

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

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

- Diarrhea is a well recognized side effect of cancer therapy
 - GVHD
 - 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

	Patients without colostomy	Patient with colostomy
1	Increase of < 4 stools/day over pretreatment	Mild increase in loose watery colostomy output compared with pretreatment
2	Increase of 4-6 stools/day, or nocturnal stools	Moderate increase in loose watery colostomy output compared with pretreatment, but not interfering with normal activity
3	Increase of 7 stools/day or incontinence; or need for parenteral support for dehydration	Severe increase in loose watery colostomy output compared with pretreatment, interfering with normal activity
4	Physiologic consequences requiring intensive care, or hemodynamic collapse	Physiologic consequences requiring intensive care; or hemodynamic collapse

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 (ie diaries or behavior logs) and effect of interventions
- QOL assessments (functional capacity)

Kornblau et al. *Journal of Pain and Symptom Management* Vol. 19 No. 2 February 2000

SPECIAL ARTICLE

Mortality Associated With Irinotecan Plus Bolus Fluorouracil/Leucovorin: Summary Findings of an Independent Panel

By Marc L. Rothenberg, Neal J. Meropol, Elizabeth A. Poplin, Eric Van Cutsem, and Scott Wadler

Treatment arm	Total Deaths		Treatment-induced Deaths	
	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	11/289	3.8	9/289	3.1
Cisplatin + bolus 5-FU/leucovorin	4/219	1.8	1/219	0.5
5-FU/leucovorin	5/278	1.8	3/278	1.1
Control + irinotecan	23		16	
Total				

Treatment arm	Treatment-induced or Unexplained Deaths		Gastrointestinal Syndrome-induced or Unexplained Deaths	
	No.	%	No.	%
Irinotecan + bolus 5-FU/leucovorin	16/635	2.5	12/635	1.9
Control + 5-FU/leucovorin	5/628	0.8	4/628	0.6
Total	21		16	

Journal of Clinical Oncology, Vol 19, No 18 (September 15, 2001): pp 3891-3907

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
 - b-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 enteroendocrine 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 crypts 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

Overview

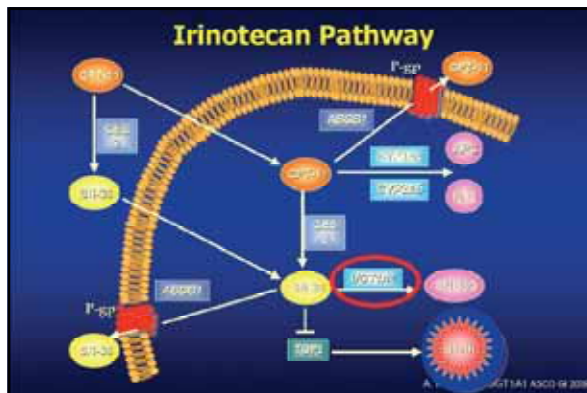
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Pharmacogenetics 5-fluorouracil

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

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

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



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

UGT1A1 genotype frequency

results of 1335 of 1405 samples

Genotype	N	%
A6/A6	582	43.6%
A6/A7	574	43.0%
A7/A7	167	12.5%
A5/A6	5	0.37%
A5/A7	3	0.22%
A6/A8	2	0.15%
A7/A8	2	0.15%

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Toxicity incidence per genotype

genotype	Iri/5FU/LV			5FU/LV		
	6/6	6/7	7/7	6/6	6/7	7/7
N (%)	263	279	87	288	257	74
Diarrhea 0-2 vs 3-4	42 (16%)	30 (10.7%)	7 (8.0%)	32 (11.1%)	14 (5.4%)	3 (4.0%)
Neutropenia 0-2 vs 3-4	67 (25.5%)	72 (25.9%)	39 (44.8%)	22 (7.6%)	19 (7.4%)	7 (9.5%)
Neutropenia 0-3 vs 4	15 (5.7%)	28 (10.1%)	14 (16.1%)	9 (3.1%)	10 (3.9%)	1 (1.3%)
Febrile neutropenia	17 (6.5%)	6 (2.1%)	10 (11.5%)	5 (1.7%)	4 (1.6%)	2 (2.7%)

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Multivariate logistic regression grade 3-4 neutropenia

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

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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

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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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Proposed algorithm for the assessment and management of treatment-induced diarrhea



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Benson, A. B. et al. J Clin Oncol; 22:2918-2926 2004

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 (\geq 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

- (grade 1-2)
- Loperamide 2 mg every 2 hours
- Start oral antibiotics
- Observe for response

• Diarrhea progressing

- (grade 3-4 with or without fever, dehydration, neutropenia, blood)

Uncomplicated treatment

Diarrhea unresolved

(grade 1-2 without fever, dehydration, neutropenia, blood)

• Outpatient evaluation

- Stool studies: C diff, salmonella, E coli, campylobacter, infectious colitis
- Check CBC and electrolytes
- Abdominal exam
- Replace fluids and electrolytes
- Discontinue loperamide and proceed with
 - Octreotide 100-150 mcg sc TID with dose escalation to 500 mcg as needed
 - Other agent (tincture of opium)

Complicated treatment

Complicated at onset

Diarrhea progressing on therapy

(grade 3-4 with or without fever, dehydration, neutropenia, blood)

• Admit to hospital

- 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

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 analgesic 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 inhibit fluid and electrolyte secretion and/or increase 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

- Description
 - synthetic opiate agonist with a chemical structure similar to that of meperidine hydrochloride.
- Mechanism
 - appears to exert its effect locally and centrally on the smooth muscle cells of the GI tract to inhibit GI motility and slow excess GI propulsion.
 - In higher doses, diphenoxylate can cause euphoria and physical dependence, and the administration of opiate antagonists can cause withdrawal symptoms in patients who have been receiving high doses of diphenoxylate.

Atropine

- Description
 - a competitive inhibitor at autonomic postganglionic cholinergic receptors
 - does not block the actions of acetylcholine at the neuromuscular junction
- Mechanism
 - 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, vasoactive intestinal peptide (VIP), insulin, glucagon, secretin, motilin, pancreatic polypeptide, growth hormone, and thyrotropin.
 - Inhibiting the secretion of serotonin and other gastroenteropancreatic 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