OBJECTIVES:

To describe the dietary and pharmacologic management of acute CTID.

DATA SOURCES:

Primary and secondary literature, and clinical experience.

CONCLUSION:

When dietary strategies do not work, or when patients present with grade 3/4 diarrhea, pharmacologic intervention is required. First-line therapy should be initiated quickly with loperamide or diphenoxylate/atropine in recommended doses. Somatostatin analogues are effective as second-line therapy or as first-line therapy for patients with grade 3/4 diarrhea.

IMPLICATIONS FOR NURSING PRACTICE:

Oncology nurses should strive to match treatment with the severity of symptoms of CTID. Whatever therapy is chosen, the goal must be to quickly control this debilitating and potentially life-threatening side effect so that primary chemotherapy and/or radiation therapy may be resumed and completed.

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MANAGEMENT OF ACUTE CANCER TREATMENT–INDUCED DIARRHEA

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TREATMENT OVERVIEW

ALTHOUGH newer chemotherapy agents and combination regimens have shown increased efficacy in controlling disease and prolonging survival, they are not without risk. For example, severe diarrhea has contributed to the death of some patients receiving irinotecan plus bolus 5-fluorouracil (5-FU)/leucovorin in recent clinical trials.[1] This unexpected mortality has led to changes in labeling that now mandate close clinical monitoring and early treatment of diarrhea in patients receiving irinotecan-based regimens. According to this new labeling, dose reductions are recommended for patients who experience chemotherapy-induced diarrhea (CID), and irinotecan therapy should not be resumed until diarrhea has completely resolved.[2]

Current guidelines for the treatment of CID were developed in 1998 by an expert multidisciplinary panel of physicians, nurses, and pharmacists.[3] These guidelines recommend (1) that all patients receiving chemotherapy known to have diarrhea as an adverse effect should be counseled and monitored closely, and (2) that diarrhea of any grade should be treated aggressively. For patients with diarrhea unresolved by dietary changes, the opioid loperamide is initially recommended. For patients with continued diarrhea despite aggressive loperamide therapy, pharmacologic treatment that acts directly to reduce excess secretion (eg, the somastostatin analogue octreotide) may be used.

TABLE 1.

Nutritional and Dietary Guidelines for Patients With Cancer Treatment-Induced Diarrhea[3-10]

General Nutritional Guidelines	Ostomy Guidelines	Foods to Avoid
Small, frequent meals		Spices that make food taste "hot"
Minimize fluid intake with meals		High-fat and fried foods
		Gas-causing foods
		Sugar alcohols
Ample intake of liquids throughout the day	Match fluid intake to	Alcohol and caffeine
30 to 35 mL/kg needed per day	output volume	High-sorbitol juices
Iso-osmotic, calorie-containing beverages		Prune, pear, sweet cherry, peach, apple
Cool or warm, not hot or cold		Very hot or cold beverages
Replace electrolytes, minerals	Check vitamin status	
Sources of sodium (Na), potassium (K), zinc (Zn), and magnesium (Mg)	B_{12}, A, D, E, K	
Adequate soluble fiber		Insoluble-fiber foods
Protein-rich foods		Gas-causing legumes
		Milk and dairy products in some patients: substitute low-lactose alternatives
Eat slowly in a relaxed atmosphere		"High-risk" foods
		Sushi, street vendors, buffets

Nutritional Management of Acute Cancer Treatment-Induced Diarrhea

Achieving proper nutrition goals is key to the management of acute cancer treatment-induced diarrhea (CTID). Nutritional management includes prevention of food-borne illness through the practice of good food safety techniques, such as hand washing, scrupulous care around raw meats, cooking foods to proper temperature, refrigerating foods promptly to below 40°F, and observing expiration/"use by" dates. Nutrition goals for patients include maintaining weight and lean body mass via adequate calorie and protein intake along with physical activity as tolerated, replacing lost fluids and electrolytes, and assuring adequate intake of vitamins and minerals. Patients with ostomies should pay particular attention to maintaining adequate intake of fluid and vitamins.

