Review Article

Evaluation and Management of Treatment-Related Diarrhea in Patients with Advanced Cancer: A Review

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Abstract
Diarrhea is a common and significant problem among patients with advanced cancer. Treatment-induced diarrhea can be severe and be associated with life-threatening dehydration and electrolyte abnormalities. The causes of diarrhea among patients with advanced cancer are diverse and some causes of diarrhea require specific therapies. Thus, careful evaluation of the underlying cause is necessary. Palliative care clinicians, particularly those dealing with patients receiving ongoing disease-modifying therapies, must be familiar with the common causes of diarrhea among cancer patients and the strategies to evaluate and manage these common and distressing symptoms. This article addresses four major issues: 1) a review of the causes of treatment-related diarrhea, focusing on diarrhea caused by chemotherapy, targeted therapies, and radiotherapy; 2) differential diagnosis and an approach to evaluation; 3) general management considerations; and 4) cause-specific issues in management. J Pain Symptom Manage 2008;36:413–423. *© 2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Diarrhea, adverse effects, diagnosis, assessment, management, palliative care, advanced cancer

Introduction

Diarrhea is a common and significant problem among patients with advanced cancer. It is defined as the frequent passage of loose stools with urgency.[1] Objectively defined, it is the passage of more than three unformed stools in 24 hours. Severe diarrhea can be debilitating and, at times, even life threatening. It contributes to dehydration, electrolyte imbalance, malnutrition, declining immune function, and pressure ulcer formation.

Increasingly, diarrhea caused by disease-modifying therapies presents a clinical challenge. Treatment-induced diarrhea can be severe and associated with life-threatening dehydration and electrolyte abnormalities.[2] Given the diverse causes of diarrhea among patients with advanced cancer and the availability of specific therapies, careful evaluation of the underlying cause is necessary. Palliative care clinicians, particularly those dealing with patients receiving ongoing disease-modifying therapies, must be familiar with the common

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causes of treatment-induced diarrhea and the strategies to evaluate and manage this common and distressing disorder.

Causes of Treatment-Related Diarrhea

Chemotherapy-Induced Diarrhea

The chemotherapy agents commonly causing diarrhea include 5-fluorouracil (5-FU), irinotecan (CPT-11), and capecitabine.[2] Diarrhea is usually a dose-related adverse effect and may be associated with other features of toxicity. Chemotherapy-induced diarrhea appears to be a multifactorial process, whereby acute damage to the intestinal mucosa (including loss of intestinal epithelium, superficial necrosis, and inflammation of the bowel wall) causes an imbalance between absorption and secretion in the small bowel.

5-Fluorouracil.

Mechanism. 5-FU causes mitotic arrest of intestinal epithelial crypt cells, resulting in an increase in the ratio of immature secretory crypt cells to mature villous enterocytes. This results in abnormal absorption and secretion of fluids and electrolytes.[3] Opportunistic infections, causing local inflammation and factors released by necrosis secondary to chemotherapy, directly stimulate intestinal secretion of fluids and electrolytes. The diarrhea associated with 5-FU therapy may be watery or bloody. Disruption of the integrity of the gut lining may permit access of enteric organisms into the blood stream, with the potential for overwhelming sepsis, particularly if the granulocyte nadir coincides with diarrhea. Severity is variable but it may be severe and at times life threatening. Pathologic changes range in severity from a mild colitis to severe necrotizing enterocolitis with pneumocystic colitis.

Risk factors. Diarrhea is most commonly observed when 5-FU is coadministered with leucovorin (LV). It is slightly more common with bolus rather than infusional administration of 5-FU/LV, in particular with high-dose LV (500 mg/m^2),[4,5] but it occurs with all administration schedules.[6] In the initial reports of weekly 5-FU/LV, diarrhea was seen in up to 50% of patients, with one-half of these requiring hospitalization for intravenous (IV) fluids[4,5] and, in one study, a 5% mortality rate.[5] Other risk factors have been identified, including unresected primary tumor, previous episodes of chemotherapy-induced diarrhea,[3] and female gender.[7,8]

Dihydropyrimidine dehydrogenase (DPD) deficiency. 5-FU is normally metabolized to inactive dihydro-5-FU after an IV dose; 80% of the drug is metabolized to the inactive dihydro-5-FU by DPD in the liver. Administration of 5-FU to patients with DPD deficiency can lead to life-threatening complications, including severe diarrhea, mucositis, and pancytopenia.[9–11] DPD deficiency is relatively common among Caucasians (3%–5%).[11] Although the diagnosis can be made by radioimmunometric assay for the DPD enzyme, this test is not a readily available, and consequently, most cases are diagnosed retroactively after severe complications. More recently, a simple breath test has been developed[12,13] and this may provide an effective screening tool.[11] Some authorities have suggested that information about DPD deficiency and its consequences be incorporated in discussions of the risks of 5-FU therapy and that patients should be offered the possibility of testing for the presence of a DPD deficiency before initiation of treatment.[14]

Irinotecan. Irinotecan can cause acute diarrhea (immediately after drug administration) or a delayed diarrhea. Immediate-onset diarrhea is caused by acute cholinergic properties and it is often accompanied by other symptoms of cholinergic excess, including abdominal cramping, rhinitis, lacrimation, and salivation. The mean duration of symptoms is 30 minutes and it usually responds rapidly to atropine.[15]

