Learning Objectives

1) Outline the key principles of the human immune response and the mechanism by which immunotherapies target various solid tumor types.

2) Examine emerging research on the clinical efficacy and safety of immune checkpoint inhibitors and identify their place in the treatment algorithm of solid tumors.

3) Identify signs and symptoms of immune-related adverse events (irAEs) associated with checkpoint inhibitor therapy and understand how to differentiate these from other etiologies, such as infection, etc.

4) Explore strategies members of the interprofessional healthcare team can employ to effectively recognize and manage irAEs in the emergency department and outpatient setting.
Cancer Statistics in the United States

• Major public health problem
  • 2017: Estimated 1.7 million new cases
  • Expected 600,920 cancer deaths
  • 2030: Projected annual incidence of 2.2 million

• Significant financial burden
  • National expenditures for cancer care:
    • $125 billion in 2010
    • Expected to reach $156 billion in 2020

Siegel RL, et al. CA Cancer J Clin 2017;
Cancer Treatment Modalities

CANCER THERAPY

CANCER IMMUNOTHERAPY: AN INTERPROFESSIONAL APPROACH TO THE MANAGEMENT OF IMMUNE-MEDIATED ADVERSE EVENTS


Immune System and Cancer Dynamic Interaction

Cancer Immunoediting

Immunosurveillance → Immunosubversion

Pre-malignant lesion → Elimination → Immunosurveillance
Advanced oncogenesis → Equilibrium → Immunoselection
Tumor growth → Escape → Immunosubversion


Cancer Immunotherapy

Rationale for Use

• To overcome the mechanisms by which tumors suppress and evade the immune response
  – Restore efficient immunosurveillance and tumor elimination, and shift the balance from immune evasion to immune protection

Disis ML. Semin Oncol. 2014.
Cancer Immunotherapy Types

The Evolving Role of Checkpoint Inhibitors in Cancer Treatment

Where Are We Now and Where are Headed?
**Immuno-regulatory Receptors**

**Activating Receptors**
- CD28
- GITR
- CD137

**Inhibitory Receptors**
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

**T-Cell Regulation**

*Immune checkpoint molecules*: inhibitory receptors on immune cells
- Modulate the duration and amplitude of immune responses and maintain self-tolerance
- Usurped by cancer cells to suppress and evade anti-tumor immune response


---

**Checkpoint Inhibitors**

- Block the immune checkpoints from being engaged
  - Unleash the immune system to attack and kill cancer cells
- Undergo rapid research and development
  - 2011: One agent to treat one tumor (melanoma)
  - 2017: Six agents approved for multiple cancers (melanoma, NSCLC, HNSCC, RCC, cHL, bladder, gastric, HCC, MSI-high solid tumors, Merkel cell carcinoma)
    - Many novel agents and new indications in the pipeline
- Revolutionize cancer therapy
  - Prolong progression-free and overall survival
  - Generally more tolerable compared with cytotoxic chemotherapy

NSCLC: non-small cell lung cancer; HNSCC: head and neck squamous cell cancer; RCC: renal cell carcinoma; HCC: Hepatocellular carcinoma; cHL: classical Hodgkin lymphoma; MSI: microsatellite instability
Immune Checkpoint Blockade
CTLA-4 and PD-1/PD-L1 Inhibitors


CTLA-4 and PD-1/PD-L1 Inhibitors

Current FDA Status and Indications
CTLA-4 Inhibitors
Ipilimumab (Human IgG1 mAb)

• Approved
  – Treatment of unresectable or metastatic melanoma
    • As monotherapy
    • In combination with nivolumab
  – Adjuvant treatment of patients with cutaneous melanoma
    with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy

• Investigational
  – Ipilimumab-nivolumab in various malignancies

www.accessdata.fda.gov/drugsatfda_docs/label/2015/125377s073lbl.pdf.

