Treatment of Immunotherapy Toxicities

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Disclosure

I have no disclosures to report relevant to the content of this presentation
Objectives

- Describe the mechanism of action of checkpoint inhibitor therapies and list the currently approved agents.

- Recognize common and serious immune-related adverse events and describe management options.
<table>
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<tr>
<th>Approach</th>
<th>Surgery</th>
<th>Radiation therapy</th>
<th>Chemo-therapy</th>
<th>Targeted therapy</th>
<th>Immuno-therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cut out tumor cells to stop growth and prevent spread</strong></td>
<td><strong>Use highly concentrated x-rays or radio-active isotopes to kill cancer cells</strong></td>
<td><strong>Use cytotoxic drugs to kill or inhibit cancer cell growth</strong></td>
<td><strong>Interfere with a mechanism required for or that supports tumor growth</strong></td>
<td><strong>Utilize the immune system’s innate ability to recognize and eliminate tumor cells</strong></td>
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<td><strong>1800s</strong></td>
<td><strong>Early 1900s</strong></td>
<td><strong>Late 1940s</strong></td>
<td><strong>2000s</strong></td>
<td><strong>2010s</strong></td>
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<tr>
<td><strong>Inaccessible tumor location; Limited efficacy if metastatic spread present</strong></td>
<td><strong>Limited efficacy if metastatic spread; May be harmful to nearby healthy tissue/vital organs</strong></td>
<td><strong>Highly toxic and may not eradicate all tumor cells, leading to high recurrence rates</strong></td>
<td><strong>Limited tumor types eligible; High efficacy but short durability not leading to tumor recurrence</strong></td>
<td><strong>Variable efficacy in different tumor types; different toxicity profiles than other agents</strong></td>
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Adapted from: www.cancerresearch.org/clinical-accelerator
Types of Immunotherapy

Non-specific Cancer Immunotherapy
- IL-2
- IFN-alpha
- Immunomodulating drugs

Adoptive Immunotherapy
- Tumor infiltrating lymphocyte therapy
- Lymphokine activated killer cell therapy
- Cytokine induced killer cell therapy
- Dendritic cell cytokine induced killer cell therapy
- Genetically engineered T-cell therapy

Monoclonal Antibodies
- Naked
- Conjugated (radio-labeled, chemo-labeled)

Targeting Immune System Checkpoints
- CTLA-4
- PD-1
- PD-L1

Cancer Vaccine Therapy
- Tumor cell vaccines
- Antigen vaccines
- Dendritic vaccines
- Vector-based vaccines

CTLA-4: cytotoxic T-lymphocyte–associated antigen-4
PD-1: programmed cell death protein 1
PD-L1: programmed cell death ligand 1
Current PD-1 and PD-L1 Inhibitors

- PD-1: trans-membrane protein on T cells, B cells and NK cells
  - Nivolumab (Opdivo™)
  - Pembrolizumab (Keytruda®)
- PD-L1: PD-ligand which is found on the surface of tumor cell
  - Atezolizumab (Tecentriq®)
  - Avelumab (Bavencio®)
  - Durvalumab (Imfinzi™)

https://www.accessdata.fda.gov/scripts/cder/daf/
PD-1/PD-L1 Therapies and Approved Indications

PD-1 and PD-L1 Inhibitors

- Melanoma
- Merkel Cell Carcinoma
- Renal Cell Carcinoma
- Microsatellite Instability-High Colorectal Cancer
- Non-Small Cell Lung Cancer
- Hodgkin’s Lymphoma
- Head and Neck Squamous Cell Cancer
- Urothelial Bladder Cancer

https://www.accessdata.fda.gov/scripts/cder/daf/
Mechanism of Action: PD-1 and PD-L1 Inhibitors

- Tumor microenvironment contains overexpression of immunosuppressive molecules
  - PD-1
  - PD-L1
  - CTLA-4
- Binding of PD-1 to PD-L1 prevents T-cell activation
- Blocking binding of PD-1/PD-L1 with a checkpoint inhibitor, cytotoxic T cells are reactivated → apoptosis
Mechanism of PD-1 and PD-L1 Inhibitors

