“-itis & -itis”: Immune Checkpoint Inhibitors Toxicity Management

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“-itis & -itis”: IMMUNE CHECKPOINT INHIBITORS TOXICITY MANAGEMENT

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The Center for Cancer Prevention and Treatment
St. Joseph Hospital of Orange
May 31, 2019
Disclosure

• Speakers’ Bureau: BMS, Merck.
• Advisory Meetings: Abbvie, Genentech.
Objectives

• Learn immune checkpoint inhibitor’s (immunotherapy) mechanism of action.
• Recognize the differences in immunotherapy side effects vs chemotherapy side effects.
• Learn initial management of immunotherapy side effects.
• Learn about the resources available for immunotherapy side effect management.
What is Immunotherapy?

• A type of therapy that affects the immune system to fight cancer.

• Many different types of immunotherapy: vaccines, small molecule compounds, monoclonal antibodies, gene therapies, cellular therapies.

• For the purpose of this talk, I will use the terms “Immunotherapy” and “Immune Checkpoint Inhibitors” interchangeably.
Key Milestones in the Evolution of Cancer Immunotherapy

- First demonstration of a "cancer vaccine" by Coley
- Hypothesis of cancer "immunosurveillance" by Thomas and Burnet
- First study with IFNα in melanoma
- The new concept of cancer "immunoediting"
- Adoptive cell transfer (ACT) for cancer
- IL-2 approved for cancer therapy
- Anti-CTLA-4 (ipilimumab) FDA approved for metastatic melanoma
- Anti-PD-1 (nivolumab) FDA approved for metastatic melanoma
- Anti-PD-1 (nivolumab) FDA approved for lung cancer
- Approvals of checkpoint inhibitors and combinations has continued across many different tumor types
- First report of the successful treatment with CAR-T cells targeting CD19 in refractory ALL

1800 - 2019

Allison & Honjo Nobel Prize

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St. Joseph Health
St. Joseph Hospital
A member of the St. Joseph Hoag Health alliance
Immune Checkpoint Inhibitor Mechanisms of Action

Immune Checkpoint Blockade: Mechanism of Action

T cell

Tumor cell or APC

Courtesy of Evan J Lipson, MD
Research to Practice
FDA approved Agents and Indications

• Ipilimumab (CTLA-4 ab)
• Cemiplimab-rwlc, Nivolumab, Pebrolizumab (PD-1 ab)
• Atezolizumab, Avelumab, Durvalumab (PD-L1 ab)
• More than 30 FDA approved Indications across multiple cancer types, and GROWING!
Immunotherapy is better tolerated

Chemotherapy

Immunotherapy

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Severe Side Effects are Rare but Do Occur

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Deaths, No. (%)</td>
<td>58 (1.08)</td>
<td>33 (0.36)</td>
<td>12 (0.38)</td>
<td>19 (1.23)</td>
</tr>
<tr>
<td>Type of fatal toxic effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>23 (40)</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (5)</td>
<td>14 (42)</td>
<td>5 (42)</td>
<td>4 (21)</td>
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<tr>
<td>Hepatitis</td>
<td>5 (9)</td>
<td>0</td>
<td>1 (8)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>9 (16)</td>
<td>4 (12)</td>
<td>3 (25)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (11)</td>
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<tr>
<td>Infectious</td>
<td>8 (14)</td>
<td>5 (15)</td>
<td>2 (18)</td>
<td>3 (16)</td>
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<tr>
<td>Hemorrhagic/thrombotic</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>1 (2)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>3 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>2 (6)</td>
<td>1 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

*JAMA Oncol. 2018;4(12):1721-1728.*
Immune side effects can involve Any Organ

- Hypophysitis
- Uveitis
- Dry mouth/mucositis
- Thyroiditis/hypothyroidism
- Pneumonitis
- Vasculitis
- Myocarditis
- Thrombocytopenia/anemia
- Hepatitis
- Adrenal insufficiency
- Rash and vitiligo
- Nephritis
- Enteritis
- Pancreatitis
- Colitis
- Autoimmune diabetes
- Neupathy
- Arthralgia

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Immune side effects are usually delayed in onset, unlike chemotherapy.
Colitis was the most common serious side effect but Myocarditis was most lethal by percentage.
American Society of Clinical Oncology (ASCO) 2018 Guideline

- Education prior to and throughout and after treatment.
- High level of suspicion for immune side effects.
- Grade 2 toxicity: hold immunotherapy and start corticosteroid (0.5-1mg/kg).
- Grade 3 toxicity: hold and start higher dose corticosteroid (1-2mg/kg IV). Consider adding infliximab or other immunomodulators if no improvement in 48-72hrs.
- Grade 4 toxicity: similar to grade 3 toxicity management plus permanent discontinuation.
Important to Slowly Taper Corticosteroid!