The delayed-onset diarrhea usually occurs at least 24 hours after drug administration and can be potentially life threatening, especially in combination chemotherapy regimens with bolus IV fluorouracil and LV.[15] The late diarrhea associated with irinotecan is unpredictable, noncumulative, and occurs at all dose levels. It is more common with high doses every three weeks than with lower weekly dosing.[15,16] The median time to onset is six to fourteen days. The mechanism of irinotecan-induced delayed diarrhea is not known, but it is believed to result from the deconjugation of CPT's metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38) glucuronide, by intestinal bacteria, thus enabling a direct effect of the active agent on colonic epithelium.[17,18] It is

suggested that the active agent binds to topoisomerase I and induces apoptosis of intestinal epithelia, leading to the disturbance in the absorptive and secretory functions of mucosa. Additionally, both irinotecan and SN-38 may also stimulate the production of proinflammatory cytokines and prostaglandins, thus contributing to an inflammatory/secretory diarrhea.[19]

Genetic factors may influence the glucuronidation of SN-38, the active metabolite of irinotecan, and thus increase this risk of diarrhea. Polymorphisms that alter UDP-glucuronosyltransferase (UGT) activities have been identified; among these is a mutation in the promoter of the UGT1A1 gene (UGT1A1*28), resulting in 5, 7, or 8, instead of 6 thymine-adenine repeats. The homozygous presence of the UGT1A1*28 polymorphism, leading to less efficient glucuronidation of SN-38, has been identified as a potential risk factor for the occurrence of delayed-type diarrhea and Grade 3–4 neutropenia.[20,21] In one study, heterozygote had a twofold elevation of risk of severe diarrhea.[22]

Capecitabine. Capecitabine, a precursor of 5-FU, is an oral fluoropyrimidine cytotoxic agent developed with the aim of providing a more effective, less toxic alternative to 5-FU, with the added advantage of oral administration. Capecitabine is converted to 5-FU in three sequential enzymatic reactions; the final one converting 5'-dFUR to 5-FU being completed by thymidine phosphorylase within tumor cells. The relative concentration of 5-FU generated in tumors is 8–14 times higher than the plasma concentrations. Administered at usual doses (2,000 mg/m^2 per day for 14 of every 21 days), the prevalence of diarrhea is 30%–40% and in 10%–20%, it is severe.[23,24]

Docetaxel. The taxane, docetaxel, commonly causes a relatively mild diarrhea. Data from Phase II and III studies indicated a prevalence of 25%–24%.[25] In most cases, the diarrhea is mild; however, cases of severe enteritis and colitis have been reported.[26]

Neutropenic enterocolitis. Neutropenic enterocolitis (also called necrotizing enterocolitis or typhlitis) is an acute life-threatening complication of chemotherapy that is most commonly observed with high-dose treatments in the setting of myeloablative therapies.[27] It is, however, also observed with nonmyeloablative therapies,[26,28] particularly with taxanes.[26,27,29]

Clinical presentation. Neutropenic enterocolitis usually occurs when the absolute neutrophil count falls below 500/μL. Patients present with fever, abdominal pain, nausea, vomiting, diarrhea, and not uncommonly, sepsis. Abdominal pain may be diffuse or localized to the right lower quadrant. Sometimes pain is absent, particularly in the patient who has received steroid therapy.

Pathogenesis. The pathogenesis of neutropenic enterocolitis is multifactorial: mucosal injury by cytotoxic drugs or other means, profound neutropenia, and impaired host defense to invasion by microorganisms.[27,30] The microbial infection leads to necrosis of various layers of the bowel wall. Anatomically, the cecum is almost always affected, and the process often extends into the ascending colon and terminal ileum. The predilection for the cecum is possibly related to its distensibility and its relatively diminished vascularization. Various bacterial and/or fungal organisms, including gram-negative rods, gram-positive cocci, anaerobes (e.g., *Clostridium septicum*), and *Candida* sp., are often seen infiltrating the bowel wall. Polymicrobial infection is frequent. Bacteremia or fungemia is also common, usually with enteric organisms, such as *Pseudomonas*, or yeasts, such as *Candida*.

Diagnostic investigations. The diagnosis is based on signs and symptoms in the appropriate clinical setting as well as imaging studies. Plain abdominal radiographs may demonstrate dilated loops of bowel, thickening of the bowel wall, "thumbprinting" resulting from bowel wall edema, or indications of a right lower quadrant mass or phlegmon. Free intraperitoneal air indicates perforation of the bowel wall. Pneumatosis intestinalis is often seen.

Computed tomography (CT) scanning is the preferred imaging modality. CT scanning techniques can evaluate the entire abdomen for pathology, especially in patients with distended loops of bowel and ileus, for whom ultrasound would not be possible. Scans commonly demonstrate concentric thickening of the bowel wall, a fluid-filled cecum, pericolic fluid collections or abscesses, pneumatosis intestinalis, and free air if an underlying perforation exists.

