

## **Emergency management of immune-related toxicities**

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The University of Manchester





- Models of emergency care for immune-related toxicities
- Case studies immune-related toxicities
- Current guidelines
- Approach to an emergency patient being treated with ICIs



Support Care Cancer DOI 10.1007/s00520-016-3470-1



COMMENTARY

# Emergency oncology: development, current position and future direction in the USA and UK

Tim Cooksley<sup>1</sup> · Terry Rice<sup>2</sup>



### CARE OF PATIENTS WITH CANCER WHO VISIT EMERGENCY

### VISUAL RESEARCH ABSTRACT

### STUDY POPULATION OBJECTIVE To determine whether continuity of care, cancer 42 820 patients who received chemotherapy or expertise or both affect outcomes in patients with radiation in the 30 days before a cancer-related cancer who require emergency department (ED) care. visit to the ED in Ontario between 2006 and 2011. DOES CONTINUITY OF CARE DOES CANCER EXPERTISE AFFECT OUTCOMES? Alternative Alternative Original Patients: Patients: general n = 42 820 hospital hospital n = 42.820hospital

### ALTERNATIVE VERSUS ORIGINAL HOSPITAL

LOWER	Admission to hospital	LOWE	
HIGHER	Return visits to the ED HR 1.06 95% CI 1.03-L11		HIGHE
NO DIFF.	F. 30-day mortality		
NO DIFF.	IFF. CT imaging		

LTERNATIVE GENERAL HOSPITAL VERSUS RIGINAL HOSPITAL OR CANCER CENTRE				
LOWER	Admission to hospital	OR 0.83 95% CI 0.79~0.88		
HIGHER	Return visits to the ED	HR 1.07 95% CI 1.03-1.11		
HIGHER	30-day mortality	OR 1.13 95% CI 1.05-1.22		
LOWER	CT imaging	OR 0.74 95% CI 0.69-0.80		

### 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 = hazards ratio; no diff. = no difference; CT = computed tomography

Source: Grewal K, Sutradhar R, Krzyzanowska MK, et al. The association of continuity of care and cancer centre affiliation with outcomes among patients with cancer who require emergency department care. CNAJ 2019;191:E436-45.

Original or

centre

other cancer

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### **Immune-related toxicities**



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Dirzeno et al. The Rheumatologist

### **Frequency of IR Toxicities**





Brahmer et al 2018. ASCO

Article in Press



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### Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center

Presented at the National Comprehensive Cancer Network 22nd annual conference, Orlando, FL, March 23-24, 2017.

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

### **Guidelines**



Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017 doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

J. B. A. G. Haanen<sup>1</sup>, F. Carbonnel<sup>2</sup>, C. Robert<sup>3</sup>, K. M. Kerr<sup>4</sup>, S. Peters<sup>5</sup>, J. Larkin<sup>6</sup> & K. Jordan<sup>7</sup>, on behalf of the ESMO Guidelines Committee<sup>\*</sup>

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CTCAE Grade	Management
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





- 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



- Alert
- BP = 100/60mmHg. Pulse = 90bpm
- Chest clear
- No focal neurology
- BM = 2.1mmols



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

### **Guidelines**



# C E Higham et al. Acute management of CKI endocrinopathies 7:5 G1-G7 EMERGENCY GUIDANCE SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE GUIDANCE GUIDANCE GUIDANCE GUIDANCE GUIDANCE

# Acute management of the endocrine complications of checkpoint inhibitor therapy

### C E Higham<sup>1</sup>, A Olsson-Brown<sup>2,3</sup>, P Carroll<sup>4</sup>, T Cooksley<sup>5</sup>, J Larkin<sup>6</sup>, P Lorigan<sup>7</sup>, D Morganstein<sup>8</sup> and P J Trainer<sup>1</sup> the Society for Endocrinology (SfE) Clinical Committee<sup>9</sup>

