Immune-Related Adverse Events Associated With Immunotherapy Check-point Inhibitors

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Disclaimer

• No financial or conflicts of interest to disclose
• The opinions expressed in this lecture are my own
Systemic Cancer Therapy

- Traditional Cytotoxic Chemotherapy
- Molecularly Targeted Therapy
- Cancer Immunotheraphy
Cancer Immunotherapy

- Process of harnessing the immune system to build an efficient and specific cytotoxic response to reject a tumor

- Therapeutic Modalities
  - Immune check-point blockade
  - Cytokines (Interferon Alpha, IL-2)
  - Prophylactic cancer vaccines
  - Therapeutic cancer vaccines
  - Oncolytic viral therapies
  - Adoptive cell therapies (Manipulation of T-cell ex vivo to be more reactive to cancer specific antigens, or promoting NK activity)
Immune checkpoint Inhibitors

• In this lecture Immune checkpoint inhibitors will be abbreviate as ICPI

• In general, check point pathways are mechanisms for the human immune system to control the immune response. Some cancers have the ability to co-opt these pathways and evade cytotoxic T-cell-mediated death.

• Below are receptors present on the surface of cytotoxic T cells. Checkpoint inhibitors bind to these protein receptors preventing the cancer from evading the immune system.

    Checkpoint inhibitor targets include:
    • PD-1,
    • PDL-1
    • CTLA-4
Immunotherapy Checkpoint Inhibitors

**PD-1 and PDL-1 inhibitors:**
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab
- Durvalumab
- Cemiplimab

**CTLA-4 inhibitors:**
- Ipilimumab
Immune checkpoint inhibitors

• Immune checkpoint inhibitors (ICPis) have shown a durable clinical benefit.

• Associated adverse effects (irAE) are very different from traditional cytotoxic chemotherapy.
  – ICPis can affect multiple organ systems such as the skin; GI tract; lungs; musculoskeletal, renal, nervous, hematologic, cardiovascular, endocrine, thyroid, adrenal, pituitary, and ocular systems.

We need to educate patients on the side effects of these medications and have a high level of suspicion that any changes may be treatment related.
ASCO Clinical Practice Guideline

• Recommendations I’m about to review are based on the ASCO Clinical Practice Guidelines published in the June 2018 Journal of clinical Oncology. They were established by a multidisciplinary, multi-organizational panel of experts in medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, urology, neurology, hematology, emergency medicine, nursing, and research trialists.

• The recommendations were expert consensus based clinical guidelines to assist providers in managing adverse side effects of immune checkpoint inhibitors while weighing benefits vs. harm.
Skin Toxicities

• Rash/inflammatory dermatitis
  – Appearances may be similar to:
    • Eczema (pruritic erythematous scaly or crusted papules or plaques)
    • Psoriasiform (well demarcated erythematous scaly papules or plaques of psoriasis)
    • Erythema multi-forme minor or major (target lesion with surrounding erythema, can progress to SJS or SCAR)
    • Lichenoid (flat top, polygonal, sometimes scaly or hypertrophic lesion)
    • Morbiliform (maculopapular)
    • Erythrodysesthesia (hand-foot-syndrome; redness, burning, numbness, itching, and superficial desquamation of the palms and soles)
    • Neutrophilic dermatosis (pustular vasculitis)

• Bullous dermatosis
  – large fluid filled blisters

• Severe Cutaneous Adverse Reactions (SCARs) examples include SJS, TEN, acute generalized exanthematous pustulosis, and DRESS/DIHS
  – Changes in the structure or function of skin, appendages, or mucous membrane. May have (+) Nikolsky sign (detached or sloughing epidermis from the dermis)
Skin Toxicities

• What to do if patient reports rash?
  – Obtain as much information about the rash.
    • When did it appear?
    • Does it itch?
    • Any new lotions, perfumes, laundry soaps, or medications?
    • Have you been outside around unfamiliar plants? Possible exposure to poison ivy/poison oak
    • What is the distribution of the rash? (Is the rash in sun exposed areas only or palms and soles of feet) Is there discomfort or sores in the nares or oropharynx?
    • Is it associated with fevers or increasing malaise, myalgia, arthralgia, ocular discomfort/photophobia, dysuria, or pain with BMs?
  – Report the new finding to the physician
  – Serial imaging of the rash may be beneficial
• Providers may request CBC, CMP, LFTs, or further serology studies to r/o other autoimmune conditions such as dermatomyositis or lupus
• Exclude other causes such as infection or other medications
• skin biopsy may be warranted
Skin Toxicities

Rash/Inflammatory Dermatitis

G1: Symptoms do not affect QOL or can be controlled with topical regimen or oral antipruritic agents

G2: Inflammatory reaction that affects QOL

G3: Same as G2, but fails to respond to interventions

G4: Rash is intolerable or unmanageable with prior intervention

Treatment recommendation

G1: Continue ICPI, tx with topical emollients, mild-mod potency topical corticosteroids, pt should avoid skin irritants and sun exposure

G2: Consider holding ICPI and monitor weekly until resolves to G1, use topical emollients and med-high potency topical corticosteroids. Consider systemic steroid taper over 4wks.

G3: Hold ICPI, use topical emollients and med-high potency topical corticosteroids, initiate system steroid taper over at least 4wks.

