Demystifying Immunotherapy Side Effects: Treatment Paradigms for the Oncology Practitioner
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Learning Objectives
• Review immunotherapy indications and approvals in oncology
• Summarize current side effect profiles of immunotherapy immune related adverse events
• Identify strategies to recognize and manage adverse events due to the use of immunotherapies

Immune Checkpoint Inhibitor Overview
• The immune system recognizes and reacts against cancers
• The immune response against tumors is often dominated by regulation or tolerance
  • Evasion of host immunity is one of the hallmarks of cancer
• Some immune responses promote cancer growth
• Defining the immune response against cancers will help in developing new immunotherapies

The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies

T cell responses to tumors
**Mechanisms of Resistance to Immunotherapy**

- Low mutation burden or "neoantigens"
- Defects in antigen processing (decreased TAP, HLA, B2M)
- Tumor immune cell exclusion (mutations in PTEN, PIK3CA, MAPK)
- Resistance to T-cell targeting (PIK3CA, IFN-γ genes)
- Inhibitory checkpoint expression
- Unfavorable microenvironment (pH, IDO, adenosine)
- Immunosuppressive cells (Treg, M2 TAM)

**Immunotherapy: Checkpoint inhibitors**

- Immune system relies on multiple checkpoints to avoid over activation on healthy cells
- Tumor cells hijack these checkpoints to escape detection
- CTLA-4 & PD-1 are upregulated on T cell surface in some cancers
- PD-L1 can be expressed on tumor cells endogenously or induced by association with T cells
- PD-1:PD-L1 interaction results in T cell suppression (anergy, exhaustion, death)

**ImmuneOncology Therapeutic Areas**

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
<th>Atezolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
<th>Ipilimumab</th>
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<tbody>
<tr>
<td>Melanoma</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Head and neck cancer</td>
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<td>X</td>
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<tr>
<td>Bladder Cancer</td>
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<tr>
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<tr>
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<td>X</td>
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<tr>
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<td>X</td>
<td>X</td>
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<td></td>
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<tr>
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<td>X</td>
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Over the next 4 years, over 20 indications are expected.

**Correlation between Tumor Mutational Burden and Objective Response Rate**


**Immunotherapy: Checkpoint inhibitors**

- In melanoma, renal cell, & other tumors, PD-L1 expression is associated with more aggressive disease
- Inhibiting CTLA-4 & PD-1 can "release the brakes"
- Checkpoint inhibitors don’t attack the tumor, they set the T cells straight
- Activity powerful enough to work in the CNS – T cells go everywhere
- Melanoma patients – on MRI, brain mets are surrounded by tons of T cells
Immune-Related Adverse Events Can Affect Any Organ System

- Cardiac
  - Myocarditis

- Gastrointestinal
  - Colitis

- Endocrine
  - Hypo- or hyperthyroidism
  - Hypoadrenalism
  - Hypoglycemia

- Immune-mediated inflammatory disease

- Nervous system
  - Neuropathy
  - Guillain-Barré syndrome
  - Myasthenia gravis–like syndrome

- Pulmonary
  - Pneumonitis

- Renal
  - Nephritis

- Skin
  - Dermatitis exfoliative
  - Vitiligo
  - Alopecia

- Uveitis
  - Iritis

- Hepatic
  - Autoimmune hepatitis

- Renal
  - Nephritis

- Immunotherapy: PD-1 inhibitors

- Nivolumab (Opdivo®) – FDA approval
  - Melanoma – unresectable or metastatic; single agent or combination with ipilimumab
  - NSCLC – metastatic, with progression on or after platinum-based chemotherapy and EGFR or ALK therapy if EGFR or ALK positive
  - Renal Cell – advanced disease who have received 1 or 2 prior therapies
  - Hodgkin Lymphoma – Relapsed/Refractory

- Summary – ORR in patients with advanced NSCLC, melanoma, renal cell carcinoma
  - 6 of 30 patients had ORR (CR or PR)
  - 30 of those 65 (46%) had response evident at first tumor eval (8wks)
  - 42 of those 65 (65%) had response lasting >1yr
  - 35 of those 65 (54%) had response ongoing at time of data analysis
  - Response persisted off the drug

- Pembrolizumab (Keytruda®) – FDA approval
  - Melanoma – unresectable or metastatic
  - NSCLC – metastatic, with progression on or after platinum-based chemotherapy and EGFR or ALK therapy if EGFR or ALK positive
  - Head and Neck Cancer – Just Approved

