Complications of Immunotherapy

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Disclosures

I have no relevant financial relationships with commercial interests pertaining to the content of this presentation.

Objectives

• Compare and contrast the side effects of immunotherapy and chemotherapy.
• Identify common signs and symptoms of immunotherapy toxicities.
• Develop care plans for the treatment of autoimmune induced complications including colitis, pneumonitis and endocrinopathies.
Checkpoint Inhibitors

- Ipilimumab
  - Melanoma

- Nivolumab
  - Melanoma
  - NSCLC

- Pembrolizumab
  - Melanoma
  - NSCLC

- Atezolizumab
  - Urothelial Carcinoma

- Avelumab
  - Urothelial Carcinoma

- Darvumab
  - Urothelial Carcinoma

NSCLC – Non-small Cell Lung Cancer, MSI-H – Microsatellite instability-high, MMR – DNA Mismatch Repair

Mechanisms of Action

- CTLA-4 Inhibitor
  - Ipilimumab

- PD-1 Inhibitors
  - Nivolumab
  - Pembrolizumab

- PD-L1 Inhibitors
  - Atezolizumab
  - Avelumab
  - Darvumab

Chemotherapy vs Immunotherapy

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Immunotherapy</th>
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<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Kill or inhibit rapidly dividing cells</td>
<td>Activate the patient's own immune system to kill cancer cells</td>
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<tr>
<td>Mechanism of Toxicity</td>
<td>Direct damage to health dividing cells</td>
<td>Autoimmune damage to healthy tissue</td>
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<td>Timing of Adverse Events</td>
<td>Generally cycle dependent</td>
<td>Delayed and variable</td>
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<td>Management of Adverse Events</td>
<td>Supportive care</td>
<td>Suppression of the immune system</td>
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Immune Related Adverse Events (irAEs)

Timing of irAEs

- Onset of occurrence is delayed
- Not associated with drug half life
- Can occur after discontinuation of therapy
- Median time to onset varies by affected tissue

Guidelines for the Management of irAEs

- European Society for Medical Oncology
  - Management of Toxicities from Immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Published July 2017

- American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) joint collaboration scheduled for release in late 2017

- NCCN Melanoma Guidelines contain brief recommendations for the management of ipilimumab, nivolumab and pembrolizumab toxicities
Treatment of irAEs

- **Steroids, Steroids, Steroids**
  - High doses
    - Prednisone 1-2 mg/kg daily
  - Long tapers
    - 4-8 weeks
- Alternative immunosuppressive agents for refractory cases
  - Infliximab, mycophenolate mofetil, tacrolimus, etc

Rash

- **Incidence**
  - Most common adverse effect of checkpoint inhibitors
    - Any grade 3-4: 5-15%
    - Severe or life threatening events are rare
- **Presentation**
  - Maculopapular rash, erythema, pustulopapular rash, urticarial dermatitis
  - Severe and fatal cases have been reported
  - DRESS, Sweet syndrome, SJS, TEN
  - Vitiligo
    - Associated with improved efficacy in patients being treated for melanoma

Treatment of Rash

- **Mild**
  - Topical steroids +/- topical antihistamines for itching
- **Moderate**
  - Systemic steroids – prednisone 0.5-1 mg/kg daily
    - Taper over 2-4 weeks
    - Hold immunotherapy until resolves to mild
- **Severe**
  - Systemic steroids – IV methylprednisolone 1-2 mg/kg daily
  - Dermatology consult
  - Discontinue immunotherapy
Colitis

- **Incidence**
  - All grades 8-23%
  - Severe or life threatening 1-7%
  - CTLA-4/PD-1 > CTLA-4 > PD-1 or PD-L1

- **Presentation**
  - Rapid onset of symptoms
  - Diarrhea
  - Abdominal Pain
  - Electrolyte abnormalities
  - Hematochezia
  - Bowel perforation

- **Work Up**
  - Rule out infectious cause
  - Consider imaging (CT or X-ray)
  - Consider sigmoido/colonoscopy +/- biopsy

Treatment of Colitis

- **Mild**
  - Supportive care – oral fluids, loperamide

- **Moderate**
  - Prednisone 1 mg/kg IV daily
  - Taper over 3-4 weeks

- **Severe**
  - Prednisone 1-2 mg/kg IV or PO equivalent daily
  - Taper over 4-8 weeks

