Immune Checkpoint Inhibitor Toxicities: What the Intensivist Needs to Know

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No conflict of interests
Objectives

• Review toxicities and workup of toxicities associated with novel immunotherapies

• Discuss available treatment options for neurologic, cardiac, and pulmonary complications related to immunotherapy
Background

- Significant improvements in cancer therapy- using the immune system to suppress tumoral activity
- Immunotherapy: Cell therapy (CARs and TCRs), monoclonal antibodies, vaccines and **Immune checkpoint inhibitors** (ICIs)
- First FDA approved was Ipilimumab (anti-CTLA4) for melanoma in 2011
- 7 have now FDA approval as single or combination therapy for multiple malignancies.
Why does toxicity occur?

- Cytotoxic T-cell have anti-tumoral effects
- Check and balances on T-cell activation and inhibition
- ICIs block T-cell suppression of CTLA4/PD-1/PDL-1 pathway and enhance immune mediated anti-tumoral activity
- Enhanced T-cell activity → high immunogenic response → Immune related adverse events (IRAEs)
How do toxicities present?

- Any organ can be affected
- Within days to months (3m) from last administration of the ICI
- Mild toxicities are more common, and usually respond to treatment
- Grade 3 and 4 toxicities: Incidence and mortality seems now to be higher than what was reported on initial studies

- Meta-analysis from 2009-2018: 613 fatal toxic events
Can we predict these toxicities?

- No specific patient characteristics have been associated to toxicities

- Severe toxicities are more common with combination therapy (anti-CTLA4: 27%, anti-PD-1/PDL-1: 16%, combination: 55%)

- Anti-CTLA4: colitis, hepatitis, skin, hypophisitis
  Anti-PDL1/PD-1: thyroiditis, pneumonitis, myocarditis

- Different distribution within malignancies?

- De-novo vs reactivation of underlying disease?

- In-vivo changes of T-cell, B-cell and NK activity (gene upregulation, cytokine profile and molecular expression) → Can this be used not only for ICI response but toxicity?
What are the Main Toxicities Observed in the ICU?
Pneumonitis

• 1-10% and is more common with anti-PD-1/PD-L1 agents and with combination therapy (15%)

• Most are mild presentations and resolve but can have 14% mortality

• Typically 3 months after last treatment but can be earlier if dual therapy

Naidoo J, et.al. JCO 2017
Pneumonitis

- Grading of symptoms as per CTCAE (Grade 3- >50% lungs and Grade 4-life threatening)

- Imaging and bronchoscopy but usually to help rule other underlying causes of respiratory failure.

- “Sarcoid-like” reactions have been described

<table>
<thead>
<tr>
<th>Radiologic Subtypes</th>
<th>Representative Image</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cryptogenic organizing pneumonia-like (n = 5, 19%)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Discrete patchy or confluent consolidation with or without air bronchograms. Predominantly peripheral or subpleural distribution.</td>
</tr>
<tr>
<td>Ground glass opacities (n = 10, 37%)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Discrete focal areas of increased attenuation. Preserved bronchovascular markings.</td>
</tr>
<tr>
<td>Interstitial (n = 6, 22%)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Increased interstitial markings, interlobular septal thickening. Peribronchovascular infiltration, subpleural reticulation. Honeycomb pattern in severe patient cases.</td>
</tr>
<tr>
<td>Hypersensitivity (n = 2, 7%)</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Centrilobular nodules. Bronchiolitis-like appearance. Tree-in-bud micronodularity.</td>
</tr>
<tr>
<td>Pneumonitis not otherwise specified (n = 4, 15%)</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Mixture of nodular and other subtypes. Not clearly fitting into other subtype classifications.</td>
</tr>
</tbody>
</table>

Naidoo J, et.al. JCO 2017
Cardiac toxicities

- Clinical presentations: Myocarditis, pericarditis, heart failure and arrhythmias

- More common with PD-1/PD-L1

- Uncommon (incidence varies on reporting system) but mortality as high as 50%

- Median incidence at 10 weeks (2w-8m)
Cardiac toxicities-Myocarditis

- Usually fulminant if left untreated and severe cardiovascular events occur even with a normal EF

- Diagnosis: Cardiac MRI and biopsy

- Multicenter registry of 8 centers of 4 years:
  - Incidence approximately 1.2% (n=35) and more common with PD-1, (2.5% with combined therapy)
  - 50% had major events (higher than general population with other causes of myocarditis)
  - No risk factors we identified (malignancy, prior treatments, EKG changes or cardiovascular risk factors)
  - Biopsy: T-cell–predominant lymphocytic infiltrate within the myocardium
  - Major CV events were associated to higher peak troponin levels

