Chemotherapy Induced Diarrhea

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October 19, 2012
Disclosures

• None.
Objectives

1. Define chemotherapy induced diarrhea

2. Outline a diarrhea grading system to aid in decision analysis

3. Identify several chemotherapy agents at high risk for causing diarrhea

4. Identify potential risk factors for the development of chemotherapy induced diarrhea

5. Through the use of clinical cases become familiar with the guidelines for the management of chemotherapy induced diarrhea
How do we define diarrhea?

- Stools that are:
  - Looser than normal
  - Increased urgency and frequency
  - More than three stools per day

- Acute (<14 days)
  - Immediate or Delayed Onset

- Persistent (>14 days)

- Chronic (>30 days)
Causes of Diarrhea in Cancer Patients

- **Chemotherapy**
  - 5-FU
  - Irinotecan
  - Others

- **Radiotherapy**
  - Pelvic

- **Enteral Feeding**

- **Drugs**
  - Laxatives
  - Antibiotics
    - Infectious
  - Antacids

- **Intestinal Obstruction**
  - Fecal Impaction

- **Malabsorption**
  - Pancreatic Cancer
  - Biliary Obstruction
  - Fistula
  - Short Bowel

- **Islet Cell Tumors**
  - Carcinoid VIPoma
  - Gastrinoma

Clinical Manifestations

- Volume depletion
- Electrolyte disorders
  - Metabolic acidosis
  - Hyponatremia
    - Free water not excreted due to ADH
  - Hypernatremia
    - Insufficient water intake to replace losses
- Renal Failure
- Higher risk of infectious complications with concomitant neutropenia
Outcomes

- Diarrhea may interfere with treatment resulting in:
  - Dosing delays
  - Dose reductions
  - Discontinuation of treatment
  - Hospitalization

- Can lead to dehydration, electrolyte abnormalities, malnutrition, renal failure, cardiovascular collapse and death

- Rate of hospitalization for toxicity secondary to chemotherapy
  - 27% for irinotecan
  - 21 to 31% for fluororacil

May be significant!
Goals of treatment? Elderly and frail?
Why does it matter?

• Patients don’t always mention it
• Incidence depends on chemotherapy regimen
  – All comers: 10% of patients
  – High incident agents: 50-80% of patients
• Often is the dose limiting toxicity

Stein A et al. Therapeutic Advances in Medical Oncology. 2010;2:51.
## Toxicity Criteria for Severity of Chemotherapy-induced Diarrhea

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
</table>
| None  | • Increase < 4 stools/day  
• No nocturnal stools | • Increase of 4-6 stools/day  
• No nocturnal stools | • Increase ≥ 7 stools/day or incontinence  
Or  
• Need for parenteral support for dehydration | • Physiologic consequences requiring ICU  
Or  
• Hemodynamic collapse |

Standard tool for assessing diarrhea severity  
*Does not include assessment of duration, volume and co-existing symptoms*  
Adapted from Benson AB et al. Journal of Clinical Oncology. 2004;14:2918.
The Consequences of Diarrhea Occurring During Chemotherapy for Colorectal Cancer: A Retrospective Study

R.B. Arbuckle, a S.L. Huber, a C. Zacker b

The Oncologist. 2000;5:250.

- Retrospective analysis
- 100 patients with colorectal carcinoma
- Receiving variety of chemotherapy regimes +/- radiotherapy
  - Bolus 5-FU, Infusional 5-FU, Capecitabine, Irinotecan
Incidence of Chemotherapy Diarrhea

5-FU Containing Chemotherapy

Diarrhea most likely to occur within first 2 cycles versus 3 or more
BUT severe high-grade diarrhea may occur during any cycle
Increased risk of diarrhea after a previous episode

Irinotecan Chemotherapy

Diarrhea most likely to occur within first 2 cycles versus 3 or more
BUT severe high-grade diarrhea may occur during any cycle
Increased risk of diarrhea after a previous episode
Chemotherapy Regimen & Highest Grade Of Diarrhea For Each Patient For Every Cycle

Percentage

Grade 0  Grade 1  Grade 2  Grade 3  Grade 4

5-FUCI  UFT  5-FU + LU  Capecitabine  Irinotecan
### Treatment Changes in 100 Patients with Diarrhea