G4: Hold ICPI, for severe consider hospital admission or dermatology consult, start systemic corticosteroids
## Skin Toxicities

### Bullous Dermatosis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>G1</td>
<td>Asymptomatic blisters covering &lt;10% BSA and no associated erythema.</td>
</tr>
<tr>
<td>G2</td>
<td>Blistering that affects QOL or covers 10-30% BSA. Deroofed vesicles or bullae.</td>
</tr>
<tr>
<td>G3</td>
<td>Skin sloughing covering &gt;30% BSA with associated pain and limiting self-care ADLs.</td>
</tr>
<tr>
<td>G4</td>
<td>Blisters covering &gt;30% BSA with associated fluid or electrolyte abnormalities.</td>
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### Treatment recommendation

<table>
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<tr>
<td>G1</td>
<td>Cessation of ICPI is not necessary. Local wound care is warranted. Patient should be monitored closely for progression to grade 2.</td>
</tr>
<tr>
<td>G2</td>
<td>Hold ICPI. If blister is unroofed pt should cover with plain petrolatum and gauze, avoid skin irritants and sun exposure. Start high-potency topical corticosteroids and reassess Q3days. Low threshold to initiate system steroid taper.</td>
</tr>
<tr>
<td>G3</td>
<td>Hold ICPI and consult with dermatology. Administer IV steroids 1-2mg/kg, tapering over at least 4wks. If bullous pemphigoid can be diagnosed long-term steroids may be avoided for rituximab instead. Consult ID if pt has signs of secondary cellulitis or neutropenia.</td>
</tr>
<tr>
<td>G4</td>
<td>Permanently discontinue ICPI. Admit pt immediately under supervision of dermatologist. Administer IV methylprednisolone 1-1mg/kg. If bullous pemphigoid can be diagnosed long-term steroids may be avoided for rituximab instead. Consult ID if pt has signs of secondary cellulitis or neutropenia.</td>
</tr>
</tbody>
</table>
Skin Toxicities

Severe cutaneous adverse reactions (SCARs)

There is no Grade 1

G2: Morbiliform exanthem cover 10-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling.

G3: Skin sloughing covering <10% BSA with mucosal involvement associated signs (eg. erythema, purpura, epidermal detachment, mucous membrane detachment)

G4: skin erythema and blistering/sloughing >10% BSA w/associated signs (listed above), and/or systemic symptoms and blood work abnormalities (eg. Elevated LFTs)

Treatment recommendation

G2: Hold ICPI. Recheck Q3 days for progression to G3 with greater BSA involvement or mucous membrane involvement. Initiate topical emollients, oral antihistamines, med-high strength topical corticosteroids, or systemic steroids.

G3: Hold ICPI. Consult dermatology. Treat skin with topical emollients, pertrolatum emollients or Dimethicone, oral antihistamines; high strength topical steroids. Admit to burn/wound services with attention to supportive care. If mucous membrane involvement of SJS or TEN, consult appropriate services.

G4: Permanently discontinue ICPI, admit immediately to burn unit or ICU with derm and wound consult, initiate IV steroids, IVIG or cyclosporine may be considered in corticosteroid-unresponsive cases.
Gastrointestinal Toxicities

- **Diarrhea** (*very very* common side effect with ICPis)
- **Colitis** (mucous in the stool, abdominal pain, fever, rectal bleeding)
- **Hepatitis**
GI toxicities

**Diarrhea**

G1: Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline.

G2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline.

G3: Increase of 7 or more stool per day over baseline; severe increase in ostomy output over baseline, limiting self-care ADL.

G4: Life-threatening consequences; urgent intervention indicated.

**Treatment Recommendation**

G1: continue ICPi; monitor for dehydration, recommend dietary changes, consider GI consult for prolonged G1 cases.

G2: Hold ICPi temporarily until toxicity resolves to G1; consider permanent d/c CTLA-4 agents and restart PD-1 agents if pt recovers to G1 or less. Systemic steroids can be offered in individual cases. Support w/anti-diarrheals once infectious process has been excluded. Consult gastroenterology for G2 or higher. Taper steroids over 4-6wks when symptoms are G1 or less.
GI toxicities

Diarrhea

Grade 3:
Seven or more stools per day over baseline; severe increase in ostomy output over baseline, limiting self-care ADL

Treatment Recommendation

Grade 3:
Consider permanent d/c of CTLA-4 agent and may restart PD-1, PDL-1 agent if pt recovers to G1 toxicity. Consider hospitalization or outpatient management of dehydration and electrolytes. Start oral steroids; if symptoms persist >3-5 days or recur after improvement then start IV steroids. Consider colonoscopy for pt on immunosuppression (anti-TNF) and are high risk for opportunistic infections, or pt who are refractory to corticosteroids.
GI toxicities

Diarrhea
Grade 4:
Life-threatening consequences; urgent intervention indicated

Treatment Recommendation
Grade 4:
Permanently discontinue treatment. Admit patient when clinically indicated; patients managed outpatient should be monitored very closely. Administer systemic corticosteroids until diarrhea reverts to Grade 1, then begin taper. Consider early infliximab 5-10mg/kg if symptoms are refractory to corticosteroids within 2-3 days. Consider lower GI endoscopy if symptoms are refractory or there is concern for new infections.
GI toxicities

Colitis

G1: Increase of less than four loose stools with or w/o blood or mucous per day over baseline, or mild ostomy output with blood or mucous.

G2: Increase of 4-6 stools w/blood or mucous per day over baseline; moderate increase in ostomy output compared to baseline.

G3: Increase of 7 or more stool w/blood or mucous per day over baseline; severe increase in ostomy output over baseline, limiting self-care ADL, Severe abdominal cramps.

G4: Life-threatening consequences; urgent intervention indicated

Treatment Recommendation

G1: No diagnostic work up is recommended. ICPI can be continued unless symptoms progress to grade 2. Monitor for dehydration similar to grade 1 diarrhea.

G2: Hold ICPI until toxicity resolves to Grade 1; consider permanent d/c CTLA-4 agents and restart PD-1 agents if pt recovers to G1 or less. Obtain CBC, CMP, TSH, ESR, CRP, stool culture, and film array. Consider testing for lactoferrin to determine who needs urgent endoscopy. Consult gastroenterology for G2 or higher.

