... These exercises often end with the caller’s tremendous expression of gratitude, thanking us for being “miracle workers”. However, it shouldn’t take a miracle to communicate and deliver high quality patient-centered care in the ED.”
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

Postow et al 2018 Uptodate
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

- Rash, pruritis
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis
Frequency of IR Toxicities

Brahmer et al 2018. ASCO
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)

- Alert
- 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
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline


ABSTRACT

Purpose
To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events in patients treated with immune checkpoint inhibitor (ICPi) therapy.
CLINICAL PRACTICE GUIDELINES

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. Kerr⁴, S. Peters⁵, J. Larkin⁶ & K. Jordan⁷, on behalf of the ESMO Guidelines Committee

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†Approved by the ESMO Guidelines Committee, May 2017.
UKONS Guidelines

Pulmonary AEs have been observed following treatment with immunotherapy and have occurred after a single dose and after as many as 48 treatments. The frequency of pulmonary AEs may be greater with immunotherapy combination therapies than monotherapy. The majority of cases reported were Grade 1 or Grade 2 and subjects presented with either asymptomatic radiographic changes (e.g., focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnea, cough, 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.

**Guideline 34. Pneumonitis**

**Mild (Grade 1)**
Clinically asymptomatic with radiographic changes only (e.g., focal ground glass opacities, patchy infiltrates).

- Management Plan:
  - Clinical Assessment & O2 SATS
  - Investigation:
    - Sputum sample for M. tuberculosis
    - baseline bloods (FBC, U & E’s, LFT’s)
    - CRP, calcium
  - Action:
    - Monitor symptoms weekly and re-image if worsening
    - Consider delay of immunotherapy
  - Decision:
    - Worsen

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

- Management Plan:
  - Clinical Assessment & O2 SATS
  - Investigation:
    - Sputum sample for M. tuberculosis
    - baseline bloods (FBC, U & E’s, LFT’s)
    - CRP, calcium
    - CT imaging (HR CT)
    - Pulmonary function test
    - Consider bronchoscopy, biopsy & BAL
    - To exclude atypical infections:
      - Beta-D-glucan
      - Ultrasound legionella and pneumococcal antigen
      - Mycoplasma serology
    - Treatment:
      - Prednisolone 0.5 – 1mg/kg/day (max. 60mg/day prednisolone) + PPI
      - If evidence of infection consider ABX as per local protocol
    - Action:
      - Hold immunotherapy
      - Consider hospital admission
      - Refer to a chest physician
      - Monitor symptoms daily with clinical examination review if symptoms worsening (with repeat imaging)
  - Decision:
    - Persist or worsen or relapse

**Severe (Grade 3-4)**
Severe new onset of symptoms limiting self-care ADL or hypoxia (O2 or worsening or AEs).

- Management Plan:
  - Clinical Assessment & O2 SATS
  - Investigation:
    - AS pneumonia (grade 3)
    - Bronchoscopy biopsy & BAL
  - Treatment:
    - IV M. tuberculosis sensitization therapy + PPI
    - Consider increasing to 4x20mg daily if clinical improvement is insufficient
  - If evidence of infection consider ABX as per local protocol
  - Discourage the use of ABX with local respiratory team
  - Action:
    - Discontinue immunotherapy
    - Activating patient
    - Refer to a chest physician
    - Monitor symptoms daily with clinical examination and repeat imaging as indicated, if symptoms worsening, repeat imaging as required

**Assess response to treatment within 72 hours**

Symptoms: Resolve or improve to mild
See steroid tapering guidance

**Persist or worsen or relapse**

If symptoms persist after 3 days of IV glucocorticoids, consult NRIF:
Utilize guidance of chest physician

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

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<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 |
Guidelines

Endocrine Connections

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

the Society for Endocrinology (SfE) Clinical Committee9

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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
- tachycardia +/- cardiac arrhythmias
- fever
- confusion/delirium
- coma
- hyponatraemia/hyperkalaemia/hypoglycaemia
- pre-renal/renal failure

