Cancer immunotherapy: successes and pitfalls for the non-oncologist

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Conflicts of interest

• DSMB for BioMetrix
Learning objectives

• Recognize basic immunotherapy and biology and its impact on cancer therapy
• Diagnose and treat immunotherapy side effects
• Identify which cancers are best suited for immunotherapy
FACT OF THE DAY

"[After immunotherapy] ... they didn’t find any cancer at all."

– JIMMY CARTER
Former U.S. President
Cancer immunotherapy wins Nobel Prize

James P. Allison

Tasuku Honjo
CHECKPOINT INHIBITOR DRUGS

‘Checkpoint’ proteins block T-cell activity. Inhibitor drugs can release the brakes on T cells at different stages.

The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.
Potter!

Images from nature.com; Pottermore.com
Melanoma: Ipilimumab better than placebo

**Figure A: Overall Survival**

- **Legend:**
  - Ipilimumab plus gp100
  - Ipilimumab
  - gp100
  - Censored

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Ipilimumab plus gp100</th>
<th>Ipilimumab</th>
<th>gp100</th>
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</thead>
<tbody>
<tr>
<td>Ipilimumab  plus gp100</td>
<td>403</td>
<td>297</td>
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<tr>
<td>Ipilimumab</td>
<td>137</td>
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<tr>
<td>gp100</td>
<td>136</td>
<td>93</td>
<td>58</td>
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</tbody>
</table>

**Figure B: Progression-Free Survival**

- **Legend:**
  - Ipilimumab plus gp100
  - Ipilimumab
  - gp100

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Ipilimumab plus gp100</th>
<th>Ipilimumab</th>
<th>gp100</th>
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<tr>
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<td>7</td>
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</tbody>
</table>

**References:**
NEJM 2010;363:711-23
Melanoma: Pembrolizumab better than ipi

A  Progression-free Survival

B  Overall Survival

NEJM 2015;372:2521-32
Melanoma: responses last!

Pre-2010: OS 6.5 months
When do we typically use immunotherapy?

• Melanoma: Adjuvant, relapsed/metastatic
• Non-small cell lung cancer: post-chemoRT, relapsed/metastatic
• Head and neck: relapsed/metastatic
• Renal cell carcinoma: relapsed/metastatic
• Hodgkin’s lymphoma: relapsed
• Hepatocellular: After failure of multikinase inhibitor
• Triple negative breast cancer: relapsed/metastatic
Adverse events (AEs) and Immune related adverse events (irAEs)
Definitions

• Adverse event: side effect associated with a medication
• Immune related adverse event: side effect due to immune activation
• CTCAE: oncology way of grading side effects
Where do irAEs occur?

- Any organ system can be affected
- Most commonly gastrointestinal tract, endocrine glands, skin, and liver.
- irAEs require multidisciplinary, collaborative approach for appropriate management
All grade side effects in IO treated patients

A All-grade adverse event

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>18.26 (16.49-20.11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10.61 (9.46-11.83)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.47 (8.43-10.58)</td>
</tr>
<tr>
<td>Rash</td>
<td>9.31 (8.29-10.41)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.39 (7.46-9.39)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7.18 (6.36-8.06)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6.07 (5.35-6.85)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.83 (5.15-6.59)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5.58 (4.92-6.31)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4.77 (4.18-5.42)</td>
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<tr>
<td>Cough</td>
<td>4.17 (3.64-4.77)</td>
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<tr>
<td>Dyspnea</td>
<td>3.88 (3.38-4.45)</td>
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<tr>
<td>Anemia</td>
<td>3.84 (3.35-4.38)</td>
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<tr>
<td>Infusion-related reaction</td>
<td>3.63 (3.15-4.17)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.60 (3.12-4.13)</td>
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</table>

B Grade 3 or higher adverse event

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>0.89 (0.69-1.14)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.78 (0.59-1.02)</td>
</tr>
<tr>
<td>AST increased</td>
<td>0.75 (0.56-0.99)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>0.71 (0.51-0.98)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0.70 (0.52-0.93)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0.67 (0.50-0.89)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.59 (0.45-0.77)</td>
</tr>
<tr>
<td>Colitis</td>
<td>0.47 (0.34-0.65)</td>
</tr>
<tr>
<td>GGT increased</td>
<td>0.47 (0.30-0.69)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0.43 (0.30-0.62)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.42 (0.30-0.59)</td>
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<tr>
<td>Lymphopenia</td>
<td>0.40 (0.26-0.60)</td>
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<td>Hyponatremia</td>
<td>0.39 (0.25-0.59)</td>
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<tr>
<td>Asthenia</td>
<td>0.34 (0.25-0.48)</td>
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<tr>
<td>Amylase increased</td>
<td>0.30 (0.17-0.47)</td>
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</table>
Immune related side effect incidence