- Former President Jimmy Carter
  - Melanoma diagnosed August 2015 – liver & brain mets
  - Surgery, radiation, pembrolizumab
  - Currently no evidence of disease including brain mets

- Disease can get worse before it gets better
- Four distinct response patterns associated with favorable overall survival (OS)
  - Response in baseline lesions
  - Stable disease with slow decline in tumor volume
  - Response following an initial increase in tumor volume
  - Response following appearance of new lesions

- Infiltration of patient immune cells can cause an initial increase in tumor volume or appearance of new lesions on imaging scans (known as pseudoprogression)
- Need 8-12 doses to accurately evaluate patient response
- However, there are inherent side effects with therapy that clinicians need to be aware of.
Immunotherapy Side Effects

Common Immune-Related AEs Associated With Checkpoint Inhibitors

Distribution of Immune-Related AEs With CTLA-4, PD-1, and PD-L1 Inhibition

Immunotherapy Side Effects

Managing Immune-Related AEs Associated With Immune Checkpoint Inhibitors

Guidelines

- NCCN
- ASCO
- SITC
Managing Side Effects with Immunotherapy

General Guidelines for Management of Immune-Related AEs

- Grade 1: asymptomatic to mild symptoms
  - Observation
  - Intervention not needed
- Grade 2: moderate symptoms
  - Local or noninvasive intervention indicated
  - Withhold drug, consider re-dose if toxicity resolves to grade ≤ 1
  - Low-dose corticosteroids likely needed
  - May be able to continue treatment
- Grade 3: medically significant but not immediately life-threatening
  - Stop immunotherapy immediately
  - Hospitalization indicated
  - High-dose steroids indicated
  - Slow steroid taper over ≥ 1 mo once toxicity resolves to grade ≤ 1
- Grade 4: life-threatening consequences
  - Urgent intervention
  - Permanently discontinue treatment

Pulmonary Toxicity: Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Pulmonary Toxicity</th>
<th>Management</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Grade 1</td>
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<tr>
<td>Grade 1-2 toxicity can be treated ≤ 1/25th lung parenchyma</td>
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<td></td>
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<tr>
<td>Grade 2</td>
<td></td>
<td></td>
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<tr>
<td>Grade 2 toxicity can be treated ≤ 1/25th lung parenchyma</td>
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<td></td>
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<tr>
<td>Grade 3</td>
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<td></td>
</tr>
<tr>
<td>Grade 3 toxicity can be treated ≤ 1/25th lung parenchyma</td>
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</tr>
</tbody>
</table>

Gastrointestinal Toxicity: Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Diarrhea/Colitis</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2-4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Biopsy-Proven Pneumonitis Is Highly Variable in Presentation

GI Toxicity

Ipilimumab-Treated Patient With Colitis

Nivolumab-Induced colitis

Melanoma, Clinical Journal 2010;34:1-2
BMC Gastroenterology 2018;8:135
Hepatic Toxicity

Grade 1
Asymptomatic; AST/ALT < 3 X ULN and/or total bilirubin < 1.5 X ULN

Grade 2
Asymptomatic; AST/ALT 3.1 - 5 X ULN and/or total bilirubin > 1.6 - 3 X ULN

Grade 3
Symptomatic; fibrosis on biopsy, compensated cirrhosis

Grade 4
 Decompensated liver function

Management
- Continue I-O therapy per protocol
- Symptomatic treatment

Follow-up
- Monitor every 3 days
- Avoid infliximab
- If worsens: treat as grade 3/4
- If improves to baseline, taper steroids over 4-6 wks
- If no improvement after 72 hrs or worsens: azathioprine, mycophenolate

Dermatologic Toxicity

Grade 1
Does not affect QoL; controlled with topical therapy or oral antipruritic

Grade 2
Inflammatory reaction; affects QoL

Grade 3
G2 that has failed to respond to interventions

Grade 4
Severe rashes unmanageable

Management
- Continue I-O therapy per protocol
- Topical emollients and/or mild - moderate potency topical corticosteroids
- Delay I-O therapy per protocol
- Oral antihistamines, topical emollients and/or moderate - high potency topical corticosteroids
- Consider: 1 mg/kg/d prednisone or equivalent
- If worsens: treat as grade 2-4
- Monitor weekly for improvement
- Improves: taper over 4 weeks
- If worsens: treat as grade 3/4
- Determine appropriateness of resuming
- Consider alternative antineoplastic if G4
- If improves to baseline, taper steroids over 4-6 wks

