Gastrointestinal Toxicities of Checkpoint Blockade

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Disclosures

• Novartis Pharmaceuticals
• Tocagen

• I will be talking about non FDA approved indications for infliximab (and other anti-TNF medications), and vedolizumab
Current metastatic melanoma 3-yr survival is now 40% (compared to <5% before 2011)

Hodi et al. NEJM. 2011; Robert et al. NEJM. 2015.
Immune therapy for cancer

• Developing tumors are recognized by adaptive immunity (e.g. mutated tumor proteins)

• Regulatory pathways (PD1/PDL1, CTLA-4) inhibit nascent antitumor responses

• Blockade of regulatory “checkpoints” has proven highly effective at activating adaptive responses against diverse malignancies

• Current treatments are only effective in a minority of patients with cancer

Sullivan and Flaherty. Clin Cancer Res. 2015
Expanding the reach of immunotherapy

- Diagnostics to monitor/predict response
- Combination and tumor directed immune therapies
- Modulation of innate immunity
- Prediction and management of immune-related adverse events (irAEs)

Expanding the reach of immunotherapy

- Diagnostics to monitor/predict response
- Combination and tumor directed immune therapies
- Modulation of innate immunity
- Prediction and management of immune-related adverse events (irAEs)
Immune-related adverse events are not just “side effects”

- Window into the biology of immune regulation in humans
- Potential insight into “sporadic” autoimmunity
- Likely complex relationship to antitumor response
Managing immune toxicities to improve cancer therapy

• Minimize morbidity/mortality from immune toxicities without inhibiting antitumor immunity

• Novel therapeutics to avoid steroids

• Concurrent treatments

• Prophylactic/preventative treatments in high risk patients

• Likely to be increasingly important with combination treatments
Is it important to avoid steroids?

Horvat et al. JCO. 2009. Single center retrospective study

- Patients only received steroids if they had an adverse event
- Anyone with a serious adverse event got steroids
- Could this response be better with alternate immune suppression?
MGH data suggests steroids inhibit the antitumor response

Metastatic melanoma treated with ipilimumab
All patients in the analysis developed hypophysitis

A)

overall survival

Percent survival

Months after starting ipilimumab

HD, median 23.3 months

LD, median not reached, $p = 0.002$

No. at risk:
LD  14  14  13  11  8  3  2
HD  50  34  20  12  7  3  2  1

B)

Time to treatment failure

Percent without additional treatment or death

Months after starting ipilimumab

HD, median 14.5 months

LD, median not reached, $p = 0.001$

No. at risk:
LD  14  13  9  8  7  3  2
HD  50  20  9  7  5  3  2  1

Similar to average ipilimumab response

Alexander Faje, Cancer, 2018
The gut is a complex barrier

- Careful immune regulation is essential to the gut
  - Dietary antigens
  - Commensal bacteria
  - Pathogenic microorganisms
  - Toxins

Abreu et al. Nat. Rev. Imm. 2010
Disruption of immune homeostasis leads to a wide-spectrum of common GI toxicities

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Gastritis
Cholangitis
Celiac

The spectrum is dependent on the pathway targeted

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Some immune-mediated diseases are not seen

- IgE-mediated food allergies
- Eosinophilic esophagitis
- Eosinophilic gastrointestinal diseases
- Does this tell us something about the role of CTLA-4 and PD-1/PD-L1 in the regulation of these (probably related) diseases?
Enterocolitis

- Enterocolitis is by far the most common GI toxicity from current checkpoint blocking antibodies

- Range of severity (many patients have indolent disease)

- Likely responsible for most treatment related diarrhea

- Often isolated to the colon, but can involve the GI tract from stomach to rectum
CTLA-4 and PD-1/PD-L1 have different regulatory roles in the gut

- More frequent and more severe
- Rapid onset
- Dose-dependent
- Rapidly resolves

Ipilimumab colitis

- More microscopic inflammation
- Indolent course
- Dose-independent (?)
- Slow resolution

PD1-blockade colitis
Clinical Features

- Watery diarrhea >> pain or cramping
- Urgency without incontinence
- Blood is rare
- Can be accompanied by nausea/vomiting

Colitis

Initial workup of checkpoint blockade induced enterocolitis

- Exclude infections: stool culture, test for C. Difficile

- CT scans are useful in some patients
  - looking for perforation or other potentially surgical complications

PD-1 blockade in Crohn’s

• 74 yoM w/ quiescent Crohn’s and metastatic sarcoma on nivolumab

• Asymptomatic off medication for many years

• two weeks after starting PD-1 blockade p/w severe abdominal pain
Checkpoint blockade can cause IBD reactivation
Checkpoint blockade can cause IBD reactivation

• Received steroids and antibiotics
• Nivolumab held
• Underwent ileocecal resection with no further complications
6 patients with pre-existing IBD (quiescent)
2 cases of colitis (33%)
Higher than average risk (5-10%)
I have seen several of these patients and they tend to be more difficult to treat
PD-1 blockade may have less of an effect on IBD

Safety of Programmed Death–1 Pathway Inhibitors Among Patients With Non–Small-Cell Lung Cancer and Preexisting Autoimmune Disorders

Giulia C. Leonardi, Justin F. Gainor, Mehmet Altan, Sasha Kravets, Suzanne E. Dahlberg, Lydia Gedmintas, Roxana Azimi, Hira Rizvi, Jonathan W. Riess, Matthew D. Hellmann, and Mark M. Awad