Abdominal ultrasonography can identify thickening of the bowel wall that produces

a target or halo sign. Indeed, bowel wall thickening of greater than 5 mm and greater than 10 mm was associated with mortality of 29% and 60%, respectively.[31] Ultrasound is useful as a follow-up tool to assess the gradual decrease in bowel wall thickening during resolution.

Targeted Therapy-Associated Diarrhea

Erlotinib and Gefitinib. Diarrhea is a common adverse effect of the epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors, erlotinib[32] or gefitinib.[33] It occurs in 40%–60% of patients, but it is rarely severe. When these agents are coadministered with 5-FU, irinotecan, and/or capecitabine, the toxicity may exacerbate.

Sorafenib. Sorafenib is an inhibitor of multiple tyrosine kinases in the vascular EGF pathway. At the recommended dose of 400 mg twice daily, it causes diarrhea in 30%–45% of patients treated; in 5%, diarrhea is severe.[34,35] For mild or moderate diarrhea, loperamide is usually effective. For more severe toxicity, stopping the drug until symptoms resolve (usually one to three days) and restarting therapy at 400 mg per day usually controls the diarrhea.

Sunitinib. Sunitinib is a multitargeted tyrosine-kinase inhibitor that is used in the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors (GISTs) after disease progression on, or intolerance to, imatinib. At the usual dose of 50 mg/day, diarrhea is seen in 40% of patients, which is severe in approximately 5%.[36]

Imatinib. Imatinib, an inhibitor of the Bcr-Abl protein tyrosine kinase used in chronic myelogenous leukemia and GIST, causes diarrhea in about 30%–50% of the patients, which is severe in 1%–5%.[37,38] Diarrhea is dose related and can be easily controlled with antidiarrheal medications. It is hypothesized that diarrhea may be related to C-Kit inhibition in the interstitial cells of Cajal, which have a pacemaker function in the intestine.[37]

Bortezomib. Diarrhea is commonly seen with the use of bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma and mantle cell lymphoma. In the pivotal studies with this agent, diarrhea occurred in 51% of patients, with 8% of the events being severe.[39]

Radiotherapy-Induced Diarrhea

Radiation injury to the lower intestine is usually encountered following treatment of cancers of the anus, rectum, cervix, uterus, prostate, urinary bladder, or testes, and as part of total body irradiation. Radiotherapy of the abdomen or pelvis damages intestinal mucosa, causing prostaglandin release and bile salt malabsorption. These two factors increase intestinal peristalsis, causing diarrhea.

Acute radiation enteritis/proctitis occurs within six weeks of therapy. Symptoms include diarrhea, cramping, rectal urgency or tenesmus, and, uncommonly, bleeding. These symptoms usually resolve without specific therapy within two to six months.[40,41]

Chronic radiation enteritis is less common. It most commonly presents as the delayed development of diarrhea, nausea, weight loss or abdominal pain, or any combination of these symptoms. It is usually associated with radiation doses greater than 45 Gy and it appears after a latency of months to years after the initial exposure.[41,42] The underlying pathology is a progressive radiation-induced endarteritis that causes intestinal ischemia. The ischemia may result in fibrosis, stricturing, ulceration, and occasionally fistula formation. The physiologic consequences of these changes include altered intestinal transit, reduced bile acid absorption, increased intestinal permeability, bacterial overgrowth, and lactose malabsorption.[41]

Other Causes of Treatment-Related Diarrhea

Medications. Excessive doses of laxatives or magnesium-containing antacids commonly result in diarrhea.

Clostridium Difficile Diarrhea. *Clostridium difficile* diarrhea occurs when the normal intestinal flora is altered, allowing *C. difficile* to flourish in the intestinal tract and produce a toxin that causes a watery diarrhea.[43] It can be triggered by repeated enemas, prolonged nasogastric tube insertion, gastrointestinal (GI) tract surgery,

and the use of antibiotics, especially penicillin (ampicillin), clindamycin, and cephalosporins. Occasionally, however, it has been reported after chemotherapy in the absence of antibiotic therapy.[44,45] The most common confirmatory study is an enzyme immunoassay for *C. difficile* toxins A and B. The test is easy to perform, and results are available in two to four hours. Specificity of the assay is high (93%–100%), but sensitivity ranges from 63% to 99%.[46]

Enteral Feeding. Tube feedings, either by nasogastric tube, gastrostomy, or jejunostomy, may be associated with the development of diarrhea.[47,48] This is a common problem, occurring in 10%–60% of patients.[49] Many potential factors may contribute to the problem and indeed it is often multifactorial.[50] The composition of formula may affect the incidence of diarrhea. Both formula osmolality and rate of delivery may be associated with diarrhea.[51] The use of fiber-containing formulas to control diarrhea related to tube feeding is controversial and evidence of efficacy is mixed.[52,53]

Contamination of the enteral formula is often a contributing or causative factor.[54,55] Recommendations to reduce the risk of contamination include hand washing before handling the feeding system, the use of clean equipment to prepare and mix feedings, jevity bag and tubing change at least once a day, limitation of "hanging time" of individual bags to under six hours, and refrigerated storage of prepared bags until use.

