CTCAE Grading Scale in Managing Immune-Mediated Adverse Events

Wendy Crabbe, MSN, APRN-BC, AOCN

UT Health San Antonio

Financial Disclosure

- **I have nothing to disclose.**

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Common Terminology Criteria for Adverse Events

- **Grade: Refer to the severity of the adverse event (AE).**
- **Grade 1: Mild, asymptomatic**
- **Management: Observation, intervention not needed.**
- **Grade 2: Moderate**
- **Management: Local or noninvasive intervention indicated**
  - **Will likely need low dose oral steroids and may be able to continue treatment**
- **Grade 3: Several or medically significant but not immediately life-threatening**
- **Management: Stop immunotherapy, hospitalization indicated, high dose steroids**
- **Grade 4: Life-threatening consequences**
- **Management: Urgent intervention, will permanently stop immunotherapy**
- **Grade 5: Death related to AE**

NCI CTCAE v4.0

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Immunotherapy Agents

CTLA-4
PD-1
PDL-1

http://www.cancernetwork.com/sites/default/files/ce_import/0198377.png

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T Cell Response: Accelerate or Break

- **T cell inhibitory signals: CTLA-4, PD-1 & LAG-3**
- **inhibitory signals "brake" the immune system and can dampen or inhibit T-cell responses. In general, without these inhibitory mechanisms, rampant autoimmune disease would emerge. Checkpoint inhibitors such as those against CTLA-4 and PD-1, however, are an advantageous example of circumventing these inhibitory signaling mechanisms.**

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CheckMate 067: Treatment-Related AE's Associated with Nivo and Ipi

Select Grade ¾ Treatment AE's, %	Nivo + Ipi (n = 313)	Nivo (n = 313)	Ipi (n = 311)
Any select AE	40	8	19
Skin	6	2	3
• Pruritus	2	0	<1
• Rash	3	<1	2
• Maculopapular rash	2	<1	<1
Gastrointestinal	15	2	12
• Diarrhea	9	2	6
• Colitis	8	<1	9
Hepatic (AST, ALT)	19	3	2
Endocrine	5	<1	2
Pulmonary (pneumonitis)	1	<1	<1

Larkin J et al. (2015). N Engl J Med, 373, 23-34.

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Immune-Related AE's with Immunotherapy

- **Skin: Dermatitis exfoliative, Erythema multiforme, Steven's-Johnson syndrome, Toxic epidermal necrolysis, Vitiligo, Alopecia**
- **Eyes: Uveitis, Iritis**
- **Endocrine: Hypothyroidism, Hyperthyroidism, Adrenal insuffiency, Hypophysitis**
- **Pulmonary: Pneumonitis, Interstitial lung disease, Acute interstitial pneumonnitis**
- **Gastrointestinal: Colitis, Enterocolitis, Necrotizing colitis, GI perforation**
- **Hepatic: Hepatitis autoimmune**
- **Renal: Nephritis autoimmune, Renal failure**
- **Neurologic: Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain-Barre, Myasthenia gravis-like symptoms**

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Immune-Mediated Colitis: Symptom Surveillance

- **Monitor for signs and symptoms**
- **Median time to onset from first dose about 10 weeks**
- **Ask patients to report any bowel habit changes promptly**
- **Rule out other cause of diarrhea**
- **Clinical Pearl: Colitis can occur without diarrhea. Important to take all GI-related symptoms seriously and evaluate.**

- **Nivoumab package insert 2014**

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Immune-Mediated Colitis: Symptom Management

Grade	Management
Mild grade 1: < or = 4 stools/day or above baseline	▪ Manage symptomatically (bland diet, PPI, antidiarrheal) ▪ Consider delaying treatment until symptoms improve
Moderate grade 2: Increase of 4-6 stools/day above baseline (persistent)	▪ Colonoscopy and steroids ▪ Low dose steroids may be sufficient ▪ Hold treatment
Severe grade 3: > 7 stools/day above baseline	▪ Initiate high dose steroids ▪ Discontinue treatment

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Immune-Mediated Hepatitis: Symptom Surveillance

- Monitor LFT's at baseline and prior to each dose of treatment
- Pts with abnormal LFT's should be monitored more frequently
- Hepatotoxicity appears worse when ipilumumab is combined with other drugs

