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?

The list of cancers that can be treated by immunotherapy keeps growing.

Can your own immune system kill cancer?

By Jacqueline Howard, CNN

Immunotherapy: Training the Body to Fight Cancer

In animal models and clinical trials, breakthrough immunotherapies are emerging.

Harnessing the Immune System to Fight Cancer

New drugs and methods of altering a patient’s own immune cells are helping some cancer patients—but not all—even when standard treatments fail.

The closest thing yet to a cure for terminal cancer?

Immunotherapy has given Sandra Sayce an extra 10 years of life, and now new combinations of the treatment may offer hope to many more patients.

The Remarkable Cancer Treatment That Helped Jimmy Carter Combat Brain Tumor

By GILLIAN MOHNEY • Mar 7, 2016, 2:57 PM ET
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

Timeline of checkpoint inhibitor approval

- **CTLA-4 Inhibitor**
  - Ipilimumab (Yervoy®) 3/2011
  - Pembrolizumab (Keytruda®) 9/2014

- **PD-1 Inhibitors**
  - Nivolumab (Opdivo®) 12/2014
  - Atezolizumab (Tecentriq®) 5/2016

- **PD-L1 Inhibitors**
  - Avelumab (Bavencio®) 3/2017
  - Durvalumab (Imfinzi®) 5/2017

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What are we “checking”?
**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
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%
  • 1-year overall survival = 69%

• **2014**: nivolumab - metastatic
  • Overall response rate = 32%
  • 1-year overall survival = 63%

• **2015**: nivolumab + ipilimumab - metastatic
  • Overall response rate = 61%
  • 2-year overall survival = 63.8%

Does this actually work?

Does this actually work?

6/12/2015 2.4cm x 2.9cm

8/31/2015 1.9cm x 2.4cm
### 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), MSI-high cancer, 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>
</tr>
</tbody>
</table>

NSCLC = non-small cell lung cancer
## 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>
Review of Toxicities

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

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!
Chemotherapy vs. Immunotherapy

Toxicity from the *drug itself*

- Nausea/vomiting
- Neutropenia, thrombocytopenia, anemia
- Hair loss
- Rash
- Diarrhea

Toxicity from *immune activation*

“*Itis-es*”

- 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*)
Hint:
Think autoimmune diseases...
Timeline of Toxicities (approximate)

Fig 2. Kinetics of appearance of immune-related adverse event.

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></th>
<th>Grade 3 or 4</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>24-27%</td>
<td>86-93%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>10-13%</td>
<td>73-80%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>16%</td>
<td>82%</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>11%</td>
<td>67%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>10%</td>
<td>62%</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>5%</td>
<td>63%</td>
</tr>
<tr>
<td>Ipi/Nivo</td>
<td><strong>54-55%</strong></td>
<td><strong>91-96%</strong></td>
</tr>
</tbody>
</table>
### How often – most common side effects

<table>
<thead>
<tr>
<th></th>
<th>Colitis(^a)</th>
<th>Rash</th>
<th>Hypophysitis(^b)</th>
<th>Hepatitis</th>
<th>Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab</strong></td>
<td>6-11%</td>
<td>40%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td>1-3%</td>
<td>20%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td>2%</td>
<td>20%</td>
<td>1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Atezolizumab</strong></td>
<td>2%</td>
<td>12%</td>
<td>1%</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Avelumab</strong></td>
<td>&lt;1%</td>
<td>9%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Durvalumab</strong></td>
<td>1-2%</td>
<td>12-13%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>6-11%</td>
</tr>
<tr>
<td><strong>Ipi/Nivo</strong></td>
<td>8-17%</td>
<td>30-50%</td>
<td>5%</td>
<td>2%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

\(^a\) Including diarrhea  
\(^b\) Including hypo/hyperthyroidism

Treatment of Toxicities

Yep. Body is definitely not a wonderland
General Principals

- Comprehensive patient education
- Be aware of common and uncommon irAE
- Immune-modulatory medications
- Contact specialty teams and/or specialty hospital
- Don’t forget supportive care
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
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.

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A. Panic – the immune system is out of control!
B. Steroids, steroids, steroids
C. **Rule out infection, then give steroids**
D. Infliximab
Colonoscopy

1. Rectum: *Inflammation
2. Rectum: *Inflammation
3. Rectum: *Inflammation
4. Sigmoid Colon: *Inflammation
5. Sigmoid Colon: *Inflammation
6. Rectum: *Inflammation
Colonoscopy

13 Descending Colon

14 Sigmoid Colon inflammation

15 Sigmoid Colon: colitis

16 Sigmoid Colon

17 Sigmoid Colon: colitis

18 Rectum: colitis
Treatment Algorithm - Colitis

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

(Grade 1 or 2)

Rule out infection
Symptomatic care

Consider Prednisone 1mg/kg

Colonoscopy for biopsy proof of colitis

Improved?

Improved originally, but now back?

Worse?