G3/4: Admit to hospital and consult gastroenterology. All workup listed for grade 2 should be obtained immediately. Start IV corticosteroids. Obtain additional labs in preparation for infliximab therapy. Avoid NSAIDs. Consider repeating endoscopy for pt who do not respond to immunosuppressive agents.
GI Toxicities

Hepatitis

G1: Asymptomatic
(AST or ALT > ULN to 3.0 x ULN and/or tbili > 1.5 xULN)

G2: Asymptomatic
(AST or ALT > ULN to ≤ 5 x ULN and/or tbili > 1.5 to ≤ 3 xULN)

G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x ULN)

G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; (AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x ULN)

Treatment Recommendations

G1: continue ICPi with close monitoring

G2: Hold ICPi and resume if toxicity recovers to Grade1, consider corticosteroid use, Infliximab may not be the most appropriate treatment for immune mediated hepatitis.

G3: Permanently d/c ICPi, monitor labs Q1-2days, immediately start corticosteroids, if no improvement after 3 days consider mycophenolate mofetil or AZA. Must test for thiopurine methyltransferase deficiency prior to using AZA. If pt fails to improve consider hepatologist referral for further w/u.

G4: Permanently discontinue ICPi. Administer IV steroids. If no improvement after 3days, consider mycophenolate mofetil. Monitor labs daily, consider inpatient monitoring. Avoid use of infliximab in immune-mediate hepatitis, hepatology consult if no improvement achieved with corticosteroids.
GI Toxicities

• Managing GI toxicities
  – Ask patients about changes in bowel habits at each visit.
  – Establish a baseline for number of loose stools per day prior to initiating ICPis and document this in the ROS.
  – Counsel patients to contact their health care provider if they experience changes in bowel habits, abdominal cramping or see blood or mucous after BMs.
  – When a patient reports diarrhea
    • Ask how many stools per day “above their baseline” they are experiencing
    • Is this accompanied by abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits such as constipation or obstipation, abdominal distention or fevers.
    • Any recent changes to their diet? Are they getting enough liquid to prevent dehydration?
    • Any changes in urine, such as tea colored urine
    • Report these findings to the patient’s oncologist
Lung Toxicities

Pneumonitis

G1: Asymptomatic, confined to one lobe or <25% of lung parenchyma

G2: Symptomatic, involves more than one lobe or 25-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL

G3: Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, limiting self-care ADL, oxygen indicated.

G4: life-threatening respiratory compromise, urgent intervention indicated (intubation)

Treatment Recommendations

G1: Hold ICPI w/radiographic evidence of pneumonitis progression. May offer one repeat CT in 3-4wks. If pt has baseline spirometry/DLCO consider repeat in 3-4wks. May resume ICPI when there is radiographic evidence of improvement or resolution. Monitor pt wkly w/Hx and PE, pulse ox, may offer CXR.

G2: Hold ICPI until symptoms resolve to G1 or less. Systemic corticosteroids, consider bronchoscopy, consider empirical antibiotics, monitor every 3 days with Hx/PE, pulse ox, consider CXR. If there is no improvement after 48-72 hr of prednisone, treat as G3.

G3/4: Permanently discontinue ICPI, Admit to hospital. Consult pulmonary and infectious disease. Start systemic steroids, if no improvement after 48 hrs may add infliximab or mycophenolate mofetil or cyclophosphamide. Bronchoscopy with BAL +/- transbronchial biopsy.
Lung Toxicities

• ICPI related pneumonitis is uncommon, but potentially serious.

• Definition of pneumonitis: inflammation of the lung parenchyma, typically identified on CT
  – CXR may show ground-glass opacities or patchy nodular infiltrates, usually involving lower lobes
  – Findings tend to be focal rather than diffuse
  – However there are no pathognomonic symptoms or radiographic features to confirm the diagnosis

• Other pulmonary side effects reported while on CTLA-4 and PD(L)-1 targeted therapies include: sarcoid-like granulomatous reactions, subpleural micronodular opacities and hilar lymphadenopathy, pleural effusions.
ICPi Related Pneumonitis

• Clinical manifestations will vary.
• Patient’s *may* present with cough, wheezing, fatigue, chest pain, or no symptoms at all.
• Time of onset can vary from 2-24 months with a median time of onset of approximately 3 months \(^3\)
• Slightly higher chance for pneumonitis in patients treated with anti-PD(L) monotherapy compared to anti-CTLA-4 monotherapy.
• Patients on combination anti-CTLA-4 and anti-PD(L)-1 typically present earlier than those on monotherapy.
Lung Toxicities

Managing Lung Toxicities

• Obtain pulse oxygenation reading at each visit.
  – Establish a baseline prior to starting ICPis and monitor for changes at each visit.
  – Hypoxia as noted by pulse oximetry could be the only sign with grade-1 pneumonitis.

• Remember pneumonitis is rare but serious

• Symptoms will vary on a patient-to-patient basis.
  – May present with cough, wheezing, fatigue, chest pain, or no symptoms at all

• Monitor patient for progressing dyspnea and report this to the physician

• Providers may order CXR, oral or IV corticosteroids, empiric antibiotics, more frequent exams with pulse ox monitoring and consider hospital admission with pulmonology consult.

• Permanent discontinuation of ICPI therapy is recommended for G3 or higher pneumonitis
Endocrine Toxicity could present as any of the following

- HA that will not go away or unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme weakness or tiredness
- Muscle aches
- Feeling cold
- Constipation
- Deeping of voice
- Weight gain or weight loss

- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Alopecia (hair loss)
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain
Endocrine Toxicities Include

- **Primary hypothyroidism**
  - Elevated TSH, normal or low free T4

- **Hyperthyroidism**
  - Suppressed TSH and high normal or elevated free T4 and/or triiodothyronine

- **Adrenal- primary adrenal insufficiency**
  - Adrenal gland failure leading to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia w/orthostasis and volume depletion d/t loss of aldosterone.

