Checkpoint inhibitors: Strategies to checkmate T-cell mediated toxicity

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Texas Society of Health-System Pharmacists
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Disclosure Statement
Adam DiPippo has no relevant financial relationships to disclose

Learning Objectives
1. Recognize signs and symptoms of immune-related adverse reactions from checkpoint inhibitors
2. Contrast the immune-related adverse reactions associated with specific checkpoint inhibitors
3. Implement a supportive care plan for a patient presenting with an immune-related adverse event
Mechanism of Action

Immune Therapy vs. Cytotoxic Therapy

<table>
<thead>
<tr>
<th></th>
<th>Immune therapy</th>
<th>Cytotoxic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Enhance anti-tumor immunity</td>
<td>Direct tumor cell kill</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Immune cells</td>
<td>Rapidly dividing cancer cells</td>
</tr>
<tr>
<td><strong>Mechanism of toxicity</strong></td>
<td>Loss of immunologic tolerance to self-antigens</td>
<td>• Off-target cytotoxicity • Drug specific toxicities from metabolism/metabolites</td>
</tr>
<tr>
<td><strong>Onset of adverse events</strong></td>
<td>Unpredictable</td>
<td>Predictable</td>
</tr>
<tr>
<td><strong>Supportive care measures</strong></td>
<td>Targets immune system</td>
<td>Targets adverse effect</td>
</tr>
</tbody>
</table>

Toxicity Incidence Summary

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Liver</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Pituitary</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*"++" = lowest relative likelihood of immune-related adverse event of any grade
*"+++" = highest relative likelihood of immune-related adverse event of any grade

Toxicity Severity Summary

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Liver</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Pituitary</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

* "++" = lowest relative likelihood of immune-related adverse event of grade 3 or 4
* "+++" = highest relative likelihood of immune-related adverse event of grade 3 or 4

Atezolizumab (Tecentriq®) prescribing information. Genentech, Inc; 2016.
Ipilimumab (Yervoy©) prescribing information. Bristol-Myers Squibb; 2015.
Pembrolizumab (Keytruda©) prescribing information. Merck Sharp & Dohme Corp; 2015.
Nivolumab (Opdivo©) prescribing information. Bristol-Myers Squibb; 2016.

Toxicity Onset Summary

PD-1/PDL-1 Inhibitors

- Rash, pruritis
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis
- Pneumonitis

**Approach to Management**

- Early identification
- Symptom management
- Improvement of symptoms
- Need to escalate supportive care
- Assess signs and symptoms prior to each cycle
- Early identification
- Symptom management


**Skin Toxicity**

- Signs and symptoms
  - Rash
  - Pruritus
  - Vitiligo
  - Oral mucositis
  - Gingivitis
  - Stevens-Johnson Syndrome (SJS)
  - Toxic Epidermal Necrolysis (TEN)
- Rash most often maculopapular and erythematous
- Rash can also be lichenoid or bullous


University of Texas MD Anderson Cancer Center, Department of Melanoma Medical Oncology.
Skin toxicity from checkpoint inhibitors. [Photograph]. 2016.
### Skin Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• Macules/papules covering &lt; 10% body surface area (BSA)</td>
</tr>
<tr>
<td></td>
<td>• With or without symptoms (pruritus, burning, tightness)</td>
</tr>
<tr>
<td>2</td>
<td>• Macules/papules covering 10-30% BSA</td>
</tr>
<tr>
<td></td>
<td>• With or without symptoms (pruritus, burning, tightness)</td>
</tr>
<tr>
<td></td>
<td>• Limiting instrumental activities of daily living (ADL)</td>
</tr>
<tr>
<td>3</td>
<td>• Macules/papules covering &gt; 30% BSA</td>
</tr>
<tr>
<td></td>
<td>• With or without associated symptoms</td>
</tr>
<tr>
<td></td>
<td>• Limiting self-care ADL</td>
</tr>
<tr>
<td>4</td>
<td>• Signs of SJS or TEN</td>
</tr>
<tr>
<td></td>
<td>• Skin sloughing covering &gt; 10% BSA with associated signs (erythema, purpura, epidermal detachment and mucous membrane detachment)</td>
</tr>
<tr>
<td>5</td>
<td>• Death</td>
</tr>
</tbody>
</table>


### Approximating BSA

#### Lund Browder Chart

![Lund Browder Chart](image)

Fecher LA, et al. Oncologist [Internet]. 2013; 18(6):733-743. Figure 3, Lund Browder chart for estimating body surface area involved by rash; p.736.

