Diarrhea: Identifying who is at increased risk and offering the appropriate management

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Overview

• Scope of the problem
• Pathophysiology
• Who is at risk?
  – Patient factors
    • Clinical characteristics
  – Treatment factors
    • Pharmacogenomics
• Appropriate management

Cancer Therapy Induced Diarrhea (CTID)
Chemotherapy Induced Diarrhea (CID)

• Diarrhea is a well recognized side effect of cancer therapy
  – G V H D
  – 5FU, irinotecan, radiation

• CID present in 50-80%
• Grade 3-5 > 30%
• Dose related, schedule dependent

Consequences of CID

Physical
Nausea
Cramping
Fatigue
Malnutrition
Dehydration
Renal insufficiency
Electrolyte imbalance
CV morbidity
Infection complications

Emotional/social
Phagophobia
Somniphobia
Inability to work
Social isolation
Body image
Sexual dysfunction

Diarrhea CTCAE version 3.0

<table>
<thead>
<tr>
<th>Patients without colostomy</th>
<th>Patient with colostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Increase of &lt; 4 stools/day over pretreatment</td>
<td>Mild increase in loose watery colostomy output compared with pretreatment</td>
</tr>
<tr>
<td>2 Increase of 4-6 stools/day, or nocturnal stools</td>
<td>Moderate increase in loose watery colostomy output compared with pretreatment, but not interfering with normal activity</td>
</tr>
<tr>
<td>3 Increase of 7 stools/day or incontinence, or need for parenteral support for dehydration</td>
<td>Severe increase in loose watery colostomy output compared with pretreatment, interfering with normal activity</td>
</tr>
<tr>
<td>4 Physiologic consequences requiring intensive care, or hemodynamic collapse</td>
<td>Physiologic consequences requiring intensive care, or hemodynamic collapse</td>
</tr>
</tbody>
</table>
Criteria for optimum measurement of cancer treatment related diarrhea

- Stool consistency graded with illustrations
- Liquid stool measured by volume
- Assessment of tenesmus or urgency, abdominal pain and cramping
- Onset and duration of diarrhea and accompanying symptoms
- Presence or absence of perianal or peristomal skin breakdown
- Patient report of self-care (e.g., diaries or behavior logs) and effect of interventions
- QOL assessments (functional capacity)


Pathophysiology 5-fluorouracil

5-fluorouracil (5-FU) may cause
- Acute damage to the intestinal mucosa
  - Mitotic arrest of intestinal epithelial crypt cells
  - Superficial necrosis
  - Extensive inflammation of the bowel wall
- Mucosal and submucosal factors (e.g., prostaglandins, leukotrienes, cytokines, and free radicals), produced directly or indirectly by the inflamed intestine, stimulate
  - Secretion of intestinal fluid and electrolytes.
  - Loss of brush border enzymes involved in the terminal digestion of carbohydrates and proteins may also contribute to secretion.
- Mitotic arrest and initiation of apoptosis in the crypts of the small intestine
  - Loss of absorptive (villous) surface
  - Imbalance in the number of absorptive and secretory cells.
- Together with the associated inflammatory cell infiltrate, these changes result in secretion of water and electrolytes, i.e., diarrhea.

Pathophysiology irinotecan

The metabolic fate of CPT-11
- Show a relationship of CPT-11-induced diarrhea to accumulation of its active metabolite SN-38 in the intestines. SN-38 generally undergoes
  - Glucuronidation in the liver but can be deconjugated in the intestines by the enzyme b-glucuronidase present in intestinal bacteria
  - Glucuronidase activity has been directly correlated with the severity of CPT-11-induced diarrhea
- The degree of intestinal mucosal damage in rats, with the most severe histologic damage seen in the cecum.
- In the rat model, cecal damage and diarrhea were reduced when antibiotics inhibited b-glucuronidase activity in the intestinal microflora, suggesting that deconjugation of SN-38 glucuronide by intestinal bacteria is the cause of CPT-11-induced diarrhea.