- **Pituitary – hypophysitis**
  - Inflammation of the pituitary varying effects on hormone function. Most commonly presenting with central adrenal insufficiency. May also have central hypothyroidism, diabetes insipidus, and hypogonadism

- **Diabetes**
  - **DM Type-II** is a combination of insulin resistance and insufficiency that may require oral or insulin therapy. May be new onset or exacerbated during tx, such as w/corticosteroid exposure.
  - **DM Type-I** results from islet cell destruction and is often acute onset with ketosis and requires insulin
Endocrine Toxicities

Primary Hypothyroidism

G1: TSH <10 mlU/L and asymptomatic

G2: Moderate symptoms; able to perform ADL: TSH persistently > 10mlU/L

G3/4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL

Treatment recommendation

G1: Continue ICPI, with close follow-up of TSH, free T4

G2: Consider holding ICPI until symptoms return to baseline. Consider endocrinology consult. Start thyroid hormone supplementation in symptomatic pt with TSH elevation and monitor every 6-8wks while titrating dose.

G3/4: Hold ICPI until symptoms resolve to baseline with appropriate supplementation. Endocrine consult. May admit for IV therapy if signs of myxedema (bradycardia, hypothermia). Thyroid supplementation and reassessment as in G2.
Endocrine Toxicities

Hyperthyroidism

G1: Asymptomatic or mild symptoms

G2: Moderate symptoms; able to perform ADL

G3/4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL

Treatment recommendation

G1: Continue ICPI, with close follow-up of TSH, free T4 Q2-3wks

G2: Consider holding ICPI until symptoms return to baseline. Consider endocrinology consult. Hydration and supportive care. Steroids are not usually required. For persistent hyperthyroidism (>6wks) workup for Graves disease.

G3/4: Hold ICPI until symptoms resolve to baseline with appropriate therapy. Endocrine consult. B-blocker for symptomatic relief. Admit if there is concern for thyroid storm and start IV steroids.
## Endocrine Toxicities

### Primary Adrenal Insufficiency

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<td>Asymptomatic or mild symptoms</td>
</tr>
<tr>
<td>G2</td>
<td>Moderate symptoms; able to perform ADL</td>
</tr>
<tr>
<td>G3/4</td>
<td>Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL</td>
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### Treatment recommendation

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<tr>
<td>G1</td>
<td>Consider holding ICPI until pt is stabilized on replacement hormone. Consult Endocrinology.</td>
</tr>
<tr>
<td>G2</td>
<td>Consider holding ICPI until pt is stabilized on replacement hormone. Endocrine consult. Specific dosing available in ASCO table.</td>
</tr>
<tr>
<td>G3/4</td>
<td>Hold ICPI until pt is stabilized on replacement hormone. Endocrine consult. Admit for IV steroids and fluids.</td>
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</table>
## Endocrine Toxicities

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<th>Pituitary – hypophysitis</th>
<th>Treatment recommendation</th>
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<tbody>
<tr>
<td><strong>G1:</strong> Asymptomatic or mild symptoms</td>
<td><strong>G1:</strong> Consider holding ICPI until pt is stabilized on replacement hormone. Consult Endocrinology.</td>
</tr>
<tr>
<td><strong>G2:</strong> Moderate symptoms; able to perform ADL</td>
<td><strong>G2:</strong> Consider holding ICPI until pt is stabilized on replacement hormone. Endocrine consult. Specific dosing available in ASCO guidelines.</td>
</tr>
<tr>
<td><strong>G3/4:</strong> Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL</td>
<td><strong>G3/4:</strong> Hold ICPI until pt is stabilized on replacement hormone. Endocrine consult. Admit for IV steroids and fluids.</td>
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Endocrine Toxicities

**Diabetes**

G1: Asymptomatic or mild symptoms; fasting glucose value >ULN (160 mg/dL); no evidence of ketosis or lab evidence of T1DM

G2: Moderate symptoms; able to perform ADL, fasting glucose >160-250 mg/dL; ketosis or evidence of TIDM at any glucose level

G3/4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL
G3: >250-500 mg/dL
G4: >500 mg/dL

**Treatment recommendation**

G1: Continue ICPI w/close follow-up and lab. May initiate oral therapy for T2DM, screen for T1DM when appropriate.

G2: May hold ICPI until glucose control is obtained. Titrate oral therapy or add insulin. Urgent endocrine consult for any pt with T1DM or admit if urgent O/P consult not available.

G3/4: Hold ICPI until toxicity reaches G1 or less. Urgent endocrine consult. Initiate insulin for all pt. Admit if there is concern for developing DKA.
Endocrine Toxicities

Managing Endocrine Toxicities

• Estimated overall incidence of clinically significant endocrinopathies with checkpoint inhibitors is ~10%
• Perform thorough review of systems at each visit.
• Notify physician of pertinent changes (see list next slide)
Endocrine Toxicities can present as any of the following symptoms:

- HA that will not go away or unusual headache patterns
- Vision changes
- Rapid heartbeat
- Increased sweating
- Extreme weakness or tiredness
- Muscle aches
- Feeling cold
- Constipation
- Deeping of voice

- Weight gain or weight loss
- Dizziness or fainting
- Feeling more hungry or thirsty than usual
- Alopecia (hair loss)
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- Urinating more often than usual
- Nausea or vomiting
- Abdominal pain
Musculoskeletal Toxicities

**Inflammatory Arthritis**

**G1**: Mild pain with inflammation, erythema, or joint swelling

**G2**: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL

**G3/4**: Severe pain associated w/signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL

**Treatment recommendation**

**G1**: continue ICPI, initiate analgesia with acetaminophen and/or NSAIDs

**G2**: Hold ICPI and resume upon symptom control and prednisone <10 mg/d. If unable to lower corticosteroid below 10mg/d after 3mo. Consider DMARD. Consider intra-articular corticosteroid injection for Lg joints and Rheumatology referral.

