Treatment-Related Diarrhea in Patients With Cancer

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Diarrhea caused by chemotherapy or radiation in patients with cancer can cause dehydration, electrolyte imbalance, malnutrition, fluid depletion, and hospitalization. In severe cases, uncontrolled diarrhea can lead to therapy dose reductions or even death. Oncology professionals may simply assess for the absence or presence of diarrhea, rather than using a standard assessment tool; they also may lack awareness regarding availability of established assessment and treatment guidelines. However, use of treatment guidelines can lead to optimal prevention and management of treatment-induced diarrhea in patients with cancer. Oncology nurses play a key role in the identification and treatment of chemotherapy- and radiation therapy-induced diarrhea.

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One of the most common side effects of treatment in patients with cancer is chemotherapy- and radiation therapy-induced diarrhea (National Cancer Institute [NCI], 2009). Diarrhea is a debilitating condition that can cause dehydration, electrolyte imbalance, malnutrition, fluid depletion, hospitalization, and even death (Saltz, 2003). Depending on the severity of diarrhea, therapy dose reductions or discontinuation of treatment can occur, resulting in less-than-optimal treatment outcomes (Muehlbauer et al., 2009).

Chemotherapy causes damage to the intestinal mucosa, resulting in necrosis of the cells that line the intestine. Those necrotic, or dead, cells increase inflammation within the intestinal mucosa, causing decreased intestinal absorption and resultant diarrhea. In addition, abdominal radiation therapy causes increased intestinal motility (Yarbro, Wujcik, & Gobel, 2011).

Although the reported prevalence and severity of diarrhea vary greatly, some chemotherapeutic regimens are associated with diarrhea rates as high as 50%–80% (Muehlbauer et al., 2009). Fluorouracil and irinotecan-based therapies have been reported to cause diarrhea in 80% of recipients, with 30% or more experiencing severe diarrhea (Arnold et al., 2005). According to the NCI (2010) Common Terminology Criteria for Adverse Events (CTCAE), more than half of patients receiving chemotherapy for colorectal cancer experience diarrhea, requiring reduction, delay, or discontinuation of therapy. Radiation-induced diarrhea is the most frequent acute toxic response for patients undergoing adjuvant or primary treatment for gastrointestinal, gynecologic, or genitourinary cancer (Kozelsky et al., 2003).

Patient Assessment

The NCI CTCAE is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer-related clinical trials and other oncology settings (NCI, 2009). The NCI CTCAE evaluate and grade diarrhea by number of stools per day, incontinence, and increase in ostomy output as compared to baseline (NCI, 2009) (see Table 1). Although the NCI CTCAE provide a standard objective foundation for evaluating treatment-induced diarrhea, additional evaluation is warranted. A detailed assessment must include hydration status and dietary intake (Benson et al., 2004). A patient self-care log or diary describing the number and consistency of stools, dietary changes, medications used to manage the diarrhea, and associated symptoms such as fever and abdominal cramping can provide the oncology practitioner with additional information necessary for optimal treatment (O'Brien, Kaklamani, & Benson, 2005).

Assessment of weight loss and reduced urine output provides important information regarding the severity of the effects of diarrhea (NCI, 2009).

Chemotherapy-induced diarrhea can be categorized as uncomplicated and complicated. Differentiating between the two categories assists in determining appropriate interventions. Uncomplicated diarrhea is defined as grade 1 or 2 toxicity without complicating signs or symptoms (Richardson & Dobish, 2007), which include moderate to severe cramping, nausea, vomiting, decreased performance status, fever, sepsis, neutropenia, bleeding, and dehydration (Cherny, 2008; Richardson & Dobish, 2007). All patients with severe (grade 3 or 4) diarrhea are considered complicated. Patients with mild to moderate diarrhea (grade 1 or 2) with one or more complicating factors also are considered complicated (Cherny, 2008; Richardson & Dobish, 2007).