CTLA-4 Inhibitors (cont.)
Tremelimumab (Human IgG2 mAb)

• Orphan drug designation
  – Malignant mesothelioma

• Investigational
  • In combination with durvalumab for various tumors

PD-1 Inhibitors

- Approved PD-1 Inhibitors
  - Nivolumab (*Human IgG4 mAb*)
  - Pembrolizumab (*Humanized IgG4 mAb*)

www.accessdata.fda.gov/drugsatfda_docs/label/2015/125554s012lbl.pdf.

Approved and Emerging Indications of PD-1 Inhibitors

NHL=Non-Hodgkin lymphoma; MSI=Microsatellite instability; SCLC=Small cell lung cancer; TNBC=Triple-negative breast cancer; Mesoth=Mesothelioma; HCC=Hepatocellular carcinoma; Oesophag=Esophageal carcinoma; GBM=Glioblastoma

Adapted from Michot JM. *Eur J Cancer*. 2016.
PD-L1 Inhibitors

- Approved PD-L1 Inhibitors
  - Atezolizumab (*Humanized IgG1 mAb*)
  - Avelumab (*Human IgG1 mAb*)
  - Durvalumab (*Human IgG1 mAb*)

Approved and Emerging Indications of PD-L1 Inhibitors

<table>
<thead>
<tr>
<th>Agents</th>
<th>Atezolizumab</th>
<th>Avelumab</th>
<th>Durvalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>Bladder</td>
<td>Bladder Merkel cell carcinoma</td>
<td>Bladder</td>
</tr>
<tr>
<td>Investigational</td>
<td>Breast cancer Hodgkin lymphoma GBM CLL/SLL Melanoma RCC Others</td>
<td>NSCLC Gastric GBM AML Ovarian RCC Others</td>
<td>NSCLC Breast cancer GBM Esophageal cancer Multiple myeloma Ovarian Others</td>
</tr>
</tbody>
</table>
Immune Checkpoint Blockade

Unique Clinical Features

Immune-Related Adverse Events (irAEs)
• By enhancing immune system function, immune checkpoint blockade can lead to autoinflammatory side effects called irAEs

Tumor Response Kinetics
• Immune-mediated response patterns may differ from those associated with conventional therapies, which has prompted the development of immune-related response criteria (irRC)

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Immune Checkpoint Blockade

Unconventional Response Patterns

Early response
Stable disease followed by slow, steady decline in tumor burden
Response after initial increase in total tumor burden

Initial increase in total tumor burden
• Infiltration of immune cells in the tumor
• Tumor flare or pseudo-progression

**CTLA-4 Blockade**  
*Kinetics of Response to Ipilimumab*

**Metastatic Melanoma**

Week 20: Regression  
Week 36: Still Regressing


---

**PD-1 Blockade**  
*Kinetics of Response to Pembrolizumab*

**Metastatic Melanoma**

**NSCLC**

Immune Checkpoint Blockade

Key Points About Evaluating Activity

• Antitumor activity may appear to be delayed compared to response times associated with cytotoxic therapies

• Patients may experience response after the appearance of progressive disease

• Development of progressive disease should be confirmed prior to discontinuation of therapy

• Development of small lesions in the presence of other responsive lesions may be clinically insignificant

• Durable stable disease may be indicative of response

Agarwala SS. Semin Oncol. 2015.

Managing Immune-Related Adverse Events (irAEs):

Optimizing Patient Outcomes with Interprofessional Collaboration
irAEs

Clinical Spectrum

• Loss of immunologic tolerance to self antigens
• Tissue damage associated with inflammatory T-cell infiltrates
  • Can involve any organ system
  • Mostly mild to moderate and reversible
  • Can be life-threatening
  • Represent a new type of oncologic emergency

Benefits of therapy outweigh potential risks, particularly when irAEs are recognized early and treated quickly

irAEs

**General Issues**

- Most irAEs occur during the first 3-4 months of therapy
  - Late irAEs, however, also can occur (eg, one episode has been seen at month 47 during maintenance phase of therapy)
  - Each irAE has different kinetics of onset and some can wax and wane, particularly colitis

