CANCER IMMUNOTHERAPY
2018

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MultiCare Regional Cancer Center
Successful anti-cancer immunity is autoimmunity

Green, The Scientist, 2014
Immunotherapy strategies

- Cancer vaccines
- Cytokines
- Adoptive T cell therapy
- Checkpoint inhibitors
- Impacts T-cell priming
- Occurs during initial interaction of T-cells with APC
- Blocks activation in the lymph nodes
- Regulates amplitude of early activation of naïve and memory T-cells
- Antibodies targeting CTLA-4
- High toxicity, little response as single agent in gynecologic cancers (OvCa)
• Impacts activation during inflammation
• Prevents T-cell expansion
• Blocks activation in the peripheral tissue
• Mechanism that limits autoimmunity
• More broadly expressed than CTLA-4
<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>2014</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma</td>
</tr>
<tr>
<td>2015</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>NSCLC</td>
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<tr>
<td></td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>NSCLC</td>
</tr>
<tr>
<td>2015</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>RCC</td>
</tr>
<tr>
<td>2015</td>
<td>Nivolumab+Ipilimumab</td>
<td>PD-1+CTLA-4</td>
<td>Melanoma</td>
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<tr>
<td>2015</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Head Neck SCC</td>
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<tr>
<td>2016</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Hodgkin lymphoma</td>
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<tr>
<td>2016</td>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Urothelial cancer</td>
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<tr>
<td>2017</td>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel cell carcinoma</td>
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<tr>
<td>2017</td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial cancer</td>
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</tbody>
</table>
Mechanism of action of cancer vaccines

Vaccine toxicities

• General
  − Fever, chills, lethargy
• Dermatologic
  − Maculopapular rash, vitiligo
• Gastrointestinal
  − Diarrhea
• Liver
  − Elevated LFTs
• Endocrine
  − None
• Other
  − Local reactions, back pain, hypotension
Cytokine toxicities

• General
  – Fever, chills, lethargy, flu-like symptoms

• Dermatologic
  – Maculopapular rash, petechial

• Gastrointestinal
  – Diarrhea, nausea, vomiting

• Liver
  – Elevated LFTs

• Endocrine
  – Thyroiditis

• Other
  – CHF, pulmonary edema, hypotension, thrombocytopenia, leukopenia, mental status changes
Adoptive T cell therapy

Cryopreserved normal donor T cells

Modification with CAR or tumor TCRs

Lymphodepleted patient

Management of toxicity

Cancer patient

Pheresis

Return to patient

Tumor biopsy

Expansion of tumor reactive TILs

Adoptive T cell toxicities

- General
  - Fever, chills, lethargy, fatigue
- Dermatologic
  - Maculopapular rash, vitiligo
- Gastrointestinal
  - Diarrhea, colitis
- Liver
  - Elevated LFTs
- Endocrine
  - Thyroiditis
- Other
  - Lymphopenia, CMV, tachycardia, hypotension, oliguria, pulmonary edema, encephalopathy, carditis
CAR-T CELL INFUSION TOXICITY MEDIATED THROUGH CYTOKINE STORM: IL-6

- AT THE PRESENT TIME, ADMINISTRATION IN A MONITORED ICU SETTING
- IL-6 INHIBITORS: TOCLIZUMAB AND SARILUMAB
T cell targets for antibody therapy

Mellman, Nature (2011)
Checkpoint inhibitor toxicities

- General
  - Fever, chills, lethargy, fatigue
- Dermatologic
  - Maculopapular rash, vitiligo
- Gastrointestinal
  - Diarrhea, colitis
- Liver
  - Elevated LFTs
- Endocrine
  - Thyroiditis
- Other
  - Lymphopenia, CMV, tachycardia, hypotension, oliguria, pulmonary edema, encephalopathy, carditis
Kinetics of immune related adverse events with ipilimumab

Weber, JCO 2012
### Immune-mediated adverse reactions for nivolumab (n=1994)

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Grades n (%)</th>
<th>Median time to onset, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis*</td>
<td>61 (3.1%)</td>
<td>3.5 (1 day to 22.3 months)</td>
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<tr>
<td>Colitis</td>
<td>58 (2.9%)</td>
<td>5.3 (2 days to 20.9 months)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>35 (1.8%)</td>
<td>3.3 (6 days to 9 months)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>12 (0.6%)</td>
<td>4.9 (1.4 months to 11 months)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>20 (1.0%)</td>
<td>4.3 (15 days to 21 months)</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>171 (9.0%)</td>
<td>2.9 (1 day to 16.6 months)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>54 (2.7%)</td>
<td>1.5 (1 day to 14.2 months)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (0.9%)</td>
<td>4.4 (15 days to 22 months)</td>
</tr>
<tr>
<td>Nephritis/renal dysfunction</td>
<td>23 (1.2%)</td>
<td>4.6 (23 days to 12.3 months)</td>
</tr>
<tr>
<td>Skin*</td>
<td>171 (9.0%)</td>
<td>2.8 (&lt;1 day to 25.8 months)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>3 (0.2%)</td>
<td>-</td>
</tr>
</tbody>
</table>
Most common adverse events with anti-CTLA-4 and anti-PD-1