- **Refractory – No improvement or worsening in 72 hours**
  - Infliximab 5 mg/kg IV once
  - Continue prednisone with slow taper
  - Consider budesonide, mycophenolate mofetil or tacrolimus

Pneumonitis

- **Incidence**
  - All grades 2-10%
  - Severe or life threatening 1-2%
  - Combination CTLA-4 & PD-1 > PD-1 or PD-L1 > CTLA-4

- **Median time to onset is 2.8 months**
  - Range 9 days to 19.2 months

- **Presentation**
  - Cough
  - Dyspnea

- **Work up**
  - Chest X-ray
  - Infectious work up
Treatment of Pneumonitis

Radiographic changes only
- Monitor for symptoms every 2-3 days

Mild/moderate symptomatic
- Prednisone 1 mg/kg daily
  - Taper over ≥ 6 weeks

Severe
- Prednisone 2-4 mg/kg IV or PO equivalent daily
  - Taper over ≥ 8 weeks
- Empiric antibiotic coverage
- Discontinue immunotherapy

Severe + onset of symptoms or worsening within 48 hours
- Infliximab 5 mg/kg IV once or mycophenolate mofetil
  - Continue prednisone

Endocrinopathies

- Incidence
  - Any grade 4-21%
  - Severe or life threatening 1-3%
- Common Conditions
  - Hypothyroidism
    - Primary or Secondary
  - Hyperthyroidism
  - Hypophysitis
  - Type 1 Diabetes
    - Incidence rate <1%
- Treatment
  - Mild
    - Hormone replacement therapy
  - Moderate
    - Consider holding checkpoint inhibitor
    - Hormone replacement therapy
  - Severe or Life Threatening
    - Discontinue checkpoint inhibitor
    - Hormone replacement therapy
    - Consider Endocrine Consult

Hepatitis

- Incidence
  - Single agent CTLA-4, PD-1 or PD-L1 inhibitors
    - Any grade 5-10%
    - Severe or life threatening 1-2%
  - Combination CTLA-4 and PD-1 inhibitors
    - Any grade 25-30%
    - Severe or life threatening 15%
- Presentation
  - Asymptomatic
  - Isolated transaminitis
- Work up
  - LFTs, INR, albumin
  - Liver screen: hepatitis panel, anti-ANA/SMA
  - Review medication
  - Consider imagine for metastasis or clot
Treatment of Hepatitis

- ALT or AST 1-2X ULN
  - Monitor LFTs weekly

- ALT or AST 2-5X ULN
  - Prednisolone 0.5 mg/kg daily
  - Taper over 2 weeks based on response

- ALT or AST 5-20X ULN
  - Prednisolone 1-2 mg/kg equivalent IV or PO daily
  - Taper over 4 weeks

- ALT or AST > 20X ULN
  - Methylprednisolone 2 mg/kg IV daily
  - Taper over ≥ 4 weeks

- Consider adding mycophenolate mofetil or tacrolimus if no improvement with steroids
- Case reports of anti-thymocyte globulin use
- Avoid infliximab due to risk of worsened hepatitis


Addition Reported irAEs

- Nephritis
- Neurologic Toxicity
  - Polynuropathy, myasthenia gravis, Guillain Barré syndrome, transverse myelitis, encephalitis, aseptic meningitis
- Cardiac Toxicity
  - Myocarditis, pericarditis, arrhythmias, LV dysfunction
- Ocular Toxicity
  - Uveitis, retinopathy
- Rheumatic Diseases

Clinical Pearls for Steroids

- High dose steroids
  - Prednisone 1-2 mg/kg daily
  - Prolonged taper based on severity of symptoms
- Prophylaxis
  - Steroid induced gastritis
    - Proton pump inhibitor or H2-antagonist
  - PCP prevention
    - Bactrim or dapsone
- Administration
  - Take early in the day to avoid sleep disturbances
  - May split into BID dosing
  - Take with food
Do steroids reduce the efficacy of immunotherapy?

No, the use of steroids for the treatment of irAEs has not been shown to affect overall survival.


5 Pillars of Immunotherapy Toxicity Management

5 Pillars of Immunotherapy Toxicity Management

Take Home Points

- As opposed to chemotherapy, the adverse effects of immunotherapy are autoimmune in nature and generally have a delayed presentation.
- The most common irAEs are rash, colitis, pneumonitis, hepatitis and endocrinopathies.
- Treatment for most irAEs is high dose steroids with a prolonged taper.
- The use of steroids for the treatment of irAE has not been shown to reduce immunotherapy efficacy.
References