Severe, potentially life threatening and possibility of hypoadrenalism: needs urgent management

Measure (alongside other acute assessment measures as indicated e.g. blood cultures):
- random serum cortisol and plasma ACTH
- U+E/LFTs/CRP/FBC/TSH/T4/glucose
- Procteine, testosterone/oesiodial, 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. injection 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

(footnotes 1 & 5)

random serum cortisol <450 nmol/l

- 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, oestrogen/testosterone, prolactin, IGF-I)
- if suspicion of hypopituitarism arrange (urgent) MRI pituitary with contrast

(footnote 6)

once clinically stable:
- 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/normal and hyponatraemia present)
- continue immunotherapy if no other contraindications

(footnote 8)

once replaced with glucocorticoids, if develops significant polyuria/polydipsia consider Diabetes Insipidus

(footnote 9)
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

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

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

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

- start oral hydrocortisone (10, 5, 5 mg) or prednisolone (3–5 mg)
- refer to specialist services (Endocrinology)
- measure remainder of pituitary profile IGF-1/TSH/T4/LH+FSH/T2orE2/prolactin
  For TFT abnormalities see Algorithm 3
- if suspicion of primary adrenal failure or ACTH elevated measure plasma renin and aldosterone
- give emergency advice about H/C: https://www.endocrinology.org/adrenal-crisis/
  https://doi.org/10.1530/EC-16-0054
- 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/T2orE2/prolactin
  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 (3–5 mg)

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 >3 mg daily will likely have a suppressed endogenous HPA axis and may have a serum cortisol measurement of <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.
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., Yaomin 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. Pilkinton, M.D., Ph.D., Laura Craigh-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 M. Taube, M.D., Luis A. Díaz, 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 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.)
Original Investigation

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

Syed S. Mahmood MD, MPH a, b, Michael G. Fradley MD c, Justine V. Cohen DO d, Anju Nohria MD e, Kerry L. Reynolds MD d, Lucie M. Heinzlerling MD, MPH f, Ryan J. Sullivan MD d, Ronprasat Damrongwalanasuk MD g, Carol L. Chen MD g, Dipti Gupta MD, MPH g, Michael C. Kirchberger MD f, Magid Awadalla MD b, Malek Z.O. Hassan MD b, Javid J. Moslehi MD b, Sachin P. Shah MD f, Sarju Ganatra MD i, Paaladinesh Thavendiranathan MD i, Donald P. Lawrence MD d, ... Tomas G. Neilan MD, MPH b, k, l, m
• 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
        - New ventricular arrhythmia or conduction system disease? (N)
          - Outpatient echo and NT-proBNP testing
      - Elevated results
        - Elevated troponin/abnormal EKG
        - If indeterminate troponin, retest to eliminate false result
          - Possible myocarditis: Admit patient
            - Stop ICI therapy; Urgent Cardiology/Cardio-Oncology consult;
              Determine whether patient is stable or unstable to dictate treatment
  - Patient with acute CV symptoms
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 presentation
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 “real world” data regarding IR and non-IR events presenting as emergencies
Future research

- 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
- Ambulatory management?
  - Is it possible to identify cohort at low risk of complications with Grade 3 toxicity?
Alternative Strategies to Inpatient Hospitalization for Acute Medical Conditions

A Systematic Review

Jared Conley, MD, PhD, MPH; Colin W. O'Brien, BS; Bruce A. Leff, MD; Shari Bolen, MD, MPH; Donna Zulman, MD, MS

**IMPORTANCE** Determining innovative approaches that better align health needs to the appropriate setting of care remains a key priority for the transformation of US health care; however, to our knowledge, no comprehensive assessment exists of alternative management strategies to hospital admission for acute medical conditions.

**OBJECTIVE** To examine the effectiveness, safety, and cost of managing acute medical conditions in settings outside of a hospital inpatient unit.
Disseminating knowledge

- IR toxicities will become more prevalent in non-Oncology hospitals
- Recognition of these complications and knowledge of their management will be increasingly important for non-Oncologists
- 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