**All-grade irAE**

<table>
<thead>
<tr>
<th>AE</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine dysfunction</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>6.07 (5.35-6.85)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2.82 (2.40-3.29)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.20 (0.91-1.55)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>0.75 (0.52-1.04)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>0.69 (0.50-0.93)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0.60 (0.42-0.82)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>0.43 (0.27-0.65)</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>0.26 (0.12-0.50)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>0.20 (0.07-0.45)</td>
</tr>
<tr>
<td>Other disorder</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.47 (8.43-10.58)</td>
</tr>
<tr>
<td>AST increased</td>
<td>3.39 (2.94-3.89)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>3.26 (2.80-3.79)</td>
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<tr>
<td>ALT increased</td>
<td>3.14 (2.71-3.62)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2.79 (2.39-3.23)</td>
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<tr>
<td>Colitis</td>
<td>1.24 (0.99-1.54)</td>
</tr>
<tr>
<td>Bilirubin increase</td>
<td>1.05 (0.75-1.41)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0.85 (0.64-1.10)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>0.29 (0.15-0.51)</td>
</tr>
</tbody>
</table>

**Grade 3 or higher irAE**

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<td>Hyperglycemia</td>
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<tr>
<td>Adrenal insufficiency</td>
<td>0.18 (0.10-0.30)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>0.18 (0.10-0.30)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0.16 (0.09-0.27)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.08 (0.04-0.13)</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>0.07 (0.02-0.16)</td>
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<tr>
<td>Thyroiditis</td>
<td>0.04 (0.01-0.10)</td>
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<tr>
<td>Hyperthyroidism</td>
<td>0.04 (0.02-0.10)</td>
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<tr>
<td>Autoimmune thyroiditis</td>
<td>0.02 (0.00-0.09)</td>
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<tr>
<td>Other disorder</td>
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<td>Bilirubin increase</td>
<td>0.15 (0.07-0.28)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>0.02 (0.00-0.07)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>0.02 (0.00-0.06)</td>
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</tbody>
</table>
Timing of irAEs

Timing of irAEs on ipilimumab

J Clin Oncol 2018; 35:34
Onset and Resolution

A. Time to onset (median, range)

- Skin (n=30 (rash only); n=171; n=16 (data for *3/4 AE only))
  - Median: 4.3
- GI (n=23; n=78; n=16 (colitis only))
  - Median: 6.3
- Pulmonary (n=13; n=11; n=26)
  - Median: 8.7
- Endocrine (n=12; n=40; n=122)
  - Median: 17.8
- Renal (n=8; n=9; n=4)
  - Median: 10.5
- Hepatic (n=3; n=29; n=8)
  - Median: 4.1

Weeks

B. Time to resolution (median, range)

- Skin
  - Median: 5.7 (0.1–46.9+) (n=24)
- GI
  - Median: 2.0 (0.1–31.0) (n=19)
- Pulmonary
  - Median: 2.0 (0.6–13.4) (n=13)
- Endocrine
  - Median: 20.6 (0.4–47.6+) (n=6)
- Renal
  - Median: 5.9 (0.7–37.6+) (n=7)
- Hepatic
  - Median: 2.0 (0.1–31.0+) (n=3)

Weeks (after onset)
Guidelines Galore!

• Multiple guidelines available
  • Choose a set of guidelines and familiarize yourself with them
Guideline websites

• SITC: https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/iraе
• ESMO: https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
• ASCO: https://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385
Management

- Consider stopping/holding the offending medication
- If moderate severity: Prednisone 1-2 mg/kg
- If severe: Methylprednisolone 2 mg/kg/day IV
Big categories of irAEs

• Pulmonary
• Gastrointestinal
• Muco-cutaneous
• Endocrinologic
• MSKL
Big categories of irAEs

- Pulmonary
- Gastrointestinal
- Muco-cutaneous
- Endocrinologic
- MSKL
Pneumonitis

- Incidence: 1%–2% of patients treated with PD-1 and/or CTLA-4
- Typical time to onset: 9–19 weeks
- Symptoms: fatigue, cough, dyspnea, hypoxemia (late)
- Differential diagnosis: infection, allergy, cardiac causes (myocarditis)

