Your Body Is A Wonderland… Or Is It?
Immune toxicities of novel antineoplastic medications

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Disclosure
I have no conflicts of interest to disclose.

I will be discussing off-label uses of prednisone, infliximab, vedolizumab, tacrolimus, mycophenolate, and budesonide.

Learning Objectives - Pharmacists
- Describe the mechanism of action of CTLA-4, PD-1, and PD-L1 inhibitors and how the differences contribute to the immune-related adverse event (irAE) profile
- Recognize the signs and symptoms of a steroid-refractory irAE and apply to a patient case
- Assess and devise a management plan for treatment of 3 long-term steroid side effects

Learning Objectives - Technicians
- Identify the currently approved brand and generic CTLA-4, PD-1, and PD-L1 inhibitors
- Define the following terms: checkpoint inhibitor, immune-related adverse event (irAE), and steroid-refractory irAE
- Recognize 3 common long-term steroid side effects

Outline
- General overview of checkpoint inhibitor biology and use in cancer
- Discussion and incidence of irAE
- Management of immune related adverse events
- Questions
I don't work in oncology… why do I care?

Can your own immune system kill cancer?

The Remarkable Cancer Treatment That Helped Jimmy Carter Combat Brain Tumor

Harnessing the Immune System to Fight Cancer

Can your own immune system kill cancer?

The Remarkable Cancer Treatment That Helped Jimmy Carter Combat Brain Tumor

Intro to Checkpoint Inhibitors

How they are taking over the cancer world!

Timeline of checkpoint inhibitor approval

Ipilimumab Yervoy® 3/2011
Pembrolizumab Keytruda® 9/2014
Nivolumab Opdivo® 12/2014
Atezolizumab Tecentriq® 5/2016
Avelumab Bavencio® 3/2017
Durvalumab Imfinzi® 5/2017

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Mechanistic Differences

CTLA-4
- Only on T-cells
- Ligands: CD80 and CD86
- Only on antigen-presenting cells
- CTLA-4 knockout mice: embryonic death from autoimmunity
- Presumed “central effect” on T-cells

PD-1
- On T, B, and NK cells
- Ligands: PD-L1 and PD-L2
- On antigen-presenting cells and tumor cells
- PD-1 knockout mice: late onset autoimmunity (Lupus-like arthritis and glomerulonephritis)
- Presumed more of “peripheral effect” on both T and B cells

What are we “checking”?

A (brief) history of melanoma:

- **1975**: dacarbazine - metastatic
  - Median overall survival = 5-11 months
  - 1-year overall survival = 27%
- **1992**: interleukin 2 (IL-2) - adjuvant
  - Complete response = 6%
  - Durable response (beyond 20 years)
- **1995**: interferon alpha-2b - adjuvant
  - 5-year overall survival: 46%
- **2011**: ipilimumab - metastatic
  - 1-year overall survival: 47%
  - 21% of all patients who received ipilimumab in trial alive at 3 years
- **2014**: pembrolizumab - metastatic
  - Overall response rate = 34%
  - 5-year overall survival = 63%
- **2014**: nivolumab - metastatic
  - Overall response rate = 61%
  - 2-year overall survival = 61.8%
- **2015**: nivolumab + ipilimumab - metastatic
  - Overall response rate = 61%
  - 2-year overall survival = 63.8%

Does this actually work?

**Current FDA approvals**

<table>
<thead>
<tr>
<th>Checkpoint inhibitor</th>
<th>FDA approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Melanoma – adjuvant or metastatic</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Squamous head and neck cancer, classical Hodgkin lymphoma, melanoma (metastatic), NSCLC, urothelial carcinoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Squamous head and neck cancer, classical Hodgkin lymphoma, melanoma (metastatic), NSCLC, renal cell, urothelial carcinoma</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>NSCLC, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Merkel cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Urothelial carcinoma</td>
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</tbody>
</table>

Does this actually work?

**Dosing**

<table>
<thead>
<tr>
<th>Checkpoint inhibitor</th>
<th>Dosing and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>3 mg/kg or 10 mg/kg every 3 weeks for 4 doses</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>200 mg or 2 mg/kg every 3 weeks</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>240 mg or 3 mg/kg every 2 weeks (1 mg/kg every 3 weeks in combination with ipilimumab for 4 doses, then 240 mg every 2 weeks)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>1200 mg every 3 weeks</td>
</tr>
<tr>
<td>Avelumab</td>
<td>10 mg/kg every 2 weeks</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>10 mg/kg every 2 weeks</td>
</tr>
</tbody>
</table>

Does this actually work?

**Review of Toxicities**

How your body might not be the wonderland you thought it was

**Question #1**

Based on your background knowledge of immunotherapy, which side effect is MOST likely to occur with a checkpoint inhibitor:

A. Alopecia (hair loss)
B. Rash
C. Vomiting
D. Anemia
E. No side effects! My body IS a wonderland!
Question #1
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D. Anemia
E. No side effects! My body IS a wonderland!

Hint: Think autoimmune diseases...