- Corticosteroids and other immunosuppressants can be used to manage almost all irAEs
  - Prolonged steroid tapers are usually required

---

**Immune Checkpoint Blockade**

*irAEs and Outcomes*

- Preclinical melanoma tumor models using CTLA-4 knock-outs have demonstrated enhanced immune-mediated tumor rejection AND immune related depigmentation, but not irAEs as seen in patients

- Correlation of irAEs with tumor response remains controversial
  - There does, however, appear to be a weak association with CTLA-4 blockade and stronger one with PD-1 blockaded, or combined checkpoint blockade

---

**CTLA-4 Blockade With Ipilimumab**

*Kinetics of irAEs in Melanoma*

![Graph showing kinetics of irAEs in Melanoma with Ipilimumab](image1)


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**PD-1 Blockade With Nivolumab**

*Kinetics of irAEs in Melanoma*

![Graph showing kinetics of irAEs in Melanoma with Nivolumab](image2)

CTCAE Severity Grade Definitions

An Adverse Event (AE) is “any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.” An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

<table>
<thead>
<tr>
<th>Severity CTCAE Grade</th>
<th>General Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (shopping, using telephone, managing money, etc).</td>
</tr>
<tr>
<td>3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living (bathing, toileting, dressing, ambulating, etc).</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
</tbody>
</table>

CTCAE= Common Terminology Criteria for Adverse Events (v 4.0)

CTLA-4 and PD-1/PD-L1 Blockade Distribution of Grade 1-2 (Low-Grade) irAEs

**CTLA-4 and PD-1/PD-L1 Blockade**

*Distribution of Grade 3-5 (High-Grade irAEs)*

![Graph showing distribution of Grade 3-5 irAEs](image)


---

**Ipilimumab vs Nivolumab vs Combo**

*irAEs Reported in ≥10% of Patients*

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Skin</td>
<td>59.1</td>
<td>5.8</td>
<td>41.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33.2</td>
<td>1.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Rash</td>
<td>28.4</td>
<td>2.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>11.8</td>
<td>1.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>46.3</td>
<td>14.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44.1</td>
<td>9.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.8</td>
<td>7.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>30.0</td>
<td>18.8</td>
<td>6.4</td>
</tr>
<tr>
<td>↑ alanine aminotransferase</td>
<td>17.6</td>
<td>8.3</td>
<td>3.8</td>
</tr>
<tr>
<td>↑ aspartate aminotransferase</td>
<td>15.3</td>
<td>6.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Endocrine</td>
<td>30.0</td>
<td>4.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.0</td>
<td>0.3</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Management of irAEs

**General Principles**

- Responsibility of all healthcare providers
- Emergency department clinicians are often the first responders
- *Early reporting by patients with close monitoring, and early intervention by healthcare providers*
- Provide thorough and continuous patient education about the signs and symptoms of irAEs
- Assess for signs and symptoms of irAEs before each immunotherapy treatment
- Know management algorithm specific to each irAE
  - Safety profiles of immunosuppressants
- Monitor and manage toxicities of immunosuppressants
  - Hyperglycemia and diabetes
  - Opportunistic infection

Patient and Caregiver Education

**Provide Contact Information**

- Whom to call
- Why to call
- When to call
- Where to call (MUST HAVE 24/7 clinician availability)

Patient Education

Signs That Require Prompt Evaluation

- **Digestive**: Diarrhea, blood or mucus in the stool, severe abdominal pain
- **Endocrine**: Fatigue, weight loss, nausea, vomiting, thirst or appetite increase, polyuria
- **Skin**: Extensive rash, severe pruritus
- **Respiratory**: Shortness of breath, coughing
- **Neurological**: Headache, confusion, muscle weakness, numbness
- **Arthralgia** or swelling joints
- **Myalgia**
- **Unexplained** fever
- **Hemorrhagic syndrome**
- **Severe loss of vision in one or both eyes**