Nutritional Management

Dietary modifications commonly are implemented to stop or lessen the severity of cancer treatment-related diarrhea (Arbuckle, Huber, & Zacker, 2000). Each
TABLE 1. Common Terminology Criteria for Adverse Events: Diarrhea

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>2</td>
<td>Increase of four to six stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>3</td>
<td>Increase of seven or more stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Note. Based on information from National Cancer Institute, 2010.

A nutritional plan should be tailored to include consideration of religious, cultural, allergy, and personal preferences. A complete dietary assessment that includes herbal supplements should be performed, as certain nutritional supplements such as saw palmetto, ginseng, milk thistle, plantago seed, and aloe can cause or exacerbate diarrhea (O’Brien et al., 2005).

Modifications to the patient’s daily dietary intake may be required (American Cancer Society [ACS], 2004). Foods that are high in fat, spicy, or contain dairy, caffeine, or alcohol should be avoided. For mild or grade 1 diarrhea, the BRAT (bananas, rice, applesauce, toast) diet can be recommended and may decrease the number of stools per day (NCI, 2009). If the BRAT diet is not tolerated, a clear liquid diet can be tried. As sugar and water (the main components of a clear liquid diet) are still absorbed well in most intestinal illnesses, this may rest the bowel and facilitate conservative resumption of solid food intake (ACS, 2004). Once solid foods are reincorporated, small frequent meals (up to six meals per day) may be suggested (Bisanz et al., 2010).

Instructing patients regarding the importance of maintaining adequate fluid intake is imperative to avoid dehydration and electrolyte imbalance. Oral intake of three to four liters of fluid per day should be encouraged (e.g., water, sports drinks, broth, weak decaffeinated teas, caffeine-free soft drinks, clear juices, gelatin). Maintenance of fluid intake is critical and inability to maintain adequate hydration is an important indication for IV fluid support. Timely institution of outpatient fluid resuscitation may minimize the need for hospitalization (Saltz, 2003). Oncology nurses need to encourage patients not only to stay hydrated but to adhere to recommended dietary modifications.

### Clinical Guidelines

The American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) provide clinical guidelines for cancer-related diarrhea (Benson et al., 2004; ONS, 2008) (see Table 2). ASCO treatment guidelines for diarrhea are classified as complicated, uncomplicated, radiation induced, and chemotherapy induced. ONS guidelines outline diarrhea management strategies as recommended for practice, likely to be effective, effectiveness not established, effectiveness unlikely, and not recommended.

### American Society of Clinical Oncology

ASCO recommendations for treatment of uncomplicated diarrhea include dietary modifications and loperamide, an oral opioid, 4 mg followed by 2 mg every four hours (not to exceed 16 mg per day). If diarrhea resolves and the causative factor is determined to be related to chemotherapy, the patient can continue with dietary modifications and discontinue the loperamide when diarrhea-free for 12 hours. Uncomplicated chemotherapy-induced diarrhea that persists should be treated with octreotide, a somatostatin analog, 100–150 mcg subcutaneously (SC), with dose escalation as needed. Loperamide should be discontinued and additional workup may be warranted. If the diarrhea resolves and the patient is receiving radiation, the patient should continue loperamide until radiation is complete. For persistent diarrhea caused by radiation, the patient should continue loperamide 2 mg every two hours. A second-line option to consider is tincture of opium. Two preparations of tincture of opium are available and, because of the variation in the amount of morphine contained in each preparation, diligent dispensing and administration is essential. Deodorized tincture of opium, the preferred preparation, contains the equivalent of 10 mg/ml morphine. The recommended dose is 10–15 drops in water every three to four hours. In patients with uncontrolled diarrhea, fluid and electrolytes likely need to be replaced as well (Benson et al., 2004).