Pathophysiology

- Widespread necrosis of crypt stem cells observed in CID and GVHD increases the risk of superinfection by opportunistic pathogens
  - Clostridium difficile, C. perfringens, Bacillus cereus, Giardia lamblia, Cryptosporidium, Salmonella, Shigella, Campylobacter and rotavirus.
  - This risk is highest in patients who may be neutropenic or immunosuppressed
- Bacterial enterotoxins
  - May induce the secretion of substances such as serotonin by enteric endocrine cells that have a direct secretory effect on the intestinal mucosa
  - Superinfection can further induce the inflammatory response and result in the destruction of the intestinal epithelium
  - Continuous loss of crypt limits the regenerative capacity of the epithelium and eventually leads to its total denudation
- This type of severe damage is often associated with bleeding and ileus

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    - Clinical characteristics
  - Treatment factors
  - Pharmacogenomics
- Appropriate management
Patients Who Experienced NCI-CTC Grade 3 or Greater Adverse Events
pooled analysis of 9 clinical trials

<table>
<thead>
<tr>
<th>Overall</th>
<th>PS 0-1</th>
<th>PS 2</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9.1</td>
<td>8.5</td>
<td>16.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.0</td>
<td>7.6</td>
<td>11.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.9</td>
<td>17.1</td>
<td>14.9</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2.5</td>
<td>2.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33.7</td>
<td>33.7</td>
<td>34.5</td>
</tr>
</tbody>
</table>

\( P \) from a logistic regression for PS as a dichotomous variable (PS 0-1 vs PS2) in a model containing for study, sex, age, and indicators for whether treatment included irinotecan and/or oxaliplatin.

Incidence of Severe Chemotherapy Toxicity by Age

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Neutropenia</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sargent SFU</td>
<td>4% *</td>
<td>8%</td>
</tr>
<tr>
<td>SFUlev</td>
<td>17% *</td>
<td>31%</td>
</tr>
<tr>
<td>Folprecht SFU</td>
<td>27% *</td>
<td>37%</td>
</tr>
<tr>
<td>oxali/5FU</td>
<td>35%</td>
<td>39%</td>
</tr>
<tr>
<td>Goldberg FOLFOX</td>
<td>43% *</td>
<td>49%</td>
</tr>
</tbody>
</table>

* statistically significant difference between age groups

Pharmacogenomics

- **Fluoropyrimidines**
  - **DPYD**: gene encoding dipyridomole dehydrogenase (DPD)
  - **DPD** catabolizes 5FU into its inactive dihydropyrimidine form
  - More than 40 different variations in DPYD have been identified as causing DPD deficiency
  - DPD deficiency results in prolonged exposure to active drug
- **TYMS**: gene encoding thymidylate synthase
  - **TS** is the target for 5FU
  - The 2R/2R variation confers a 1.4-2.5-fold increased risk for adverse events
  - TS deficiency results in excess of "free" 5FU
- **Irinotecan**
  - **UGT1A1**: gene encoding UDP-glucuronosyl transferase 1A1 (UGT1A1)
  - Enzyme conjugates SN-28 predominantly to form a glucuronide metabolite.
  - UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism.

5-Fluorouracil metabolism

- **DPD Deficiency Mechanism of Action**
  - Variations in DPYD can lead to DPD insufficiency
  - This results in an inability to inactivate 5-FU leading to increased levels of active drug in the system that can result in greater toxicity

- **TS Deficiency Mechanism of Action**
  - Variations in TYMS can lead to altered TS expression
  - Lower levels of the TS enzyme can lead to
    - Increased levels of active 5-FU
    - Toxicity
Pharmacogenetics
5-fluorouracil

About 1 in 14 (7%) patients treated with 5-FU have Grade 3-4 toxicity associated with a DPYD or TYMS gene variation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (unselected)</th>
<th>Overall Grade 3-4 toxicity</th>
<th>DPYD and Grade 3-4 toxicity</th>
<th>DPYD and toxicity relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morel</td>
<td>n = 487</td>
<td>9%</td>
<td>60%</td>
<td>7-fold</td>
</tr>
<tr>
<td>Schwab</td>
<td>n = 683</td>
<td>16%</td>
<td>50%</td>
<td>3-fold</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (unselected)</th>
<th>Overall Grade 3-4 toxicity</th>
<th>TYMS and Grade 3-4 toxicity</th>
<th>TYMS and toxicity relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta analysis</td>
<td>n = 200</td>
<td>22%</td>
<td>52%</td>
<td>2.5 fold</td>
</tr>
<tr>
<td>Schwab</td>
<td>n = 683</td>
<td>16%</td>
<td>22%</td>
<td>1.4 fold</td>
</tr>
</tbody>
</table>

Does UGT1A1*28 homozygosity predict for severe toxicity in patients treated with 5-fluorouracil and irinotecan?