Patients selected for tube feeding are often hypoalbuminemic. Some data suggest that hypoalbuminemia predisposes patients to diarrhea by decreasing osmotic pressure and causing edema in the intestinal mucosa.[56]

Celiac Plexus Block. Celiac plexus block is commonly associated with a self-limiting acute diarrhea. Occasionally, diarrhea may be persistent.[57] This diarrhea may be amenable to treatment with atropine.[58]

Differential Diagnosis of Diarrhea in Patients with Advanced Cancer

There are other common causes of diarrhea in patients with advanced cancer and these often need to be considered in the differential diagnosis. Occasionally, fecal impaction or partial bowel obstruction can manifest as alternating constipation and diarrhea. Fecal impaction results in bacterial degradation of stools above the level of impaction, resulting in fluid stool leaking past the impacted mass, sometimes with incontinence. In some instances, diarrhea may be caused by comorbidities such as inflammatory bowel disease (IBD) and thyroxicosis.

Cancers can cause malabsorption syndromes by a number of mechanisms. Each of these is characterized by increased fecal fat. Pancreatic cancer may be associated with obstruction of the pancreatic duct, pancreatic exocrine failure, or biliary obstruction.[59] In some cases, patients who have undergone either Whipple's procedure or a gastrectomy with a roux-en-y may develop bacterial overgrowth within the efferent loop, which may result in a malabsorption syndrome.[60] Resection of more than 100 cm of ileum can hinder the reabsorption of bile acids, causing a watery diarrhea.[61] Ileal resection also causes a disaccharidase deficiency, resulting in carbohydrate malabsorption and an osmotic diarrhea.

Colectomy reduces the water absorbing capacity that occurs in the colon, which cannot be fully compensated by the small bowel and also can result in diarrhea. Changes in intestinal anatomy may cause bacterial overgrowth, resulting in diarrhea.

A number of pancreatic islet cell tumors may be associated with severe secretory diarrhea with hypokalemia.[62] Vasoactive intestinal protein-secreting tumors may cause severe life-threatening watery diarrhea. Similar problems may be seen in some patients with carcinoid syndrome. Less severe diarrhea may be observed with gastrinomas causing a Zollinger Ellison Syndrome. Finally, diarrhea is also sometimes observed with medullary carcinoma of the thyroid[63] and GIST.[64]

Assessment

The U.S. National Cancer Institute's grading for the severity of diarrhea is presented in Table 1. In the setting of chemotherapy-induced diarrhea, it is an important consideration in treatment selection (see below).

The assessment of a patient with possible treatment-induced diarrhea should include a detailed medical history, dietary history, medication review, description of stools, and

Table 1
U.S. National Cancer Institute Common Toxicity Criteria for Grading of Diarrhea

Toxicity	0	1	2	3	4
Patients without a colostomy	None	Increase of <4 stools/d over pretreatment	Increase of 4–6 stools/d or nocturnal stools	Increase of ≥7 stools/d	>10 stools/d
	None	None	Moderate cramping, not interfering with normal activity	Severe cramping and incontinence, interfering with daily activities	Grossly bloody diarrhea and need for parenteral support
Patients with a colostomy	None	Mild increase in loose, watery colostomy output compared with pretreatment	Moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	Severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	Physiological consequences requiring intensive care; hemodynamic

Adapted from Ref. 80.

a physical examination focused on the identification of dehydration, and abnormalities of the abdominal and rectal areas. When appropriate, abdominal radiographs can be ordered to evaluate for abdominal obstruction or fecal impaction. Biochemical parameters should be checked for evidence of dehydration, hypokalemia, or renal impairment. If enteric infections are suspected, stool samples should be sent for fecal leukocytes, *C. difficile* toxins A and B, and culture for organisms including *C. difficile*, *Salmonella*, *Escherichia coli*, *Campylobacter*, and infectious colitis. As described above, when neutropenic enterocolitis is suspected, CT imaging of the abdomen should be undertaken and additional prognostic information may be obtained by ultrasound evaluation of bowel wall thickness.

General Principles in the Management of Diarrhea

Patients must be rehydrated either orally, or when appropriate, by parenteral infusion. In cases of large volume diarrhea, there is the potential for very rapid dehydration with risk of prerenal impairment or even, in extreme cases, shock. Patients may suffer electrolyte imbalance, particularly hypokalemia. Because a transient lactase deficiency with lactose malabsorption can occur with any form of mucosal injury to the GI tract, milk products should be avoided. Special attention should be given to patients who are incontinent of stool due to the risk of pressure ulcer formation. Skin barriers should be used to prevent skin irritation caused by fecal material.

Antidiarrheal Medications

Opioids. Loperamide is generally the opioid of choice because it has local activity in the gut and is absorbed only minimally (this accounts for the lack of systemic effects).[65] It reduces stool weight, frequency of bowel movements, urgency, and fecal incontinence in acute and chronic diarrhea. Loperamide can be started at an initial dose of 4 mg followed by 2 mg every two to four hours or after every unformed stool.[66] Other opioids, such as tincture of opium, morphine, or codeine, can be used.