### Skin Toxicity

<table>
<thead>
<tr>
<th>Toxicity (%)</th>
<th>All</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>15</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>4-12</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>4.26</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>14-33</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>20-35</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>8-21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-19</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>24-35</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>2</td>
</tr>
</tbody>
</table>

Full citation in Reference List.
### Skin Toxicity Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Specific Immunotherapy Management</th>
<th>Supportive Care</th>
</tr>
</thead>
</table>
| 1     | Continue                          | - Topical moisturizers  
- Oral antihistamines if pruritus  
- Topical corticosteroids Low potency 
  *If no improvement in 72 hours* |
| 2     | Hold                              | - Topical corticosteroids Moderate to high potency  
  *If no improvement in 72 hours*  
- Oral: 0.5-1 mg/kg/day prednisone  
- 1-2 week taper after symptoms improve  
- Oral antihistamines if pruritus |
| 3     | Permanently discontinue           | - May consider re-challenging if reaction not SJS or TEN  
- Risk versus benefit evaluation |
  *Hospitalization indicated  
- Dermatology consult recommended  
- IV: 2 mg/kg/day methylprednisolone  
- Consider additional immunosuppression for persistent symptoms  
- After symptoms improve, taper over >4 weeks  
- Consider dermatology consult |
| 4     | Hospitalization indicated         | - Dermatology consult recommended  
- IV: 2 mg/kg/day methylprednisolone  
- Consider additional immunosuppression for persistent symptoms  
- After symptoms improve, taper over >4 weeks |


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### Gastrointestinal Toxicity

- **Signs and symptoms**
  - Diarrhea or increased bowel movements
  - Increased ostomy output
  - Bloody stool
  - Mucous in stool
  - Abdominal pain
- **Possible Complications**
  - Colitis
  - Small bowel obstruction
  - Gastrointestinal perforation

Ipilimumab (Yervoy©) prescribing information. Bristol-Myers Squibb; 2015.
Pembrolizumab (Keytruda©) prescribing information. Merck Sharp & Dohme Corp; 2015.
Nivolumab (Opdivo©) prescribing information. Bristol-Myers Squibb; 2016.
### Gastrointestinal Toxicity

#### Incidence

<table>
<thead>
<tr>
<th>Toxicity [%]</th>
<th>Atezolizumab (20, 21, 22, 23)</th>
<th>Pembrolizumab (23, 24)</th>
<th>Nivolumab (9, 10, 11, 12, 13, 14, 17, 18, 19)</th>
<th>Ipilimumab (8, 14, 16)</th>
<th>Ipilimumab + Nivolumab (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>7-20</td>
<td>1-2</td>
<td>&lt; 1-2</td>
<td>23-33</td>
<td>3-6</td>
</tr>
<tr>
<td>Colitis</td>
<td>1</td>
<td>1-2</td>
<td>&lt; 1-2</td>
<td>8-12</td>
<td>5-9</td>
</tr>
</tbody>
</table>

*Null citations to references*
### Gastrointestinal Toxicity Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Specific Immunotherapy Management</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue</td>
<td>• Anti-diarrheals as needed&lt;br&gt;• Fluid replacement&lt;br&gt;<strong>If no improvement in 24 hours</strong></td>
</tr>
<tr>
<td>2</td>
<td>Hold&lt;br&gt;• Resume only if improves to grade \leq 1&lt;br&gt;and patient taking \leq 7.5 mg/day prednisone equivalents&lt;br&gt;• Combination anti-diarrheals&lt;br&gt;• Fluid replacement&lt;br&gt;• Consider budesonide&lt;br&gt;<strong>If no improvement in 24 hours</strong></td>
<td>• Oral: 2 mg/kg/day prednisone&lt;br&gt;• After symptoms improve, taper over \geq 4 weeks</td>
</tr>
</tbody>
</table>

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### Pulmonary Toxicity

- **Pneumonitis**
  - Inflammation of lung parenchyma

- **Signs and symptoms**
  - Shortness of breath
  - New or worsening cough
  - Chest pain
  - Decreased oxygen saturation
  - Radiographic changes
Pulmonary Toxicity

Teply BA, et al. Oncology [Internet]. 2014;28(11 Suppl 3): Figure 3, Different radiographic patterns of checkpoint blockade-associated pneumonitis seen on CT scanning in a single patient treated with ipilimumab and nivolumab; [about p. 8].

Pulmonary Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pneumonitis</th>
</tr>
</thead>
</table>
| 1     | Asymptomatic  
|       | • Radiographic changes only |
| 2     | Symptomatic  
|       | • Medical intervention indicated  
|       | • Limiting instrumental ADL |
| 3     | Severe symptoms  
|       | • Limiting self-care ADL  
|       | • Oxygen indicated |
| 4     | Life-threatening respiratory compromise  
|       | • Impending tracheotomy or intubation |
| 5     | Death |


Incidence

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab (16, 39)</th>
<th>Pembrolizumab (6, 40)</th>
<th>Nivolumab (9, 10, 11, 12, 13, 14, 18)</th>
<th>Ipilimumab (8, 14, 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity (%)</td>
<td>All Grade 3/4</td>
<td>All Grade 3/4</td>
<td>All Grade 3/4</td>
<td>All Grade 3/4</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
<td>1</td>
<td>2-6</td>
<td>&lt;1-3</td>
</tr>
<tr>
<td></td>
<td>1-5</td>
<td>&lt;1*</td>
<td>0-1.5</td>
<td>&lt;1*</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Postmarketing case reports of single agent grade 3 immune pneumonitis
*Five fatalities in dose-finding study (1 mg/kg and 3 mg/kg [2 patients each]; 10 mg/kg [one patient])
### Pulmonary Toxicity Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Specific Immunotherapy Management</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue</td>
<td>Monitor for symptoms every 72 hours</td>
</tr>
</tbody>
</table>
| 2     | Hold                              | Consult pulmonary and infectious diseases services  
|       | • Resume only if improves to baseline and patient taking < 7.5 mg/day prednisone equivalents | Monitor for symptoms daily  
|       | • Oral: 1 mg/kg/day prednisone    | After symptoms improve, taper over > 4 weeks |