ASCO guidelines for treatment of complicated chemotherapy-induced diarrhea include IV fluids with octreotide 100–150 mg SC three times daily—with dose escalation to 500 mg three times daily until controlled—and an antibiotic treatment (fluoroquinolone) until diarrhea-free. Laboratory work-up, including fecal occult blood, fecal leukocytes, *Clostridium difficile*, *Escherichia coli*, *Salmonella*, and *Campylobacter*, should be done, as well as a complete blood count and basic metabolic panel plus electrolytes. The ASCO guidelines suggest that hospitalization be considered for patients with grade 2 diarrhea that does not resolve after 24 hours of high-dose loperamide. Hospitalization is recommended for all patients with severe diarrhea (grades 3 and 4) (Benson et al., 2004).

### Oncology Nursing Society

ONS Putting Evidence Into Practice (PEP) resources are designed to provide evidence-based interventions for patient care and teaching (additional information and description of the ONS PEP categories of evidence are located at www-ons-org/Research/PEP/Topics). Interventions incorporated to prevent and treat chemotherapy- or radiation therapy-induced diarrhea essentially are pharmacologic and are based on best-available evidence (ONS, 2008).

Recommended for practice: For chemotherapy-induced diarrhea, loperamide 4 mg followed by 2 mg orally every four hours is the standard first-line therapy. High-dose loperamide (2 mg orally every two hours; 4 mg every four hours at night) has shown moderate effectiveness in controlling diarrhea associated with irinotecan chemotherapy. That dose should not be given for more than 48 hours. In addition, octreotide 100 mcg SC three times daily for three days, then 50 mcg SC three times daily for three days, is recommended.
No recent studies specifically addressing radiation-induced diarrhea reached the level of evidence needed to be recommended for practice; however, the use of loperamide and diphenoxylate continue to be recommended as the standard of practice for patients with mild symptoms (Benson et al., 2004).

**Likely to be effective:** For chemotherapy-induced diarrhea, octreotide 150 mcg SC three times daily for five days may be effective. Octreotide 30–40 mg intramuscularly 7–14 days prior to day 1 of chemotherapy, then every 28 days up to six doses, or octreotide long-acting release 20–30 mg monthly may be considered. One option for treatment of radiation-induced diarrhea is 100 mcg SC three times daily until resolution of diarrhea. Octreotide may be titrated upward from 150 to 500 mcg SC administered three times daily until symptoms are controlled. That dose may be more effective than standard doses in patients with chemotherapy-induced diarrhea who fail loperamide (Benson et al., 2004).

Probiotics are “live microorganisms, which when administered in adequate amounts, confer a health benefit on the host,” (Food and Agriculture Organization of the United Nations & World Health Organization, 2001, p. 7). The use of probiotics may be effective in preventing radiation-induced diarrhea in high-risk patients undergoing radiation to the lower abdomen and pelvis. In particular, the administration of VSL#3® strain, beginning on the first day of radiation and until the end of the radiation treatment period, resulted in a significant difference in the number of bowel movements and toxicity of diarrhea in a study of 409 patients undergoing pelvic radiation following surgery for sigmoid, rectal, or cervical cancers (Delia et al., 2007). In another study, *Lactobacillus acidophilus* significantly reduced diarrhea when given to patients during pelvic radiation (Marteau, de Vrese, Cellier, & Schrezenmeir, 2001). Researchers using psyllium fiber during pelvic radiation for prostate or gynecologic cancer found that 1–2 teaspoons daily was effective in reducing the incidence and severity of diarrhea (Murphy, Stacey, Crook, Thompson, & Panetta, 2000). Psyllium fiber and probiotic supplementation, including VSL#3, *Lactobacillus acidophilus*, and *Rhodotorula*, are likely to be effective in the prevention of radiation-induced diarrhea (Chitapanarux et al., 2010; Delia et al., 2007; Singh, 2007). Additional research is needed to determine the optimal probiotic strain(s), dosage(s), and timing of administration.

