Checkmate to Immune Checkpoint Inhibitor Toxicity

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Pharmacy Grand Rounds
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Objectives

• Describe the mechanism of the currently approved check point inhibitors and their characteristics with respect to their immune-related adverse effects

• Identify signs/symptoms of the adverse effects with the immune checkpoint inhibitors

• Outline a strategy for management of immune-related adverse effects management including diarrhea/colitis, endocrine dysfunction and hepatitis
The Evolving Role of Immunotherapy

- Chemotherapy: Non-specific, rapidly dividing cells
- Immunotherapy: Stimulates the immune system
  - Non-specific immunotherapies/adjuvants
    - E.g. Aldesleukin in melanoma and renal cell carcinoma
  - Cancer vaccines
  - Immune checkpoint inhibitors (ICPI)
    - Overexpression of CTLA-4, PD-1 and PD-L1 in the microenvironment

CTLA-4: Cytotoxic T-lymphocyte associated antigen,
PD-1: Programmed cell death protein,
PD-L1: programmed cell death protein ligand.

Villadolid et al. *Transl Cancer Res* 2015; 4(5), 560
Mechanism of Action

Atezolizumab

Ipilimumab

Nivolumab, Pembrolizumab
Spectrum of ICIP Therapy

ICPI Blockade

Timeline of ICPIs

3/28/2011 - Ipilimumab for advanced melanoma

9/4/2014 - Pembrolizumab for advanced melanoma

12/22/2014 - Nivolumab for advanced melanoma

10/1/2015 - NIVO/IPI for advanced melanoma

5/18/2016 - Atezolizumab for advanced urothelial carcinoma
### CTLA-4 and PD-1 polymorphisms

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Polymorphism</th>
<th>Ethnic group of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroiditis, Graves’ disease and Hashimoto’s disease</td>
<td>CTLA-4</td>
<td>European</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>CTLA-4</td>
<td>European, Asian</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>CTLA-4</td>
<td>European</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>CTLA-4</td>
<td>South American</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>CTLA-4, PD-1</td>
<td>European</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>CTLA-4, PD-1</td>
<td>European, Asian</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>CTLA-4</td>
<td>European</td>
</tr>
</tbody>
</table>

-Similar presentations to the adverse effects of ICPIs

Villadolid et al. *Transl Cancer Res* 2015; 4(5), 560
Immune-Related Adverse Effects

- Mechanism: Unrestrained T cell activation → development of autoimmune manifestations
  - Self-tolerance is maintained through CTLA-4 and PD-1/PD-L1 axis
  - Most data from melanomas

- *Immune related adverse event or irAE
  - Several other terms used
    - “drug related adverse event” or “event of special interest”
irAE Site and Effect

- Hypophysitis
- Hypothyroidism
- Adrenal insufficiency
- Diarrhea
- Arthralgias
- Rash and vitiligo
- Hepatitis
- Pneumonitis
- Dry Mouth
- Uveitis and orbital inflammation

“LEGs” Acronym
- Liver
- Endocrine
- GI
- Skin

Incidence
## Common Terminology Criteria for Adverse Events

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Moderate; minimal intervention indicated</td>
</tr>
<tr>
<td>3</td>
<td>Severe or medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death related to adverse event</td>
</tr>
</tbody>
</table>