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Immune-Mediate Heptatis: Symptom Management

- Rule out other causes of LFT abnormalities
- Increase LFT monitoring
- Corticosteroid treatment with grade 2 or higher LFT's
  - Prolonged taper may be required
- Mycophenolate may be useful (immunosuppressant)
- LFT abnormalities appear to be dose dependent

LFT	Grade 1	Grade 2	Grade 3	Grade 4
Bilirubin	> ULN to 1.5	> 1.5 to 3.0x	>3.0 to 10.0x	> 10.0 x ULN
ALT/AST	>ULN to 2.5x	>2.5 to 5.0x	> 5.0 to 20.0x	> 20.0x ULN
Albumin	<LLN to 3 g	< 3 to 2 g/dL	< 2 g/dL	--

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Immune-Mediated Dermatitis

- Reported in up to 40% of pts with anti-CTLA-4 and anti-PD-1 agents
- Occasionally severe rashes
- Onset within a few weeks of starting or several weeks/months into therapy
- Severity driven by symptoms
- Rule out other etiologies
- Generally not infusion related

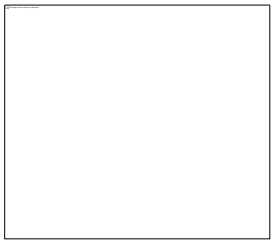

Image courtesy of Matthew M. Burke, MBA, RN, MSN, APRN-BC and clinicaloptions.com

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Immune-Mediated Dermatitis: Symptom Management

Severity	Management
Mild/moderate (rash/pruritus) Grade 1	▪ Topical nonsteroidal cream, antihistamine, oatmeal baths ▪ Skin care: Moisturize, sunscreen, avoid sun
Persistent (> 1 week) or interferes with ADL's Grade 2	▪ Moderate-potency steroids creams or ▪ Moderate-dose oral steroids
Severe Grade 3 or >	▪ D/C treatment ▪ High-dose steroids ▪ Avoid rapid steroid taper

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Immune-Mediated Endocrinopathies

- Can be serious or fatal if not managed correctly
- Hypophysitis, thyroid disease and primary adrenal insufficiency have all been reported as well as insulin-dependent diabetes
- Check TSH, free T3 & T4 at baseline and prior to each dose
- Monitor glucose
- Time to onset may be much later; median 11 weeks
- Endocrinopathies may be permanent
- Grade 1: Asymptomatic or mild symptoms, observation, no intervention
- Grade 2: Moderate symptoms, may need thyroid replacement
- Grade 3: Severe or medically significant, may need hospitalization, insulin or hormone replacement
- Grade 4: Life-threatening consequences, urgent intervention

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Immune-Mediated Endocrinopathies: Symptom Management

- Hormone replacement, corticosteroids
- Possibly delay treatment (usually not for thyroid)
- Co-syntropin stimulation test prior to starting steroidsor send to endocrinologist
- Many endocrinopathies can be controlled if hormone levels are stable with < 7.5 mg of prednisone, treatment can be continued.
- Pre-existing thyroid disorder does not predispose pts for developing additional endocrinopathies as far as we know.
- Grade 3 & 4 AE's discontinue therapy

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Immune-Mediated Pneumonitis

- Fairly uncommon, but potentially serious (3% of pts)
  - Deaths have been reported
  - Need to carefully monitor pts
- Pts at increased risk for pneumonitis
  - NSCLC in the setting of chronic lung inflammation
  - Heavily pretreated pts
  - Combination of CTLA-4 and PD-1 agents
  - Prior radiation to lung
  - History of COPD
- Grade 1: Asymptomatic, may show up on xray or CT scan, intervention not indicated
- Grade 2: Symptomatic, medical intervention indicated
- Grade 3: Severe symptoms; limiting self care ADL, oxygen needed

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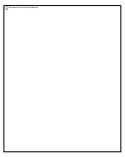
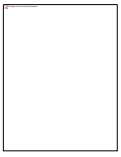
Immune-Related Pneumonitis: Signs and Symptoms

