Management of Immune Checkpoint Inhibitor Related Toxicities

A Webinar for HealthTrust Members
November 12, 2018
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Learning Objectives

- Identify the mechanism of action of immune checkpoint inhibitors (ICPis)
- Discuss the management of the most common ICPi-related toxicities
- Demonstrate the importance of patient and clinical communication prior to and during treatment with ICPis
Introduction

- Indications for use are expanding rapidly

- Adverse events can affect many different body systems at varying times during treatment

- Patient and clinician education are essential for the safe use of this class of medications
Mechanism of Action

- Checkpoint pathways: part of human immune system that control the immune response

- Can be manipulated to help cancer cells evade cytotoxic T-cell mediated death
  - Turn “off” immune system response to cancer cells

- ICPis prevent receptors and ligands from binding, thereby disrupting signaling
  - Turn “on” immune system response to cancer cells
## ICPi Targets

### CTLA-4 Pathway
- Cytotoxic T-lymphocyte associated-4 (CTLA-4) receptor on cytotoxic T cells
- Binds to CD80/CD86 ligands on cells

### PD-1 Pathway
- Programmed cell death protein 1 (PD-1) receptor on cytotoxic T cells
- Binds to programmed death-ligand 1 (PD-L1) on cells
CD80/CD86 expressed on cancer cell

Binds to CTLA-4 receptor on T cell

Immune response off
CD80/CD86 expressed on cancer cell

Binding to CTLA-4 blocked by CTLA-4 inhibitor

Immune response on
PD-L1 expressed on cancer cell

Binds to PD-1 receptor on T cell

Immune response off
PD-L1 expressed on cancer cell

Binding to PD-1 blocked by PD-1 inhibitor

Immune response on
Question 1

Which of the following is expressed on T cells and is a target of immune checkpoint inhibitors?

A. CD80
B. CD86
C. PD-1 receptor
D. PDL-1
Question 1 - Answer

Which of the following is expressed on T cells and is a target of immune checkpoint inhibitors?

A. CD80
B. CD86
C. PD-1 receptor
D. PDL-1
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Target</th>
<th>Indication (s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Yervoy</td>
<td>CTLA-4</td>
<td>Colorectal, melanoma, renal cell carcinoma</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Keytruda</td>
<td>PD-1 receptor</td>
<td>Many</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Opdivo</td>
<td>PD-1 receptor</td>
<td>Many</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Tecentriq</td>
<td>PD-L1 (ligand)</td>
<td>NSCLC, Urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Imfinzi</td>
<td>PD-L1 (ligand)</td>
<td>NSCLC, Urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Bavencio</td>
<td>PD-L1 (ligand)</td>
<td>Merkel cell carcinoma, Urothelial carcinoma</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>Libtayo</td>
<td>PD-1 receptor</td>
<td>Cutaneous squamous cell carcinoma</td>
</tr>
</tbody>
</table>

*not an all inclusive list
General Management

- Patient and family caregivers should receive timely and up-to-date education on:
  - Medication
  - Mechanism of action
  - Possible immune-related adverse events (irAEs)

- Prior to initiating therapy and continuous throughout treatment and beyond

- New symptom onset – suspect the immunotherapy
## Immune-related Adverse Events - Onset

<table>
<thead>
<tr>
<th>Organ</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Variable</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>5-10 weeks</td>
</tr>
<tr>
<td>Lung</td>
<td>2-24 months (median: 3 months)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Variable, typically ~1-5 months</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5-12 weeks</td>
</tr>
</tbody>
</table>

**Estimations only – can occur at any point during and after treatment with an immune checkpoint inhibitor**
General Management

- Immune-related adverse events
  - Graded according to the CTCAE
    - Common Terminology Criteria for Adverse Events (version 5.0)
    - Different criteria for each organ
General Management

Grade 1
- Continue ICPi with close monitoring
- Exceptions: cardiac, hematologic, neurologic