General nutrition guidelines for patients with CTID include eating small, frequent meals and making those meals rich in protein (Table 1).[4,5] Liquids should be taken primarily between meals, so as to avoid over filling at meal times and to maintain adequate fluid intake throughout the day. Eating slowly in a relaxed atmosphere is also important for patients. Soluble fibers, such as oats, pectin, guar, and psyllium (the same types of fiber that may help reduce blood cholesterol levels) may help bind fluid to improve stool volume and quality and nutrient absorption.[6-9] Examples of foods containing soluble fibers include cooked oatmeal and oat bran, barley, applesauce, citrus fruits, potatoes, cooked carrots, and bananas and banana flakes. For maximum success, nutritional guidelines need to take into account patient preferences and limitations, such as ethnic preferences, food tolerances, caregiver availability, and cost.

Diarrhea-promoting foods and beverages should be avoided (Table 1). These include spices such as curry, chili powder, pepper sauce, cayenne, and paprika. Alcohol and caffeine should also be avoided because of their stimulation of intestinal motility, and because alcohol is injurious to the gastrointestinal mucosa. Juices that are high in sorbitol content, such as prune, pear, sweet cherry, peach, apple, and grape juices, should be avoided as well. Lower osmolality fluids, such as one half strength Kool-Aid (Kraft Foods, North Field, IL), low-calorie cranberry juice, or broth should be encouraged. Because sodium can aid the absorption of liquid, electrolyte-containing low carbohydrate drinks such as Gatorade (PepsiCo, Purchase, NY) and Pedialyte (Abbott Laboratories, Abbott Park, IL) are good choices. In some patients, milk is an acceptable choice, though others will develop lactose intolerance because of mucosal injury.[10] In these patients, low-lactose foods such as Lactaid (McNeil Nutritionals, Springhouse, PA) milk, live-culture yogurt, aged cheeses, and soy-based products may be substituted. Insoluble fibers, or "roughage," should be

avoided because they can increase stool bulk and movement of waste through the intestines. Insoluble fibers are found in whole grain cereals, breads and pastas, brown rice, wheat bran, popcorn, many vegetables, and the skins of fruits and root vegetables. Sugar alcohols, including sorbitol, xylitol, maltitol, and mannitol can stimulate severe flatulence and diarrhea. These may be found in food that is labeled as "sugar free" or in high-protein bars, and can be found by checking the ingredient lists of food labels. Finally, herbal supplements that induce diarrhea should be avoided, such as aloe, buckthorn, cascara, flaxseed, manna, milk thistle, panax ginseng, psyllium seed, rhubarb root, and senna.[11-13]

Other considerations in the treatment of CTID include assessing the patient for the presence of exocrine pancreatic deficiency, which may occur in patients with malignancies that have necessitated either partial gastrectomy or pancreatectomy.[14] Such patients may have need for supplemental pancreatic enzymes.[15] Other supplements that have been considered for use in cancer patients include probiotics, guar extracts, and glutamine. Probiotics are viable, nonpathogenic microorganisms that may have beneficial effects on the host gastrointestinal tract.[16,17] A suggested benefit of probiotics in reducing diarrhea has been seen in one study of radiation-induced diarrhea.[16,17] Partially hydrolyzed guar gum has also been shown to reduce diarrhea in septic patients receiving total enteral nutrition and in patients with irritable bowel syndrome.[18] The amino acid glutamine has also been evaluated as an aid to decreasing diarrhea in CTID, but the results have been mixed. One study with CID induced by 5-FU showed that oral glutamine (18 g/day) might have a protective effect.[19] However, a study using low-dose glutamine (4 g twice daily) during pelvic radiation therapy failed to find any benefit of glutamine in reducing diarrhea.[20]

Pharmacologic Management of Acute Chemotherapy Treatment-Induced Diarrhea

Overview of Antidiarrheal Medications

Intestinal transit inhibitors. Pharmacologic agents used to control and treat acute CTID fall into two general classes: intestinal transit inhibitors that prolong transit time through the bowel, and antisecretory agents that decrease fluid secretion and thereby help to "solidify" intestinal contents. Patients with presumed or documented *Clostridium dificile* diarrhea should be treated with metronidazole or vancomycin. Intestinal transit inhibitors, which include loperamide (eg, Imodium; McNeil-PPC), diphenoxylate plus atropine (eg, Lomotil; Pfizer, New York, NY), and opium ("DTO," tincture of opium) are most commonly prescribed as first-line therapy.