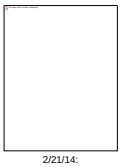
- **Shortness of breath, Dry cough**
- **New or increasing oxygen needs, or Decreasing O2 sat on room air**
- **May be detected just on imaging**



11/15/2013:
Prepneumonitis



1/21/14:
Pneumonitis



2/21/14:
Improved with steroids; taper completed 3/7/14

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Immune-Related Pneumonitis: Symptom Management

- **Grade 1: Close observation and is seen on outside films, get those films and compare to previous and obtain chest xray of CT chest**
- **Grade 2: Low dose steroids, may delay treatment**
- **Grade 3: May need hospitalization and high dose parenteral steroids, discontinue treatment**

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Other Immune-Related AE's

- **Immune-related AE's include**
  - **Ocular manifestations: conjunctivitis, uveitis, and scleritis**
  - **Neurologic complications: Guillain-Barre syndrome, inflammatory myopathy, aseptic meningitis, temporal arteritis, and posterior reversible encephalopathy syndrome**
  - **Sarcoidosis**
  - **Systemic vasculitis, including renal disease**
  - **Autoimmune pancreatitis**
  - **Hematologic: including red cell aplasia, pancytopenia, autoimmune neutropenia, and acquired hemophilia A**
    - **Follow National Comprehensive Cancer Network (NCCN) guidelines for the prevention and treatment of cancer-related infections, which recommend considering Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole, atovaquone, or pentamidine for patients treated with 20 mg of prednisone equivalent daily for at least four weeks. The role of prophylactic antiviral or antifungal medication in these patients requires further study**

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Keys to Optimal Pt Management

- **Education of healthcare team (including ER staff), pts, and caregivers**
- **Rapid and timely intervention**
  - **Corticosteroids for some intolerable grade 2 immune-related AE's and any grade ¾ immune-related AE's**
  - **Grade 2 (moderate) immune-mediated toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity is grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day or equivalent) should be started if symptoms do not resolve within a week**
  - **SLOW taper of glucocorticoids**
  - **Grade 3 or 4 (severe or life-threatening) immune-mediated toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) should be given. When symptoms subside to grade 1 or less, steroids can be gradually tapered over at least one month. If IV steroids do not work after 3 days, administer infliximab (5 mg/kg) rather than continue with a prolonged course of high-dose IV corticosteroids**

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Special Populations

- **Pregnancy and lactation**
  - **Antibodies are known to cross placental barrier**
  - **Pregnancy category C: immune checkpoint inhibitors not recommended**
  - **Advise pts to use highly effective contraception while on therapy and for 6 months after**
  - **Safety of breast-feeding has not been studies**

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Infusion Reactions

- **Infusion reactions with checkpoint inhibitors are very rare**
  - **Reported in up to 10% of pts (usually less)**
  - **Usually mild: Stop the infusion and restart at a lower rate**
  - **No steroids: pre-medications are often not necessary**
  - **As with any infusion, monitor carefully and have emergency medications available**

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Communicating with Patients

- **How do we explain this complicated process to pts and their caregivers?**
  - **Gas and brake pedal analogy**
  - **Pressing the gas pedal = restoring T-cell activity and starting immune response against tumor**
  - **Brake pedal = immune checkpoint**
  - **Lifting the foot off the brake = enabling T cell–mediated immune response to continue**
  - **"Removing muzzle off the dog" analogy**

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Pt Education on Immunotherapy

- **Unique MOA and time to response**
- **Toxicity profiles differ from standard chemotherapy**
  - **Early recognition of immune-related AE's essential**
  - **Immune-related AE's infrequent, treatable, and respond well to steroids**
  - **Know Whom and When to call for AE's**
  - **These new therapies are helping many people**
- **Reinforce teaching points at every point of contact (phone or visit)**
  - **Notify healthcare team if the pt is admitted to another hospital**

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Pseudo-progression vs Disease Progression

Patient Factors	Disease Progression	Pseudo-progression
Performance status	Deterioration of PS	Stable or better
Systemic symptoms	Worsen	+ or –
Symptoms of tumor enlargement	Present	+ or –
Tumor burden	Increase	Initial increase then decrease
Baseline	Appear and increase in size	Appear then remain stable and/or respond
New lesions	Evidence of tumor growth	Evidence of immune-cell infiltration
Biopsy may reveal		

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Case Study #1: J.G.