Nivolumab
Pembrolizumab
Atezolizumab
Avelumab
Durvalumab

Ipilimumab

Tumor

Physiological Implications of PD-1/PD-L1 Therapies

- PD-1/PD-L1 interaction between malignant cells and T cells allows tumor to evade immune response
- PD-1 and PD-L1 inhibitors bind to PD-1/PD-L1 → immune response
  - Reactivation of tumor-specific cytotoxic T lymphocytes
    - Increased T cell proliferation and activity
    - Pro-inflammatory reactions
- Generates atypical tumor responses resulting in dysimmune toxicities
  - Immune-related adverse events (irAEs)
Immune-related Adverse Events (irAEs)

- Auto-immune toxicity to normal tissue due to immune activation
  - May affect any organ system
    - Grade 1 - 2: mainly affect skin and gut
    - Grade 3 - 4: mainly affect GI tract
  - Safety profiles vary per tumor type

- Incidence
  - All grades: 70%
  - Grades 3 - 4: 7 – 19%

- Discontinuation rate of PD-1/PD-L1 due to irAEs
  - 3 – 8%
Immune-related Adverse Events (irAEs)

- Toxicities do not appear to be dose-related, cumulative
- No relationship between symptom onset and efficacy/disease regression
- Timeline of symptom onset

Immune-related Adverse Events (irAEs)
Organ Systems Affected by PD-1/PD-L1

- **Skin**
  - Maculopapular rash, vitiligo, psoriasis, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms

- **Gastrointestinal tract**
  - Enterocolitis, gastritis, pancreatitis, celiac disease

- **Endocrine glands**
  - Thyroid disease, hypophysitis, adrenal insufficiency, diabetes

- **Lungs**
  - Pneumonitis, pleural effusion, sarcoidosis
Organ Systems Affected by PD-1/PD-L1

- **Nervous system**
  - Peripheral neuropathy, aseptic meningitis, Guillain-Barré syndrome, encephalopathy, myelitis, meningo-radiculoneuritis, myasthenia gravis

- **Liver**
  - Hepatitis

- **Kidneys**
  - Granulomatous interstitial nephritis, lupus-like glomerulonephritis

- **Hematological cells**
  - Hemolytic anemia, thrombocytopenia, neutropenia, pancytopenia
Organ Systems Affected by PD-1/PD-L1

- Musculo-articular system
  - Arthritis, myopathies
- Heart
  - Pericarditis, cardiomyopathy
- Eyes
  - Uveitis, conjunctivitis, blepharitis, retinitis, choroiditis, orbital myositis
Common irAEs with PD-1/PD-L1 Inhibitors

- Incidence > 10%
  - Fatigue
  - Rash, pruritus
  - GI: Nausea, diarrhea, colitis
  - Arthralgia
  - Pneumonitis, pneumonia
  - Hepatitis, increased liver enzymes
  - Endocrinopathies
Risk Factors for irAEs

- Personal/family history of auto-immune diseases
  - Psoriasis, lupus, ulcerative colitis, diabetes, etc.

- Tumoral infiltration
  - Focal immune reconstitution inflammatory syndrome

- Opportunistic pathogens
  - Inflammatory reaction against a previous chronic pathogen

- Concomitant medications and job-related exposures
  - Environmental exposures may increase risk of autoimmune diseases
How to Manage Patients with a History of Autoimmune Diseases?

- If autoimmune disease is controlled, provider may consider treatment with PD-1/PD-L1 therapy
  - Case reports show autoimmune disease may remain stable
    - ie. vitiligo – no disease worsening
  - Endocrine deficiencies which are controlled with substitutive treatment
- Treatment decision should weigh risk versus benefit for individual patient
- Increased monitoring should occur to prevent worsening of autoimmune disease
Toxicity Management

- GI, Hepatic, Renal irAE → rapid resolution
- Skin, Endocrine irAE → gradual improvement
- Early onset < 2 months
- Late onset > 2 months

• Physical
• Imaging
• Labs (CBC, CMP, CRP, Coags, TSH)
Immune-related Adverse Event: Fatigue

- Most frequently reported irAE with PD-1/PD-L1 inhibitor

- Incidence
  - Anti-PD-1: 16 – 37%
  - Anti-PD-L1: 12 – 24%

- Usually mild in severity

- Pathogenesis – poorly understood
  - Rule out other causes – endocrine?
Immune-related Adverse Events (irAEs)
Immune-related Adverse Events: Dermatologic

- Vitiligo
  - Seen most in patients with melanoma
  - Incidence: ~8% of melanoma patients on anti-PD-1/PD-L1 therapy
  - Hua and colleagues prospectively followed metastatic melanoma patients (n = 67) on pembrolizumab therapy
    - 25% developed vitiligo
    - Objective response to treatment associated with incidence of vitiligo
    - All patients who developed vitiligo were alive at analysis
      - Median follow-up: 441 days

