

# RADIATION & YOUR PATIENT



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*Clostridium difficile*, a bacteria that excretes diarrhea-causing toxins

## Assessing and treating radiotherapy-associated diarrhea

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Cancer treatment-related disruptions of normal gastrointestinal function are a common clinical challenge and usually include constipation or diarrhea.<sup>1,2</sup> Treatment-related diarrhea can lead to patient dehydration and nutritional and electrolyte imbalances and hypokalemia; rapid dehydration can lead to shock.<sup>1,3</sup> In severe cases, reductions in therapeutic radiation doses or even the discontinuation of radiotherapy are necessary.<sup>1,3</sup> Untreated, severe cases of treatment-related diarrhea can be fatal.<sup>1,3</sup>

Radiation therapy-associated diarrhea is the most common acute toxicity among patients undergoing whole-body, pelvic, and abdominal radiotherapy, and is particularly frequent among patients receiving abdominal or pelvic radiotherapy for colorectal, anal, cervical, uterine, prostate, bladder, or testicular cancers.<sup>1,3</sup> Both chemotherapy and radiation therapy can cause diarrhea; when treatments kill nontarget, healthy cells in the mucosal lining of the intestines, absorption of GI fluids is disrupted, contributing to diarrhea.<sup>1,3</sup> Damaged intestinal mucosa also release prostaglandins and disrupt absorption of bile salts, hastening intestinal peristalsis and the movement of fluids and fecal matter through the intestines.<sup>1,3</sup> Radiotherapy-associated diarrhea tends to be more severe than diarrhea associated with other treatments.<sup>1</sup>

Chronic or delayed diarrhea associated with radiation enteritis can appear months or even years after radiotherapy and is typically associated with total radiation doses greater than 45 Gy.<sup>3</sup> It is less common than acute radiotherapy-associated diarrhea.<sup>3</sup> Triggered by delayed intestinal ischemia, fibrosis, and ulceration, chronic radiotherapy-associated diarrhea frequently occurs with nausea, weight loss, and abdominal pain.<sup>3</sup>

Numerous treatments other than radiotherapy can cause treatment-associated diarrhea and interventions vary depending in part on the causative treatment modality or agent.<sup>2</sup> Careful assessment of the patient's treatment regimen is therefore necessary before attributing the diarrhea to radiotherapy.<sup>3</sup> For example, chemotherapeutic agents such as docetaxel (Docefrez, Taxotere, generics), 5-fluorouracil (5-FU) and its precursor capecitabine (Xeloda), and irinotecan (Camptosar,

generics), are each associated with diarrhea.<sup>2,3</sup> Targeted agents like bortezomib (Velcade), erlotinib (Tarceva), sorafenib (Nexavar), sunitinib (Sutent), and imatinib (Gleevec) also include diarrhea among their treatment-associated toxicities.<sup>3</sup> Enteral tube feeding, laxatives, and magnesium antacids are common causes of diarrhea, as well.<sup>3</sup>

Bacterial enteritis involving *Salmonella*, *Escherichia coli*, and *Campylobacter* can cause diarrhea among cancer patients. Another increasingly common and very serious cause of diarrhea, is intestinal infection with *Clostridium difficile*, a bacteria that excretes diarrhea-causing toxins.<sup>3,4</sup> *C difficile*-associated diar-

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rhea (CDAD) is frequently a hospital-acquired condition, associated with nasogastric intubation, GI surgery, cytostatic chemotherapies, antibiotic therapy, proton pump inhibitors, and inadequate hand hygiene.<sup>3,4</sup> Patients undergoing treatment for head and neck carcinomas appear to be at particular risk for *C difficile* infections and CDAD.<sup>4</sup> Morbidity and mortality are high among patients with CDAD, and one recent retrospective study estimated approximately 40% of cases result in interruption of radiotherapy treatments.<sup>4</sup> In addition to intensive patient screening for *C difficile* infection, avoiding tube feeding when possible and restricting the administration of antibiotics (particularly the fluoroquinolone moxifloxacin) and proton pump

inhibitors appear to be associated with reduced CDAD risks.<sup>4</sup>

### ASSESSING PATIENTS

When treatment-related diarrhea is suspected, assessment includes determining the clinical grade of diarrhea; obtaining patient medical, medication, and dietary histories (including herbal supplements such as saw palmetto, ginseng, milk thistle, plantago seed, or aloe, which can cause diarrhea<sup>1</sup>); laboratory analysis of stools (including fecal leukocyte testing, *C difficile* toxins A and B tests, and bacterial cultures); dehydration assessment; and physical examination.<sup>3</sup> Diarrhea does not preclude bowel obstruction or fecal impaction; when these are suspected, diagnostic abdominal imaging should be ordered.<sup>3</sup> Possible neutropenic enterocolitis is also assessed with abdominal CT.<sup>3</sup>

The National Cancer Institute (NCI) grades diarrhea severity on a scale of 0 to 5 (0 represents an absence of diarrhea, 5 represents death).<sup>1,5</sup> Treatment-related diarrhea is sometimes categorized more simply as complicated or uncomplicated, but these designations are typically limited to chemotherapy-induced diarrhea. Grade 1-2 diarrhea with no cramping, nausea, or vomiting; fever; or neutropenia is classified as uncomplicated, whereas grade 3-4 diarrhea with moderate-to-severe cramping, nausea or vomiting, fever, neutropenia, sepsis, bleeding, dehydration, or diminished performance status is classified as complicated.<sup>3</sup>