Management of irAEs

*General Principles for Non-Oncology Clinicians*

- Emergency department clinicians will often be the first line of defense
- Maintain a high degree of suspicion
- Obtain thorough oncologic treatment history
  - Look beyond current therapy for late-onset or waxing/waning irAEs
- Infections, disease progression/pseudo-progression and other etiologies should be ruled out or deemed unlikely as contributing to the irAEs
- *Early contact with primary oncologist*
- Know management algorithm specific to each irAE
**Relevant Resources**

**CTCAE severity grade**

**Guidelines for Management of Immunotherapy Toxicities**
- **ASCO/NCCN**: Scheduled to be released end of 2017

---

**Management of irAEs**

*Based on CTCAE Severity Grade*

<table>
<thead>
<tr>
<th>Severity CTCAE Grade</th>
<th>Patient Care Setting</th>
<th>Steroids</th>
<th>Other Immunosuppressive Drugs</th>
<th>Immunotherapy and Subsequent Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ambulatory</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Continue</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory</td>
<td>Not recommended upfront</td>
<td>Topical steroids or systemic steroids oral 0.5-1 mg/kg/d for persistent grade 2</td>
<td>Not recommended</td>
</tr>
<tr>
<td>3</td>
<td>Hospitalization</td>
<td>Systemic steroids oral or IV 1-2 mg/kg/d for 3 d then reduce to 1 mg/kg/d</td>
<td>Consider for patients with unresolved symptoms after 3 days of steroid course Organ specialist advised</td>
<td>Suspend and discuss resumption based on risk/benefit ratio with patient</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalization</td>
<td>Systemic steroids IV methylprednisolone 1-2 mg/kg/d for 3 d and then reduce to 1 mg/kg/d</td>
<td>Consider for patients with unresolved symptoms after 3 days of steroid course Organ specialist advised</td>
<td>Discontinue permanently</td>
</tr>
</tbody>
</table>

irAEs
Dermatitis

- Most common:
  - Rash
  - Pruritis
  - Vitiligo

- Rare: toxic epidermal necrolysis (TEN), Steven-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS)

- Vitiligo is associated with good clinical responses to anti-PD-1 MoAbs in patients treated for melanoma


Dermatitis
Presentation and Findings

Back:
Confluent red rash

Right upper arm:
Vacuolar changes (magnification x20)

Back:
Papular lesions (Close up)

Anti-CD8 staining:
Extensive epidermal exocytosis (magnification x20)

**Dermatitis Management**

- Encourage the preventative use of moisturizers
- Photograph, document, and follow
- Mild (grade 1)
  - Topical therapies including emollient skin creams, oral anti-histamines, mild strength topical steroid creams
- Moderate (grade 2)
  - Check patient weekly for improvement
  - Consider holding immunotherapy
  - Topical emollients, medium-high strength topical steroids, oral anti-histamines
- Severe (grade 3+)
  - Hold/discontinue immunotherapy until back to grade 1
  - Topical emollients, oral antihistamines and high strength topical steroids
  - Consider systemic corticosteroids 0.5–1 mg/kg


**irAEs**

**Diarrhea, Colitis and Enteritis**

- Diarrhea is a common irAE (37% all grade and 12% grades 3/4) with ipilimumab; less common with PD-1 blockade
  - Diarrhea: quantitative manifestation for colitis
  - Enteritis/Colitis: qualitative assessment via endoscopic and/or radiographic studies
- Colonoscopy or sigmoidoscopy shows diffusely erythematous, friable, and occasionally ulcerated mucosa
- Colon biopsy usually demonstrates inflammatory colitis with CD4>CD8 infiltrate in interstitium
- Can rarely lead to gastrointestinal perforation (1%), profound ileus or megacolon requiring surgery