**G3/4**: Hold ICPI temporarily and refer to rheumatology, may resume therapy when symptoms are G1.
## Musculoskeletal Toxicities

### Myositis

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<th>Stage</th>
<th>Description</th>
<th>Treatment Recommendation</th>
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</thead>
<tbody>
<tr>
<td>G1:</td>
<td>Mild weakness with or w/o pain.</td>
<td>Continue ICPI, if CK is elevated and pt has muscle weakness, may offer oral corticosteroids, and tx as G2. Offer acetaminophen or NSAIDS if there are not contraindications.</td>
</tr>
<tr>
<td>G2:</td>
<td>Moderate weakness with or w/o pain, limiting age appropriate instrumental ADL</td>
<td>Hold ICPI temporarily, may resume upon symptom control. Refer to rheumatology or neurology. May require permanent d/c if EMG or muscle bx are abnormal.</td>
</tr>
<tr>
<td>G3/4:</td>
<td>Severe weakness with or without pain, limiting self-care ADL</td>
<td>Hold ICPI temporarily and refer to rheumatology, may resume therapy when symptoms are G1. Permanently d/c if any evidence of myocardial involvement. Consider admit for supplemental care. Consider plasmapheresis or IVIG. Consider immunosuppressant therapy such as MTX, AZA, MMF.</td>
</tr>
</tbody>
</table>
Musculoskeletal Toxicities

Polymyalgia – like syndrome

G1: Mild stiffness and pain

G2: Moderate stiffness and pain, limiting age appropriate instrumental ADL

G3/4: Severe weakness with or without pain, limiting self-care ADL

Treatment recommendation

G1: continue ICPI, Offer acetaminophen or NSAIDS if there are no contraindications.

G2: Consider holding ICPI temporarily, initiate corticosteroids, if no improvement after 4wks escalate to G3. Consider rheumatology referral.

G3/4: Hold ICPI and may resume, in consultation w/rheumatology, if recovers to G1 or less. Toxicity returning upon rechallenging have been reported. Initiate corticosteroids.
Musculoskeletal Toxicities

Managing Musculoskeletal Toxicities

• Monitor for new joint pain or weakness after starting ICPI therapy
• Document changes in ROS and notify provider
• Although myositis is rare it should be considered in patients who report inability to lift arms or lack the muscle strength to stand.
  – Check CK level
• Reports of severe muscle pain w/o appreciable weakness could represent PMR-like syndrome.
  – Check ESR and CRP as these may be dramatically elevated
• Consider rheumatology referral.
  – In cases of oligoarthritis intra-articular corticosteroids may be warranted.
Renal Toxicities

**Nephritis**

G1: creatinine level increase of > 0.3mg/dL; creatinine 1.5-2 x over baseline

G2: creatinine 2-3x above baseline

G3: creatinine > 3x baseline or >4mg/dL

G4: Life threatening consequences; dialysis indicated

**Treatment recommendation**

G1: Consider temporarily holding ICPI, evaluate for other etiologies (recent IV contrast, meds, fluid status) and baseline renal function.

G2: Temporary hold ICPI, consult nephrology, evaluate for other causes, initiate corticosteroids if no other etiology is found.

G3: Permanently d/c ICPI, admit to hospital

G4: Consult nephrology, initiate dialysis, administer corticosteroids.
Renal Toxicities

Managing Nephritis

• Estimated incidence of acute kidney injury (AKI) associated with ICPI is ~1-2% w/single agent and ~4.5% with combination Nivolumab and Ipilimumab.

• Monitor creatinine weekly or prior to every dose

• Routine UA not indicated unless you suspect UTI

• Exclude other causes for renal insufficiency. If no potential alternative cause of AKI can be identified then forgo renal biopsy and proceed with immunosuppressive therapy.

• Consider nephrology consult for severe cases
Nervous System Toxicities

• **Myasthenia gravis**
  – Fatigable or fluctuating muscle weakness, generally more proximal than distal.
  – Frequently has ocular and/or bulbar involvement (ptosis, extraocular movement abnormalities leading to double vision, facial muscle weakness, dysphagia, dysarthria)
  – May occur with myositis and/or myocarditis
  – Respiratory symptoms may require evaluation tor/o pneumonitis, myocarditis

• **Guillain–Barré syndrome**
  – Progressive, most often symmetrical muscle weakness w/absent or reduced DTRs.
  – Often starts with sensory symptoms/neuropathic pain localized to lower back and thighs. (typically ascending weakness, but not always) may involve facial, respiratory, and bulbar and oculomotor nerves.
  – May have dysregulation of autonomic nerves.
Nervous System Toxicities

• **Peripheral Neuropathy**
  – Presents as asymmetric or symmetric sensory, motor, or sensory motor deficits
  – Hypo- or areflexia or sensory ataxia
  – Numbness and paresthesia may be painful or painless
  – Focal mononeuropathies such as facial neuropathies/Bell palsy

• **Autonomic Neuropathy**
  – Nerves that control involuntary bodily functions are damaged.
  – May affect BP, temp control, digestion, bladder function, and sexual function
  – There has been a case of severe enteric neuropathy with ICPI. It can present with GI difficulties such as new severe constipation, nausea, urinary problems, sexual dysfunction, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension
Nervous System Toxicities

