Emergency management of immune-related toxicities

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Post MASCC Brussels, Brussels, Nov 2019

@acutemed2
Overview

- Description of immune-related toxicities
- Current guidelines
- Approach to an unwell patient on checkpoint inhibition
- Case studies
Mechanism of checkpoint inhibitors

- PD-1 inhibitors
  - Nivolumab
  - Pembrolizumab

- CTLA-4 inhibitors
  - Ipilimumab
  - Tremelimumab

- PD-L1 inhibitors
  - Atezolizumab
  - Durvalumab
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

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73) P<0.001

Combination Checkpoint Inhibition

A Progression-free Survival

B Overall Survival

Wolchok et al.
NEJM
2017
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

![Graph showing the timing of IR toxicities over time. The graph plots toxicity grade against time in weeks. Different lines represent different toxicities: Rash, pruritus, Liver toxicity, Diarrhea, colitis, and Hypophysitis. Each toxicity peaks at different times.](image)
Frequency of IR Toxicities

A. Distribution of grade 1-2 IRAEs

B. Distribution of grade 3-5 IRAEs

Brahmer et al 2018. ASCO
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.

¹Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; ²Department of Gastroenterology, Kermel 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 Royal Infirmary, Aberdeen, UK; ⁵Department of Medicine, Center 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

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†Approved by the ESMO Guidelines Committee May 2017.
<table>
<thead>
<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
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

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-mediated 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/hyperkalemia/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/FT/FT4/TSH/T3/glucose
- Prolactin, testosterone/oestriol, 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 8 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
- 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

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 3–5mg per day)
- consider primary adrenal failure: assess renin/aldosterone (particularly if ACTH elevated/normal and hyponatraemia present)
- continue immunotherapy if no other contraindications
Guidance for possible mild/moderate immune-mediated HPA toxicity

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 (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/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/TorE2/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 (3–5mg)

- 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 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.
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
High dose steroids for IR HPA toxicity associated with reduced survival

A) Percent survival

- LD, median not reached, $p = 0.002$
- HD, median 23.3 months

No. at risk:

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<td>50</td>
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<td>after</td>
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<td>ipilimumab</td>
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<td>20</td>
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<td>8</td>
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B) Percent without additional treatment or death

- LD, median not reached, $p = 0.001$
- HD, median 11.4 months

No. at risk:

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C) Death

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<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th>Forest Plot</th>
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<tr>
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<table>
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<td>LD vs HD</td>
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<td>LDH*</td>
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<td>16.75</td>
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<td>0.69</td>
<td>0.33-1.52</td>
<td>0.34</td>
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* log transformed
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

- 65 year old male
- Metastatic ureteric carcinoma
- Completed 4 cycles of Pembro
- Presents with:
  - Fatigue
  - Fever
  - Osmotic symptoms
Clinical examination

- Alert
- Temp = 38°C
- Dry
- BP = 110/70mmHg Pulse = 130bpm
- RR = 28 O₂ SATS = 98% (AIR)
- Chest clinically clear
- Abdo and neuro examination unremarkable
Immune-related DKA

- BM = 29.8 mmols
- pH = 7.29, BE = -10.7

- IV insulin infusion
- Bolus of basal insulin
- Judicious fluid resuscitation
- Careful K+ management
- No role for steroids
- Need long term insulin management
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
Myasthenia and Myocarditis

Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan

Shigeaki Suzuki, Nobuhisa Ishikawa, Rumie Konoeda, Nobuhiko Seki, Satoshi Fukushima, Kikuko Takahashi, Hisashi Ubara, Yoshikazu Hasegawa, Shinichiro Inomata, Yasushi Otani, Kenji Yokota, Takashi Hirose, Ryo Tanaka, Norihiro Suzuki, Makoto Matsui
Abatacept for severe IR myocarditis

Salem et al NEJM 2019
Emergency presentation data

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**Annals of Emergency Medicine**

**An International Journal**

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**Articles in Press**

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**Article in Press**

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


*Imad El Majzoub, MD, Aiham Qdaiaat, MD, Kyaw Z. Thein, MD, Myint A. Win, MD, Myat M. Han, MD, Kalen Jacobson, MD, Patrick S. Chaffari, MD, Michael Projean, RN, Cielito Reyes-Gibby, PhD, Sai-Ching J. Young, MD, PhD*
Emergency oncology: development, current position and future direction in the USA and UK

Tim Cooksley¹ • Terry Rice²
Perspective

Ambulatory emergency oncology: A key tenet of future emergency oncology care
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

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 and reduce morbidity/mortality in life-threatening IR toxicity?
- Novel therapies for severe life-threatening toxicity
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
• Ambulatory management of IR toxicities
• Education of patients and health care professionals