- Two retrospective studies comprising 12 patients with UC or Crohn’s treated with PD-1/PD-L1
- Few patient details in the study, but all had minimal/no evidence of ongoing disease
- None flared while on PD-1 blockade, but they had a higher incidence of unrelated irAEs

Menzies et al. Ann. Oncol. 2017; Leonardi et al. JCO. 2018
Endoscopic Appearance

Colitis

Normal

Who needs to undergo endoscopy

- Grade 3/4 diarrhea and anyone who is sick enough to be admitted

- Persistent grade 2 disease (sometimes even grade 1)

- Atypical symptoms: bleeding, pain, fevers

- Atypical onset: months after discontinuation of immunotherapy, <7 days after starting, rapid escalation

- Diarrhea on investigational combinations, or other drugs that cause diarrhea
Extent of disease: UC type pattern

• Typically a pan-colitis
• Regional variability

Table 2. Site of inflammation on colonoscopies of patients with anti-CTLA-4 enterocolitis. Variation in the denominator is due to incomplete colonoscopy.

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<td>Ascending colon</td>
<td>27/33</td>
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Crohns type disease does occur

Crohns type disease does occur

- Nivolumab (13 months)
  - previously treated with ipiliumumab/nivolumab, and BRAF/MEKi

- Rare (on the order of 1%)

- This patient was treated with infliximab and a duodenal stent
Microscopic colitis

- Can be high grade based on diarrhea criteria
- Responds to budesonide
- Does not require discontinuation of checkpoint blockade
- More common with anti-PD-1
How similar is checkpoint colitis to IBD?

• Typically a pan colitis (more similar to UC)
• Deep ulcers and strictures are rare
• Fistulas don’t seem to occur
• Typically a monophasic course
Upper GI manifestations would be rare in IBD

- Enteritis is common (25% or more), only seen in Crohn’s
- Diarrhea disproportionate to colonic disease severity (enteritis?)
- Both of these occur exclusively in Crohn’s and rarely involve the entire stomach or small bowel

Checkpoint induced Celiac Disease

- Approximately 5% of cases of immunotherapy induced diarrhea
- Responds to a gluten free diet
- Variable response to steroids
- May be (partially) reversible

Not all adverse symptoms are adverse events

73 yo woman w/ uveal melanoma metastatic to the liver on ipilimumab p/w epigastric pain and reflux

• Non responsive to high dose PPI

• No prior history of GERD

• Symptoms onset shortly after initiation of ipilimumab
Pathology

melanocytes
S100 positive: melanoma
Histology of Typical Checkpoint Colitis

- Lymphocytic and neutrophilic infiltrate
- Prominent epithelial apoptosis
- Crypt abscesses, rare granulomas reported
- Preserved crypt architecture
Treatment of grade 3/4 checkpoint colitis

- Most patients respond to systemic steroids, and can be weaned over a period of several weeks

- Large case series reported 12/41 (<1/3) patients to be steroid-refractory (Beck et al. JCO. 2006)
  - MGH and other recent experience closer to 50% inadequate response
  - PD-1 blockade may be more likely to be refractory

- No rigorous studies of steroid dose
  - 1-2 mg/kg IV solumedrol, 40-60 mg oral prednisone
TNFα is a key mediator of checkpoint colitis

- Infliximab is highly effective in steroid refractory disease
  - Several small cases series (Beck et al. JCO. 2006), multiple other reports, incorporated into all guidelines

- Indications for infliximab
  - No/minimal response to steroids after 2-3 days
  - Recurrence on steroid taper
  - Colonic ulcers on endoscopy (?)

- Responses typically occur within days (1-3 doses)
  - PD-1 blockade colitis is more likely to be refractory
Infliximab is associated with a trend toward increased survival in patients with ipilimumab associated diarrhea.

Resistance to infliximab

- We have seen this very rarely at MGH
  - The question is not addressed adequately in the literature

- Most cases appear to be infectious (C Diff >> CMV, aspergillus)
  - We always rescope and obtain biopsies

- Where infections are rigorously excluded and colitis is still macroscopically severe, other options include:
  - bowel rest (TPN)
  - vedolizumab (integrin inhibitor)
  - CTLA-4-Ig (?)
  - Surgery
Next steps

• Mechanistic studies focusing on the immune mechanisms of colonic inflammation
  • Identify new targets
  • Understand the relationship to antitumor response

• Trials of novel therapeutic strategies
  • Integrin inhibitors
  • Anti-cytokine therapies
  • Microbiome (?)

• Endoscopy/pathology based treatment guidelines
  • Drug specific?
## Acknowledgements

**MGH Oncology**
- Ryan Sullivan
- Donald Lawrence
- Keith Flaherty
- Krista Rubin

**MGH GI**
- Ramnik Xavier
- Andy Chan
- Dan Pratt
- Molly Thomas

**MGH SIIC**
- Alexandra-Chloe Villani
- Riley Fadden

**Novartis**
- Glenn Dranoff

**Dana-Farber Cancer Institute**
- Stephanie Dougan
- Kai Wucherpfennig
- Elizabeth Buchbinder
- Steve Hodi
- Patrick Ott

**MIT**
- Michael Birnbaum

**MGH GI**
- Ramnik Xavier
- Andy Chan
- Dan Pratt
- Molly Thomas

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