<table>
<thead>
<tr>
<th>Treatment Change</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change</td>
<td>44</td>
</tr>
<tr>
<td>Dosing delay</td>
<td>8</td>
</tr>
<tr>
<td>Discontinue therapy</td>
<td>15</td>
</tr>
<tr>
<td>Dosing decrease</td>
<td>22</td>
</tr>
<tr>
<td>Two or more changes</td>
<td>11</td>
</tr>
</tbody>
</table>
Worst Offenders
Fluoropyrimidines

- 5-FU, Capecitabine
- Bolus > infusion
- Anecdotally: Diarrhea worse with capecitabine
- Clinical factors predictive:
  - Female, Ethnicity (Caucasian), Diabetes
    - Complete deficiency of dihydropyrimidine dehydrogenase (DPD)
    - Partial deficiency 3-5% of patients
- Few papers attempt to address or understand mechanism
- Mitotic arrest of interstitial crypt cells
  - Decreased fraction of villus enterocytes & surface area

Irinotecan

• Commonly used in colon, small cell lung, sarcoma

1. **Acute diarrhea (lasts ~ 30min)**
   - Caused by acute cholinergic properties
   - Cholinergic excess
     - abdominal cramping, rhinitis, lacrimation, salivation
   - Responds to atropine (CCMB orders atropine std)

2. **Delayed onset-diarrhea (>24 hours)**
   - Median onset 6 – 14 days
   - Unpredictable, non-cumulative, at all dose levels
   - Watch combination chemotherapy
     • bolus IV fluorouracil and LV
Diagnosis: **Metastatic Colorectal Cancer**

Planned Course: **FOLFIRI regimen q 2 weeks**

<table>
<thead>
<tr>
<th>Height: _____ cm</th>
<th>Weight: _____ kg</th>
<th>BSA: _____ m²</th>
</tr>
</thead>
</table>

Allergies: 

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**FOLFIRI Regimen Criteria for Use:**

Patients with the following criteria will be eligible for treatment. Please check-off the appropriate criteria for each cycle to be administered. Thank you.

- ☐ Colorectal cancer Stage IV or
- ☐ Locally advanced or locally recurrent colorectal cancer and
- ☐ Patient functioning at ECOG level of 0, 1 or 2.

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**PHYSICIAN'S ORDERS**

<table>
<thead>
<tr>
<th>MEDICATION ADMINISTRATION RECORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE</td>
</tr>
</tbody>
</table>

Notify physician before administering full doses of chemotherapy if platelets $< 100 \times 10^9 /L$ or ANC $< 1.5 \times 10^9 /L$.

Initiate therapy in sequence specified below.

1. **Establish IV of NaCl 0.9% 250 mL for medication administration on chemotherapy days.**

2. **Dexamethasone _____ mg (usually 12 mg) po**
   - 30 min. before chemotherapy.

3. **Ondansetron _____ mg (usually 8 mg) IV over 15 min. in NaCl 0.9% 50 mL before chemotherapy**

4. **Atropine _____ mg (usually 0.5 mg) IV Push over 2-3 min. Range 0.25 mg - 1.0 mg**

5. **Irinotecan _____ mg (usually 180 mg/m²) IV in**
Metabolism of Irinotecan

1. Direct mucosal damage
2. Altered luminal environment
   - Altered colonization?
3. Altered mucine gene expression?

- SN-38 and SN-38G excreted via urine and bile
- Mass spectrometer studies – fecal route 63.7% of drug

Stein A et al. Therapeutic Advances in Medical Oncology. 2010;2:51.
Incidence of Grade 3/4 Diarrhea with Chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU (bolus)</td>
<td>12%</td>
</tr>
<tr>
<td>5-FU (bolus) + LV</td>
<td>37%</td>
</tr>
<tr>
<td>5-FU (infusion)</td>
<td>6-13%</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>11%</td>
</tr>
<tr>
<td>Irinotecan (late)</td>
<td>16-22%</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>11-24%</td>
</tr>
<tr>
<td>Docetaxel/Paclitaxel</td>
<td>4%</td>
</tr>
</tbody>
</table>