"Tincture of opium" is a widely used antidiarrheal agent. It is often recommended as an alternative to loperamide. Deodorized tincture of opium contains the equivalent of 10 mg/mL morphine and the recommended dose is 10–15 drops in water every three to four hours.[67] It is important not to confuse this with paregoric, which is a camphorated (alcohol-based) tincture. The latter is a less-concentrated preparation that contains the equivalent of 0.4 mg/mL morphine. The recommended dose is one teaspoon (5 mL) in water every three to four hours.[67]

Somatostatin Analogs. In cases of severe or persistent diarrhea, the somatostatin analog octreotide should be considered. Octreotide has multiple antidiarrheal actions, including

suppression of release of insulin, glucagon, vasoactive intestinal peptide, and gastric acid; reduction in motility; and increased absorption of water, electrolytes, and nutrients from the GI tract.[68] The usual starting dose for octreotide is 100–150 μg SC/IV three times daily. Because there is a dose-response relationship with regard to the antidiarrheal effect, the dose can be titrated up to 500 μg subcutaneous (SC)/IV three times daily or by continual IV infusion 25–50 μg/h.[69] Recently, a microencapsulated, long-acting formulation of octreotide has been developed for once monthly intramuscular dosing. This formulation has demonstrated efficacy in resolving severe diarrhea and preventing further episodes of diarrhea in patients receiving ongoing therapy.[70]

Other Agents. Budesonide is an orally administered, topically active steroid with high activity in IBD, a 90% first pass effect in the liver and, therefore, low systemic availability. It is commonly used in the management of diarrhea in patients with low-to-medium grade IBD. One small study has demonstrated efficacy of oral budesonide in the management of chemotherapy-induced diarrhea that was refractory to loperamide.[71]

Specific Management Guidelines

Acute Chemotherapy-Induced or Radiotherapy-Induced Diarrhea

Standard guidelines for management of acute treatment-induced diarrhea were published in 2004.[69] Patients are classified as uncomplicated or complicated on the basis of clinical features and this classification guides treatment approach.

"Uncomplicated" Diarrhea.

Step 1: Patients with Grade 1 or 2 diarrhea and no other complicating signs or symptoms may be classified as "uncomplicated" and managed conservatively with oral hydration and loperamide. Initial management of mild-to-moderate diarrhea should include dietary modifications (e.g., eliminating all lactose-containing products and high-osmolar dietary supplements). The patient should be instructed to record the number of stools and report other serious symptoms (e.g., fever or dizziness on standing). Loperamide should be started at an initial dose of 4 mg followed by 2 mg every four hours or after every unformed stool (not to exceed 16 mg/d). If diarrhea resolves with loperamide, the patients should be instructed to continue dietary modifications and to gradually add solid foods to their diet. In the case of chemotherapy-induced diarrhea, patients may discontinue loperamide when they have been diarrhea-free for at least 12 hours.

Step 2: If mild-to-moderate diarrhea persists for more than 24 hours, the dose of loperamide should be increased to 2 mg every two hours, and oral antibiotics may be started as prophylaxis for infection.

Step 3: If mild-to-moderate chemotherapy-induced diarrhea has not resolved after 24 hours on high-dose loperamide (48 hours total treatment with loperamide), the patient should be seen in the physician's office or outpatient center for further evaluation, including complete stool and blood work-up. Stool work-up should include evaluation for pathogens. Fluids and electrolytes should be replaced as needed. Loperamide should be discontinued and the patient should be started on a second-line antidiarrheal agent, such as octreotide (100 μg to 150 μg starting dose, with dose escalation as needed) or other second-line agents (e.g., oral budesonide or tincture of opium).

"Complicated" Chemotherapy-Induced Diarrhea. Patients with mild-to-moderate diarrhea complicated by moderate-to-severe cramping, nausea, and vomiting; diminished performance status, fever, sepsis, neutropenia, bleeding, or dehydration; and patients with severe diarrhea, are classified as "complicated." These patients should be evaluated further, monitored closely and treated aggressively.

Aggressive management of complicated cases usually necessitates hospital admission and involves IV fluids; octreotide at a starting dose of 100–150 μg three times daily (25–50 μg/h) if the patient is severely dehydrated, with dose escalation up to 500 μg three times daily until diarrhea is controlled, and administration of antibiotics (e.g., fluoroquinolone). These patients should be evaluated with complete blood count, electrolyte profile, and a stool work-up evaluating for blood, fecal leukocytes, *C. difficile*, *Salmonella*, *E. coli*, *Campylobacter*, and infectious colitis.

Chronic Radiation Therapy-Induced Diarrhea

Opioid antidiarrheal agents are recommended, but are relatively contraindicated in patients with obstructive symptoms. Antibiotics may reduce diarrhea in patients in whom there is evidence of bacterial overgrowth on breath testing.[72] Most recently, there is accumulating anecdotal evidence that hyperbaric oxygen therapy may help relieve symptoms of chronic radiation enteritis.[73–75]

Management of Neutropenic Enterocolitis

Management of neutropenic enterocolitis is challenging and the risk of mortality is high. There are roles for both medical and surgical interventions.