No specific terminology for irAEs

CTCAE: Common terminology criteria for adverse events

NCI. CTCAE v4.03. Accessed 12/28/16
<table>
<thead>
<tr>
<th>irAEs (Grade 3 - 4)</th>
<th>IPI in MEL</th>
<th>PEM in MEL</th>
<th>NIVO in MEL</th>
<th>PEM in LC</th>
<th>NIVO in LC</th>
<th>ATZ in UC and LC</th>
<th>IPI+NIVO in MEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>23-33 (3-6)</td>
<td>14-17 (1-3)</td>
<td>11-19 (0-2)</td>
<td>8 (1)</td>
<td>8-10 (0-3)</td>
<td>8</td>
<td>44 (9)</td>
</tr>
<tr>
<td>Colitis</td>
<td>8-12 (7-9)</td>
<td>2-4 (1-3)</td>
<td>1 (&lt;1)</td>
<td>1 (1)</td>
<td>1 (&lt;1)</td>
<td>1</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1-7 (0-2)</td>
<td>1-2 (1-2)</td>
<td>3-6 (2-3)</td>
<td>1-3 (&lt;1)</td>
<td>1-3 (&lt;1)</td>
<td>1-6 (&lt;1-2)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>Rash</td>
<td>15-21 (1-2)</td>
<td>13-15 (0)</td>
<td>9-22 (&lt;1)</td>
<td>10 (0.2)</td>
<td>4-11 (0-1)</td>
<td>1</td>
<td>28 (3)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>2-4 (0)</td>
<td>9-11 (0)</td>
<td>5-11 (0)</td>
<td>NR (0)</td>
<td>NR (NR)</td>
<td>NR</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2-4 (0)</td>
<td>9-10 (&lt;1)</td>
<td>4-9 (0)</td>
<td>8 (&lt;1)</td>
<td>4-7 (0)</td>
<td>NR</td>
<td>15 (&lt;1)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1-2 (&lt;1)</td>
<td>3-7 (0)</td>
<td>2-4 (&lt;1)</td>
<td>2-4 (0)</td>
<td>1-2 (0)</td>
<td>NR</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>2-4 (2)</td>
<td>&lt;1 (&lt;1)</td>
<td>&lt;1 (&lt;1)</td>
<td>&lt;1 (&lt;1)</td>
<td>NR (NR)</td>
<td>NR</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

Distribution of irAEs Based on Class

Distribution of irAEs Based on Class

All Grades
- Anti-CTLA-4: up to 90%
- Anti-PD-1: 70%
- Anti-PD-L1: 7% (all irAEs), although Systemic corticosteroids used in 22%

Approximate Median Appearances of irAEs

- Rash: Week 5
- Diarrhea: Week 7
- Hepatitis: Week 8
- Pneumonitis: Week 11
- Endocrinopathies: 10-24 week median

Source:
Question #1

Which of the following statements is correct with regards to pembrolizumab?

1. Pembrolizumab targets CTLA-4
2. Skin rash is a more frequent irAE than hypothyroidism
3. Hepatitis is a more frequent irAE than diarrhea with pembrolizumab
4. Pembrolizumab targets PD-1 on the tumor cell
irAE: Management

• No prospective, randomized studies
• Management based on following
  • Safety reports, patient case reports
  • Expert opinion
  • Knowledge of autoimmune diseases
General irAE Management

<table>
<thead>
<tr>
<th>Severity CTCAE grade</th>
<th>Type of patient care</th>
<th>*Steroids</th>
<th>Other immunosuppressive drugs</th>
<th>Immunotherapy and subsequent approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ambulatory</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory</td>
<td>Topical steroids or systemic steroids oral 0.5–1 mg/kg/d</td>
<td>Not recommended</td>
<td><strong>Suspend temporarily</strong></td>
</tr>
<tr>
<td>3</td>
<td>Hospitalization</td>
<td>Systemic steroids oral or IV 1–2 mg/kg/d for 3 d then reduce to 1 mg/kg/d</td>
<td>Considered if symptoms resolved after 3–5 d of steroids. Organ specialist advised.</td>
<td>Suspend and discuss resumption based on risk/benefit ratio with patient</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalization/ICU</td>
<td>Systemic steroids IV methylprednisolone 1–2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d</td>
<td>Considered if symptoms resolved after 3–5 d of steroids. Organ specialist advised.</td>
<td>Discontinue permanently</td>
</tr>
</tbody>
</table>

*If steroids initiated, consider slow taper over several weeks

**Exception of skin or endocrine manifestations where immunotherapy could be maintained

Diarrhea and Colitis

- GI irAE: 8-33% in all ICPI
- Diarrhea: Increase in frequency of stools
- Colitis: Abdominal pain or colonic inflammation
  - Ipilimumab induced colitis has features to Crohn’s disease
    - Physical features (colonoscopic assessment)
      - Mucosal erythema
      - Ulcerations
    - Histologic features of Crohn’s disease
      - Lymphocytic and neutrophil inflammation
      - Cell infiltration with cryptitis