Sources:
Targeted Therapy

- Numerous drugs of different classes:
  - EGFR tyrosine-kinase inhibitors (Erlotinib, Gefitinib)
  - Tyrosine kinase inhibitor (Sorafenib, Sunitinib)
  - Bcr-Abl inhibitor (Imatinib)
  - Proteasome inhibitor (Bortezomib)

- Mechanisms poorly understood possibly related to excess of secretion of chloride in the bowel leading to secretory diarrhea

http://dx.doi.org/10.3747/co.19.1054
Incidence of Grade ¾ Diarrhea with Chemotherapy – Targeted Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>6%-12%</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>3%</td>
</tr>
<tr>
<td>Sorafenib/Sunitinib</td>
<td>2-8%</td>
</tr>
<tr>
<td></td>
<td>(24% - Grade 2-3)</td>
</tr>
<tr>
<td>Imatinib</td>
<td>45% (grade ?)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>8-9%</td>
</tr>
</tbody>
</table>

Is there a way to predict?

**Patient Factors**
- Age
- Sex
- Performance Status
- Other bowel pathology

**Therapy-related Factors**
- Drugs
- Schedule
- Previous chemotherapy diarrhea
- Concomitant chemo/radiotherapy of abdominal-pelvic region

Drug and Schedule

- Dependent on chemotherapy type
  - 5-fluorouracil, irinotecan
  - Oral Agents
    - Capecitabine
    - Molecular targeted agents
- Dependent on administration
  - Bolus/infusional
  - Weekly vs q3 weekly vs other
- Dose-related adverse effect
Predictive Factors specific for Irinotecan-Related Diarrhea

- Weekly administration
- Genetic factors – UGT1A1*28 polymorphism
- Gilbert syndrome
- Crigler-Najjar syndrome Type I

Treatment

• Non-pharmacologic
  – Aggressive oral rehydration with water, salt and sugar containing fluids
  – Avoidance of aggravating foods

• Pharmacologic
Guidelines

• Two NCI trials with IFL regimen:
  – N9741 – advanced metastatic colorectal cancer
  – Cancer and Leukemia Group B adjuvant treatment trial C89803

• Both of these trials IFL (irinotecan/bolus 5-FU/LV) was administered according to the Saltz regimen

• Mortality:
  – 2.5% with IFL regimen
  – 0.8% with bolus weekly 5-FU/LV

• Most of the deaths attributed to GI toxicity and cardiovascular events
• Quite a concern as patients in the C89803 trial were receiving potentially curative adjuvant therapy

BCCA Guidelines on the Management of Chemotherapy-Induced Diarrhea
October 2004
www.bccancer.bc.ca

Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian Working Group on Chemotherapy-Induced Diarrhea

J.A. Maroun MD,* L.B. Anthony MD,† N. Blais MD,‡ R. Burkes MD,§ S.D. Dowden MD,|| G. Dranitsaris MPharm,‖ B. Samson MD,** A. Shah MD,‖‖ M.P. Thirlwell MD,‖‖‖ M.D. Vincent MD,$$$ and R. Wong MD$$$
Mr. Runnings is a 79-year-old with advanced colon cancer who has completed chemotherapy with oxaliplatin, irinotecan, and fluorouracil. Six days after chemotherapy he develops diarrhea. After the 3rd episode his daughter calls and asks if there is anything that can be done?

What can you do for him?
EVALUATE

• History of onset & diarrhea duration
• # stools & composition
• Fever, dizziness, abd pain/cramping, weakness
• Medications
• Dietary review

UNCOMPLICATED
• Grade 1 – 2 diarrhea
• No complicating signs or symptoms

COMPLICATED
• Grade 3 – 4 diarrhea
or
• Grade 1 – 2 with $\geq 1$ symptom:
  • Dehydration • neutropenia
  • Cramping, fever • sepsis • bleeding
  • Nausea/vomiting ($\geq$ Grade 1 – 2)
  • Decreased ECOG

ADDED RISK FACTORS

MANAGEMENT - UNCOMPLICATED

• Stop all lactose containing products, alcohol and high-osmolar supplements
• Drink 8 – 10 large glasses clear liquids/day (Gatorade or broth)
• Each frequent small meals (bananas, rice, applesauce, toast, plain pasta)
• Record number of stools
• Grade 2: Hold cytotoxic chemo until symptoms resolve, consider dose reduction

