Management of immunotherapy-related adverse events

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Mortality of Immunotherapy

- HDIL2
  - Infection
  - Cardiac arrhythmias
- Ipilimumab
  - Colitis, perforation
- PD1 antibodies
  - Pnemonitis
Morbidity of Immunotherapy

- Fatigue
- Rash/Pruitis
- Pituitary dysfunction
- Hepatotoxicity

- Patients are living longer and some patients may be cured
  - Long term adverse events may not yet be known

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Following the patient third dose of ipilimumab, he calls your clinic with 10 nonbloody loose stools in the last 24 hours despite lomotil.

What is the best next step in management?

a. Call in a 1 week steroid taper, such as a medrol dose pack
b. Hold further ipilimumab, the diarrhea will resolve on its own without further intervention as long as no additional treatment is given
c. Hold further ipilimumab, treat with steroids and taper over 4-6 weeks if improved. Restart ipilimumab once diarrhea is resolved
d. Discontinue ipilimumab. Start 1mg/kg of steroids and consider hospital admission.
The interval from last dose of ipilimumab to the onset of symptoms of enterocolitis

![Graph showing the interval from last dose of ipilimumab to the onset of symptoms of enterocolitis.](image)


The number of doses of ipilimumab given before the onset of symptoms of enterocolitis

![Graph showing the number of doses of ipilimumab given before the onset of symptoms of enterocolitis.](image)

Case Presentation

- Your patient is started on 1mg/kg daily of steroids but continues to have abdominal pain and diarrhea after 2 days of steroids and bowel rest
- What do you do next?
  - Up the steroids to BID
  - Infliximab 5mg/kg or 10mg/kg
  - Nothing, needs more time to recover
- Same patient does well on oral steroids, but begins to have recurrent diarrhea when steroids are tapered
Gl irAEs: Overview

• Diarrhea is a frequent irAE
  – Most cases are mild or moderate
  – Biopsy demonstrates inflammatory colitis and T-cell infiltrates
  – Most cases respond to either symptomatic treatment or steroids (needs 4-6 week taper)
  – Can rarely lead to GI perforation (<1%) requiring surgery

• When do you retreat?

GI toxicity induced by Ipilimumab

• Inflammation can be anywhere in GI tract (eg, mucositis and gastritis, enteritis but most commonly colitis)
• Diarrhea: requires attention
  – New and watery
  – Increased frequency >50% baseline
  – Duration
  – Bloody
• Grade 1 and 2
  – Treat symptomatically
  – Rule out other causes
  – No need for systemic steroids; can try budesonide
  – Follow closely for resolution
Dermatologic irAEs: Overview

• Common irAEs
  – Mostly low grade
  – Rash, pruritus, and vitiligo
  – Most resolve with symptomatic therapy: moisturizers, benadryl, hydroxyzine
  – Corticosteroids for more severe cases (can try short course, but flare possible)
  – T-cell infiltrate seen on biopsy specimens of the skin


Fig 1. Toxic events during CP-675,206 administration
Endocrinopathy irAEs: Overview

- Occurs with both ipilimumab and PD1 antibodies, higher rate with PD1 antibodies
- Symptoms: fatigue, nausea, amenorrhea, impotence, hypotension, hyponatremia, hypoglycemia, and eosinophilia
  - If strong suspicion for adrenal crisis (dehydration and hypotension), start stress-dose steroids
  - If suspect hypophysitis, head MRI with pituitary cuts; visual field testing
  - Hormone replacement; consider trial of high-dose steroids
- Can you retreat?

Pnemonitis irAEs: Overview

- Occurs with both ipilimumab (1%) and PD1 antibodies, higher rate with PD1 antibodies (3% of melanoma patients)
- Patients present SOB, cough, hypoxia
- Grade 1 may demonstrate on scans without symptoms
- For symptomatic patients
  - Rule out other causes
  - Consider bronchoscopy
  - Steroids (1mg/kg) with prolonged taper for symptomatic cases

Beck. J Clin Oncol. 2006;24:2283
Nivolumab Induced Pneumonitis

Alternative irAEs

- **Hepatotoxicity**
  - Monitor LFTs q3 weeks
  - If greater than 5x upper limit of normal, increasing bili, treatment with steroids is indicated
  - Liver failure has been seen
- **Neurotoxicity**
  - Any neurologic complaints should be taken seriously – Guillain-Barre, Myasthenia Gravis have been reported.
  - Neuropathy most common neurologic complaint
Management of irAEs

- Patient education for early recognition of irAEs
- Aggressive work-up and management for moderate/severe events
- Nonspecific complaints might reflect endocrine (eg, pituitary) toxicity
- Corticosteroids are effective
- Consider Infliximab in refractory cases
- Algorithms established for the management of irAEs
- Combination therapies are showing higher toxicity rates, but similar types of toxicities are seen