The initial treatment for neutropenic colitis is medical, with the administration of broad-spectrum antibiotics, granulocyte colony-stimulating factors, nasogastric decompression, IV fluids, bowel rest, and serial abdominal examinations.[27,30,76] In most patients, these measures are sufficient, and symptoms resolve after correction of the neutropenia. The administered antibiotics should have a broad spectrum of activity to cover enteric gram-negative organisms, gram-positive organisms, and anaerobes. Causative microorganisms include *Pseudomonas*, *Staphylococcus aureus*, *E. coli*, and Group A *Streptococcus*.[76] In cases that do not respond to antibacterial agents, amphotericin should be considered, because fungemia is common.[27,77] Blood transfusions may be necessary because the diarrhea is often bloody. Anticholinergic, antidiarrheal, and opioid agents should be avoided because they may aggravate ileus.

The indications for, and timing of, surgical intervention are controversial. The mortality of patients who fail to respond to medical interventions is high and many patients may not be salvageable. Nonetheless, in selected patients, surgery may be helpful to avoid progressive bowel necrosis, perforation, and to help control sepsis. Commonly cited indications for surgery include: 1) persistent GI bleeding after correction of thrombocytopenia and coagulopathy; 2) evidence of intraperitoneal perforation; 3) abscess formation 4) clinical deterioration despite aggressive supportive measures; and 5) to rule out other intra-abdominal processes such as bowel obstruction or acute appendicitis.[27,30,76,78,79]

If exploratory surgery is performed, resection of grossly involved bowel is necessary. All necrotic material must be resected, usually by a right hemicolectomy, ileostomy, and mucous fistula. Failure to remove the necrotic focus in these severely immunocompromised patients is potentially fatal.[78,79] Primary anastomosis is not generally recommended in such severely immunocompromised patients because of the increased incidence of anastomotic leak.[78,79] Because anastomotic leak in this setting is almost always fatal, primary anastomosis should be considered only for uncomplicated cases in patients with no systemic sepsis or organ failure.

Conclusions

Diarrhea may pose a major management issue for cancer and palliative care clinicians. There is a clinical imperative for clinicians to be familiar with the common causes of treatment-induced diarrhea, its evaluation, and management strategies. Treatment-induced diarrhea remains a fertile domain for ongoing clinical and basic investigation. Better understanding of the mechanisms of these diverse syndromes may help facilitate new approaches to prophylaxis and risk reduction, and the development of more effective approaches to acute and long-term management.

References

1. Alderman J. Diarrhea in palliative care. J Palliat Med 2005;8(2):449–450.

2. Arnold RJ, Gabrail N, Raut M, et al. Clinical implications of chemotherapy-induced diarrhea in patients with cancer. J Support Oncol 2005;3(3): 227–232.

3. Cascinu S, Barni S, Labianca R, et al. Evaluation of factors influencing 5-fluorouracil-induced diarrhea in colorectal cancer patients. An Italian Group for the Study of Digestive Tract Cancer (GISCAD) study. Support Care Cancer 1997;5(4):314–317.

4. Petrelli N, Herrera L, Rustum Y, et al. A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol 1987;5(10):1559–1565.

5. Petrelli N, Douglass HO Jr, Herrera L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective

randomized phase III trial. Gastrointestinal Tumor Study Group. J Clin Oncol 1989;7(10):1419–1426.

6. Meta-Analysis Group In Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. Meta-Analysis Group In Cancer. J Clin Oncol 1998;16(11):3537–3541.

7. Chansky K, Benedetti J, Macdonald JS. Differences in toxicity between men and women treated with 5-fluorouracil therapy for colorectal carcinoma. Cancer 2005;103(6):1165–1171.

8. Sloan JA, Goldberg RM, Sargent DJ, et al. Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. J Clin Oncol 2002;20(6):1491–1498.

9. Harris BE, Carpenter JT, Diasio RB. Severe 5-fluorouracil toxicity secondary to dihydropyrimidine dehydrogenase deficiency. A potentially more common pharmacogenetic syndrome. Cancer 1991;68(3):499–501.

10. Houyau P, Gay C, Chatelut E, et al. Severe fluorouracil toxicity in a patient with dihydropyrimidine dehydrogenase deficiency. J Natl Cancer Inst 1993; 85(19):1602–1603.

11. Mercier C, Ciccolini J. Profiling dihydropyrimidine dehydrogenase deficiency in patients with cancer undergoing 5-fluorouracil/capecitabine therapy. Clin Colorectal Cancer 2006;6(4):288–296.

12. Mattison L, Ezzeldin H, Carpenter M, et al. Rapid identification of dihydropyrimidine dehydrogenase deficiency by using a novel 2-13C-uracil breath test. Clin Cancer Res 2004;10:2652–2658.

13. Mattison LK, Fourie J, Hirao Y, et al. The uracil breath test in the assessment of dihydropyrimidine dehydrogenase activity: pharmacokinetic relationship between expired 13CO2 and plasma [2-13C]dihydrouracil. Clin Cancer Res 2006;12(2):549–555.

14. van Kuilenburg AB. Screening for dihydropyrimidine dehydrogenase deficiency: to do or not to do, that's the question. Cancer Invest 2006;24(2): 215–217.

15. Hecht JR. Gastrointestinal toxicity or irinotecan. Oncology (Williston Park) 1998;12(8 Suppl 6):72–78.

16. Abigerges D, Armand JP, Chabot GG, et al. Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. J Natl Cancer Inst 1994;86(6):446–449.