Postow MA. Am Soc Clin Oncol Educ Book. 2015;
irAEs

Diarrhea, Colitis and Enteritis

- Typical presentation is quick escalation of uncontrollable diarrhea not responsive to typical anti-diarrheal therapies
- Early intervention with corticosteroids is essential to prevent escalation and bowel perforation
- Infliximab is used in steroid-refractory cases
- Endoscopic evaluation
- Supportive care
  - Dietary modification, fluid repletion, electrolyte supplementation, anti-motility agents

Colitis and Enteritis

Management – Grade 1,2

- Rule out other causes
  - Bacterial (ie, *Clostridium difficile*)
  - Parasitic
- Treat symptomatically (antidiarrheals, fluid and electrolyte supplementation)
- No corticosteroids unless persistent
- Follow closely for resolution

Postow MA. Am Soc Clin Oncol Educ Book. 2015;

Colitis and Enteritis
Management – Grade 3,4

• Discontinue therapy

• Assess duration, magnitude, and symptomatology to determine need for hospitalization

• High dose corticosteroids 1–2 mg/kg per day
  – Slow taper, over 8-12 weeks

• If persists (>72 hours), consider infliximab 5mg/kg (TNF-blocking antibody)

• Rare: pancreatitis and small bowel enteritis


irAEs
Hepatitis

• Liver function test (LFT) elevations may be associated with symptoms of hepatotoxicity (jaundice, right upper quadrant pain, vomiting) or may be completely asymptomatic; many patients have other non-specific symptoms (fever, malaise)

• LFT must be assessed prior to administration of each dose of checkpoint inhibitors

• All subjects must meet LFT criteria before each dose of checkpoint inhibitors
  – With no liver metastases <2.5X ULN for AST, ALT
  – With liver metastases; <5X ULN for AST, ALT, <2.5X ULN for total bilirubin

Hepatitis
Management – Grade 2

- Elevation LFTs >3-5 x ULN requires close attention
- Hold therapy
- Intensified monitoring; labs twice a week
- Consider disease burden, medications, infections, particularly viral; other metabolic disorders; imaging;
- Consider corticosteroid therapy 1mg/kg/day if persistent; if no improvement increase to 2mg/kg/day


Hepatitis
Management – Grade 3/4

- LFTs >5x or total bilirubin >3x ULN
  - Permanently discontinue therapy
  - Intensified monitoring; labs every 1-3 days until begin to resolve
  - High dose steroids, eg, methylprednisolone 1-2 mg/kg/day; if LFTs decrease convert to oral steroids
  - If after 3 days, no improvement or rebound, add mycophenolate
  - Consult with a hepatologist and consider a liver biopsy
  - If no improvement in 5-7 days, add tacrolimus or anti-thymocyte globulin (ATG); Infliximab is not recommended

irAEs

**Endocrinopathies**

- Thyroid dysfunction
  - Hypothyroidism > hyperthyroidism
- Panhypopituitarism (hypophysitis)
- Pancreatitis
- Adrenal insufficiency
- Type 1 diabetes mellitus


**Endocrinopathies**

**Thyroid Dysfunctions**

- Up to 10% (all grades) with ipilimumab or anti-PD-1/PD-L1
- TSH and FT4 at baseline and before each cycle of ipilimumab or at least monthly with anti-PD-1/PD-L1
- Hyperthyroidism:
  - Most cases resolve spontaneously, with subsequent development of hypothyroidism
  - Use beta-blocker as initial management, if symptomatic
  - Consider prednisone 0.5mg/kg for painful thyroiditis
  - Consider anti-thyroid medications if anti-TSH receptor antibody +
- Hypothyroidism: thyroid hormone replacement
  - Typically do not require corticosteroid therapy
- Suspension of checkpoint inhibitors rarely necessary
  - Withhold therapy in symptomatic hyperthyroidism until symptoms controlled

**Endocrinopathies**

*Hypophysitis*

- Can present with severe headache, fatigue, weakness, memory loss, impotence, personality changes, and visual impairment
- Pituitary dysfunction can cause downstream effects on all hormone levels
- Differential includes CNS metastases
- Monitor TSH before each dose
- Diagnostic MRI with pituitary cuts and laboratory evaluation of hormone levels