The opioid loperamide decreases intestinal motility via direct effects on the smooth muscles of the intestinal wall. Therapy is initiated at 4 mg, and repeated at 2 to 4 mg every 2 to 4 hours, up to a maximum of 16 mg/day in irinotecan-induced diarrhea.[3] Side effects of loperamide are usually mild and infrequent, and may include abdominal pain, abdominal distention, dry mouth, and drowsiness. Patients should be instructed not to drive during their consumption. Diphenoxylate is an opiate analogue that inhibits intestinal peristalsis and reduces the defecation reflex. Because diphenoxylate has codeine-like properties, atropine has been added in low doses to discourage abuse of diphenoxylate. To treat CTID, it is administered in tablet form (as diphenoxlate 2.5 mg/atropine 0.025 mg) to a maximum of eight tablets per day. Adverse reactions are more common than with loperamide, and include dry mouth, flushing, tachycardia, urinary retention, abdominal pain, drowsiness, sedation, and confusion. Diphenoxylate should be used with extreme caution in patients with renal and/or liver failure. Atropine can also be used alone.[21] Because some of the early gastrointestinal symptoms (within 24 hours of the infusion) associated with irinotecan infusion (cramping, diarrhea) may be cholinergic-mediated, atropine is also sometimes used in this setting. However, its use is controversial. The recommended dose of atropine is 0.25 mg to 1 mg given intravenously or subcutaneously (SC) before irinotecan, or as treatment when symptoms appear.

Opium is a controlled narcotic substance with a similar mechanism of action as diphenoxylate. It is formulated as tincture of opium (a solution in alcohol) and administered as 0.6 mL every 4 to 6 hours. Factors to consider when choosing among these drugs include toxicity, cost, and availability. Loperamide has the most favorable toxicity profile, especially in the elderly and patients with underlying liver dysfunction. Tincture of opium is the least expensive, at approximately $0.60/day, but is a controlled substance. Diphenoxylate/atropine costs approximately six times more per day than tincture of opium and is available by prescription. Loperamide is available over the counter, with an intermediate daily cost.

TABLE 2.

Comparative Efficacy of Chemotherapy-Induced Diarrhea/Radiation-Induced Diarrhea Therapies[19-23]

	Intestinal Transit Inhibitors (Opioid Analogues)	Antisecretory Therapy (Octreotide SC)
Cascinu et al, 1993[23] (N = 41)	15% complete response* with loperamide 3.4 days of therapy needed	90% complete response with octreotide 6.1 days of therapy needed†
Gebbia et al, 1993[24] (N = 40)	30% complete response with loperamide	80% complete response with octreotide*
Barbounis et al, 2001[25] (N = 13)	No response (loperamide-refractory)	92% response with octreotide
Zidan et al, 2001[26] (N = 32)	No response (loperamide-refractory)	94% response with octreotide
Yavuz et al, 2002[27] (N = 61)	54% discontinued primary RT when RID was treated with diphenoxylate-atropine	18% discontinued primary RT when RID was treated with octreotide‡

Abbreviations: RT, radiation therapy; SC, subcutaneous; RID, radiation-induced diarrhea.
*Complete response defined as the absence of diarrhea at 24 and 48 hours.
†$P \leq .001$ *v* loperamide.
‡$P = .003$ *v* diphenoxylate.

Antisecretory agents. Octreotide is a synthetic analogue of the hormone somatostatin with a multifactorial mechanism of action: enhancement of fluid and electrolyte absorption, reduction of splenic blood flow, decrease of intestinal motility, and inhibition of fluid secretion across the gut wall. The recommended starting dose of octreotide for the treatment of CTID is 100 μg to 150 μg injected subcutaneously (SC) BID, with titration up to 500 μg SC TID.[3] Octreotide is also available in a long-acting form that is given intramuscularly (IM) every 28 days (octreotide LAR [long-acting release] depot). With this formulation, therapeutic drug levels are not reached until 10-14 days after the first dose, so it should not be used for the treatment of acute CTID. It is, however, sometimes used prophylactically as secondary prevention. Side effects associated with octreotide include constipation, ileus, biliary sludge, and hyperglycemia. Pain and redness at the injection site are often reported. Although the cost of octreotide SC is not insignificant, $50 to $250/day, it is usually prescribed for only 3 to 7 days.