Re-evaluate in 2-3 days

- ? Fecal calprotectin or c-reactive protein
- Clostridium difficile
- IV fluids
- Anti-diarrheals
Treatment Algorithm - Colitis

Severe
≥ 7 stools per day over baseline
(Grade 3 or 4)

Rule out infection
Symptomatic care
Methylprednisolone
1-2 mg/kg IV

Prednisone 1mg/kg
Continue until G1, then slowly taper

Improved?
Improved originally, but now back?
Worse?
Re-evaluate in 2-3 days

Colonoscopy for biopsy
proof of colitis

References:
Treatment Algorithm - Colitis

- **Improved?**
- **Taper prednisone over 4 weeks**
- **May be ok to restart immune therapy**

Re-evaluation in 2-3 days

**References:**
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
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.

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D. Vedolizumab 300 mg
E. Consult Gastroenterology
## Steroid-Refractory Colitis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Infliximab**       | • Continue steroids  
                       |   • 5 mg/kg once, may be given again in 2 weeks                        |
| **MMF/Tacrolimus**   | • Limited information; expert opinion  
                       |   • No goal level established                                          |
| **Vedolizumab**      | • Anti-integrin α4β7 antibody (gut specific)  
                       |   • 300 mg at 0, 2, and 6 weeks                                       |
| **Colectomy**        | • Urgent cases  
                       |   • Infliximab, other immune therapy failure                          |
Can we prevent this?

- Budesonide: non-absorbed oral steroid
- Weber, et al:
  - Stage III unresectable or Stage IV melanoma
  - 1:1 to concomitant budesonide vs. placebo
  - Grade ≥ 2 diarrhea rate
    - Ipilimumab + budesonide = 32.7%
    - Ipilimumab + placebo = 35%
  - 2-year overall survival
    - Ipilimumab + budesonide = 40.5%
    - Ipilimumab + placebo 41.7%
- No difference in diarrhea/colitis rates
- Do not recommend using as prophylaxis
- Many irAE algorithms mention budesonide as an option in G1 treatment of colitis

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
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
Skin body surface area – Rule of 9’s

<table>
<thead>
<tr>
<th>Anatomical Surface</th>
<th>%BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>9%</td>
</tr>
<tr>
<td>Anterior trunk</td>
<td>18%</td>
</tr>
<tr>
<td>Posterior trunk</td>
<td>18%</td>
</tr>
<tr>
<td>Arms</td>
<td>9% each</td>
</tr>
<tr>
<td>Legs</td>
<td>18% each</td>
</tr>
<tr>
<td>Genitalia</td>
<td>1%</td>
</tr>
</tbody>
</table>
Treatment Algorithm - Rash

Mild or Moderate ≤ 30% BSA

(Grade 1 or 2)
Maculopapular
Papulopustular

Symptomatic care

- IV fluids
- Topical steroids
- Lotions/creams
- Oral antihistamines

Consider Prednisone 1mg/kg

Biopsy proof of drug reaction

Improved?

Improved originally, but now back?

Worse?

Re-evaluate in 2-3 days

Treatment Algorithm - Rash

Severe
≥ 30% BSA

(Grade 3 or 4)
Maculopapular
Papulopustular
Bulla
Exfoliative/ulcerative

Symptomatic care
Methylprednisolone
1-2 mg/kg IV

Biopsy proof of drug reaction

Prednisone 1mg/kg
Slowly taper

Improved?

Improved originally, but now back?

Worse?

Re-evaluate in 3-5 days

Treatment Algorithm - Rash

Improved?

Taper prednisone over 4 weeks

May be ok to restart immune therapy

Re-evaluation in 3-5 days

Endocrinopathies from immune therapy

HYPOPHYSITIS
- More common in men
- More common in CTLA-4 inhibitors over PD-1 or PD-L1 inhibitors
- Symptoms: headache, asthenia, fatigue, nausea, weakness, lethargy, erectile dysfunction, and loss of libido
- Steroids + gland replacement

HYPO OR HYPERTHYROID
- More common in women
- Slightly more common in PD-1 or PD-L1 over CTLA-4 inhibitors
- Hypothyroid
  - Only necessary to treat when symptomatic
  - Levothyroxine
- Hyperthyroid
  - Methimazole, Propylthiouracil
  - Endocrine consult suggested

OTHERS
- Type 1 Diabetes mellitus
  - Treated as normal T1DM
- Adrenal insufficiency/Adrenal crisis
  - Hydrocortisone is drug of choice
  - Endocrine consult preferred
  - Emergency

Oncologist 2016;21(7):804-16.
Managing Steroids

- Hyperglycemia
- Hypertension
- Infections
- Osteopenia
- Skin Breakdown
- GI upset/ulcers

- Daily calcium and vitamin D supplementation
- Every other year BMD
- Thick cream/ointments for comfort
- Aggressive wound care
- Usually a good thing!
- Monitor for diabetic patients

- More monitoring for current diabetic patients
- Develop a plan for monitoring a non-diabetic patient
- May need to adjust or start medications
- PJP pneumonia
  - Prophylaxis
  - Fungal – mucocutaneous
    - Treatment only
- Prophylaxis with PPI
- Discourage concurrent use of NSAIDs

- GI upset/ulcers
- Increased appetite

- Thick cream/ointments for comfort
- Aggressive wound care
- Daily calcium and vitamin D supplementation
- Every other year BMD
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
Question #5

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
Questions?

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