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Miguel D. Regueiro, MD, FACP
December 16, 2021 at Noon Eastern

Week 1, 2022
Management of Pancreatic Pseudocysts
Mohit Girotra, MD
January 6, 2022 at Noon Eastern

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American College of Gastroenterology
Disclosures:

**Speaker:**
Shilpa Grover, MD, MPH
Senior Physician Editor, Gastroenterology, UpToDate, Wolters Kluwer Inc.

**Moderator:**
Matthew Townsend, MD, MSc, MPP
Dr. Townsend, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

*All of the relevant financial relationships listed for these individuals have been mitigated

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**Acute Gastrointestinal Toxicity of Oncologic Therapy: What Every Gastroenterologist Should Know**

Shilpa Grover, M.D., M.P.H.
Director, Onco-Gastroenterology Program
Brigham and Women's Hospital
Gastrointestinal Toxicity

- 60% of patients have acute GI complications during cancer therapy
- Adverse effects can impact ongoing care
  - Interruption or withdrawal of antineoplastic therapy
  - Concomitant immunosuppression
  - Health care costs
- Long-term sequelae can significantly impact quality of life

Abola et al. Annals Oncology 2014
Brahmer et al. JCO 2018

Unique Aspects of GI Disease in Cancer Patients

- Attenuated signs of inflammation
- Atypical clinical presentation
- Higher incidence of specific infections in immunocompromised patients
- Toxicity may present after completion of treatment
Case 1

- 65-year-old man
- Advanced non-small cell lung cancer (EGFR positive) on erlotinib
- Mild abdominal pain and diarrhea (5/day) within 1 week of treatment
- Laboratory studies
  - White cell count (per µl) 5,390
  - Stool microbiologic evaluation, *C. difficile* negative

Abdominal CT
All of the Following are Appropriate Strategies to Treat Diarrhea Associated with a Targeted Agent Except:

A. Withhold erlotinib
B. Loperamide
C. Octreotide
D. Mesalamine

### Targeted Cancer Therapies: GI toxicity

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Indications</th>
<th>Incidence (Grade 3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecule EGFR TKI</td>
<td>Erlotinib</td>
<td>NSCLC</td>
<td>90% (15%)</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td>Pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>TKI with anti-VEGF activity</td>
<td>Sorafenib</td>
<td>HCC</td>
<td>30-79% (3-17%)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td>RCC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
<td>Thyroid cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regorafenib</td>
<td>Sarcoma, GIST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>Pancreatic NET</td>
<td></td>
</tr>
<tr>
<td>Multi-targeted TKI</td>
<td>Imatinib</td>
<td>CML</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>ALL</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Bosutinib</td>
<td>GIST</td>
<td>76-84%</td>
</tr>
</tbody>
</table>
### Targeted Cancer Therapies: GI toxicity

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Indications</th>
<th>Incidence (Grade 3-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other multitargeted TKI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK inhibitors</td>
<td>Crizotinib</td>
<td>NSCLC</td>
<td>49% (1%)</td>
</tr>
<tr>
<td></td>
<td>Ceritinib</td>
<td></td>
<td>86% (6%)</td>
</tr>
<tr>
<td>MEK inhibitors</td>
<td>Trametinib</td>
<td>Metastatic melanoma</td>
<td>50% (&lt;5%)</td>
</tr>
<tr>
<td></td>
<td>Cobimetinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histone deacetylase inhibitor</td>
<td>Vorinostat</td>
<td>Cutaneous T cell-lymphoma</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>Panobinostat</td>
<td>Refractory multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Proteosome inhibitor</td>
<td>Bortezomib</td>
<td>Multiple myeloma</td>
<td>51% (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Constipation</td>
<td>24%</td>
</tr>
<tr>
<td>Immunomodulatory drugs</td>
<td>Pomalidomide</td>
<td>Multiple myeloma</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide</td>
<td>Kaposi sarcoma</td>
<td></td>
</tr>
</tbody>
</table>

### How do Targeted Agents Cause Diarrhea?

- EGFR signaling pathway dysregulation → Increased Cl⁻ secretion
- VEGF(R) inhibitors reduce capillaries networks → Epithelial hypoxia, pancreatic exocrine insufficiency
- KIT inhibition in interstitial cells of Cajal → Altered gut motility
- Alteration in gut microbiota
- Direct colonic crypt damage
Grading Diarrhea Severity: CTCAE v 5.0