JAMA Dermatol 2016; 152: 45-51.
Immune-related Adverse Events: Dermatologic

- **Pruritus**
  - Incidence all grades: 13 – 20%
  - Grades 3 and 4 (severe) incidence: <2.5%

**Management of Pruritus**

**Mild**
- Continue immunotherapy
- Treat with high-potency topical steroids

**Moderate**
- Consider holding immunotherapy
- Treat with high-potency topical steroids, oral antihistamines (cetirizine, hydroxyzine); dermatology consultation

**Severe**
- Hold immunotherapy
- Treat with prednisone/methylprednisolone 0.5 – 1 mg/kg/day, GABA agonists (gabapentin, pregabalin); Urgent dermatology consultation
Immune-related Adverse Events: Dermatologic

- **Rash**
  - Proposed mechanism: blockade of antigen expressed on tumor surface and the dermo-epidermal junction
  - Incidence: 15% of patients

- **Types**
  - Maculopapular
  - Lichenoid dermatitis
  - Bullous pemphigoid
  - Stevens Johnson Syndrome (SJS)
  - Toxic Epidermal Necrolysis (TEN)

Maculopapular Rash: Grading

- **CTCAE Classification**
  - Grade 1: macules/papules covering < 10% of BSA with or without symptoms
  - Grade 2: macules/papules covering 10-30% of BSA with or without symptoms; limiting ADLs
  - Grade 3: macules/papules covering >30% of BSA with or without symptoms; limiting self-care ADLs
  - Grade 4: papulopustular rash associated with life-threatening superinfection; SJS or TEN covering >30% of BSA and requiring ICU admission
Management of Skin Rash

Mild
- Continue immunotherapy
- Use moderate potency topical steroids, oral antihistamines for itching;
- Use topical emollients; Avoid irritants, sun exposure

Moderate
- Consider holding immunotherapy
- Use high potency topical steroids and/or prednisone 0.5 – 1 mg/kg/day, oral antihistamines for itching, topical emollients

Severe
- Hold immunotherapy
- Treatment with high potency topical steroids, Prednisone 0.5 – 1 mg/kg/day (increase if no improvement), treat until grade 1 then wean over 4 – 6 weeks;
- Urgent dermatology consultation

NCCN Guidelines Management of Immunotherapy-Related Toxicities Version 1.2018
Immune-related Adverse Events (irAEs)
Immune-related Adverse Events: Endocrinopathies

- **Pituitary**
  - Hypophysitis – uncommon
  - Acute symptoms: headaches, photophobia, dizziness, nausea/emesis, fevers or anorexia
  - Non-acute symptoms: fatigue, possible weight loss

- **Thyroid**
  - Hypothyroidism > Hyperthyroidism
  - Proposed mechanism: mediated by T-cells
  - Incidence: 5 – 10%
    - Commonly Grade 1 or 2
  - Routine monitoring, at baseline, then at least monthly (TSH, FT4)
Immune-related Thyroid Dysfunction Management

<table>
<thead>
<tr>
<th>TSH</th>
<th>Free T4</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>- (normal)</td>
<td>No symptoms, monitor If symptoms, consider replacement if TSH &gt; 10</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>No symptoms, monitor If symptoms, initiate thyroid replacement</td>
</tr>
<tr>
<td>- (normal)</td>
<td>↑</td>
<td>Repeat, if still elevated, refer to endocrinologist</td>
</tr>
<tr>
<td>- (normal)</td>
<td>↓</td>
<td>No symptoms, recheck; Check AM cortisol (may indicate hypopituitarism)</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>No symptoms, monitor If symptoms, hyperthyroidism: beta-blockers, thyroid antibodies and uptake scan</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>Check AM cortisol (may indicate hypopituitarism)</td>
</tr>
</tbody>
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**Hypothyroidism** (↓ FT4 with ↑ TSH) OR (Normal FT4 with TSH > 10)
- Treatment: levothyroxine 0.5 – 1.5 mcg/kg
- With hormone replacement, continue anti-PD-1/PD-L1 therapy