Chemotherapy vs. Immunotherapy

Toxicity from the drug itself
- Nausea/vomiting
- Neutropenia, thrombocytopenia, anemia
- Hair loss
- Rash
- Diarrhea

Toxicity from immune activation
- “Ils-itis”
- Colitis (inflammation of the colon)
- Pneumonitis (inflammation of the lining of the lungs)
- Hypophysitis (inflammation of the hypophyseal gland)
- Hepatitis (inflammation of the liver)
- Rash (aka skin-itis)

Timeline of Toxicities (approximate)

Toxicity Grading
CTCAE: Common Terminology Criteria for Adverse Events
- Grade 1: mild; asymptomatic or mild symptoms; intervention not indicated
- Grade 2: moderate; minimal, local, or non-invasive intervention indicated
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization indicated
- Grade 4: life-threatening; urgent intervention indicated
- Grade 5: death related to AE

Subjective grade (reportable symptom)
- Dry mouth grade 2: “moderate symptoms; oral intake alterations”

Objective grade (lab value)
- Alanine aminotransferase (ALT) increased grade 2: “>3.0-5.0 x ULN”

How often – any adverse event

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade 3 or 4</th>
<th>All Grades</th>
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</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>24-27%</td>
<td>88-93%</td>
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<tr>
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<td>10-13%</td>
<td>73-80%</td>
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<td>Nivolumab</td>
<td>16%</td>
<td>82%</td>
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<tr>
<td>Atezolizumab</td>
<td>11%</td>
<td>67%</td>
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<td>Avelumab</td>
<td>10%</td>
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</tr>
<tr>
<td>Durvalumab</td>
<td>5%</td>
<td>63%</td>
</tr>
<tr>
<td>Ipil+Nivo</td>
<td>54-55%</td>
<td>91-96%</td>
</tr>
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</table>
How often – most common side effects

<table>
<thead>
<tr>
<th></th>
<th>Colitis</th>
<th>Rash</th>
<th>Hypophysitis</th>
<th>Hepatitis</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>avelumab</td>
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<td>0%</td>
<td>1%</td>
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<td>1%</td>
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<tr>
<td>durvalumab</td>
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<td>0%</td>
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<td>1%</td>
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<tr>
<td>ipil/nivo</td>
<td>0-11%</td>
<td>0%</td>
<td>1%</td>
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</tbody>
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*Including diarrhea

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**Treatment of Toxicities**

Yep. Body is definitely not a wonderland.

JH is a 72-year-old man with metastatic melanoma. He was treated with 4 cycles of combination nivolumab/ipilimumab.

Five days after his last dose, JH was admitted for 8-10 watery bowel movements per day and abdominal pain over the last 3 days.

What do we do next?
A. Panic – the immune system is out of control!
B. Steroids, steroids, steroids
C. Rule out infection, then give steroids
D. Infliximab
Steroid

Ann Oncol 2015;26:2375

Colonoscopy

Colonoscopy for biopsy proof of colitis

Re-evaluate in 2-3 days

Mild or Moderate
6 stools/day per day over baseline, per rectal bleeding, abdominal pain, or large bowel inflammation

Rule out infection

Symptomatic care

Prednisone 1mg/kg

Colostomy - you don't really need it anyway

Consider Methylprednisolone 4-8mg/kg IV

Modest response to 5mg/kg or

or

Large dose to 10mg/kg, taper slowly

Re-evaluate in 2-3 days

Worse?

Improved?

Worsen originally, but now back?

Consider Infliximab every 8 weeks

腸内細菌症

C. Difficile

Question #3

JH initially improves with the steroids after 3 days. He is discharged from the hospital with a course of steroids to start a taper in 2 weeks. 6 days after discharge, he starts to have increasing frequency of diarrhea and is admitted to our service again. He receives a dose of infliximab, but still has diarrhea.

What do we do next?

A. PANIC!! This time we really have a problem

B. Double the steroid dose to 2 mg/kg and give another dose of infliximab to 5 mg/kg

C. Colostomy – you don’t really need it anyway

D. Vedolizumab 300 mg

E. Consult Gastroenterology

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SS is a 90 year old gentleman who came in with a diffuse rash covering both legs, trunk, back, arms, and it has just moved up to his face. He was also complaining of fevers, but not itching. He started pembrolizumab for metastatic melanoma 8 weeks ago and has received a total of 2 doses.

What should we do next (all that apply)?
A. Oatmeal bath
B. OTC hydrocortisone cream
C. Prednisone 1 mg/kg
D. Infliximab 5 mg/kg
E. Consult Dermatology

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### Skin body surface area – Rule of 9’s

**Anterior Surface**
- Head and neck: 9%
- Anterior trunk: 18%
- Arms: 9% each
- Legs: 18% each
- Genitalia: 1%

**Posterior Surface**
- Trunk: 18%
- Sacral region: 1%
- Lower extremities: 24% each

### Treatment Algorithm - Rash

**Biopsy proof of drug reaction**

**Mild or Moderate**

[Grade 1 or 2]
- Neurologic/psychiatric
- Other

**Symptomatic care**
- IV fluids
- Topical steroids
- Lotions/creams
- Oral antihistamines

**Consider Prednisone 1 mg/kg**

**Re-evaluate in 2-3 days**

**Improved?**

**Improved originally, but now back?**

**Worse?**
CB is a 65 year old gentleman with a history of diabetes. Your plan is to start a prednisone taper for colitis – decreasing by 10 mg every week, starting at 1 mg/kg, or 90 mg. While he was taking the 90 mg he was using insulin glargine 50 units at bedtime, as well as insulin lispro sliding scale of 1:10 correction starting at a blood glucose of 150 mg/dL three times daily with meals.

How should we manage his insulin during the taper (all that apply)?
A. Decrease the insulin glargine by 10 units with each drop of prednisone
B. Have CB stop taking his meal-time insulin
C. Continue current regimen
D. Hold insulin glargine when blood glucose is < 100 mg/dL
E. Consult Endocrinology
Conclusions

- Immune therapy is an exciting and emerging type of therapy for a variety of oncologic conditions
- Response rates are improving with newer therapies
- Side effects can be mild, but are typically immune-related
- Grade 3-4 immune therapies required immediate attention and expert consultation
- Steroids require close monitoring and the least effective dose to prevent unneeded side effects