<table>
<thead>
<tr>
<th>Grade</th>
<th>Diarrhea Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt;4 stools/day</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4-6 stools/day</td>
</tr>
<tr>
<td>3</td>
<td>Increase of ≥7 stools/day</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Management of Diarrhea Due to Targeted Therapy

- **Assessment:** Severity, risk factors, presence of alarm signs
- **Evaluation:** Infection, dehydration, neutropenia

- **Grade 1-2**
  - Oral hydration
  - Lactose-free, BRAT diet
  - Withhold targeted agent
  - Loperamide only if stool cx negative

- **Grade 3-4 or alarm symptoms**
  - Withhold targeted agent
  - Consider hospitalization
  - IV fluids, antibiotics
  - High-dose octreotide
  - Endoscopic evaluation if no improvement in 24 hrs

- **Persistent symptoms**
  - Colestipol, octreotide
  - DTO*

- **Symptom resolution**
  - Restart targeted agent at reduced dose

- **Progressive symptoms**
  - Restart targeted agent at reduced dose/consider alternatives
**Case 2**

- 43-year-old with rectal cancer
- Neoadjuvant chemotherapy (5-FU) and XRT → low anterior resection
- Adjuvant FOLFOX x 10 cycles
- Metastatic disease → FOLFIRI + bevacizumab
- 6 months later: Increasing abdominal pain and rectal bleeding
- Colonoscopy: Ulcer at the anastomotic site

**VEGF-Inhibitor Associated GI Perforation**
Mechanism of GI Perforation

- Ulceration in areas of tumor necrosis
- Mesenteric ischemia
- Disturbed platelet-endothelial cell homeostasis
- Impaired healing

GI Perforation

- Anti-VEGF antibody bevacizumab
- Incidence 0.9%, mortality 30%
- GI perforation also associated with other targeted agents
  - Small-molecule EGFR inhibitors (erlotinib and gefitinib)
  - Phosphoinositide 3-kinase (PI3K) inhibitors (idelalisib)
  - MEK inhibitor (trametinib)
- Incidence varies with primary and dose
Risk Factors for GI perforation

Established risk factors
- Concurrent radiation
- Corticosteroid use
- Tumor in situ
- Peritoneal carcinomatosis
- Surgery
- Colonic stent placement

Perforation can occur in the absence of risk factors
At sites distant to the tumor

Strategies to Decrease Risk of GI Perforation

Patients who require surgery
Hold VEGF-inhibitor for 6 weeks before and 4 weeks after surgery

Patients undergoing endoscopy
Individualized management based on urgency and risk (procedure and oncologic)
Case 3

70-year-old man with renal cell carcinoma

Starts cabozantinib

Asymptomatic

Laboratory studies
CMP normal, no anion gap, lactic acid 0.5 mmol/ml

Cabozantinib is Held - What is the Best Next Step?

A. Emergent exploratory laparotomy
B. Empiric antibiotics
C. Intermittent high-flow oxygen therapy
D. Close outpatient observation
Pneumatosis Intestinalis

- Presence of gas within the wall of the small or large intestine
- Median duration 3 months after initiation of targeted agents
- Can involve the normal bowel
- 70% asymptomatic
- Assess for alarm signs
  - Acute abdomen, lactic acidosis, portal venous gas
- Management similar to PI from other causes
- High recurrence rate

Case 4

60-year-old M with metastatic NSCLC, congestive heart failure (NYHA class III)
Carboplatin, bevacizumab, pemetrexed x 6 cycles
Maintenance bevacizumab, pemetrexed
Disease progression → atezolizumab
6 weeks later develops diarrhea (8 stools/day)
Case 4

Evaluation

*Clostridioides difficile, cultures: negative*
Abdominal CT: fluid filled colon

Management

Checkpoint inhibitor withheld
Prednisone (1 mg/kg/day) initiated

72 hrs later - diarrhea persists (8-9 loose stools/day)

What is the Best Next Step?

A. Start loperamide and colestipol

B. Oral prednisone (2 mg/kg/day)

C. IV methylprednisolone (2 mg/kg/day)

D. Urgent endoscopic evaluation
**Checkpoint Inhibitor Colitis**

![Image of colon and histology](image)

---

**Immune Checkpoint Inhibitors**

- Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
  - Ipilimumab

- Programmed cell death-1 (PD-1) receptor
  - Pembrolizumab, Nivolumab, Cemiplimab, Dostarlimab

- Programmed cell death ligand-1 (PD-L1)
  - Durvalumab, Atezolizumab, Avelumab
What Are the Immunologic Checkpoints?