Immune-related Adverse Events: Endocrinopathies

► Diabetes mellitus
  ► Proposed mechanism: mediated by specific CD8 T-cells as blockade of PD-1/PD-L1 pathway occurs
  ► Type 1 DM > Type 2 DM
    ► Loss of beta cells of islets of Langerhans
  ► Management: Steroids
    ► Unknown if steroid use can prevent loss of beta cells
    ► Steroids will contribute to worsening control of blood glucose
  ► Insulin replacement/regulation of BG → restart anti-PD-1/PD-L1 therapy
Management of Hyperglycemia

New onset hyperglycemia
<200 mg/dL
and/or
History of Type II DM with low suspicion of DKA

Continue immunotherapy
Monitor serial BG with each dose, diet and lifestyle modifications (if needed, medical therapy); Consider endocrine consultation

New onset fasting glucose
> 200 mg/dL or
Random BG > 250 mg/dL or
History of Type II DM with fasting BG > 250 mg/dL

Evaluate patient for DKA →
If negative, manage as above
If positive for DKA workup, see below

Patient with DKA

Hold immunotherapy
Inpatient management, per institutional guidelines; Insulin management per inpatient team
Endocrine consultation

DKA: diabetic ketoacidosis
NCCN Guidelines Management of Immunotherapy-Related Toxicities Version 1.2018
Immune-related Adverse Events (irAEs)
Immune-related Adverse Events: Hepatotoxicity

- Hepatitis
  - Incidence: 5 – 10%
    - Grade 3 accounts for 1 – 2%
  - Typically asymptomatic
  - Monitor liver enzymes
    - Serum transaminases, bilirubin at baseline and prior to each treatment
      - If elevated → rule-out other causes
    - Consider a liver biopsy if necessary for differential
Management of Hepatitis

**Mild**
If AST/ALT > ULN - 3x ULN, monitor with increased frequency
Continue immunotherapy

**Moderate**
If AST/ALT 3 – 5x ULN, hold immunotherapy
Recheck AST/ALT every 3 – 5 days, if rising, consider
prednisone 0.5 – 1 mg/kg/day, taper over at least 4 weeks

**Severe**
If AST/ALT 5 – 20x ULN, permanently discontinue immunotherapy
Initiate prednisone 1 – 2 mg/kg/day, taper over at least 4 weeks, monitor
LFTs every 1 – 2 days, hepatology consultation

**Life-threatening**
If AST/ALT > 20 x ULN, permanently discontinue immunotherapy and
inpatient admission for management
Initiate methylprednisolone/prednisone 2 mg/kg/day, taper slowly as
tolerated, monitor LFTs daily, urgent hepatology consultation

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Management of Hepatitis Cont’d

Patient worsening despite steroid management

If on PO steroids →
Change to IV Methylprednisolone

If on IV steroids →
Add mycophenolate mofetil 500 – 1000 mg PO bid

If worsens on mycophenolate mofetil →
Consider addition of tacrolimus* and consult hepatology

* Use of infliximab is contraindicated due to increased risk of hepatotoxicity

Immune-related Adverse Events (irAEs)
Immune-related Adverse Events: Gastrointestinal Toxicity

- CTLA-4 inhibitors > anti-PD-1/PD-L1 therapy
- Incidence Colitis
  - Grade 3 – 4: only 1 – 2%
- Symptoms
  - Diarrhea > nausea/vomiting > abdominal pain
- Endoscopic findings
  - Normal mucosa
  - Inflammation
    - Mild erythema
    - Severe inflammation (mucosal friability/ulceration)
Management of Diarrhea/Colitis

Consider holding immunotherapy
Mild: <4 liquid stools/day > baseline, no symptoms of colitis; Symptomatic management (fluids, antidiarrheal agents), close monitoring

Hold immunotherapy
Moderate: 4-6 liquid stools/day > baseline with colitis symptoms not interfering with ADLs
Initiate IV methylprednisolone 1 mg/kg/day, convert to prednisone when tolerated
If no response in 2 – 3 days: Increase methylprednisolone to 2 mg/kg/day, consider infliximab*

Grade 3: Discontinue immunotherapy, consider resuming alternative agent
Grade 4: Permanently discontinue immunotherapy
Severe: > 6 liquid stools/day > baseline with colitis symptoms interfering with ADLs
Inpatient admission: IV fluids, electrolytes, consult GI service, consider colonoscopy
Initiate IV methylprednisolone 2 mg/kg/day, if no response in 2 days, consider infliximab*

For moderate and severe diarrhea: treat until symptoms improve to Grade ≤ 1, then taper over 4 – 6 weeks