Mahmood SS, et.al. J Am Coll Cardiol. 2018
Neurotoxicity

• Until recently were considered to be rare (<1% incidence) but higher incidences now being reported (1%-12% of patients receiving therapy)

• Neuro iAEs compromise 6-15% of all immune checkpoint inhibitor AE related mortality. Unclear data on morbidity

• Clinical Presentations:
  • Neuromuscular disorders: Guillain-Barre Syndrome and Myasthenia Gravis
  • Seizures
  • Posterior Reversible Encephalopathy Syndrome (PRES)
  • Encephalitis, aseptic meningitis
  • Transverse myelitis
  • Cerebral edema
  • Encephalopathy
Neurotoxicity

- Routine diagnostic workup (antibodies for MG, paraneoplastic titers, EEG, EMG)
- Findings on MRI have significant variability
- Lumbar puncture with lymphocytosis can be suggestive, but there is variability in findings—useful to rule out infectious process
Neurotoxicity: Guillain-Barre and Myasthenia Gravis

• Data available is from case series, however in general poor response to treatment and morbidity is significant

• Can be typical presentations or variants (ie: bulbar symptoms alone are common)

• Highly associated to myositis (complicating clinical picture) and myocarditis

• Close monitoring in the ICU

• Treatment is similar to non ICI related: Piridostigmine, corticosteroids, IVIg, plasmapheresis
Other organ toxicities:

• **Endocrine:**
  - Different to all other IRAEs they don’t reverse after discontinuation of therapy
  - Hypophysitis (6.4% incidence with combination therapy, 8-9 weeks after therapy)
  - Hypo/hyperthyroidism and adrenal crisis can occur therefore monitoring of serial cortisol, ACTH levels and thyroid function
  - Diabetes insipidus
  - De-novo DM <1% (presenting as either DKA or HHS)

• **Nephrotoxicity**
  - 2% to 5% (when combination therapy)
  - Acute interstitial nephritis or minimal change disease
  - Increased risk when underlying auto-immune disease? Or “2nd hit”? 

• **Gastrointestinal:**
  - Colitis, pancreatitis and hepatitis
Diagnosis

• Differential diagnosis should be kept and treated concomitantly when necessary (ie: antibiotics for possible infectious causes while ruling out pneumonitis)

• Biopsy - can be considered (colitis, myocarditis, pneumonitis, nephrotoxicity)
  - helpful to rule out other conditions
  - does it play a role in “customizing therapy”? 
## Treatment

- Guidelines by ASCO, ESMO, SITC and others

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>ASCO</strong></td>
<td></td>
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</tr>
<tr>
<td>Pulmonary</td>
<td>corticosteroids (1-2 mg/kg methylpred)</td>
<td>mycophenolate, IVlg, infliximab or cyclophosphamide</td>
</tr>
<tr>
<td>Neurological</td>
<td>corticosteroids (1-2 mg/kg or 1gr methylpred)</td>
<td>IVlg or plasmapheresis. Rituximab</td>
</tr>
<tr>
<td>Cardiac</td>
<td>corticosteroids (1-2 mg/kg or 1gr methylpred)</td>
<td>mycophenolate, infliximab or ATG</td>
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<tr>
<td><strong>ESMO</strong></td>
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<td>Pulmonary</td>
<td>corticosteroids (1-2 mg/kg methylpred)</td>
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</tr>
<tr>
<td>Neurological</td>
<td>corticosteroids (1-2 mg/kg methylpred)</td>
<td>plasmapheresis or IVlg, azathioprine, cyclosporine, mycophenolate</td>
</tr>
<tr>
<td>Cardiac</td>
<td>corticosteroids (&quot;high dose&quot;)</td>
<td>mycophenolate, infliximab or ATG</td>
</tr>
<tr>
<td>Others:</td>
<td>methylprednisolone 4 mg/kg/day</td>
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Treatment: General Approach

• Discontinuation of the agent (can they be restarted?)

• Corticosteroids:
  • start with prednisone 0.5 mg/kg daily and increase to 1-2mg/kg methylprednisolone up to pulse dose.
  • Prolonged taper of 4 to 6 weeks

• For steroid refractory:
  • Cyclophosphamide, tacrolimus, mycophenolate, ATG
  • Plasmapheresis and IVIg
Treatment: Directed Therapy

• More than 10% of patients require additional immunosuppressant

• Consider using early in certain severe AEs such as myocarditis

• Biopsy driven?
  • T-cell -IL-6, IL-1R, IL-12 and IL-23 blockade
  • B-cell: anti-CD20
  • Monocytes: anti-TNFα