• **Aseptic Meningitis**
  – May present with HA, photophobia, and neck stiffness
  – Often afebrile, but could be accompanied by fever
  – Mental status is typically normal which distinguishes this from encephalitis
  – Possible N/V

• **Encephalitis**
  – Confusion, altered behavior, HA, seizures, short-term memory loss, focal weakness, speech abnormality

• **Transverse myelitis**
  – Bilateral acute or subacute weakness or sensory changes, often with increased DTRs
# Nervous System Toxicities

## Myasthenia Gravis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>G2</td>
<td>Some symptoms interfere w/ADL</td>
</tr>
<tr>
<td>G3/4</td>
<td>Limiting self-care and aide warranted, weakness limits ability to walk, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressing symptoms, or MGFA severity class 3-4 moderate to severe generalized weakness to myasthenic crisis</td>
</tr>
</tbody>
</table>

## Treatment recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>N/A</td>
</tr>
<tr>
<td>G2</td>
<td>Hold ICPI, Consult Neurology, may resume ICPI only if symptoms resolve. Pyridostigmine and corticosteroid dosing described in ASCO guidelines.</td>
</tr>
<tr>
<td>G3/4</td>
<td>Permanently d/c ICPI, Admit to hospital, may need ICU-level monitoring. Corticosteroids and IVIG dosing described in ASCO guidelines. May benefit from plasmapheresis.</td>
</tr>
</tbody>
</table>
Nervous System Toxicities

Guillain-Barré syndrome

G1: mild, none

G2: Moderate, some interference w/ADL, symptoms concerning to patient

G3/4: Severe, limiting self-care and aid warranted, weakness limits ability to walk, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressing symptoms

Treatment Recommendations

G1: N/A

G2-4: Discontinue ICPI, Admit to hospital w/ICU –level monitoring available. Frequent neurochecks and pulmonary function monitoring, non-opioid management of neuropathic pain. IVIG and corticosteroid dosing available in ASCO guidelines, consider plasmapheresis.
Peripheral Neuropathy

G1: Mild, no interference w/function and symptoms not concerning to pt. Note: any cranial nerve problem should be managed as moderate

G2: moderate, some interference w/ADL, no gait or weakness but symptoms concerning to pt

G3/4: Severe, limiting self-care, assistive devices warranted, weakness limiting walking or resp. problems (foot drop, leg weakness) Severe may be Guillain-Barré syndrome and should be managed as such.

Treatment Recommendations

G1: Low threshold to hold ICPi and monitor symptoms weekly if planning to continue ICPi

G2: Hold ICPi and resume once return to GI, consider corticosteroids, neurontin, pregabalin, or duloxetine for pain

G3/4: Permanently D/C ICPi, Admit patient, Neurologic consult, Initiate IV methylprednisolone as per Guillain-Barré syndrome management
Nervous System Toxicities

**Autonomic Neuropathy**

G1: Mild, no interference w/function and symptoms not concerning to pt.

G2: Moderate, some interference w/ADL, symptoms concerning to patient

G3/4: Severe, limiting self-care and aids warranted

**Treatment Recommendations**

G1: Low threshold to hold ICPi and monitor symptoms weekly if planning to continue ICPi

G2: Hold ICPi and resume once return to GI, consider corticosteroids,

G3/4: Permanently D/C ICPi, Admit patient, Neurologic consult, Initiate IV methylprednisolone as per ASCO guidelines
Nervous System Toxicities

Aseptic Meningitis

G1: Mild, no interference w/function and symptoms, not concerning to pt. Note: Any cranial nerve problem should be managed as moderate

G2: Moderate, some interference w/ADL, symptoms concerning to pt (ie, pain but no weakness or gait limitation)

G3/4: Severe, limiting self-care and aids warranted

Treatment Recommendations

• Hold ICPi
  – Admit to hospital for testing
  – Consult Neurology
  – Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results return.
  – Discuss resuming tx w/pt only after taking into account risk vs. benefits.
Nervous System Toxicities

Encephalitis

G1: Mild, no interference w/function and symptoms not concerning to pt.

G2: Moderate, some interference w/ADL, symptoms concerning to patient

G3/4: Severe, limiting self-care and aids warranted

Treatment Recommendations

• Hold ICPi
  – Admit to hospital for testing
  – Consult Neurology
  – Lumbar puncture
  – Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results return.
  – MRI brain, EEG is seizures present
  – Discuss resuming tx w/pt only after taking into account risk vs. benefits.
Nervous System Toxicities

Transverse Myelitis
G1: Mild, no interference w/function and symptoms not concerning to pt.

G2: Moderate, some interference w/ADL, symptoms concerning to patient

G3/4: Severe, limiting self-care and aids warranted

Treatment Recommendations
• Permanently discontinue ICPi
  – Admit to hospital for testing
  – Consult Neurology
  – Obtain MRI brain and spine w/thin axial cuts through region of suspected abnormality.
  – Lumbar puncture
  – Strongly consider IVIG and methylprednisolone dosing per ASCO guidelines
Nervous System Toxicities

Managing neurologic toxicities

- ICPI related neurologic toxicities were initially reported with an incidence of 1%, however more recent analysis suggests it might be more common. Fortunately, grade 3 and 4 adverse events are estimated to be <1% across all ICPIs (4,5)

- Most neurologic events are mild; HA and peripheral sensory neuropathy (4)

- **What should we do if patient reports new HA or numbness tingling, weakness?**
  - Obtain labs to exclude metabolic etiology (CMP, Mg, B12, folate, TSH)
  - Rule out CNS progression of cancer (may need MRI brain or spine)
  - Ask about hxo seizures or seizure-like activity
  - Monitor for infectious causes
Hematology Toxicities

• **Autoimmune Hemolytic Anemia**
  – A condition in which RBCs are destroyed and removed from the bloodstream before their normal lifespan is over.
  – Symptoms include: weakness, paleness, jaundice, dark-colored urine, fever, inability to do physical activity

• **Acquired TTP**
  – A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenia purpura, fever, renal abnormalities, and neurologic abnormalities, such as seizures, hemiplegia, and visual disturbances.