---

**Hypophysitis Management**

- Hold checkpoint inhibitors if moderate-severe symptoms
- Methylprednisolone 1mg/kg/day IV with a taper over ≥ 4 weeks if CNS symptoms
- Obtain endocrine consult
- Replace deficient hormones
  - Replace hydrocortisone 1 week before thyroid hormone supplement
- Symptoms will resolve with treatment
  - Slow return of some endocrine function
  - Most patients require life-long hydrocortisone supplement
- Use stress dose hydrocortisone in perioperative period and critical illness
  - Educate patient about stress dose steroid, emergency hydrocortisone injection, and medical alert bracelet

---


**Endocrinopathies**

*Type 1 Diabetes Mellitus*

- Rare, <1%, more common with anti-PD-1/PD-L1
- May occur with rapid onset anytime during therapy
- Monitor serum glucose at baseline and prior to each cycle of checkpoint inhibitor
- Obtain endocrine consult
  - C-peptide and diabetes related autoantibodies*
- Require life-long insulin therapy
- Role of high-dose steroid unclear
  - Exacerbate hyperglycemia
  - No data to suggest high-dose steroid can prevent total β cell loss
- Resume checkpoint inhibitors once blood sugar well-controlled

*Glutamic acid decarboxylase 65 (GAD-65) antibody; Tyrosine phosphatase islet 2 antibody (IA-2); Insulin autoantibody (IAA)*

**irAEs**

*Neurological Toxicities*

- Relatively infrequent (~1% all grades) with IPI or PD-1
  - Possible underestimation due to lack of recognition or under-reporting
- Heterogeneous presentations:
  - Numbness, tingling, foot drop, localized muscle weakness, or generalized ascending motor and diaphragmatic weakness
  - Headache, seizure, altered mental status, syncope
- Neurologic events reported so far:
  - Myasthenia gravis (MG)-like syndrome
  - Guillain-Barre syndrome (GBS)
  - Limbic encephalitis, aseptic meningitis
  - Peripheral neuropathy, facial nerve palsy, enteric neuropathy
  - Posterior reversible leukoencephalopathy

Neurological Toxicities
Management

• Hospitalize if moderate-severe symptoms
• Obtain neurology consult!
• Rule out hypophysitis, stroke, CNS metastases, paraneoplastic syndromes, infectious etiologies, metabolic derangement
• Typical work up:
  – Complete blood counts and metabolic panels
  – Hormone levels, toxicity screen, paraneoplastic panels
  – Lumbar puncture
  – MRI brain and/or spine
  – EEG
  – EMG and nerve conduction study


Neurological Toxicities
Management

• Withhold checkpoint inhibitors
• Empiric anti-infectives +/- anti-convulsants
• Methyprednisolone 2 mg/kg/day with a prolonged taper over 6-8 weeks
• Consider IVIG, plasmapheresis and other immunosuppressants (mycophenolate, tacrolimus, azathioprine, rituximab) if grades 3-4 and without resolution of symptoms within 48 hours
• Multi-disciplinary support:
  – Pain management
  – PT, OT, speech therapy

irAEs

Pneumonitis

- Uncommon, 2-4% all grades, 1-2% grades ≥ 3
  - Higher incidence with combined checkpoint blockade
- Check pulse oximetry in all patients at baseline and before each cycle of checkpoint inhibitor(s)
- Obtain chest X-ray in anyone with SOB, chronic cough, increased sputum, and have a low threshold for CT chest
  - Radiographic findings may lag behind the patient’s symptoms
- Rule out infectious etiology and disease progression
- High dose steroids starting at 1-2 mg/kg with taper over 6-8 weeks
- Add infliximab or mycophenolate if without relief after 48 hours
- Consider empiric anti-infectives