74 y.o. male with tibial mets of melanoma: 7 X 1 X 3.5 cm lesion with bone destruction

- On combination therapy with nivolumab and ipilumumab
- After cycle 2, he is dx with pneumonitis and successfully treated with HD prednisone taper
- Now off steroids with no resp. issues
- A few days before schedule visit for cycle 3, he calls c/o watery stoos, 1 per hr, blood in stool, abd. Discomfort and severe weakness
- He lives 200 miles from clinic
- Due to his very severe symptoms, he was advised to go to the ED
- ED staff were immediately made aware that this pt is receiving immunotherapy and likely has immune-related colitis and may be at risk for perforation
- CT abdomen showed moderate colitis and diverticulosis without diverticulitis; stool + for occult blood
- Colonoscopy showed changes consistent with IBD; bx of colonic mucosa reveals moderate idiopathic colitis
- J.G. is referred to GI specialist
- Stool evaluated for bacteria and viral gastroenteritis, parasitic and C.difficile infection, all negative
- Pt treated with oral steroids of prednisone 1 mg/kg with quick resolution of symptoms
- Prednisone tapered after symptoms resolved

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- J.G. calls again that his stools are again watery, approx. 15 times in half a day. What do you do?
- Symptoms reported to oncologist
- J.G. is admitted and given high-dose methyprednisone 60 mg BID and 1 dose of infliximab at 5 mg/kg, followed by oral steroids
- He was discharged when diarrhea/colitis resolved to grade 1 with 2 BM's/day and a prolonged prednisone taper over > 4 weeks

Colitis is most likely to occur between the second and third doses of ipilumumab

If the pt has a grade 2 rash, proceed with treatment.

Grade 3 rash would exhibit vesicles, bullous lesions and desquamation and treatment would be held, the pt given high dose steroids with taper. If the rash resolved to grade 1 they can usually resume treatment.

- Rash can continue weeks to months after completion of ipilimumab and, at times, can re-flare. If on steroids, tapering slowly helps. Continue with supportive care.

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Case Study #2: G.B.

59 y.o. male, nonsmoker with hx of NSCLC, adenocarcinoma

- Relapsed after cisplatin/pemetrexed and single agent docetaxel
- Histology: adenocarcinoma with EGFR, ALK, and KRAS wild type
- ECOG PS: 1, continues to work
- PD-L1 assay is positive for PD-L1 expression
- Initiated pembrolizumab and tolerated well except for fatigue
- 12 week restaging scans: mixed response with some disease improvement and some areas of PD and possible new small pulmonary nodules
- G.B continued on pembolizumab
- At 5 months, he developed mild DOE, most noticeably while climbing stairs with dry cough triggered by laughing and exercise
- Chest xray: Bilateral patchy airspace disease
- What are you worried about
- What are the next steps?
- Pembrolizumab is held and G.B. is sent to pulmonologist
- Not able to perform PFT's due to coughing
- Started on prednisone 100 mg/day with slow taper
- At 12 weeks, tapered off steroids to 2.5 mg/day
- DLCO performed: 60% of predicted
- PET reveals moderate improvement in inflammatory airway disease
- What do you do now?

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- Another pt receiving immunotherapy is here for their 4th cycle of ipilumumab and is ambulatory but complaining of fatigue, stating she is "very, very tired," with a headache and mild nausea but able to eat and drink; in bed all day yesterday and difficulty performing usual activities
- Do not give the fourth dose and report signs and symptoms to the oncologist. The etiology of the symptoms is not known, but moderate or profound fatigue with immunotherapy to be is not expected to be normal. It is known that toxicities can happen anytime, even though this patient was seen a few days earlier. The severe headache is also not normal. In metastatic melanoma, patients are at high risk for brain metastases. Patients should be evaluated for possible causes such as infection, sepsis, brain metastases, and endocrine toxicity.
- It is important to note that if patients have severe symptoms of hypotension, electrolyte imbalance (low sodium, high potassium), and dehydration, they may possibly be in adrenal crisis and should be hospitalized and treated with methylprednisolone 1-2 mg/kg IV followed by oral prednisone 1/2 mg/kg/day.

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