Results of the PETACC3-EORTC 40993-SAKK 60/00 trial comparing Iri/5FU/FA with 5FU/FA in stage II-III colon cancer patients

AD Roth, P Yan, D Dietrich, R Fiocca, G Bodoky, R Labianca, D Cunningham, E Van Cutsem, F Bosman, S Tejpar
Roth, A 2008 Gastrointestinal Symposium abstract 277

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N (%)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A6/A6</td>
<td>582</td>
<td>43.6%</td>
</tr>
<tr>
<td>A6/A7</td>
<td>574</td>
<td>43.0%</td>
</tr>
<tr>
<td>A7/A7</td>
<td>167</td>
<td>12.5%</td>
</tr>
<tr>
<td>A5/A6</td>
<td>5</td>
<td>0.37%</td>
</tr>
<tr>
<td>A5/A7</td>
<td>3</td>
<td>0.22%</td>
</tr>
<tr>
<td>A6/A8</td>
<td>2</td>
<td>0.15%</td>
</tr>
<tr>
<td>A7/A8</td>
<td>2</td>
<td>0.15%</td>
</tr>
</tbody>
</table>

Roth, A 2008 Gastrointestinal Symposium abstract 277

<table>
<thead>
<tr>
<th>Toxicity incidence per genotype</th>
<th>Iri/5FU/LV</th>
<th>5FU/LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>genotype</td>
<td>6/6</td>
<td>6/7</td>
</tr>
<tr>
<td>N (%)</td>
<td>263</td>
<td>279</td>
</tr>
<tr>
<td>Diarrhea 0-2 vs 3-4</td>
<td>42</td>
<td>(16%)</td>
</tr>
<tr>
<td>Neutropenia 0-3 vs 4</td>
<td>67</td>
<td>(25.9%)</td>
</tr>
<tr>
<td>Neutropenia 0-3 vs 4</td>
<td>15</td>
<td>(5.7%)</td>
</tr>
<tr>
<td>Faebrile Neutropenia</td>
<td>17</td>
<td>(6.5%)</td>
</tr>
</tbody>
</table>

Roth, A 2008 Gastrointestinal Symposium abstract 277
Multivariate logistic regression
grade 3-4 neutropenia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Chi square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>0.0148</td>
<td>0.90</td>
</tr>
<tr>
<td>Number of cycle</td>
<td>0.0206</td>
<td>0.89</td>
</tr>
<tr>
<td>Age / 60 y</td>
<td>2.8647</td>
<td>0.09</td>
</tr>
<tr>
<td>Gender (F&gt;M)</td>
<td>12.2304</td>
<td>0.0003</td>
</tr>
<tr>
<td>Performance status (0&gt;1)</td>
<td>6.0087</td>
<td>0.014</td>
</tr>
<tr>
<td>UGT1A1 7/7 (present&gt;absent)</td>
<td>15.1990</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Roth, A 2008 Gastrointestinal Symposium abstract 277

Conclusions

- UGT1A1 7/7 is associated with a
  - decreased incidence of diarrhea
  - increased incidence of grade 3-4 neutropenia and febrile neutropenia

- Basal bilirubin correlated with UGT1A1 7/7 but does not predict toxicity

- Multivariate LR analysis shows UGT1A1 7/7, female gender, PS influence grade 3-4 neutropenia

- Most grade 3-4 neutropenia occurred independent of UGT1A1 genotype

Conclusions who is at risk?

- Risk of diarrhea is not affected by age or PS
- Risk of neutropenia is increased in advanced age, not affected by PS
- Consequences of diarrhea are affected by age, PS and risk of neutropenia

- Genetic
  - About 1 in 14 (7%) patients treated with 5-FU have Grade 3-4 toxicity associated with a DPYD or TYMS gene variation
  - UGT1A1 7/7 polymorphism is associated with a decreased risk of diarrhea (but increased risk of neutropenia)

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Evaluation at first report

- Evaluate
  - Obtain history of onset and duration of diarrhea
  - Describe number of stool and stool composition
  - Assess for fever, dizziness, abd pain/cramping, weakness (risk of sepsis, bowel obstruction, dehydration)
  - Medication profile
  - Dietary profile
**Assess risk**

**Uncomplicated**
- CTC grade 1-2 diarrhea with no complicating signs or symptoms

**Complicated**
- CTC grade 3-4 diarrhea or grade 1-2 with one or more of:
  - Cramping
  - Nausea/vomiting (≥ grade 2)
  - Decreased PS
  - Fever
  - Sepsis
  - Neutropenia
  - Bleeding
  - Dehydration