Infusion Related Reactions

• Stop infusion
• Give IV:
  – Diphenhydramine 50 mg
  – Ranitidine 50 mg
• Med choice by symptom:
  – Fever, chills, headache, diaphoresis
    • Acetaminophen, ibuprofen or naproxen
  – Rigors
    • IV meperidine 50 mg-can be given every 5 minutes times 3
• If does not resolve in 30 minutes or worsens
  – Consider IV steroids or epinephrine
• After symptom resolution, restart infusion at 50% infusion rate
General guidelines

• Low grade (1-2) toxicities
  – Observe
  – Hold drug
  – Topical steroids
• Medium grade (2-3) toxicities
  – Hold drug
  – Oral systemic steroids
  – Closer monitoring
• High grade (3-4) toxicities
  – Admit
  – IV steroids
• Steroid-refractory toxicities
  – Other immunosuppressive agents
## Management of grade 3 and 4 events

<table>
<thead>
<tr>
<th>Type and Severity of irAE</th>
<th>Initial Management</th>
<th>Additional Immunosuppression</th>
<th>Immunosuppression Tapering Schedule</th>
</tr>
</thead>
</table>
| **Colitis and/or diarrhea**  
Grade 3-4  
- Increase of ≥7 stools per day over baseline  
- Abdominal pain, fever, and change in bowel habits | • Admit to hospital for intravenous corticosteroid therapy (methylprednisolone 1-2 mg/kg daily dose)  
• Supportive care including intravenous fluids, supplemental oxygen, and antibiotics as needed  
• Withhold hepatotoxic drugs  
• Consider further diagnostic imaging or procedures | **Colitis and/or diarrhea**  
- If no improvement after 3 days, give infliximab 5 mg/kg  
- Can redo infliximab after 2 weeks if needed | **Colitis and/or diarrhea**  
- Rapidly tapering course of steroids as tolerated over 4-6 weeks  
- Increase steroids if diarrhea flares and then restart tapering |
| **Hepatitis**  
Grade 3-4  
- Aspartate transaminase and/or alanine transaminase levels >5 times ULN  
- Total bilirubin level >3 times ULN | | **Hepatitis**  
- If no improvement after 3 days, start mycophenolate mofetil 500-1000 mg every 12 hours | **Hepatitis**  
- Rapidly tapering course of steroids as tolerated; discontinue mycophenolate mofetil once tapered to prednisone 10 mg daily |
| **Pneumonitis**  
Grade 3-4  
- Severe, life-threatening symptoms  
- Worsening hypoxia | | **Pneumonitis**  
- If no improvement after 48 hours, start additional agent as above or cyclophosphamide | **Pneumonitis**  
- Taper steroids slowly over 6 weeks  
- Mycophenolate mofetil management as above if needed |
Management of colitis

Adapted from the YERVOY irAR Management Guide
Management of hepatitis

Determine Severity of Hepatitis

Mild or Moderate
- AST or ALT >5 to ≤8 x ULN
- Bilirubin >3 to ≤5 x ULN

Management
- Omit scheduled ipilimumab dose
- Investigate for other causes hepatic injury
- Monitor LFT’s closely

Hepatitis Controlled
- Resume ipilimumab if AST and ALT ≤5 x ULN, and bilirubin ≤3 x ULN

Follow up

Ongoing LFT Elevation
- Omit ipilimumab until AST and ALT ≤5 x ULN, and bilirubin ≤3 x ULN

Severe
- AST or ALT >8 x ULN
- Bilirubin >5 x ULN

Permanently stop ipilimumab
- Administer high-dose IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day)
- Monitor LFT’s closely
- Investigate for other causes hepatic injury

Hepatitis Controlled
- Taper steroids over at least one month
- Increase steroid dose and taper more slowly if LFT’s increase during taper, see below

Additional Immunosuppressive Therapy
- Consider adding alternative immunosuppressant such as mycophenolate mofetil 500 mg bd
- Consider high-dose pulsed IV corticosteroids (15 mg/kg methylprednisolone daily for 3 days)*

Steroid Refractory

Adapted from the YERVOY irAR Management Guide
T cells continue to evolve even after drug is cleared

- When toxicities occur is variable
- Early and late
- Prolonged treatment
- May need to treat again

Responses as late as 106 weeks

Weber, Oncologist, 2008
Summary

- Prompt recognition of unique immune related toxicities
- Grade severity
- Toxicities may persist and elaborate even after stopping drug
- Consult subspecialty services
  - Pulmonary, endocrinology, dermatology, GI, etc.
- With more FDA indications--very rare side effects
- Immune combinations may lead to higher rates of adverse events