• **Hemolytic Uremic Syndrome**
  – A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia
Hematology Toxicities

• **Aplastic Anemia**
  – Condition in which the body stops making enough new blood cells

• **Lymphopenia**
  – An abnormally low level of lymphocytes in peripheral blood (PB); counts of < 1,500/mm³

• **Immune Thrombocytopenia**
  – An autoimmune disorder characterized by immunologic destruction of otherwise normal platelets (PLT).

• **Acquired Hemophilia**
  – Disorder characterized by the development of autoantibodies (inhibitors) directed against plasma coagulation factors
## Hematologic Toxicities

<table>
<thead>
<tr>
<th>Autoimmune Hemolytic Anemia</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: Hgb &lt; LLN to 10 g/dL</td>
<td>G1: continue ICPI with close clinical follow-up and labs</td>
</tr>
<tr>
<td>G2: Hgb &lt; 10-8 g/dL</td>
<td>G2: Hold ICPI and strongly consider permanent d/c. Start corticosteroids</td>
</tr>
<tr>
<td>G3: Hgb &lt; 8 g/dL</td>
<td>G3: Permanently d/c ICPI. Consult hematology, consider admission and RBC transfusion, start folic acid 1mg daily</td>
</tr>
<tr>
<td>G4: Life threatening consequences, urgent intervention indicated</td>
<td>G4: Permanently d/c ICPI, Consult hematology, admit pt, start IV corticosteroids, RBC transfusion</td>
</tr>
</tbody>
</table>
Hematologic Toxicities

**Acquired TTP**

G1: Evidence of RBC destruction (schistocytosis) w/o anemia, renal insufficiency, or thrombocytopenia

G2: Evidence of RBC destruction (schistocytosis) w/o clinical consequence with G2 anemia, renal insufficiency, or thrombocytopenia

G3: Lab findings w/clinical consequences (G3 thrombocytopenia, anemia, renal insufficiency >2)

G4: Life threatening consequences (eg, CNS hemorrhage or thrombosis/embolism or renal failure)

**Treatment Recommendations**


G4: Hold ICPi and consult hematology. Hematologist may initiate PEX and methylprednisolone, and may consider rituximab
Hematologic Toxicities

**Hemolytic Uremic Syndrome**

G1/2: Evidence of RBC destruction (schistocytosis) w/o clinical consequences of anemia, thrombocytopenia grade 2.

G3: lab findings w/clinical consequences (eg, renal insufficiency, petechiae)

G4: Life threatening consequences (eg, CNS thrombosis/embolism or renal failure)

**Treatment Recommendations**

G1/2: Continue ICPi w/close clinical follow-up and labs, supportive care

G3/4: Permanently d/c ICPi. Begin therapy with eculizumab 900mg wkly x 4 doses, 1200mg week 5, then 1200mg every 2wks and RBC transfusion per guidelines
Hematologic Toxicities

Aplastic Anemia

G1: Nonsevere, >0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with marrow cellularity < 25%, peripheral platelet count > 20,000; reticulocyte count >20,000

G2: Severe, hypocellular marrow < 25% and two of the following: ANC < 500, Peripheral platelet count < 20,000; and reticulocyte < 20,000

G3/4: Very Severe, ANC < 200, PLT < 20,000; reticulocyte < 20,000; plus hypocellular marrow < 25%

Treatment Recommendations

G1: Consider holding ICPi and provide growth factor support, close clinical follow-up and labs. Supportive transfusions PRN.

G2: same as G1, with hematology consult and daily lab checks. Hematology will consider adding ATG + cyclosporine, HLA typing and BM evaluation for transplant if pt is candidate, ALL blood products should be irradiated and filtered,

G3/4: same at G2, but hold ICPi and consult hematolgy. For refractory cases hematologist may consider adding eltrombopag plus supportive care
Lymphopenia

G1/2: 500-1,000 peripheral blood (PB) lymphocyte count

G3: 250-499 PB lymphocyte count

G4: < 250 PB lymphocyte count

Treatment Recommendations

G1/2: Cont. ICPI

G3: Continue ICPI with weekly CBC, initiate CMV screening

G4: Consider holding ICPI, initiate *mycobacterium avium complex prophylaxis* and *Pneumocystis jirovecii prophylaxis*, CMV screening, HIV/hepatitis screening-if not already done, Consider EBV testing if evidence of lymphadenopathy/hepatitis, fevers, hemolysis consistent w/lymphoproliferative disease
Hematologic Toxicities

Immune thrombocytopenia
G1: PLT count < 100/µL
G2: PLT count < 75/µL
G3: PLT count < 50/µL
G4: PLT count < 25/µL

Treatment Recommendations
G1: Continue ICPI with close follow exam and lab

G2: Consider holding ICPI until AE is G1, start corticosteroids and consider IVG

G3: Hold ICPI and start corticosteroids and consider IVIG. Monitor for improvement, if not resolved interrupt tx.