**Uncomplicated management**
- Stop all lactose-containing products, alcohol, high-osmolar supplements
- Drink 8-10 glasses of clear liquids daily
- Eat frequent small meals (BRAT)
- Instruct patient to keep record of output and symptoms
- For grade 2 diarrhea: hold cytotoxic therapy, consider subsequent dose reduction

**Uncomplicated treatment**
- Administer standard dose loperamide
  - 4 mg followed by 2 mg every 4 hours or after every unformed stool
  - Reassess 12-24 hours later

**Diarrhea resolving**
  - Continue dietary modifications
  - Gradually add solid foods
  - Discontinue loperamide after 12 hour diarrhea-free interval

**Diarrhea unresolved**
  - Loperamide 2 mg every 2 hours
  - Start oral antibiotics
  - Observe for response

**Diarrhea progressing**
  - Loperamide 2 mg every 2 hours
  - Start oral antibiotics
  - Observe for response
/End of one page

**Complicated treatment**

**Complicated at onset**
- Octreotide 100-150 mcg sc TID with dose escalation to 500 mcg or IV 25-50 mcg/hour
- Intravenous fluids and electrolyte evaluation
- Stool evaluation
- Antibiotics

**Diarrhea progressing on therapy**
- Octreotide 100-150 mcg sc TID with dose escalation to 500 mcg as needed
- Other agent (tincture of opium)
- Intravenous fluids and electrolyte evaluation
- Stool evaluation
- Antibiotics

**Cancer therapy modifications**
- Persistent grade 2 or any grade 3-4 should have dose reduction
- Radiation induced diarrhea does not necessarily follow this same algorithm
Loperamide

- **Description**
  - Chemically related to opioids, it does not exhibit anesthetic or opiate-like effects, even at high doses
  - Tolerance to the antidiarrheal effect of loperamide has not been observed, and it does not appear to produce physical dependence

- **Mechanism**
  - Interferes with peristalsis by a direct action on the circular and longitudinal muscles of the intestinal wall to slow motility.
  - Directly inhibits fluid and electrolyte secretion and/or increases water absorption.
  - By increasing the transit time of the intestinal contents, loperamide reduces fecal volume, increases the bulk density and the viscosity of the feces, and decreases the loss of electrolytes and fluids from the body.

Diphenoxylate/Atropine

- **Diphenoxylate**
  - Synthetic opiate agonist with a chemical structure similar to that of meperidine hydrochloride.
  - In higher doses, diphenoxylate can cause euphoria and physical dependence.

- **Atropine**
  - Competitive inhibitor at autonomic postganglionic cholinergic receptors.
  - Decreased gastric secretion; and decreased GI motility.
  - The anticholinergic effects of atropine are generally insignificant when Lomotil® is used in normal doses.

Octreotide

- **Description**
  - Parenteral synthetic analog of the naturally occurring hormone somatostatin

- **Mechanism**
  - Inhibits the secretion of both pituitary and gastrointestinal hormones including serotonin, gastrin, vasodilatory intestinal peptide (VIP), insulin, glucagon, secretin, motilin, pancreatic polypeptide, growth hormone, and thyrotrpin.
  - Inhibiting the secretion of serotonin and other gastrointestinal peptides results in increased intestinal absorption of water and electrolytes, decreased pancreatic and gastric acid secretions, and increased intestinal transit time.

Opium

- **Description**
  - Opium tincture is an alcoholic solution containing 50 mg of anhydrous morphine (as granulated or sliced opium) per 5 ml. The ethanol concentration is 17—21%.
  - Paregoric is 25-times less potent than opium tincture. The concentration difference between these products is the reason that the total dose of opium tincture is given in drops or a fraction of a milliliter while the total dose of paregoric is given as 5—10 ml or as 1—2 teaspoonfuls.

- **Mechanism**
  - Opiate agonists increase smooth muscle tone in the antral portion of the stomach, the small intestine (especially the duodenum), the large intestine, and the sphincters.
  - Opiate agonists also decrease secretions from the stomach, pancreas, and biliary tract. The combination of effects of opiate agonists on the GI tract results in constipation and delayed digestion.

Conclusions

**Appropriate Management**

- Risk assessment for uncomplicated vs complicated diarrhea
  - Number, frequency, consistency
  - Clinical signs/symptoms
  - Laboratory assessment for infection/dehydration
- Dietary restrictions, medication profile
- Frequent re-assessment of symptoms and efficacy of intervention