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### Pulmonary Toxicity Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Specific Immunotherapy Management</th>
<th>Supportive Care</th>
</tr>
</thead>
</table>
| 3 or 4| Permanently discontinue          | Hospitalization indicated  
|       | • Consult pulmonary and infectious diseases service  
|       | • IV: 2 mg/kg/day methylprednisolone | Consider additional immunosuppression for persistent symptoms  
|       | • After symptoms improve, taper over > 4 weeks |


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### Patient Case

**Immune-related pneumonitis**
Patient Case

NO is a 52 year old male with metastatic non-small cell lung cancer on treatment with nivolumab

• He presents to clinic on cycle 12 day 1 of therapy complaining of worsening dyspnea on exertion, cough and mild fever
• These symptoms are impacting some of his daily activities but he is still able to care for himself
• Chest x-ray shows consolidation in the left lower lobe of the lung

Questions

• What are three things that should be in the differential diagnosis at this point?
  – Infection
  – Disease progression
  – Immune-related pneumonitis

It is decided that NO has Grade 2 immune-related pneumonitis from nivolumab

• How would you recommend managing NO's Cycle 12 of nivolumab?
  – Continue
  – Hold
    • Resume only if improves to baseline and patient taking ≤ 7.5 mg/day prednisone equivalents
  – Permanently discontinue
Patient Case

• What supportive care measures should be considered?
  – Oral corticosteroids
    • What dose?
      – 1 mg/kg/day prednisone
    • What duration?
      – After symptoms improve, taper over > 4 weeks
  – What adjunctive medications can we recommend?
    • Inhalers or nebulizer treatments as needed

Pituitary Toxicity

• Hypophysitis
  – Inflammation of the pituitary gland
• Signs and symptoms
  – Fatigue
  – Headache
  – Nausea/Vomiting
  – Visual changes
  – Myalgia
  – Loss of appetite

Workup

  – Adrenocorticotropic hormone (ACTH) and cortisol
  – Thyroid stimulating hormone (TSH) and Free T4
  – Luteinizing hormone (LH) and Follicle stimulating hormone (FSH)

  – Testosterone (if male)
  – Prolactin
  – MRI to look for pituitary inflammation
Pituitary Toxicity

Incidence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>&lt; 1.5</td>
</tr>
<tr>
<td>Ipilimumab + Nivolumab</td>
<td>8</td>
</tr>
</tbody>
</table>

Hypophysitis

- Normal Results: Continue None
- Abnormal Results Moderate Symptoms: Hold
  - Resume only if symptoms improve and patient taking ≤7.5 mg/day prednisone equivalents
- Abnormal Results Severe Symptoms: Permanently discontinue
  - Hospitalization indicated
  - Endocrine consult
  - Replace appropriate hormones as indicated
  - IV: 2 mg/kg/day methylprednisolone
  - After symptoms improve, taper over ≥4 weeks

Supportive Care

- Endocrine consult
- Replace appropriate hormones as indicated
- Oral: 1 mg/kg/day prednisone
- After symptoms improve, taper over >4 weeks

Summary

- Immune-related adverse events from checkpoint inhibitors can affect any organ system
- Organ systems particularly susceptible to toxicity include:
  - Skin
  - Gastrointestinal tract
  - Lungs
- Toxicity can occur at any time during or after treatment
Conclusions

• Use of checkpoint inhibitors will continue to expand
  – More indications
  – More patients

• Pharmacists have a key role in the care of patients on checkpoint inhibitors
  – Patient education on early reporting
  – Early identification of adverse effects
  – Frequent follow-up
  – Treatment modifications

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Post-Assessment Question 1

1. Which immune-related adverse event is correctly matched with an associated sign or symptom from checkpoint inhibitors?
   A. Hypotension due to cytokine release syndrome
   B. Irregular heart rate due to QTc prolongation
   C. Visual changes due to hypophysitis
   D. Hand foot syndrome due to dermatitis
Post-Assessment Question 2

2. Which immune-related adverse event is more frequently associated with nivolumab compared to ipilimumab?
   A. Rash
   B. Pneumonitis
   C. Diarrhea
   D. Colitis

Post-Assessment Question 4

3. CT is a 64 year old male receiving ipilimumab for metastatic melanoma.
   • He presents to clinic for Cycle 3 clearance and is experiencing Grade 3 gastrointestinal toxicity

Which of the following is the most appropriate supportive care measure for CT's symptoms?
   A. Fluid replacement orally
   B. Methylprednisolone 2 mg/kg/day IV
   C. Budesonide 3 mg PO TID
   D. Prednisone 1 mg/kg/day PO