Grade 2
- Consider holding ICPis and resume when toxicity improves to Grade 1 or better

Grade 3
- Hold ICPis and initiate high-dose corticosteroids

Grade 4
- Permanent discontinuation of ICPIs
- Exception: endocrinopathies
General Management

- Key goal: early intervention with corticosteroids
- Close consultation with disease-specific subspecialties encouraged
- Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor activity
- Avoid premedication with corticosteroids when possible
  - Potential mitigation of immunotherapeutic effectiveness in prophylactic setting
## Monitoring Parameters

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Frequency during immunotherapy treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>Every 2–3 weeks</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>Every 2–3 weeks</td>
</tr>
<tr>
<td>TSH and free T4</td>
<td>Every 4–6 weeks</td>
</tr>
<tr>
<td>Morning ACTH and cortisol</td>
<td>Every 2–3 weeks</td>
</tr>
</tbody>
</table>
Special Populations

- Autoimmune conditions
- Solid organ transplant
- Prior stem cell transplant
Immune-related Adverse Events

- Skin
- Gastrointestinal
- Lung
- Endocrine
Skin Toxicities

- Many different etiologies
  - Maculopapular rash
  - Pruritis
  - Bullous dermatitis
  - Stevens Johnson Syndrome (SJS)
  - Toxic epidermal necrolysis (TEN)
Skin Toxicities - Rash

Grade 1

- Continue ICPI
- Treat symptomatically
  - Oral antihistamine
  - Topic emollients
  - Moderate potency topical steroids
- Avoid skin irritants and sun exposure
Skin Toxicities - Rash

Grade 2

• Consider holding ICPI with weekly monitoring
• If not resolved, interrupt treatment until improved to Grade 1
• Treatment
  • Topical emollients, oral antihistamines
  • Medium to high potency topical steroids
  • Consider adding oral corticosteroid
  • Prednisone (or equivalent) 0.5–1mg/kg daily until improved to Grade 1, then taper over at least 4 weeks
Skin Toxicities - Rash

Grade 3

• Hold ICPI
  • Consult dermatology to determine appropriateness of resuming ICPI
• Treatment
  • High potency topical steroids AND
  • Oral corticosteroid
    • Prednisone (or equivalent) 0.5–1mg/kg until improved to Grade 1, then taper over at least 4 weeks
Skin Toxicities - Rash

**Grade 4**

- Hold ICPi
  - Consult dermatology to determine appropriateness of resuming ICPi upon resolution of skin toxicity and steroids reduced to prednisone <10mg
- Admit with direct oncology and dermatology involvement
- Treatment
  - Systemic corticosteroid
    - Methylprednisolone (or equivalent) 1–2 mg/kg with slow tapering when toxicity resolves
  - Consider alternative neoplastic therapy
## Skin Toxicities - Pruritis

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3/4</th>
</tr>
</thead>
</table>
| • Continue ICPI  
• High potency topical steroids | • Consider holding ICPI until Grade 1  
• Oral antihistamines  
• Dermatology consult | • Hold immunotherapy  
• Prednisone 0.5–1 mg/kg/day  
• GABA agonists  
• Consider apreptitant  
• Consider omalizumab  
• Urgent dermatology consult |
Skin Toxicities – Blistering Disorders

DERMATOLOGIC ADVERSE EVENT(S)  ASSESSMENT/GRADING  MANAGEMENT

Bullous dermatitis<sup>c,k</sup>  
Urgent dermatology consultation for skin biopsy  
Mild (G1)<sup>n</sup>  
• Hold immunotherapy<sup>i</sup>  
• High potency topical steroids

Stevens-Johnson syndrome (SJS)<sup>m</sup>  
Toxic epidermal necrolysis (TEN)<sup>m</sup>  
Urgent dermatology consultation for skin biopsy  
Moderate (G2)<sup>o</sup>  
• Hold Immunotherapy until <G1<sup>l</sup>  
• Prednisone/methylprednisolone 0.5–1 mg/kg/day<sup>g</sup>