17. Takasuna K, Hagiwara T, Hirohashi M, et al. Inhibition of intestinal microflora beta-glucuronidase modifies the distribution of the active metabolite of the antitumor agent, irinotecan hydrochloride (CPT-11) in rats. Cancer Chemother Pharmacol 1998;42(4):280–286.

18. Alimonti A, Gelibter A, Pavese I, et al. New approaches to prevent intestinal toxicity of irinotecan-based regimens. Cancer Treat Rev 2004;30(6): 555–562.

19. Yang X, Hu Z, Chan SY, et al. Novel agents that potentially inhibit irinotecan-induced diarrhea. Curr Med Chem 2005;12(11):1343–1358.

20. Iyer L, Das S, Janisch L, et al. UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenomics J 2002;2(1): 43–47.

21. Toffoli G, Cecchin E, Corona G, et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. J Clin Oncol 2006;24(19):3061–3068.

22. de Jong FA, Kehrer DF, Mathijssen RH, et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1*28 genotype screening: a double-blind, randomized, placebo-controlled study. Oncologist 2006;11(8): 944–954.

23. Van Cutsem E, Findlay M, Osterwalder B, et al. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. J Clin Oncol 2000;18(6):1337–1345.

24. Walko CM, Lindley C. Capecitabine: a review. Clin Ther 2005;27(1):23–44.

25. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095–2103.

26. Ibrahim NK, Sahin AA, Dubrow RA, et al. Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. Lancet 2000;355(9200):281–283.

27. Bremer CT, Monahan BP. Necrotizing enterocolitis in neutropenia and chemotherapy: a clinical update and old lessons relearned. Curr Gastroenterol Rep 2006;8(4):333–341.

28. Ferrazzi E, Toso S, Zanotti M, Giuliano G. Typhlitis (neutropenic enterocolitis) after a single dose of vinorelbine. Cancer Chemother Pharmacol 2001;47(3):277–279.

29. D'Amato G, Rocha Lima C, Mahany JJ, Muro-Cacho C, Haura EB. Neutropenic enterocolitis (typhilitis) associated with docetaxel therapy in a patient with non-small-cell lung cancer: case report and review of literature. Lung Cancer 2004; 44(3):381–390.

30. Davila ML. Neutropenic enterocolitis. Curr Treat Options Gastroenterol 2006;9(3):249–255.

31. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol 2001;19(3): 756–761.

32. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. Oncologist 2005;10(7):461–466.

33. Cersosimo RJ. Gefitinib: an adverse effects profile. Expert Opin Drug Saf 2006;5(3):469–479.

34. Kane RC, Farrell AT, Saber H, et al. Sorafenib for the treatment of advanced renal cell carcinoma. Clin Cancer Res 2006;12(24):7271–7278.

35. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356(2):125–134.

36. Rock EP, Goodman V, Jiang JX, et al. Food and Drug Administration drug approval summary: sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist 2007;12(1):107–113.

37. Guilhot F. Indications for imatinib mesylate therapy and clinical management. Oncologist 2004;9(3):271–281.

38. Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 2002; 8(10):3034–3038.

39. Berenson JR, Jagannath S, Barlogie B, et al. Safety of prolonged therapy with bortezomib in relapsed or refractory multiple myeloma. Cancer 2005;104(10):2141–2148.

40. Babb RR. Radiation proctitis: a review. Am J Gastroenterol 1996;91(7):1309–1311.

41. Bismar MM, Sinicrope FA. Radiation enteritis. Curr Gastroenterol Rep 2002;4(5):361–365.

42. Jain G, Scolapio J, Wasserman E, Floch MH. Chronic radiation enteritis: a ten-year follow-up. J Clin Gastroenterol 2002;35(3):214–217.

43. Poutanen SM, Simor AE. *Clostridium difficile*-associated diarrhea in adults. CMAJ 2004;171(1): 51–58.

44. Jarvis B, Shevchuk YM. Recurrent *Clostridium difficile* diarrhea associated with mitoxantrone and etoposide: a case report and review. Pharmacotherapy 1997;17(3):606–611.

45. Yamazawa K, Kanno H, Seki K, et al. Life-threatening *Clostridium difficile*-associated diarrhea induced by paclitaxel-carboplatin combination chemotherapy. Acta Obstet Gynecol Scand 2001; 80(8):768–769.

46. Schroeder MS. *Clostridium difficile*-associated diarrhea. Am Fam Physician 2005;71(5):921–928.

47. Whelan K, Hill L, Preedy VR, Judd PA, Taylor MA. Formula delivery in patients receiving enteral tube feeding on general hospital wards: the impact of nasogastric extubation and diarrhea. Nutrition 2006;22(10):1025–1031.

48. Reese JL, Means ME, Hanrahan K, et al. Diarrhea associated with nasogastric feedings. Oncol Nurs Forum 1996;23(1):59–66. discussion 66–68.

49. American Gastroenterological Association. Medical Position Statement: guidelines for the use of enteral nutrition. Gastroenterology 1995;108(4): 1280–1281.

50. Burns PE, Jairath N. Diarrhea and the patient receiving enteral feedings: a multifactorial problem. J Wound Ostomy Continence Nurs 1994;21(6): 257–263.

