Emergency management of immune-related toxicities

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Overview

• Models of emergency care for immune-related toxicities
• Case studies immune-related toxicities
• Current guidelines
• Approach to an emergency patient being treated with ICIs
Emergency oncology: development, current position and future direction in the USA and UK

Tim Cooksley¹ • Terry Rice²
Emergency Oncology Models

CARE OF PATIENTS WITH CANCER WHO VISIT EMERGENCY

OBJECTIVE
To determine whether continuity of care, cancer expertise or both affect outcomes in patients with cancer who require emergency department (ED) care.

STUDY POPULATION
42,820 patients who received chemotherapy or radiation in the 30 days before a cancer-related visit to the ED in Ontario between 2006 and 2011.

1. DOES CONTINUITY OF CARE AFFECT OUTCOMES?

<table>
<thead>
<tr>
<th>Alternative Versus Original Hospital</th>
<th>Admission to hospital</th>
<th>Return visits to the ED</th>
<th>30-day mortality</th>
<th>CT imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOWER</td>
<td>OR 0.78 (95% CI 0.74-0.83)</td>
<td>HR 1.06 (95% CI 1.03-1.11)</td>
<td>NO DIFF.</td>
<td>NO DIFF.</td>
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<tr>
<td>HIGHER</td>
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<tr>
<td>NO DIFF.</td>
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</tbody>
</table>

2. DOES CANCER EXPERTISE AFFECT OUTCOMES?

<table>
<thead>
<tr>
<th>Alternative General Hospital Versus Original Hospital or Cancer Centre</th>
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</thead>
<tbody>
<tr>
<td>Admission to hospital</td>
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<tr>
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<td>CT imaging</td>
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</tbody>
</table>

Cancer expertise of an institution rather than continuity of care may be an important predictor of outcomes following emergency treatment of patients with cancer.

Note: OR = odds ratio; HR = hazard ratio; no diff. = no difference; CT = computed tomography
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Immune-related toxicities

- Encephalopathy, aseptic meningitis, parasthesias, 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
Frequency of IR Toxicities

Brahmer et al. 2018. ASCO
Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center


Imad El Majzoub, MD, Aiham Qdaisat, MD, Kyaw Z. Thein, MD, Myint A. Win, MD, Myat M. Han, MD, Kalen Jacobson, MD, Patrick S. Chaffari, MD, Michael Prejean, RN, Cielito Reyes-Gibby, PhD, Sai-Ching J. Yeung, MD, PhD
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 Committee⁸

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

†Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via La Taddei 4, CH-6962 Viganello-Lugano, Switzerland, E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee, May 2017.
## General approach to IR toxicities

<table>
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<tr>
<th>CTCAE Grade</th>
<th>Management</th>
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</table>
| 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)

- 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
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

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⁸Department of Endocrinology, Chelsea and Westminster Hospital, London, UK
⁹The Society for Endocrinology, Woodlands, Bradley Stoke, Bristol, UK
Guidance for life-threatening immune-related HPA toxicity

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/S/LFTs/CRP/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. 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
(footnotes 1 & 5)

- stop adrenal insufficiency management
- reassess cause of signs and symptoms
(footnote 6)

random serum cortisol <450 nmol/l
(footnotes 1 & 5)

- 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
(footnote 7)

once replaced with glucocorticoids, if develops significant polyuria/polydipsia consider Diabetes Insipidus
(footnote 9)

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 serum renin/aldosterone (particularly if ACTH elevated/normal and hyponatraemia present)
- continue immunotherapy if no other contraindications
Steroid management of IR HPA toxicity

Original Article

High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma

Alexander T. Faje MD, Donald Lawrence MD, Keith Flaherty MD, Christine Freedman RN, Riley Fadden NP, Krista Rubin NP, Justine Cohen MD, Ryan J. Sullivan MD

First published: 05 July 2018 | https://doi.org/10.1002/cncr.31629 | Cited by: 4
Collaboration is key

Correspondence

Emergency management of immune-related hypophysitis: Collaboration between specialists is essential to achieve optimal outcomes

Tim Cooksley MBChB (Hons), MRCP (Acute), Claire Higham MBBS, DPhil, Paul Lorigan MBBCH, FRCP, Peter Trainer MBChB, MD

First published: 23 October 2018 | https://doi.org/10.1002/cncr.31789
Case Study

- 47 year old male
- Metastatic melanoma
- Completed 2 cycles of Ipi/Nivo
- Presents with:
  - Severe and rapidly progressively dyspnoea
  - Dry cough
  - Myalgia/fatigue
Clinical examination

• Unwell. Extremely dyspnoeic
• Apyrexial
• BP = 140/70mmHg Pulse =130bpm
• RR = 40 O₂ SATS = 82% (AIR)
• Chest clinically clear
• Abdo and neuro examination unremarkable
Emergency management

• Cultures – including Viral N+T swabs, PCP screen and β-Glucan
• Urgent HRCT
• Too unwell for bronchoscopy

• High flow Oxygen
• IV Methylprednisolone 2mg/kg - PPI and antimicrobial prophylaxis
• IV Co-Amoxiclav
• Chest physio
• Agreement with ICU colleagues for IPPV if required
• Given IV infliximab (5mg/kg) at 24 hours given severity of illness
Immune-mediated granulomatous pneumonitis
Clinical progress

• Excellent clinical progress over 72 hours
• High flow oxygen weaned
• 3 days of IV methylprednisolone (2mg/kg)
• Cultures and β – Glucan negative
• Weaned to oral prednisolone
• Commenced on Mycophenolate Mofetil 500mg BD
• Discharged at 5 days with early clinic follow up
1 week later
Case presentation

- 57 year old male with metastatic papillary renal cell carcinoma
- C1 Ipi/Nivo
- Presents with rapid onset of diplopia
Case presentation
Emergency management

• Commenced on IV methylprednisolone (1mg/kg)
• Pyridostigmine 60mg TDS
• Monitoring FEV1

• EMG – Abnormal jitter analysis in facial muscles

• IV Immunoglobulins (1g/kg)

• Excellent clinical progress
• Converted to weaning oral prednisolone and MMF 500mg BD
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.
Antibiotics and ICIs

ORIGINAL ARTICLE

Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer

L. Derosa1,2,3, M. D. Hellmann1,5,6, M. Spaziano2, D. Halpenny8, M. Fidelie1,2,3, H. Rizvi9, N. Long8, A. J. Plokdowski8, K. C. Arbour4, J. E. Chait4,5, J. A. Rouche10, L. Zitvogel1,2,3,11, G. Zalcman12, L. Albige13,13,14, B. Escudier7,13,14 & B. Routy12,13,15,16

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• 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 and reduce morbidity/mortality in life-threatening IR toxicity?
Future research

- Biomarkers for prediction of those at risk
- Biomarkers for detection
- Antibiotic therapy and risk of infection
- 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?
• 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
• Education of patients and health care professionals