Severe (G3)<sup>p</sup>  
• Permanently discontinue immunotherapy  
• Prednisone/methylprednisolone 1–2 mg/kg/day<sup>g</sup>  
• Inpatient care required  
• Urgent dermatology and ophthalmology consultation

Life-threatening (G4)<sup>q</sup>  
• Permanently discontinue immunotherapy  
• Inpatient care required  
• Urgent dermatology and ophthalmology consultation  
• Methylprednisolone/prednisone 1–2 mg/kg/day<sup>g</sup>
## Diarrhea/Colitis

<table>
<thead>
<tr>
<th>Diarrhea Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4-6 stools per day over baseline; IV fluids indicated &lt;24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL;</td>
<td>Increase of ≥7 stools per day over baseline; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL;</td>
<td>Life – threatening consequences (eg hemodynamic collapse)</td>
<td>Death</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colitis Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, pathologic or radiographic findings only</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Abdominal pain, fever, change in bowel habits with ileus, peritoneal signs</td>
<td>Life – threatening consequences (eg perforation, bleeding, ischemia, necrosis, toxic megacolon)</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
GI Toxicities – Diarrhea/Colitis

Grade 1

• Fewer than 4 bowel movements above baseline per day and no colitis symptoms
• Consider holding ICPI
• Treatment
  • Loperamide
  • Hydration
  • Close monitoring
GI Toxicities – Diarrhea/Colitis

- Necessary tests for patients presenting with Grade 2–4
  - Stool evaluation to rule out infectious etiology
    - Culture
    - C. Difficile
    - Ova and parasites
  - Abdominal/pelvic CT with contrast
  - GI consultation
GI Toxicities – Diarrhea/Colitis

Grade 2

- Hold immunotherapy
- Consult gastroenterology
- Systemic corticosteroids: methylprednisolone 1 mg/kg/day with slow taper over 4-6 weeks when toxicity resolves
- No response in 2–3 days
  - Increase to 2mg/kg/day
  - Consider infliximab
  - If infliximab refractory, consider vedolizumab
GI Toxicities – Diarrhea/Colitis

Grade 3

- Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity
- Consider inpatient care
- Systemic corticosteroids: methylprednisolone 1 mg/kg/day with slow taper over 4–6 weeks when toxicity resolves
- No response in 2–3 days
  - Consider infliximab
  - If infliximab refractory, consider vedolizumab
GI Toxicities – Diarrhea/Colitis

Grade 4

- Permanently discontinue immunotherapy
- Consider inpatient care
- Systemic corticosteroids: methylprednisolone 1 mg/kg/day with slow taper over 4–6 weeks when toxicity resolves
- No response in 2–3 days
  - Consider infliximab
  - If infliximab refractory, consider vedolizumab
A 65-year old female presents for her next dose of nivolumab (Opdivo). She reports a two-day history of 10 stools per day (usually ~1 BM per day). Which medication should be initiated for the management of diarrhea?

A. Loperamide  
B. Methylprednisolone  
C. Infliximab  
D. Vedolizumab
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A. Loperamide
B. Methylprednisolone
C. Infliximab
D. Vedolizumab
Lung Toxicities – Pneumonitis

Grade 1

• Hold immunotherapy
• Monitor patients weekly with history and physical, with or without a chest xray
• May resume ICPI with radiographic evidence of improvement or resolution
• If no improvement, treat as Grade 2
Lung Toxicities – Pneumonitis

Grade 2

• Hold immunotherapy until resolution to Grade 1 or less
• Consider empiric antibiotics, bronchoscopy with BAL
• Prednisone 1–2 mg/kg/day; slow taper by 5-10 mg/week over 4-6 weeks when toxicity resolves
• Monitor every 3–7 days
• If no improvement after 48–72 hours of steroids, treat as Grade 3
Lung Toxicities – Pneumonitis