- Median onset of 7-24 weeks

## Diarrhea and Colitis Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 4 stools per day over baseline</td>
<td>Supportive care (BRAT diet), bowel rest and hydration as indicated. Continue ICPI therapy</td>
</tr>
<tr>
<td>2</td>
<td>4-6 stools/day over baseline, abdominal pain, or blood/mucus in the stool</td>
<td>Supportive care, antidiarrheal treatment (may mask higher grade toxicity). If symptoms &gt; 1 week, initiate prednisone 0.5 mg/kg/day. Hold ICPI, resume therapy when prednisone ≤7.5 mg and symptoms back to baseline</td>
</tr>
<tr>
<td>3 or 4</td>
<td>≥7 stools/day over baseline, signs of bowel perforation or ileus, fever</td>
<td>Discontinue ICPI therapy. Start corticosteroids 1 -2 mg/kg/day (hold until ID results if patient stable), IV hydration. Consider early escalation to infliximab 5 mg/kg after 48-72 hours if no improvement from steroids. Consider mycophenolate if still refractory.</td>
</tr>
</tbody>
</table>

- Need to watch for rebound diarrhea when initiating steroid taper

Steroid-Refractory Diarrhea and Colitis

• Infliximab IV 5 mg/kg dose
  • Preferred agent
  • Recommended in NCCN Melanoma Guidelines
  • Single dose usually sufficient

• Mycophenolate

• Tacrolimus

• Vedolizumab
  • 300 mg IV at 0, 2 and 6 weeks

• Colectomy in select patients

Hsieh, AH, et al. BMJ Case Reports 2016; doi:10.1136/bcr-2016-216641
Prevention of Diarrhea

• Unresectable stage III or IV melanoma receiving ipilimumab
  • Ipilimumab dose 10 mg/kg Q 3 weeks
  • Prophylactic budesonide 9 mg daily vs placebo
  • Did not affect rate of Grade ≥2 diarrhea
    • Rate of 32.7% vs 35% for budesonide and placebo respectively
    • Response rates of 12.1% vs 15.8%

• Not recommended

Hypothyroidism

• ~2-10% incidence with single ICPIs
• Typical presentation of inflammatory, painless, thyroiditis
  • Fatigue most common symptom
• Can occur after subclinical hyperthyroidism
• Suppressed TSH levels may be due to high dose steroids
  • E.g. treatment of other irAEs
  • Evaluation of morning ACTH and cortisol levels


TSH: Thyroid stimulating hormone
ACTH: Adrenocorticotropic hormone
Hypothyroidism Management

Check TSH, FT4, FT3 at baseline and periodically throughout therapy

1. TSH low or <0.01 with normal or high FT4 or T3
   • Potentially acute thyroiditis
   • Repeat TFT’s 3-6 weeks

2. TSH 5-10, normal FT4 or T3
   Repeat thyroid function tests in 3-6 weeks

3. TSH >10 with normal or low FT4 & T3
   Begin thyroid replacement if symptomatic
   May consider repeating TFT’s in 2-4 weeks if asymptomatic

1) Levothyroxine at 1.6mcg/kg or 75-100mcg/daily
2) Repeat TFT’s in 4-6 weeks

FT4: Free T4
FT3: Free T3

Hypophysitis

• Inflammation of pituitary gland
  • Low production of pituitary hormones
    • Diagnosis with low ACTH and cortisol levels with symptoms
    • Radiographic evidence of pituitary gland swelling
  • <1% incidence with PD-1 inhibitors
  • 1.8% in ipilimumab trial in advanced melanoma

• Headaches, fatigue, visual disturbances
  • Hyponatremia and hypoglycemia may be present
  • FSH, LH, prolactin, GH and TSH may also be affected

FSH: follicle-stimulating hormone, LH: Luteinizing hormone, GH: growth hormone, ACTH: adrenocorticotropic hormone