- CTLA-4 and PD-1/PD-L1 are regulatory pathways that inhibit the immune response
  - Associated with tolerance
  - Prevention of autoimmunity

Blocking CTLA-4 Reactivates T cells
PD-1 Immunologic Checkpoint

- Interaction of PD-1 on activated T cells by its ligands renders them non-functional

PD-1 Immunologic Checkpoint

- Blocking PD-1/PD-L1 pathway reactivates T cells
Immune Related Adverse Events

- IrAE in 15-90% of patients

**Skin**
- Exfoliative dermatitis
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia

**Cardiac**
- Myocarditis

**Renal**
- Acute kidney injury

**GI tract**
- Colitis
- Gastroparesis
- Enteritis
- Hepatitis
- Pancreatitis

**Pulmonary**
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

**Eye**
- Uveitis
- Iritis

**Endocrine**
- Hypophysitis
- Adrenal insufficiency
- Autoimmune thyroid disease

**Neurologic**
- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barré
- Myasthenia gravis

**Incidence and Timing of Colitis**

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea</th>
<th>Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Anti-CTLA-4</td>
<td>23-33</td>
<td>3-6</td>
</tr>
<tr>
<td>monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-PD-1/PD-L1</td>
<td>11-19</td>
<td>1-3</td>
</tr>
<tr>
<td>monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>44-45</td>
<td>9-11</td>
</tr>
</tbody>
</table>

Weber JS et al. JCO 2012
Grover et al. ASCO Edbk 2018

American College of Gastroenterology
Clinical Presentation

• Median onset 6-8 weeks after initiation
• Frequent watery stools, bloody diarrhea is rare
• Mild to moderate abdominal pain
• Associated urgency and fecal incontinence
• Atypical presentation constipation and tenesmus
• Colitis-related mortality rate 2-5%

Abdominal Imaging

CT features

- Bowel wall thickening
- Fat stranding
- Mucosal hyperenhancement
- Fluid-filled colon
- Mesenteric vessel engorgement

Diffuse Colitis Pattern
Segmental Colitis Associated with Diverticulosis (SCAD)
Abdominal CT: Low Sensitivity for ICI Colitis

- Retrospective review of 6920 solid tumor patients who received ≥1 course of ICI
  - 100 had biopsy-proven colitis
    - Anti CTLA-4 (n=25), anti PD-1/PD-L1 (n=48), combination ICI (n=38)
- Of the 111 CT scans performed
  - 55 (50%) diagnostic for colitis
  - 12 (10%) equivocal
  - 44 (40%) non-diagnostic
- Sensitivity of abdominal CT for ICI colitis
  - Combination therapy: 63%
  - CTLA-4: 56%
  - PD-1/PD-L1: 35% (p=0.03)

Who Should Undergo Abdominal CT?

- Indications
  - Grade 3 or 4 diarrhea
  - Severe abdominal pain
  - Abdominal distension
  - Significant abdominal tenderness
  - Peritoneal signs
- Rationale
  - Serves to rule out complications of colitis
- Limitation:
  - Abdominal CT has low sensitivity for ICI colitis
Laboratory Evaluation

<table>
<thead>
<tr>
<th>Stool evaluation</th>
<th>Blood tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool culture</td>
<td>Complete blood count with differential</td>
</tr>
<tr>
<td>Clostridioides difficile</td>
<td>Comprehensive metabolic panel</td>
</tr>
<tr>
<td>Ova and parasites</td>
<td>IgA-tissue transglutaminase antibody, IgA</td>
</tr>
<tr>
<td>Rotavirus and Norovirus</td>
<td>TSH</td>
</tr>
<tr>
<td>Fecal calprotectin</td>
<td></td>
</tr>
<tr>
<td>Additional testing in patients with risk factors</td>
<td>Vibrio, Aeromonas, Listeria, Yersinia</td>
</tr>
</tbody>
</table>

Colonoscopy/Sigmoidoscopy

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent grade ≥2 diarrhea (&gt;4 stools/day)</td>
</tr>
<tr>
<td>Steroid-refractory diarrhea</td>
</tr>
<tr>
<td>Significant abdominal pain</td>
</tr>
<tr>
<td>Hematochezia</td>
</tr>
</tbody>
</table>
Endoscopic Appearance is Not Specific