Grade 3/4

- Permanently discontinue immunotherapy
- Inpatient care
- Consider pulmonary and infectious disease consults
- Bronchoscopy with BAL to rule out infection and malignant lung infiltration
- Consider empiric antibiotics
- Methylprednisolone IV 1–2 mg/kg/day until symptoms improve to Grade 1 or less, then taper over ≥6 weeks
- If no improvement after 48 hours, consider:
  - Infliximab
  - Mycophenolate mofetil
  - Intravenous immunoglobulin
Endocrine Toxicities

Educate patients to inform health care provider immediately if they experience any of the following:

- Headaches that will not go away
- Unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme tiredness or weakness
- Muscle aches
- Weight gain or weight loss
- Dizziness or fainting

- Feeling more hungry or thirsty than usual
- Hair loss
- Changes in mood or behavior
- Feeling cold
- Constipation
- Voice gets deeper
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain
Thyroid Hormone Supplementation

- Patients without risk factors: full replacement estimated with ideal body weight-based dose = 1.6 mcg/kg/day
- Elderly, frail, or multiple comorbidities: consider titrating up from low dose, starting at 25–50 mcg/day
Other Endocrine Toxicities

- Hypophysitis
- Primary Adrenal Insufficiency
- Diabetes
- Hyperthyroidism

*Refer to NCCN/ASCO guidelines for management recommendations*
Immune-related Adverse Events

- Can occur in many other organs/body systems
- Refer to NCCN/ASCO guidelines for management recommendations
Immunotherapy Rechallenge

- Depending on severity of adverse event and organ system involved

- Use caution when considering restarting immunotherapy after significant iRAE
  - Close follow-up to monitor for recurrent symptoms
Immunotherapy Rechallenge

- In general, resumption of immunotherapy following grade 2 iRAEs can be considered upon resolution to ≤ Grade 1.

- See NCCN guidelines for organ-specific considerations.
Patient Education Concepts

- Immunotherapy Background
- Side Effects
- Monitoring & Treatment Response
Immunotherapy Background

- Immune system helps distinguish healthy cells from abnormal cells
- Tumor cells can block the ability of the immune cell to recognize them as foreign
- Immune checkpoint inhibitors prevent tumors from evading the body’s natural immune system
Side effects

- Immunotherapy side effects differ from other types of cancer treatment
- Can affect one or several different organ systems
- Can occur at any time during or after treatment is completed
- Combination therapy may increase severity of adverse events
- Alert other health care providers about receiving immunotherapy
Monitoring & Treatment Response

- **Managing side effects early** can help with treating them effectively
  - Communication between patient/family and treatment center is essential
- Symptoms that may be considered unrelated (diarrhea) are often signs of immune checkpoint inhibitor side effects
- Regular monitoring will be done to assess treatment response
- May take longer to see a response
Patient Education Tools

- Every visit: ask about new symptoms or changes in health
- Questionnaires or standardized assessments
- Wallet cards with symptoms to watch for and how to reach health care provider
Question 3

A patient is planning to start pembrolizumab and will be educated on this medication prior to initiation. Which of the following are important counseling points for a patient beginning treatment with immunotherapy?

A. Adverse effects can occur in many organs and at any time during treatment
B. Immune checkpoint inhibitors are tolerated better than standard chemotherapy
C. Be sure to inform your oncology care team of new symptoms or changes to your health
D. All of the above
E. A and C
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B. Immune checkpoint inhibitors are tolerated better than standard chemotherapy
C. Be sure to inform your oncology care team of new symptoms or changes to your health
D. All of the above
E. A and C
Conclusion

- Immune checkpoint inhibitor use is growing, with more medications and indications being studied.
- Patients should be monitored closely for adverse events and treated according to published guidelines.
- Patient and clinician education are essential for the safe use of this class of medications.
References


Q&A

To ask the presenter a question, simply type it into the “chat” box within the WebEx tool bar.

Be sure that you select “Host” when submitting your question in the chat.
Thank you!

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