Immune-Mediated Endocrinopathies: Symptom Management

- Thyroid dysfunction (no steroids)
  - Endocrinology consult
  - Initiate thyroid replacement therapy for TSH elevation or symptomatic hyperthyroidism
  - Administer medical treatment for symptomatic hyperthyroidism
- Hypophysitis
  - Asymptomatic: hold therapy, evaluate pituitary function, and initiate hormone replacement therapy
  - Symptomatic: discontinue therapy, evaluate pituitary function, MRI, hormone replacement therapy

- Adrenal insufficiency
  - Grade 2: hold therapy and initiate appropriate hormone replacement therapy with hydrocortisone
  - Grade 3/4: discontinue therapy and administer 1.2 mg/kg/day prednisone or equivalent
  - Hormone replacement therapy if symptomatic with abnormal labs
  - Suspected adrenal crisis: discontinue therapy, rule out sepsis, stress dose of IV steroids with mineralocorticoid activity

Case Studies on Immunotherapy Side Effects
Case 1 (Sam): Pt With Newly Diagnosed Stage IV Squamous NSCLC

- A 61-year-old man was recently diagnosed with stage IV squamous NSCLC
- He has bone metastasis and an ECOG PS of 1
- On biopsy, his tumor has high PD-L1 expression (TPS of 60%)
- Patient is treated with palliative RT to rib lesion for pain control and started on pembrolizumab

Baseline

6.5 mos later

Case 1 (Sam): Complications on Anti–PD-1 Therapy

- Patient presents with dyspnea, a nonproductive cough, and a fever that he has had for the past 2 weeks

Case 2 (John): Pt With Stage IV Adenocarcinoma on Investigational Combination Therapy

- A 68-year-old man diagnosed with stage IV lung adenocarcinoma
- Pathology testing was negative for EGFR mutations, ALK and ROS1 translocations; 10% PD-L1 expression by IHC (22C3)
- ECOG PS of 1
- Elected to begin treatment with first-line ipilimumab in combination with nivolumab on a clinical trial
- He achieved a PR after 4 cycles
- 5 mos into therapy, pt presents with 1-wk history of abdominal cramping, intermittent diarrhea, and hematochezia (grade 2)

Case 3 (Claire) Blurry Vision

- 63-year-old woman with melanoma and brain metastasis
- Received gamma-knife treatment 6 weeks ago
- Started on single-agent pembrolizumab 2 weeks ago
- 6 days prior to admission, developed blurry vision accompanied with headache and shortness of breath
- Exam shows mild lid lag in both eyes, respiratory exam normal
- CT chest shows 1cm RLL nodule. No evidence of other abnormalities
- MRI brain shows improved brain metastasis. No other intracranial abnormalities

Past Medical History

- Presented in 2014 with cutaneous ulcerated melanoma of scalp
- Received wide local excision and neck dissection
- Started on clinical trial with vemurafenib vs. placebo
- Eight months following trial initiation, developed asymptomatic brain metastasis

Clinical Course

- Admitted, neurology consulted. Pyridostigmine started. Concerns for pneumonia in posterior field. Myasthenia panel ordered
- Day 0: Prednisone 60mg qday and IVIG started on the day
- Day 4: Acetylcholine receptor Ab returned positive. Switched to 1000mg methylprednisolone
- Day 7: Started plasmapheresis
- Day 9: Worsening shortness of breath. Intubated
- Day 12: Patient opted to withdraw care. Terminally extubated

Was this related to immunotherapy?
Patient Case #4 (Michael)

- 61-year-old man with pancreatic cancer recently treated with pembrolizumab
- Following 4th cycle, developed chills and low-grade temp to 100.1° which resolved
- Patient was on Daptomycin secondary to VRE in the hospital, after 14 days of treatment patient’s cultures were negative
- Progressive lower back pain starting in 4 weeks ago
  - Pain begins in lower back, legs go numb for 20 seconds, then sensation returns with throbbing pain in back and legs
  - Assumed due to vertebral mets, referred to XRT with no relief
- After 4 months of starting treatment, developed lower extremity weakness and inability to walk.