Pneumonitis

• Workup
  • Chest x-ray and/or CT scan: Radiographic findings of ground-glass lesions and/or disseminated nodular infiltrates
  • Bronchoscopy (if diagnosis in doubt)
  • PFT (pulmonary function testing)
  • Blood gas

• Treatment
  • Steroid therapy (guided by radiographic/symptomatic response)
  • Prophylactic antibiotic/antifungal therapy during high-dose steroid
  • Mycophenolate mofetil, cyclophosphamide, IVIG, or infliximab in severe cases

Big categories of irAEs

• Pulmonary
• Gastrointestinal
• Muco-cutaneous
• Endocrinologic
• MSKL
Diarrhea and/or Colitis

• Incidence:
  • Up to 30% with anti-CTLA4 therapy (ipilimumab) with 7% severe
  • Severe in 2% of PD1 pathway drugs (nivolumab, pembrolizumab, etc.)
• Typical time to onset: 6–8 weeks in CTLA-4 or CTLA-4/PD-1, longer in PD-1

Diarrhea and/or Colitis (cont.)

• **Symptoms**
  • Abdominal cramping, pain
  • Anorexia, dyspepsia
  • Diarrhea +/- blood
  • Possible to have colitis without diarrhea

• **Workup**
  • Stool for *C. diff*, ova and parasite, blood
  • CT abdomen/pelvis with IV contrast to evaluate for colonic thickening and dilatation
  • Colonoscopy with biopsy if diagnosis unclear

Image courtesy Brianna Hoffner, University of Colorado.

Diarrhea and/or Colitis (cont.)

- Work-up (cont.): Sigmoidoscopy/colonoscopy may be done if diagnosis is unclear

- Treatment:
  - Observation if mild (grade 1)
  - Initial therapy: Steroids (1 mg/kg) if grade 2 or worse (4-6 BMs/day)
  - Diarrhea/colitis with one checkpoint inhibitor does not prohibit use of another

Hepatitis

• Incidence
  • 2-9% with ipilimumab
  • Approximately 0.5% with anti-PD1
  • Typical time to onset: 8–12 weeks in single agent, sooner in combination

• Symptoms
  • Abdominal bloating or pain, dyspepsia, jaundice, and nausea
  • Usually asymptomatic and diagnosed based on elevated LFT

Hepatitis (cont.)

• Workup
  • Hepatitis panel to evaluate for infectious cause
  • CT and/or ultrasound to evaluate for liver metastases or cholelithiasis
  • Biopsy (if needed)

• Treatment
  • High-dose steroid (prednisone 1–2 mg/kg)
  • Mycophenolate mofetil with steroid for severe cases
  • Infliximab is contraindicated due to hepatotoxic effects
  • Check labs every 1–2 days

Big categories of irAEs

- Pulmonary
- Gastrointestinal
- Muco-cutaneous
- Endocrinologic
- MSKL
Skin

• Incidence:
  • Most common irAE
  • Anti–PD-1: Approx. 40% in melanoma vs. 17% in NSCLC
• Time to onset: 6 weeks
• Symptoms: Pruritis, vitiligo, rash, erythema
• Work up: biopsy if unclear
• Treatment: topical steroids if mild, systemic if severe

Image courtesy Brianna Hoffner, University of Colorado.

Big categories of irAEs

- Pulmonary
- Gastrointestinal
- Muco-cutaneous
- Endocrinologic
- MSKL
Endocrinopathies

• Incidence: 5%–10% Many endocrine disorders do not resolve, require lifelong replacement

• Median time to onset: Variable (early for thyroid, late for other)

• Symptoms
  • Hypothyroid/hyperthyroid
  • Hypophysitis
  • Adrenal insufficiency
  • Diabetes type 1

Thyroid Disorders

- Incidence: Hypothyroidism in 5-10%
- Typical time to onset: Can be fast (2-4 weeks)
- Symptoms: typical for thyroid disease
- Work up
  - High TSH, low/normal T4 or T3 indicate primary hypothyroidism
  - Low/normal TSH, low T4 suggests hypothyroidism secondary to pituitary
  - TPO antibodies, thyrotropin-binding inhibitory immunoglobulins

TPO = thyroid peroxidase.

Thyroid Disorders (cont.)