TREATMENT

Loperamide: Initially 4 mg followed by 2 mg q4h or after every unformed stool

Reassess 12 – 24 hours later

RESOLVING

• Watch diet
• D/C loperamide after 12 hr diarrhea free

Reassess 12 – 24 hours later

PERSISTANT

• ↑ Loperamide 2 mg q2h
• Start oral antibiotics
• If RT-induced no antibiotics

Grade 3 – 4 or symptoms
Loperamide vs Diphenoxylate

**Loperamide**
- Does not cross BBB
- Via opioid receptor
- Inhibits peristalsis & prolongs transit time
- Decreases fecal volume
- Diminishes fluid and electrolyte loss
- Increases tone on anal sphincter

**Diphenoxylate + atropine**
- Brand: Lomotil
- Crosses the BBB
- Addition of atropine is to decrease abuse potential
- Via opioid receptor
- Inhibits peristalsis & prolongs transit time
- Decreases fecal volume
- Diminishes fluid and electrolyte loss
- Increases tone on anal sphincter

Randomized trials – two weak studies
Double Blinded Cross-Over Study Comparing Loperamide Codeine and Diphenoxylate in the Treatment of Chronic Diarrhea

K. R. PALMER, C. L. CORBETT, and C. D. HOLDSWORTH
Gastroenterology Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom

Gastroenterology. 1980;79:1272

- Double blinded, cross-over trial
- 30 individuals (chronic diarrhea)
  - Only 15 completed the study
- Solid stool greatest with loperamide
- Incontinence greatest with diphenoxylate
- Side effects diphenoxylate > codeine > loperamide

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Capsules per day (± SEM)</th>
<th>Stool frequency Mean (± SEM) Range</th>
<th>% Solid stool (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>2.3 (0.3) (4.6 mg)</td>
<td>1.8 (0.3) 0-6</td>
<td>67.8 (8.8)</td>
</tr>
<tr>
<td>Codeine</td>
<td>2.3 (0.3) (10.3 mg)</td>
<td>1.9 (0.3) 1-5</td>
<td>58.4 (6.7)</td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td>2.5 (0.3) (12.5 mg)</td>
<td>1.9 (0.3) 1-5</td>
<td>36.3 (6.6)</td>
</tr>
</tbody>
</table>

* Differs significantly from loperamide and codeine (P < 0.01).

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Loperamide</th>
<th>Codeine</th>
<th>Diphenoxylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>2</td>
<td>27*</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Headaches</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>29</td>
<td>39*</td>
</tr>
</tbody>
</table>

* Differs from Loperamide (P < 0.01). * Differs from Loperamide (P < 0.05)
You suggest to Mr. Runnings that he start taking lopareamide 4 mg PO initially, and 2 mg with every bowel movement. He initially gets control, but with further telephone calls increases dose to 2 mg q2h. Unfortunately, his diarrhea continues but he is feeling okay, and is able to increase his oral intake. He denies symptoms of hypovolemic

What can you do for him?
PERSISTANT despite ↑ loperamide

OFFICE/**OUTPATIENT SETTING
• Consider hospital admission
• Stool work-up
  • Blood, fecal leukocytes, Clostridium difficile, Salmonella, Escherichia coli, Campylobacter, infectious colitis
• CBC, electrolytes
• Abdominal examination
• Replace fluids & electrolytes
• Discontinue loperamide & start 2nd line agent
• Octreotide 100 mcg subcut TID (up to 500mcg TID)
• RT induced: Continue loperamide, no work-up required
Octreotide Versus Loperamide in the Treatment of Fluorouracil-Induced Diarrhea: A Randomized Trial

- 41 patients
  - Grade II or III diarrhea
  - Randomized: octreotide or loperamide
    - Octreotide 100 mcg subcut BID x 3 days
    - Loperamide 4 mg then 2mg q6h x 3 days
- No confounding factors
  - No previous diarrhea < 3 months
  - No antibiotics
- 5-FU +/- LV or 5-FU +/- interferon