- Erythema
- Edema
- Mucosal friability
- Superficial ulcerations
- Erosions

Deep Ulceration is Rare
Segmental Colitis

Mucosa Can Appear Normal
Histology is Not Specific

- Active colitis pattern
  - Neutrophilic inflammation
  - ↑ Intraepithelial lymphocytes
  - ↑ Apoptotic crypt epithelial cells
  - Granulomas are rare
  - Features of chronicity are limited or absent
- Can resemble infectious colitis

---

Histology is Not Specific

- Lymphocytic colitis-like pattern
  - Lymphoplasmacytic inflammation in lamina propria
  - Intraepithelial lymphocytosis in surface epithelium
  - Scattered crypt epithelial apoptosis
- Collagenous colitis-like pattern
- Other patterns
  - GVHD-like pattern
  - Mixed

---

Grover S, Srivastava A, Cancer, 2019
Why is Endoscopic Evaluation of the Colon Needed?

- Rules out alternative etiologies
- Confirms the diagnosis
- Endoscopic severity - prognostic information
- Consequences of steroids and biologics
- Informs decision to rechallenge

Verheijden R et al, Clin Cancer Res 2020
Mooradian et al, JTC 2020

Extracolonic Gastrointestinal Toxicity

- Concomitant enteritis in 25%
- Isolated enteritis with PD-1/PD-L1 inhibitors

Tang et al, Scand J Gastro, 2019
Checkpoint Inhibitor Gastritis

- Usually associated with enteritis
- Rare cases isolated

Johnsilla M et al, Histopathology 2019

Checkpoint Inhibitor Esophagitis

- Patchy peripapillary increase in lymphocytes
- Scattered necrotic cells

Chen F, Liu A et al, Curr Probl Cancer. 2020
Esophagitis Dissicans Superficialis

Sloughing esophagitis

Who Should Undergo An Upper Endoscopy?

- Upper GI symptoms
  - Upper abdominal pain
  - Nausea/vomiting
  - Bloating
- Upper GI tract involvement on imaging
- Patients with diarrhea undergoing flexible sigmoidoscopy
- Recent colitis due to other causes
  - *C. difficile* infection
Checkpoint Inhibitor Colitis: Management

- Based on the severity of symptoms
- Early assessment for alarm features
  - Severe abdominal pain
  - Fever/sepsis
  - Bloody diarrhea
  - Moderate to severe nausea/vomiting
  - Hypovolemia
  - Neutropenia

Management of Severe (Grade 3 and 4) Colitis

- Consider hospitalization
- High dose intravenous corticosteroids (methylprednisolone 1-2 mg/kg/day)
- IV fluids, replete electrolytes
- Avoid antidiarrheals, lactose-free diet
- Early evaluation for contraindication to biologic (IGRA TB, Hepatitis B and C)

Improvement

- Convert to equivalent dose oral prednisone
- Taper prednisone over 6-8 weeks (10 mg q4 days)

Persistent (≥ 3 days) or progressive symptoms

- Infliximab (5 mg/kg)
- Partial response: infliximab (additional dose 5-10 mg/kg)
- Vedolizumab is an alternative
- Colectomy for toxic megacolon or perforation
Rates of exacerbation of enterocolitis are higher
• Patients with IBD 19%
• Patients with microscopic colitis 75%

Management
• Most patients managed medically, 1 colectomy, no deaths
• All required permanent discontinuation of immunotherapy
• Patients with pre-existing IBD/microscopic colitis may be treated with ICIs
  • Baseline assessment of disease severity
  • Close monitoring for potential enterocolitis flares

Investigational Treatments
• Fecal microbiota transplant

Others:
• Janus kinase (JAK) inhibitor: Tofacitanib
• IL-12/IL-23 inhibitor: Ustekinumab
• Recombinant CTLA-4 IgG: Abatacept
Avoid NSAIDs

• Concomitant with ICI

Anti-Integrin/Anti-TNF

• Concomitant with ICI

Other strategies with unclear role

• Vitamin D
  • Low levels associated with increased risk of ICI colitis
  • Unclear if decreases risk of ICI colitis
• Budesonide
  • No role for ileal release budesonide in primary prevention
  • Role in prevention of recurrence is unclear

Take Home Points

Incidence of acute GI complications of oncologic treatment is high

Targeted agents and immune checkpoint inhibitors can cause several GI complications

Symptoms can be mild and presentation can be atypical or delayed

Early evaluation has important treatment implications

Multidisciplinary care improve patient outcomes
Thank you

grover@bwh.harvard.edu

Questions?

Speaker: Shilpa Grover, M.D., M.P.H.

Moderator: Matthew Townsend, MD, MSc, MPP
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