• Management
  • Thyrotoxicosis
    • Supportive beta-blockers
    • Hold immunotherapy
    • Radioactive iodine uptake generally inaccurate
    • Generally self-limiting
    • Monitor for subsequent hypothyroidism
  • Hypothyroidism
    • Hormone replacement

Hypophysitis

• Incidence: <5% with PD-1 alone, 10% with combination
• Typical time to onset: >6-12 weeks
• Symptoms: Headache, fatigue, muscle weakness, hypotension, bowel changes
• Work up: Inflammation of the pituitary resulting in low release of all or some of the following pituitary hormones
  • ACTH
  • TSH
  • FSH
  • LH
  • Growth hormone (prolactin)

Hypophysitis (cont.)

• Treatment
  • High-dose steroid for critical illness
  • Low-dose glucocorticoid to alleviate headache/fatigue
  • Replace pituitary hormone deficiencies (start with adrenal insufficiency)
  • Call your friendly, neighborhood endocrinologist

Diabetes Mellitus

• Incidence: <5%

• Typical time to onset: 6-12 weeks

• Symptoms: patients generally present in DKA

• Workup
  • CMP, UA
  • GAD65 antibodies

• Treatment: insulin

DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65.

irAE summary

• irAE are varied in type, severity and timing
• High index of suspicion for everything
• Steroids are the initial therapy: Prednisone 1-2 mg/kg
• Talk to the oncologist
Fun fact #1: irAE = better response?
Fun fact #2: baseline steroids are bad

- Study identified PD-L1 naïve patients with advanced NSCLC from two cancer centers treated with single-agent PD-L1
- Common indications for steroid: dyspnea, fatigue, brain mets
- Baseline corticosteroid /= 10mg prednisone = worse outcome

J Clin Oncol 2018;36:2872-2878
Fun fact #3: Antibiotics might decrease response
Audience response!

Which of the following metastatic cancers is not an indication for immunotherapy?

- ER/PR positive breast cancer
- Head and neck squamous cell carcinoma
- Metastatic melanoma
- Metastatic renal cell carcinoma
Case 1

• 61-year-old man with metastatic non-small cell lung cancer
• Starts single agent pembrolizumab
• After 1 month presents with anxiety, sweating, tremor
Case 1 audience response

Which of the following is the most likely diagnosis?

• Neutropenic fever
• Immune-related thyroid disease
• Immune-related CNS toxicity
• Shaking with excitement to see his oncologist
**Case 1 (cont.)**

<table>
<thead>
<tr>
<th></th>
<th>Pre-tx</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
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<tbody>
<tr>
<td>TSH</td>
<td>1.9</td>
<td>&lt;0.076</td>
<td>&lt;0.0005</td>
<td>8.14 (H)</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.82 (L)</td>
<td>1.42</td>
<td>3.19 (H)</td>
<td>0.46 (L)</td>
</tr>
</tbody>
</table>

- Hold immunotherapy
- Start metoprolol
Case 2

• 56 y/o man with metastatic renal cell
• Starts single agent nivolumab
• At 10 weeks presents to PCP with cough, SOB, hypoxemia
Case 2 audience response

• Which of the following is not appropriate?
  
  • Stop nivolumab
  • Start prednisone 2 mg/kg
  • Call your patient’s oncologist
  • Start infliximab
Case 2 (cont.)

- Workup
  - Call your friendly oncologist
  - CT scans

- Management
  - Prednisone 1-2 mg/kg
  - Consider antibiotics
Case 3

- 49 y/o man with metastatic melanoma
- Starts nivolumab + ipilimumab
- After 2 month
  - Massive neck tumors almost gone
  - Complains of progressive vision loss
Case 3 audience response

What should you do next?

• Non-urgent ophtho referral for cataracts
• Urgent ophtho referral for evaluation
• Modify his anti-hypertensive regimen
<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starts nivo/mpi</td>
<td>6 weeks</td>
</tr>
<tr>
<td></td>
<td>G2 Uveitis</td>
</tr>
<tr>
<td>12 weeks</td>
<td>G3 hepatitis</td>
</tr>
<tr>
<td>14 weeks</td>
<td>G1 vitiligo</td>
</tr>
<tr>
<td>18 weeks</td>
<td>G1 hepatitis</td>
</tr>
<tr>
<td>48 weeks</td>
<td>G1 uveitis</td>
</tr>
</tbody>
</table>

**irAE tx**
- 6 weeks: Ophtha Steroids Hold IO
- 12 weeks: Resume nivo
- 14 weeks: Hold nivo Steroids (2 mg/kg)
- 18 weeks: Resume nivo
- 48 weeks: Resume nivo

**Cancer outcome**
- Partial response
- Complete response
Learning summary

• Describe some basic biology of how immunotherapy works
• Identify the benefits of immunotherapy in cancer
• Recognize immunotherapy side effects and how to treat them