<sup>1</sup>Department 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 <sup>2</sup>The Clatterbridge Cancer Centre, Bebbington, Wirral, UK <sup>3</sup>The University of Liverpool, Brownlow Hill, Liverpool, UK <sup>4</sup>Department of Endocrinology, Guy's & St. Thomas' NHS Foundation Trust, London, UK <sup>5</sup>Department of Acute Medicine, UHSM and Christie Hospital NHS Foundation Trust, Manchester, UK <sup>6</sup>Skin Unit, Royal Marsden Hospital, London, UK <sup>7</sup>Department of Medical Oncology, Christie Hospital NHS Foundation Trust, Manchester, UK <sup>8</sup>Department of Endocrinology, Chelsea and Westminster Hospital, London, UK <sup>9</sup>The Society for Endocrinology, Woodlands, Bradley Stoke, Bristol, UK

### **Guidance for life-threatening immune-related HPA toxicity**



(footnote 9)

Management of a life-threateningly unwell (CTCAE grade 3-4) patient Assess for the following signs/symptoms: hypotension (systolic BP <90 mmHg)</li> postural hypotension (>20mmHg drop in BP tachycardia +/- cardiac arrythmias from standing to sitting) fever dizziness / collapse confusion/delirium hypovolemic shock coma abdominal pain, tenderness and guarding hyponatraemia/hyperkalemia/hypoglycemia nausea and vomiting 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 (footnote 1) U+Es/LFTs/CRP/FBC/TSH/fT4/glucose (footnote 2) Prolactin, testosterone/oestradiol, LH/FSH (footnote 3) Treat as adrenal insufficiency as per Society for Endocrinology Emergency Endocrine Guidance: (footnote 4) 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 random serum cortisol <450 nmol/l (footnotes 1 & 5) (footnotes 1 & 5) stop adrenal insufficiency management continue i.v./i.m./infusion of hydrocortisone reassess cause of signs and symptoms until clinically stable (usually 24-48 hrs) (footnote 6) assess for additional underlying conditions if response is delayed (footnote 6) review ACTH results once clinically stable: measure remainder of pituitary function if not convert to oral hydrocortisone (initially already measured (LH/FSH, 20/10/10 mg to reduce to maintenance of oestradiol/testosterone, prolactin, IGF-I) 10/5/5 mg) or oral prednisolone (maintenance if suspicion of hypopituitarism arrange 3-5mg per day) (urgent) MRI pituitary with contrast consider primary adrenal failure: assess (footnote 7) renin/aldosterone (particularly if ACTH elevated/normal and hyponatremia present) (footnote 8) once replaced with glucocorticoids, if develops continue immunotherapy if no other significant polyuria/polydipsia consider Diabetes

Insipidus

C. NO. W. C. C. SOCHER, M. 9864 (1994)

contraindications





Original Article

High-dose glucocorticoids for the treatment of ipilimumabinduced 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





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





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



- Unwell. Extremely dyspnoeic
- Apyrexial
- BP = 140/70mmHg Pulse =130bpm
- RR =  $40 O_2 \text{ SATS} = 82\% \text{ (AIR)}$
- 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



Manchester University



### **Clinical progress**



- Excellent clinical progress over 72 hours
- High flow oxygen weaned
- 3 days of IV methylprednisolone (2mg/kg)

• Cultures and  $\beta$  – Glucan negative

- Weaned to oral prednisolone
- Commenced on Mycophenolate Mofetil 500mg BD

• Discharged at 5 days with early clinic follow up

### 1 week later







- 57 year old male with metastatic papillary renal cell carcinoma
- C1 lpi/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.





**ORIGINAL ARTICLE** 

Annals of Oncology 29: 1437–1444, 2018 doi:10.1093/annonc/mdy103 Published online 30 March 2018

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

L. Derosa<sup>1,2,3†</sup>, M. D. Hellmann<sup>4,5,6†</sup>, M. Spaziano<sup>7</sup>, D. Halpenny<sup>8</sup>, M. Fidelle<sup>1,2,3</sup>, H. Rizvi<sup>9</sup>, N. Long<sup>8</sup>, A. J. Plodkowski<sup>8</sup>, K. C. Arbour<sup>4</sup>, J. E. Chaft<sup>4,5</sup>, J. A. Rouche<sup>10</sup>, L. Zitvogel<sup>1,2,3,11</sup>, G. Zalcman<sup>12</sup>, L. Albiges<sup>1,3,13,14</sup>, B. Escudier<sup>1,13,14</sup> & B. Routy<sup>1,2,3,15,16\*</sup>





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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?





- 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