G4: Hold ICPI and consult hematology. Start IVIG and corticosteroids, if unsuccessful may consider rituximab, thrombopoietin, or more-potent immunosuppression. Consult ASCO hematology guideline for details
## Hematologic Toxicities

### Acquired Hemophilia

**G1: Mild**, 5%-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood

**G2: Moderate**, 1%-5% of normal factor activity in blood, 0.01-0.05 IU/mL whole blood

**G3/4: Severe**, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood

### Treatment Recommendations

**G1:** Hold ICPi and resume only after reviewing risk vs. benefits with pt. Administer corticosteroids, transfusion support, and hematology consult

**G2:** same as G1, Hematologist may start factor replacement, prednisone +/- Rituximab v. cyclophosphamide.

**G3/4:** Permanently d/c ICPi. Admit pt, consult hematology for management
Hematologic Toxicities

Managing Hematologic Toxicities:

• Incidence rates are low.
  – Estimated rates of grade 1-4 anemia is approximately 11%, and ~5.4% for grade 3 and 4\(^{(6,7)}\)
  – Estimated rates of thrombocytopenia is ~8% for all grades and ~4.3% for grade 3 and 4. \(^{(6)}\)

• Educate patients regarding:
  – Risks of therapy
  – Importance of routine follow-up visits and lab draws
  – Importance of reporting new symptoms

• Consider other etiology, such as new drugs or insect or spider bites, declining nutrition, or infections
Cardiovascular Toxicities

Divided into two categories:

1. Myocarditis, Pericarditis, Arrhythmias, impaired ventricular function with heart failure and vasculitis
2. Venous Thromboembolism

- Median onset of diagnosis was 10wks, but CV adverse events could appear as early as week 2 or as late as week 32

- Incidence of CV irAEs < 0.1% based on pharmaceutical safety data

- Combination (nivolumab and ipilimumab) had greater rates of cardiovascular complications than nivolumab alone (0.28% vs. 0.06%)
Cardiovascular Toxicities

Myocarditis, pericarditis, arrhythmias, impaired ventricular function w/HF and vasculitis

G1: Abnormal cardiac biomarker testing, including abnormal ECG

G2: Abnormal screening tests w/mild symptoms

G3: Moderately abnormal testing or symptoms with mild activity

G4: Moderate to severe decompensation, IV meds or intervention required, life-threatening condition

Treatment Recommendations

• All grades warrant w/u and intervention given potential for cardiac compromise

• Consider the following:
  – Hold ICPI and permanently d/c if greater than G1 events occur.
  – high-dose corticosteroids
  – Admit and consult cardiology
Cardiovascular Toxicities

Venous Thromboembolism

G1: Venous thrombosis (eg, superficial thrombosis)

G2: Venous thrombosis (eg, uncomplicated DVT), medical intervention indicated

G3: Thrombosis (eg, uncomplicated PE [venous], nonembolic cardiac mural [arterial] thrombus, medical intervention indicated

G4: Life-threatening (eg, PE, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated

Treatment Recommendations

G1: continue ICPI, warm compress, clinic surveillance

G2/3: continue ICPI, manage according to CHEST, ACC, and/or AHA guidelines, consider cardiology consult, start LMWH

G4: Permanently d/c ICPI, admit patient and consult cardiology, further clinical management indicated based on symptoms
Managing CV Toxicities

• Identify, document, and notify provider of concerning symptoms:
  – Palpitations
  – Arrhythmia
  – Chest pain
  – Shortness of breath
  – Peripheral edema
  – Fatigue
  – Pleural effusion
  – Increased vein or skin sensitivity
  – Cyanosis accompanied by unexplained fever can be concerning for DVT
  – Pleuritic pain, dyspnea, cough, wheezing, or hemoptysis are concerning for PE
Ocular Toxicities

- **Uveitis/iritis**
  - Inflammation of the middle layer of the eye

- **Episcleritis**
  - Inflammatory condition affecting the episcleral tissue between the conjunctiva and sclera in the absence of infection

- **Belpharitis**
  - Inflammation of the eyelid that affects the eyelashes or tear production
Ocular Toxicities

**Uveitis/Iritis**

**G1:** Asymptomatic

**G2:** Anterior uveitis, medical intervention required

**G3:** Posterior or panuveitis

**G4:** 20/200 or worse

**Treatment Recommendations**

**G1:** Refer to ophthalmology within 1wk, prescribe artificial tears

**G2:** Urgent ophthalmology referral. Hold ICPi until ophthalmology eval.

**G3:** Urgent ophthalmology referral. Permanently discontinue ICPi

**G4:** Emergent ophthalmology referral. Permanently d/c ICPi, consider infliximab or TNF-alpha blockers for severe or cases refractory to standard tx.
# Ocular Toxicities

<table>
<thead>
<tr>
<th>Episcleritis</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1: Asymptomatic</td>
<td>G1: refer to ophthalmology within 1wk, prescribe artificial tears</td>
</tr>
<tr>
<td>G2: Vision 20/40 or better</td>
<td>G2: Urgent ophthalmology referral. Hold ICPi until ophthalmology eval.</td>
</tr>
<tr>
<td>G3: Symptomatic and vision worse than 20/40</td>
<td>G3: Urgent ophthalmology referral. Permanently discontinue ICPi</td>
</tr>
<tr>
<td>G4: 20/200 or worse</td>
<td>G4: Emergent ophthalmology referral. Permanently d/c ICPi, consider infliximab or TNF-alpha blockers for severe or cases refractory to standard tx.</td>
</tr>
</tbody>
</table>
Ocular Toxicities

Blepharitis

– No formal grading

– Treatment recommendations include warm compresses and lubrication drops, continue ICPI unless symptoms persist despite supportive care or become serious
Ocular Toxicities

Management of Ocular Toxicities:

- Identify, document, and notify provider of high risk symptoms:
  - New blurry vision
  - Change in color vision
  - Photophobia
  - Distortion
  - Scotomas
  - Visual field changes
  - Double vision
  - Tenderness
  - Pain with eye movement
  - Eyelid swelling
  - Proptosis
Citations


9. online.epocrates.com/drugs