### MANAGING RADIOTHERAPY-ASSOCIATED DIARRHEA

The primary goals of intervention are to rehydrate and stabilize the patient, and to control the diarrhea with medication and dietary modification.<sup>1,3,6,7</sup> Milk and milk products should be avoided because lactose malabsorption caused by lactase deficiency frequently accompanies intestinal mucosal damage.<sup>3</sup> Animal

fats, spicy foods, caffeine, alcohol, and certain herbal supplements (listed above) should also be avoided.<sup>1</sup> The BRAT diet (banana, rice, applesauce, and toast) can reduce stool frequency.<sup>1</sup>

The clinical evidence-based treatment for radiotherapy-associated diarrhea is sparse compared with that for chemotherapy-associated diarrhea.<sup>8</sup> Aspirin may be helpful with radiotherapy-associated diarrhea.<sup>7</sup> Mild or uncomplicated cases are treated with oral rehydration and antidiarrheal medication with opioids.<sup>1,3,8</sup> Loperamide [Imodium, generics] is the gold standard, administered as an initial dose of 4 mg followed by 2 mg every 2 hours, or noncamphorated deodorized tincture of opium, administered as 10 mg/mL morphine, 10-15 drops in water every 3 to 4 hours.<sup>1,3,8</sup> Tincture of opium is generally considered a second-line medication for diarrhea control.<sup>1,3</sup>

Patients should be asked to report fever, dizziness upon standing, and the number of stools. After the diarrhea wanes, patients should be instructed to continue avoiding dairy products and other diarrhea-causing foods, including caffeinated drinks, and begin to eat solid foods in small-serving-size meals up to 6 times a day.<sup>1,3</sup> Patients can be provided with a simple list of acceptable and prohibited foods and drinks. The critical importance of hydration should be emphasized; patients should be instructed to drink 3 to 4 liters of fluid daily, including water, broth,

decaffeinated teas or soft drinks, sports drinks, and clear juices.<sup>1</sup>

If diarrhea persists, prophylactic antibiotic therapy should be considered.<sup>3</sup> If diarrhea persists for more than 24 hours, intestinal infection should be suspected and appropriate tests obtained, rehydration and electrolyte replacement continued as needed, and opioid therapy discontinued; hospitalization should be considered.<sup>1,3</sup>

As with tincture of opium, octreotide (Sandostatim, generics), with dose escalation as needed from an initial dose of 100 to 150 mcg, is a second-line antidiarrheal treatment for low-grade (grade 1-2) diarrhea.<sup>3</sup> Octreotide appears to be effective for treating grade 2-3 loperamide-refractory radiotherapy-associated diarrhea among rectal cancer patients who had been treated with concomitant fluorouracil chemoradiotherapy.<sup>8</sup> Subcutaneous octreotide (100 mcg 3 times daily) appears to be superior to diphenoxylate (Lomotil, Lonox; 10 mg daily), an opioid antidiarrheal, in patients with grade 2-3 diarrhea who are undergoing radiotherapy only.<sup>8</sup>

Hospitalization, aggressive treatment, and vigilant monitoring, including complete blood counts, electrolyte assessment, and stool evaluations for blood, fecal leukocytes, and bacterial cultures, are indicated for patients with severe diarrhea.<sup>1</sup> Treatment includes IV hydration, octreotide (100 to 150 mcg 3 times daily) and antibiotic therapy.<sup>1,3</sup>

Chronic radiotherapy-associated diarrhea can be treated with antidiarrheal medications unless contraindicated by symptoms of bowel obstruction; support for hyperbaric oxygen therapy remains anecdotal.<sup>3</sup>

### PREVENTIVE MEASURES

Octreotide and sucralfate (Carafate, generics) are not indicated as a diarrheal prophylactic or preventive for radio-

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therapy patients.<sup>6,9</sup> A phase 3, double-blind clinical trial of prophylactic octreotide to prevent diarrhea among patients undergoing pelvic radiotherapy found no benefit over placebo, and found that some GI symptoms, including patient-reported nocturnal bowel movements and bloody stool were more frequent among patients receiving octreotide.<sup>9</sup>

In contrast, probiotics (orally administered live gut bacteria) might prevent radiotherapy-associated diarrhea, administered alone starting on day 1 of pelvic or abdominal radiotherapy or with psyllium fiber (1 to 2 teaspoons daily), which absorbs intestinal fluids.<sup>1,8</sup> Strain VSL#3 (VSL Pharmaceuticals, Inc.) administered daily through radiotherapy is associated with significantly reduced bowel movements and diarrhea incidence among patients receiving pelvic radiotherapy who had undergone surgical resection of colorectal and cervical cancers.<sup>8</sup> *Lactobacillus acidophilus* NDCO 1748 is also associated with significant reductions in pelvic radiotherapy-associated diarrhea.<sup>8</sup>

The Oncology Nursing Society evidence-based guidelines for managing

radiotherapy-related diarrhea indicate selenium (Selsun, generics), sulfasalazine (Azulfidine, generics), and pentosan polysulfate (Elmiron) are unlikely to benefit patients with radiotherapy-associated diarrhea.<sup>1,6</sup> ■

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