51. Hiebert JM, Brown A, Anderson RG, et al. Comparison of continuous vs intermittent tube feedings in adult burn patients. JPEN J Parenter Enteral Nutr 1981;5(1):73–75.

52. Bass DJ, Forman LP, Abrams SE, Hsueh AM. The effect of dietary fiber in tube-fed elderly patients. J Gerontol Nurs 1996;22(10):37–44.

53. Collier P, Kudsk KA, Glezer J, Brown RO. Fiber–containing formula and needle catheter jejunostomies: a clinical evaluation. Nutr Clin Pract 1994; 9(3):101–103.

54. Okuma T, Nakamura M, Totake H, Fukunaga Y. Microbial contamination of enteral feeding formulas and diarrhea. Nutrition 2000;16(9):719–722.

55. Mickschl DB, Davidson LJ, Flournoy DJ, Parker DE. Contamination of enteral feedings and diarrhea in patients in intensive care units. Heart Lung 1990;19(4):362–370.

56. Schwartz DB, Darrow AK. Hypoalbuminemia-induced diarrhea in the enterally alimented patient. Nutr Clin Pract 1988;3(6):235–237.

57. Chan VW. Chronic diarrhea: an uncommon side effect of celiac plexus block. Anesth Analg 1996;82(1):205–207.

58. Cataldo R, Potash M. Atropine as a treatment of diarrhea after celiac plexus block. [letter; comment]. Anesth Analg 1996;83(5):1131–1132.

59. Wakasugi H, Hara Y, Abe M. A study of malabsorption in pancreatic cancer. J Gastroenterol 1996; 31(1):81–85.

60. King CE, Toskes PP. Malabsorption following gastric resection. Major Probl Clin Surg 1976;20: 129–146.

61. Hofmann AF. Bile acid malabsorption caused by ileal resection. Arch Intern Med 1972;130(4): 597–605.

62. Eriksson B, Oberg K, Skogseid B. Neuroendocrine pancreatic tumors. Clinical findings in a prospective study of 84 patients. Acta Oncol 1989; 28(3):373–377.

63. Zamir D, Polychuck I, Leibovitz I, et al. Diarrhea and hypokalemia as primary manifestations of medullary carcinoma of the thyroid. Am J Med 2002;113(5):438–439.

64. Jothi SP, Miller S. Gastrointestinal carcinoid tumor in a patient with chronic diarrhea. Arch Intern Med 2002;162(1):95–96.

65. Ruppin H. Review: loperamide—a potent antidiarrhoeal drug with actions along the alimentary tract. Aliment Pharmacol Ther 1987;1(3):179–190.

66. Cascinu S, Bichisao E, Amadori D, et al. High–dose loperamide in the treatment of 5-fluorouracil-induced diarrhea in colorectal cancer patients. Support Care Cancer 2000;8(1):65–67.

67. Lesar T. Prescribing errors involving medication dosage forms. J Gen Intern Med 2002;17(8): 579–587.

68. Szilagyi A, Shrier I. Systematic review: the use of somatostatin or octreotide in refractory diarrhoea. Aliment Pharmacol Ther 2001;15(12):1889–1897.

69. Benson AB 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004; 22(14):2918–2926.

70. Rosenoff S. Resolution of refractory chemotherapy-induced diarrhea (CID) with octreotide long-acting formulation in cancer patients: 11 case studies. Support Care Cancer 2004;12(8): 561–570.

71. Lenfers BH, Loeffler TM, Droege CM, Hausamen TU. Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. Ann Oncol 1999;10(10):1251–1253.

72. Beer WH, Fan A, Halsted CH. Clinical and nutritional implications of radiation enteritis. Am J Clin Nutr 1985;41(1):85–91.

73. Huddy JE, Patel P, Johnson MW, et al. Hyperbaric oxygen as a treatment for malabsorption in a radiation-damaged short bowel. Eur J Gastroenterol Hepatol 2006;18(6):685–688.

74. Marshall GT, Thirlby RC, Bredfeldt JE, Hampson NB. Treatment of gastrointestinal radiation injury with hyperbaric oxygen. Undersea Hyperb Med 2007;34(1):35–42.

75. Neurath MF, Branbrink A, Meyer zum Buschenfelde KH, Lohse AW. A new treatment for severe malabsorption due to radiation enteritis [Letter]. Lancet 1996;347(9011):1302.

76. Avigan D, Richardson P, Elias A, et al. Neutropenic enterocolitis as a complication of high dose chemotherapy with stem cell rescue in patients with solid tumors: a case series with a review of the literature. Cancer 1998;83(3):409–414.

77. Starnes HF Jr, Moore FD Jr, Mentzer S, et al. Abdominal pain in neutropenic cancer patients. Cancer 1986;57(3):616–621.

78. Urbach DR, Rotstein OD. Typhlitis. Can J Surg 1999;42(6):415–419.

79. Moir CR, Scudamore CH, Benny WB. Typhlitis: selective surgical management. Am J Surg 1986; 151(5):563–566.

80. National Cancer Institute. Cancer therapy evaluation program common toxicity criteria, version 2.0. Bethesda, MD: National Institutes of Health, 1999, p. 11.