Subcutaneous Octreotide Versus Loperamide for Treating Diarrhea

One of the advantages of opioid therapy in the treatment of diarrhea is its rapid onset of effect. High-dose loperamide (16 capsules a day) has been successful in the treatment of 5-FU–induced (grade 1/2) diarrhea in patients with colorectal cancer.[22] However, up to 50% of patients with severe (grades 3/4) diarrhea did not respond to opioids.[22] In a randomized trial of octreotide SC 100 μg twice daily versus loperamide 8 mg daily for the treatment of CID after 5-FU therapy, Cascinu et al[23] showed that octreotide induced a higher rate of complete response* than loperamide: 90% of patients treated with octreotide versus 15% of patients treated with loperamide had a complete response (Table 2). No side effects were observed in either treatment arm.[23] Similarly, in another study of CID secondary to a variety of therapies, Gebbia et al[24] showed that octreotide SC 500 μg three times daily induced complete response in 80% of patients versus 30% of patients treated with loperamide 12 mg daily ($P < .001$). The time from initiation of therapy to achievement of complete response was also significantly shorter in those receiving octreotide, 3.4 days versus 6.1 days, ($P = .001$). Side effects with octreotide included mild abdominal pain in 15% of cases and pain at the injection site in 15% of patients.

Subcutaneous Octreotide in Opioid-Refractory Diarrhea

More recently, trials of octreotide have been conducted in patients who did not respond to loperamide for the treatment of CID. In a trial

*Complete response was defined as the absence of diarrhea at 24 and 48 hours.

by Barbounis et al[25] conducted in patients with irinotecan-induced grade 3/4 diarrhea, 92% of patients who did not respond to loperamide 16 mg daily subsequently responded to octreotide SC 500 μg three times daily. Side effects in the octreotide-treated patients were mild. One patient complained of flushing and mild itching, while five patients complained of pain at the injection site. In a second trial, Zidan et al[26] reported that 94% of loperamide-refractory patients responded to octreotide for the treatment of diarrhea secondary to a variety of agents, including fluorouracil, leucovorin, irinotecan, cyclophosphamide, methotrexate, and/or cisplatin. No side effects related to octreotide were observed.

Acute radiation-induced diarrhea may also be treated more effectively with octreotide than with conventional therapy. In patients with grade 2/3 acute radiation-induced diarrhea, Yavuz et al[27] showed that octreotide SC 100 μg three times daily resolved diarrhea more quickly than diphenoxylate/atropine 2.5 mg four times daily. In addition, this study found that significantly fewer patients required discontinuation of their pelvic radiotherapy with octreotide: 18% versus 54% with opioid therapy ($P = .003$). No side effects were seen in either arm. Therefore, these patients benefited by achieving their maximum possible dose intensity as well as alleviation of distressing symptoms.

Dose Response to Subcutaneous Octreotide in Colorectal Cancer

A prospective, randomized trial was conducted by Goumas et al[28] to evaluate the optimal dosing of octreotide SC in patients with loperamide-refractory diarrhea secondary to 5-FU. A complete response was obtained in 90% of patients treated with 500 μg three times daily, compared with 61% of patients treated with 100 μg four times daily. The total daily dose of 1,500 μg/day was well tolerated. The statistically significant difference in efficacy ($P = .018$) supports a dose-response effect of octreotide SC. These investigators suggested that the higher dose, while more expensive, may be more cost-effective because of reduced hospitalization if diarrhea is better controlled.

Conclusion

The management of acute CTID requires prompt and aggressive treatment of diarrhea of any grade.[3] The treatment should be matched with the severity of the symptoms of CID and radiation-induced diarrhea. Proper management should always include dietary and nutritional guidelines. When these measures alone do not suffice, or in patients who present with grade 3/4 diarrhea, pharmacologic intervention is required. First-line therapy with loperamide or diphenoxylate/atropine in recommended doses should be initiated quickly. Recent clinical studies of octreotide show that somatostatin analogues, with their multifactorial mode of action, are effective as second-line therapy for the treatment of loperamide-refractory diarrhea, or as first-line therapy for patients with grade 3/4 diarrhea. Whatever therapy is chosen, the goal is to quickly control this debilitating and potentially life-threatening side effect so that primary chemotherapy and/or radiation therapy will not be interrupted.

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