Oncologic History
- T4N3M1 lung cancer
- Excellent response to 1st-line pembrolizumab, with 90% resolution of RUL and pleural lesions
- Known vertebral metastases remained stable throughout course
- No history of autoimmune disease, arthritis, radiculopathy
- Right upper lobe lesion with poorly differentiated NSCLC
- PD-L1>50%, EGFR wt, ALK negative

Clinical History
- Other suggestions of N1 increased pain, Chemohepatic, bone pain
- No IV on imaging, Metastatic OS
- Hospitalization with anti-inflammatory, nausea, vomiting, high protein, hypoglycemia, nephritis, hypokalemia
- Developed neurotoxicity, neurological disturbance, hearing loss, vision disturbance, upper-lower limb weakness
- Lower extremity weakness, lower extremity weakness, toe numbness, no improvement of symptoms, but continued pain
- Patient LP in 1/2016 showed cytology positive for malignant cells

- Was this due to Daptomycin or something else?

Musculoskeletal side-effects of anti-PD-1 therapy

Combination Immune Checkpoint therapy

- Anti-CTLA-4 and PD-1 combination therapy has been evaluated
- Higher incidence of G3/4 toxicities
  - However, flipped dosing schedule has seemed to show a reduced overall toxicity profile
- Management same as previously discussed
- Reasonable to resume therapy with PD-1 monotherapy upon resolution of toxicities

Treatment-Related Adverse Events in >2% of Patients Treated Beyond Progression

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Any grade, n (%)</th>
<th>Grade 3 or 4, n (%)</th>
<th>Any grade, n (%)</th>
<th>Grade 3 or 4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with an event</td>
<td>25 (69)</td>
<td>1 (3)</td>
<td>23 (64)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>11 (31)</td>
<td>0</td>
<td>8 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (28)</td>
<td>0</td>
<td>10 (28)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td>9 (25)</td>
<td>1 (3)</td>
<td>8 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>4 (11)</td>
<td>0</td>
<td>4 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>3 (8)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>2 (6)</td>
<td>0</td>
<td>2 (6)</td>
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</table>

Summary

1. PD-1/PD-L1 therapies have shown promising activity with realized results in numerous cancers, with continued approvals on the horizon.
2. Clinical management of toxicities is crucial for continued therapy and side effect management.
3. Systemic corticosteroids play a key role in the management of moderate-severe immune-mediated toxicities
# Pembrolizumab Dose Adjustments

<table>
<thead>
<tr>
<th>Severity</th>
<th>Action</th>
<th>Action (pembrolizumab dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 or 3</td>
<td>Hold and administer corticosteroids; may reduce if resolves to ≤ grade 1</td>
<td>Discontinue and administer corticosteroids.</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
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</tbody>
</table>

### Toxicity

#### Colitis
- **Grade 2 or 3**: Hold and administer corticosteroids; may reduce if resolves to ≤ grade 1.
- **Grade 4**: Discontinue and administer corticosteroids.

#### Hypophysitis (symptomatic)
- **Grade 2**: Hold and administer corticosteroids and hormone replacement as indicated.
- **Grade 3 or 4**: Hold if DRR is discontinuous, administer corticosteroids and hormone replacement as indicated.

#### Hyperthyroidism
- **Grade 3**: Hold, administer corticosteroids and treat appropriately. Discontinue if recurs.
- **Grade 4**: Hold, administer corticosteroids and treat appropriately; discontinue if dose does not resolve to ≤ grade 2 or if recurs.

#### Hypothyroidism
- **Isolated, any grade**: Treat with hormone replacement therapy.
- **Grade 2**: Hold and administer corticosteroids as appropriate.
- **Grade 3 or 4**: Discontinue and administer corticosteroids as appropriate.

### Nivolumab Dose Adjustments

<table>
<thead>
<tr>
<th>Severity</th>
<th>Action</th>
<th>Action (nivolumab dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 or 3 diarrhea or colitis</td>
<td>Withhold dose</td>
<td></td>
</tr>
<tr>
<td>Grade 4 diarrhea or colitis</td>
<td>Withhold dose when administered as a single agent</td>
<td></td>
</tr>
<tr>
<td>Grade 4 diarrhea or colitis</td>
<td>Withhold dose when administered with ipilimumab</td>
<td></td>
</tr>
</tbody>
</table>

#### Hepatitis
- **Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal**: Hold dose.
- **AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal**: Permanently discontinue.

#### Hypophysitis
- **Grade 2 or 3 hypophysitis**: Withhold dose.
- **Grade 4 hypophysitis**: Permanently discontinue.

#### Adrenal Insufficiency
- **Grade 2 adrenal insufficiency**: Withhold dose.
- **Grade 3 or 4 adrenal insufficiency**: Permanently discontinue.