<table>
<thead>
<tr>
<th>iAE Indications</th>
<th>Protocols</th>
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<tbody>
<tr>
<td>Anti-IL-2 blockade</td>
<td>Severe iAE during acute phase: severe or refractory arthritis; chronic</td>
</tr>
<tr>
<td></td>
<td>inflammatory; demyelinating; polyadenosine; pyrimidin-like reactions;</td>
</tr>
<tr>
<td></td>
<td>eosinophilic; myeloid; meningitis; myocarditis; mesothelioma;</td>
</tr>
<tr>
<td></td>
<td>T-cell-IL-6, IL-1R, IL-12 and IL-23 blockade</td>
</tr>
<tr>
<td>Anti-IL-6 blockade</td>
<td>Severe iAE during acute phase: severe or refractory arthritis; large</td>
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<tr>
<td></td>
<td>vessel vasculitis: overtis; myocarditis; pneumonia; myocarditis</td>
</tr>
<tr>
<td>Intervascular Immunoglobulins</td>
<td>Guillain-Barré syndrome, sepsis and chronic inflammatory demyelinating</td>
</tr>
<tr>
<td></td>
<td>polyadenosine; subarach and chronic inflammatory neuropathies: immune</td>
</tr>
<tr>
<td></td>
<td>neurectopic immune thrombo-ocipital facial nerve palsies; myocarditis</td>
</tr>
<tr>
<td></td>
<td>Transverse myelitis, enteric neuropathy, encephalitis, atypical meningitis</td>
</tr>
<tr>
<td>Anti-CD20 depletion</td>
<td>Systemic lupus erythematosus; severe Sjögren's syndrome; ANCA-associated</td>
</tr>
<tr>
<td></td>
<td>vasculitis; cutaneous vasculitis; autoimmune antiterlergic gangliopathy;</td>
</tr>
<tr>
<td></td>
<td>sensory gangliopathy, nephritis, myocarditis; transverse myelitis; entry</td>
</tr>
<tr>
<td></td>
<td>encephalitis; atypical meningitis; hepatitis</td>
</tr>
<tr>
<td>Anti-IL-12 blockade</td>
<td>Severe colitis and anti-TNFα refractory colitis: severe or refractory</td>
</tr>
<tr>
<td></td>
<td>arthritis: anti-IL-12 refractory iAEs</td>
</tr>
<tr>
<td>Anti-TNFα blockade</td>
<td>Severe colitis: hepatitis; severe or refractory arthritis; nephritis</td>
</tr>
<tr>
<td></td>
<td>uveitis; pneumonia; myocarditis</td>
</tr>
<tr>
<td>Anti-IL-17 blockade</td>
<td>T-cell-IL-17 refractory colitis: severe or refractory arthritis</td>
</tr>
<tr>
<td>Anti-TNFα blockade</td>
<td>T-cell-IL-17 refractory colitis: severe or refractory arthritis</td>
</tr>
<tr>
<td>Anti-integrin 4 blockade</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Anti-IL-23 and anti-IL-12</td>
<td>Acute phase: severe, or anti-TNFα refractory colitis: severe or anti-TNFα</td>
</tr>
<tr>
<td>blockage</td>
<td>refractory pouchitis: severe or refractory arthritis</td>
</tr>
<tr>
<td>Janus kinase inhibitor</td>
<td>Severe or refractory arthritis</td>
</tr>
</tbody>
</table>

Table: New therapeutic strategies for the management of intermediate adverse events

Conclusion

• Wide variety in clinical presentation therefore intensivists should consider IRAEs from Immune checkpoint inhibitors as part of the differential.

• No clear risk factors prior to treatment identified yet.

• Low incidence, but high mortality once admitted to the ICU therefore quick and aggressive treatment with collaboration of subspecialties and oncologists is of great importance.

• Important to work up the patient for non-ICI related causes of organ failure (ie: infections, myocardial infarction, etc...)

• Treatment is mainly corticosteroids, with guidelines varying on recommendations of refractory cases. Therefore experienced physicians should be called to help with management.
Learning Assessment Question #1

• What are the two types of targets of checkpoint inhibitors?
  a) Anti-PD-1
  b) Anti-PDL-1
  c) Anti-CTLA4
  d) All of the above
Learning Assessment Question #1

- What are the two types of targets of checkpoint inhibitors?
  a) Anti-PD-1
  b) Anti-PDL-1
  c) Anti-CTLA4
  d) All of the above
Learning Assessment Question #2

• Which is NOT a toxicity associated to checkpoint inhibitors?
  a) Myocarditis
  b) Pneumonitis
  c) Myasthenia Gravis
  d) Hypophysitis
  e) Acute myocardial infarction
Learning Assessment Question #2

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QUESTIONS?