• Octreotide - Diarrhea resolved in 90% patients at three days
  – Majority took 3 days for resolution
• Loperamide – Diarrhea resolved in 15% of patients at three days
COMPLICATED

• Grade 3 – 4 diarrhea
  or
• Grade 1 – 2 with $\geq 1$ symptom:
  • Dehydration  • neutropenia
  • Cramping, fever  • sepsis  • bleeding
  • Nausea/vomiting ($\geq$ Grade 1 – 2)
  • Decreased ECOG

ADMIT TO HOSPITAL

• IV fluids, antibiotics
• Stool work-up, CBC, electrolytes
• Octreotide 100 – 150 mcg subcut/IV TID w/ max 500 mcg TID
  • Infusion at 25 – 50 mcg/hr
• D/C cytotoxic chemotherapy until symptoms resolve, reduce dose chemotherapy
Ms. Jones is a 52-year-old lady diagnosed with stage IV adenocarcinoma of the lung. She has completed cisplatin & gemcitabine x 4 cycles but progressed. She was recently discharged from hospital where she was treated for uncomplicated cellulitis. After her discharge she was started on Erlotinib, but calls today to say she has had three episodes of diarrhea. Is this normal?
Unique Issues to Oral Therapy

• Unacceptable side effects for patients may lead to discontinuation of treatment
  – Issue of compliance with oral medications

• Oral compounds induce chronic diarrhea that may persist throughout treatment
  – Often dose related
  – Time of onset is widely varied, median 14 days

• Alterations in GI physiology may alter the pharmacokinetics and pharmacodynamics of targeted therapy & concomitant medications
Two Questions

1. What is the risk of clostridium difficile diarrhea in patients on chemotherapy?

2. Guidelines do not address targeted therapy, alternative management or the same?
Prospective study of chemotherapy-induced *clostridium difficile* infection in lung cancer patients

Toi Y et al. Journal of Clinical Oncology. 2012; suppl; abstr e19521

- 345 consecutive patients (492 cycles)
- Variety of chemotherapy drugs
- 36 of 492 cycles (7.3%) showed Grade 2 or worse diarrhea
- *C. difficile* infection was confirmed in 8 of 36 regimens (22.2%)
- *C. difficile* infection more frequently observed in regimens containing irinotecan than other anticancer drugs
EGFR-TKI Inhibitors

- Although diarrhea frequent, usually mild to moderate
- Early management is key:
  - To prevent dose reduction or discontinuation
- Management similar to cytotoxic induced
- If grade 3/4 dose reduction or discontinuation may be required
  - Not based on clinical trials

Case-3

Mr. Ross is a 65 year old diagnosed with stage IV colon cancer. He has just completed of FOLFIRI during which time he had 5+ episodes of diarrhea. It was well controlled with Imodium.

He wonders if he should prophylaxis for the diarrhea before it starts for cycle 2?
Prophylaxis

• Current recommendations
  – Octreotide LAR 30 mg IM q 28 days if previous grade 3 – 4 diarrhea

• RTOG-0315
  – Randomized Phase III 226 patients receiving chemoradiotherapy for anal & rectal cancer
    • Did not prevent incidence or reduce severity of diarrhea
    • No improvement in quality of life benefit

• Extrapolate to chemotherapy only?
  • Also a Canadian multiphase study in progress
Other Options?

- Dozens of small studies looking at:
  - Non-absorbable antibiotics
    - Neomycin
  - Chrysin
    - No difference
  - Glutamine
    - No difference
  - Activated charcoal
  - Thalidomide
  - Omega-3 fatty acids
  - Oral alkalisation

**Bottom Line:** No benefit
Not presently part of current published practice guidelines
Summary-1

- Chemotherapy induced diarrhea is a common problem

- Most commonly seen in irinotecan and fluorouracil chemotherapy but with increasing use of targeted therapy it remains a common problem

- Diet modification, and loperamide remain mainstay for management

- Currently no data to support combined loperamide & lomotil use
• Octreotide is an proven option if conservative measures are not effective

• No role for octreotide prophylaxis

• In non-resolving diarrhea or recently hospitalized patients evaluating for clostridium difficile infection is important even in the absence of previous antibiotic use
Questions?