Pneumonitis

-Radiographic and Histopathology Findings

Immune Checkpoint Blockade

**Other irAEs**

- Pancreatitis
  - Amylase/lipase elevation but rarely symptomatic
  - Amylase/lipase monitoring NOT indicated
  - Corticosteroid NOT recommended for asymptomatic elevations in serum amylase and lipase in the absence of other signs or symptoms of pancreatic inflammation
- Arthritis
  - Late manifestation with chronic PD-1/PD-L1
  - Often exacerbation of pre-existing arthritis
  - NSAIDs and/or acetaminophen for mild discomfort
  - Prednisone 10-20mg or intra-articular steroid injection if moderate symptoms
  - Prednisone 0.5-1 mg/kg and rheumatology consult if severe

Immune Checkpoint Blockade

**Other irAEs**

- Nephritis (rare)
  - Monitor BUN, Cr, and electrolyte panel at baseline and before each cycle of checkpoint inhibitors
  - Rule out dehydration, UTI, obstruction, drug reaction
  - CT scans show stranding = inflammation
  - Consider steroids: 0.5-1 mg/kg/day for Cr >1.5-3 x ULN or 1-2 mg/kg/day if Cr >3 x ULN
  - Nephrology consult if grade 3+ or persistent grade 2
- Uveitis
  - Redness, change in vision; ophthalmology evaluation
  - Topical corticosteroid eye drops
  - Systemic corticosteroid for severe ocular/orbital inflammation

Postow MA. Am Soc Clin Oncol Educ Book. 2015;
Immune Checkpoint Blockade

*irAEs in Elderly Patients*

- No difference in incidence of toxicity or grade of toxicity for the use of IPI or PD-1 under or over 65
- The overall survival for those treated with ipilimumab does not vary significantly by age
- It appears that ipilimumab and PD-1/PDL1 antibodies can be safely given to those at any age
- Caution should be used in using IPI or IPI/NIVO in those functionally over 80 with co-morbidities, who will not tolerate the colitis or prolonged steroid taper very well

---

**Key Take Home Points**

- Immune checkpoint blockade is associated with unique clinical features
  - *irAEs* → contemporary type of oncologic emergency
    - Can affect any organ system at anytime during therapy
    - Tumor flare/pseudo-progression is possible

- *Early recognition and effective management of irAEs is crucial to optimal use of checkpoint inhibitors*
  - Maintain high index of suspicion
  - Early communication with primary oncologist
Abbreviation Key

ACTH: Adrenocorticotropic hormone
AE: adverse event
AML: acute myelogenous leukemia
BNP: B-type natriuretic peptide
cHL: Chronic Hodgkin Lymphoma
CMV: Cytomegalovirus
CTCAE: Common terminology criteria for adverse events
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
DRESS: drug rash with eosinophilia and systemic symptoms
EBV: Epstein-Barr virus
EC: emergency center
EEG: electroencephalogram
FSH: follicle-stimulating hormone
FT4: free T4
GBM: glioblastoma multiforme
HNSCC: Head and Neck Squamous Cell Carcinoma
igG2: immunoglobulin G2
irAE: Immune-related adverse events
irRC: immune-related response criteria
IVIG: intravenous immunoglobulin
LFT: liver function test
LH: luteinizing hormone
mAb: monoclonal antibody
MSI-high: Microsatellite instability high
NSCLC: Non-small cell lung cancer
O&P: ova and parasite
PD-1/PD-L1: Programmed Death 1/ Programmed Death Ligand 1
RCC: Renal cell carcinoma
SOB: shortness of breath
TEN: toxic epidermal necrolysis
TSH: thyroid stimulating hormone
ULN: upper limit of normal
UTI: urinary tract infection
WBC: white blood cell count

Notes
REFERENCES AND SUGGESTED READING


Weber JS, Antonia SJ, Topalian S, et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): a pooled analysis. Presented at the American Society of Clinical Oncology 2015 Annual Meeting; May 29-June 2, 2015; Chicago, IL, USA.


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