Steroid Taper


*Infliximab dosing: 5 mg/kg up to q2weeks
Immune-related Adverse Events (irAEs)
Immune-related Adverse Events: Pulmonary

- **Pneumonitis**
  - Anti-PD-1/PD-L1 therapy > CTLA-4 inhibitors
  - Incidence
    - All grades: 2 – 4%
    - Grade 3 or 4: 1 – 2%
      - Incidence is similar across tumor types and with varying dose
  - Symptoms may include: new cough, upper respiratory infection, shortness of breath or hypoxia
    - Rule out disease progression or lung metastases
    - CT Scan can help with differential diagnosis

Management of Pneumonitis

**Grade 1**

Hold immunotherapy
Asymptomatic; Monitor and reassess in 1 – 2 weeks
Work-up: Chest imaging (CT with contrast preferred or X-ray), pulse oximetry

**Grade 2**

Hold immunotherapy
Presence of new/worsening symptoms (dyspnea, cough, chest pain); Monitor and reassess every 3 – 7 days
Consider infectious workup, bronchoscopy with BAL, chest imaging; Start antibiotics if infection suspected
Initiate methylprednisolone/prednisone 1 – 2 mg/kg/day, if no improvement within 72 hours, treat as grade 3

**Grade 3/4**

Permanently discontinue immunotherapy
Severe new symptoms, new or worsening hypoxia, life threatening difficulty breathing, ARDS
Inpatient admission: infectious workup, pulmonary and ID consultation, bronchoscopy with BAL, consider empiric antibiotics
Initiate IV methylprednisolone 1 – 2 mg/kg/day
If no improvement or worsening after 48 hours, add infliximab*, mycophenolate mofetil or IVIG

**Steroid Taper**

Grade 2: Treat until Grade ≤ 1, taper over 4 – 6 weeks
Grade 3 – 4: Treat until Grade ≤ 1, taper over ≥ 6 weeks

*Infliximab dosing: 5 mg/kg up to q2weeks
General Principles of Immunosuppressive Therapy

- Corticosteroid use to treat irAE has NOT been shown to reduce anti-tumor activity
  - Routine premedication with steroids (nausea, infusion reactions) is not recommended due to potential mitigation of anti-tumor activity in the prophylactic setting
- Longer steroid tapers may be required for some irAE
  - Pneumonitis
  - Hepatitis
- Prophylactic treatments should be considered
  - Pneumocystis jiroveci pneumonia → if on prednisone ≥ 20 mg/day for ≥ 4 weeks
  - Fungal infections → if on prednisone ≥ 20 mg/day for ≥ 6 weeks
Sequelae of Prolonged Immunosuppression

Prolonged Immunosuppression

Corticosteroids use > 4 weeks

Immunomodulatory Medications

Opportunistic infections
- Insomnia
- Mood disturbances
- Gastritis
- Diabetes
- Hypertension
- Osteoporosis
Clinical Pearls of Prolonged Corticosteroid Use

- **Insomnia**
  - Dosing in AM or if BID, PM dosing earlier in day

- **GI Upset**
  - Administer with meals
  - Consider H2RB or PPI for reflux (especially in high risk patients: NSAID use, anticoagulation)

- **Diabetes**
  - Routine blood glucose monitoring is recommended
  - Consider initiation of oral agents/insulin for optimal control
  - Endocrine consultation

- **Osteoporosis**
  - Optimize Vitamin D levels
  - Supplementation with calcium
  - Provide education to minimize risk
  - Greatest risk if patient on steroids > 3 months
Conclusions for Management of Checkpoint Inhibitor Toxicities

- Anti-PD-1/PD-L1 agents are relatively well-tolerated (Grade 1 or 2 irAE)
- Every organ system can be affected
  - Patient education of prompt reporting of symptoms is imperative
- Grade 3 or 4 irAE are rare but possibly life-threatening
  - Urgent management with corticosteroids/immunomodulatory agents may be necessary
Self-Assessment Question

1. Which of the following is **NOT** a PD-1/PD-L1 inhibitor?
   
   a) Durvalumab  
   b) Ipilimumab  
   c) Nivolumab  
   d) Pembrolizumab  
   e) Atezolizumab
Self-Assessment Question

1. Which of the following is true about irAE of PD-1/PD-L1 inhibitors?
   a) Toxicities do not appear to be dose-related
   b) Incidence of all grades of toxicity is ~70%
   c) No relationship exists between symptom onset and efficacy
   d) All of the above
Treatment of Immunotherapy Toxicities

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