## Hypophysitis Management

<table>
<thead>
<tr>
<th>Grade or Sign</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue ICPI with close follow-up; consider hormone replacement in *physiologic doses</td>
</tr>
<tr>
<td>2</td>
<td>Hold ICPI until grade ≤ 1</td>
</tr>
<tr>
<td>3</td>
<td>Delay further ICPI therapy, 1-2 mg/kg prednisone daily then taper to *physiologic doses</td>
</tr>
<tr>
<td>4 or mass effect on MRI</td>
<td>Stop ICPI therapy, initiate , 1-2 mg/kg prednisone daily then taper to *physiologic doses</td>
</tr>
</tbody>
</table>

- Replacement of other hormones as indicated
  - Thyroxine, testosterone/estrogen, growth hormone, desmopressin

*Consider prednisone 15-20 mg in the morning and 5-10 mg in the afternoon

irAEs: Hepatitis

- Liver transaminases most affected
  - AST, ALT
  - Some cases of elevated bilirubin, hepatomegaly
  - Usually asymptomatic

- Incidence <10% with ICPI monotherapy
  - Formal diagnosis: liver biopsy with diffuse T-cell infiltration
  - Diagnosis of exclusion
<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST or ALT &gt; 2x and ≤ 5.0x ULN and/or Total bili ≤ 3.0 x ULN</td>
<td>AST or ALT &gt; 5.0x ULN and/or Total Bili &gt; 3.0 x ULN</td>
</tr>
<tr>
<td>• Hold therapy, resume after resolution to baseline</td>
<td>• Permanently discontinue therapy</td>
</tr>
<tr>
<td>• Rule out other causes</td>
<td>• Initiate 1-2 mg/kg prednisone</td>
</tr>
<tr>
<td>Monitor 1-2 weekly until resolution to grade &lt;2 (or baseline)</td>
<td>• *Consider MMF 500 mg every 12 hours or azathioprine if steroid refractory</td>
</tr>
<tr>
<td>• Start steroids at 0.5-1 mg/kg prednisone</td>
<td></td>
</tr>
<tr>
<td>• Taper over 1 month</td>
<td></td>
</tr>
</tbody>
</table>

*Avoid infliximab due to hepatotoxicity
Steroids for irAEs and Impact on Efficacy

- Horvat et al. – Ipilimumab, single center
  - Metastatic melanoma (n=298)
  - 35% steroid therapy, 10% anti-TNFα
  - No difference in OS (p=0.6) or TTF (p=0.86) in those treated for irAEs vs no treatment

- Weber et al – Nivolumab pooled analysis
  - Metastatic melanoma (n=576)
  - Patients with irAE had greater ORR than those that did not (48.6% vs 17.8%, p <0.001)
  - ORR for IM vs none was 29.8% vs 31.8% (P= 0.736)

- Steroids do not appear to affect efficacy
Patient Case Question #2

• AP is a 56 year old male is undergoing cycle #5 of pembrolizumab for his metastatic melanoma (unresectable, stage III). He complains of significant fatigue and headaches during this visit. He is undergoing a steroid taper for a skin rash secondary to pembrolizumab. Which of the should be considered to be checked during this visit?

1. TSH
2. ACTH
3. Cortisol level
4. All the above
Patient Case Question #3

- AP’s metastatic melanoma progressed after 10 cycles of pembrolizumab. It was decided to go to ipilimumab/nivolumab for second line therapy. He has admitted after 3 cycles of therapy due to dehydration and AKI secondary to diarrhea. After steroids, which is the preferred agent for steroid refractory diarrhea?

  A. Infliximab
  B. Tacrolimus
  C. Mycophenolate
  D. Azathioprine
Future Considerations and Questions

• Unclear which agents for steroid refractory irAEs
  • Sequence of Agents after steroids?
  • Need prospective data

• Currently CTCAE does not address irAE
  • Version 5 appears to not discuss
  • New criteria specifically for irAE?

• Is there a difference between the PD-L1 and the other ICPIs?
Conclusions

• Clinicians need to recognize irAEs of ICPIs
  • “LEGS” and beyond
• irAEs first line treatment is corticosteroids
  • Unclear of which agents if steroid refractory
    • Infliximab preferred if diarrhea
    • Mycophenolate preferred if hepatitis
• Treatment with steroids do not appear to impact efficacy
  • Should not impact decision to initiate therapy
Checkmate to Immune Checkpoint Inhibitor Toxicity

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