• Need to taper prednisone slowly over 4-6 weeks to prevent relapse.
• Depending on the initial severity of immune side effect, Immunotherapy may be resumed when side effects improve to grade 1 and daily prednisone dose of $\leq 10\text{mg/day}$.
What I Need to Know about my Immunotherapy

The Center for Cancer Prevention and Treatment
St Joseph Hospital, Orange
Immunotherapy Wallet Card

- Your nurse will give you an ‘immunotherapy wallet card’
- Keep this card in your wallet at all times
- Present this card to any urgent care or emergency department
- This card helps any healthcare provider identify you as someone undergoing immunotherapy who needs special follow up and care

Back

ADVICE TO HEALTH CARE PROFESSIONALS

Autoimmune side effects:
- Diarrhea and Colitis
- Hepatotoxicities
- Pneumonitis
- Addison’s Disease
- Endocrinopathies
- Neuropathies
- Renal Toxicities
- Skin Rashes

Required blood tests:
- CBC
- Complete Metabolic Panel
- Random Cortisol/ACTH
- Thyroid function test
- If patient has dyspnea, order Chest CT

Steroids are frequently indicated in the management of side effects and may be given.

Courtesy of Enza Nguyen, RN, MSN, ANP-BC
Include in the Past Medical History Section of Medical Record

- Immune-related adverse events can occur even months after treatment has been discontinued.
- Part of the differential diagnosis when patients get sick.
Free Tools for immune side effect management: NCCN Guidelines

<table>
<thead>
<tr>
<th>Gastrointestinal Adverse Event(s)</th>
<th>Assessment/Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (G1)</td>
<td>Stool evaluation to rule out infectious etiology⁰&lt;br&gt; - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture&lt;br&gt; - C. difficile&lt;br&gt; - Ova &amp; parasites; molecular testing for <em>Giardia</em> and <em>Cryptosporidium</em> spp and <em>E. histolytica</em>; consider microsporidia, <em>Cyclospora/isoaspora</em> spp&lt;br&gt; - Viral pathogens testing when available&lt;br&gt; - Based on institutional availability, consider lactoferrin/calprotectin&lt;br&gt; - Consider abdominal/pelvic CT with contrast&lt;br&gt; - Consider GI consultation&lt;br&gt; - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy</td>
<td>Consider holding immunotherapy⁹&lt;br&gt; - Loperamide or diphenoxylate/atropine&lt;br&gt; - Hydration&lt;br&gt; - Close monitoring¹¹</td>
</tr>
<tr>
<td>Moderate (G2) or Severe (G3–4)</td>
<td>- Hold immunotherapy⁹&lt;br&gt; - Prednisone/methylprednisolone¹ 1 mg/kg/day¹</td>
<td>- No response in 2–3 days:&lt;br&gt;   - Increase dose to 2 mg/kg/day¹&lt;br&gt;   - Consider adding infliximab⁷</td>
</tr>
<tr>
<td></td>
<td>- G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity⁹&lt;br&gt; - G4: Permanently discontinue immunotherapy agent responsible for toxicity⁹&lt;br&gt; - Consider inpatient care for provision of supportive care&lt;br&gt; - Intravenous (IV) methylprednisolone¹ 2 mg/kg/day¹&lt;br&gt; - No response in 2 days:&lt;br&gt;   - Continue steroids, consider adding infliximab⁷&lt;br&gt;   - If infliximab-refractory, consider vedolizumab</td>
<td></td>
</tr>
</tbody>
</table>
Free Tools for immune side effect management: ONCOASSIST

www.oncoassist.com
Conclusion

• Immune Checkpoint Inhibitors have revolutionized Cancer treatment, and the use is expected to grow over time.
• Immune side effects are usually manageable with prompt recognition and corticosteroid use.
• Immune side effects can occur even after treatment as been discontinued.
• Adherence to guidelines optimize immune side effects management.