**Benefits balanced with harms:** Diarrhea caused by 5-fluorouracil and calcium folinate infusion in colorectal cancer may be managed with amifostine 800 mg/m² weekly. Oncology nurses need to be aware of the side effects of this medication. Amifostine can cause a sharp drop in blood pressure, as well as nausea, vomiting,

### TABLE 2. Comparison of ASCO and ONS Evidence-Based Guidelines

<table>
<thead>
<tr>
<th>Topic</th>
<th>American Society of Clinical Oncology (ASCO)</th>
<th>Oncology Nursing Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment</td>
<td>Dietary modifications; Loperamide 4 mg followed by 2 mg every four hours</td>
<td>Dietary modifications; Loperamide 4 mg followed by 2 mg every four hours</td>
</tr>
<tr>
<td>Diarrhea refractory to loperamide: mild to moderate diarrhea (ASCO) or grade 2 or 3 (ONS)</td>
<td>CID: Octreotide 100–500 mcg with dose escalation as needed or tincture of opium or budesonide</td>
<td>Likely to be effective for CRID: 150 mcg octreotide SC TID for five days</td>
</tr>
<tr>
<td></td>
<td>RID: Continue loperamide 2 mg every two hours; replace fluid and electrolytes</td>
<td>Likely to be effective for RID: Octreotide 100 mcg SC TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: According to the Oncology Nursing Society, budesonide’s effectiveness is not established; however, the American Society of Clinical Oncology recommends it.</td>
</tr>
<tr>
<td>Complicated (ASCO) or severe (ONS) diarrhea</td>
<td>Complicated CID: IV octreotide 100–150 mcg SC or IV TID with dose escalation until controlled, and an antibiotic (fluoroquinolone); hospitalization may be necessary; stool workup; laboratory tests</td>
<td>Recommended for severe CID: Octreotide 100 mcg SC TID for three days, then 50 mcg SC TID for three days</td>
</tr>
<tr>
<td></td>
<td>Complicated RID: Hospitalization may not be necessary; continue loperamide; may not need octreotide, and antibiotics may worsen</td>
<td>Likely to be effective for severe CID: 30 mg long-acting repeatable octreotide intramuscularly 7–14 days prior to day 1 of chemotherapy, then every 28 days up to six doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Likely to be effective for RID grade 2 or 3: Octreotide 100 mcg SC TID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: ONS did not offer recommendations for RID higher than grade 3.</td>
</tr>
<tr>
<td>Prevention</td>
<td>The American Society of Clinical Oncology states that no definitive data exist, but the future is promising.</td>
<td>Effectiveness not established: Budesonide, oral alkalization, charcoal, and levofloxacin for irinotecan-induced diarrhea; probiotics and glutamine for CID prevention</td>
</tr>
<tr>
<td>Important facts</td>
<td>Assessment recommendations: Increase monitoring (weekly assessment of gastrointestinal toxicity); blood tests no more than 48 hours prior to chemotherapy; increased management such as antibiotic treatment if diarrhea lasts more than 24 hours; discontinue chemotherapy if severe CID, may lead to death</td>
<td>Benefits balanced with risks: Amifostine infusion; neomycin for irinotecan-induced diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effectiveness not established: Antioxidants (vitamins E and C) for treatment for RID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effectiveness unlikely: Sulfasalazine and selenium supplementation for prevention of RID; pentosan polysulfate for treatment of RID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recommended for practice: Sucralfate for prevention of RID</td>
</tr>
</tbody>
</table>

CID—chemotherapy-induced diarrhea; CRID—chemotherapy- and radiation-induced diarrhea; RID—radiation-induced diarrhea; SC—subcutaneously
chills, and dizziness. The benefit of this drug must outweigh the risks before use (Tsavaris et al., 2003).

Neomycin, an antibiotic that prevents intestinal absorption of SN-38 (the active metabolite of irinotecan), often is used in patients receiving irinotecan chemotherapy. Oral neomycin 660 mg three times daily administered for three consecutive days starting two days before irinotecan (de Jong et al., 2006), or 1,000 mg three times a day continuously from two days prior to five days after the second cycle of treatment (Kehrer et al., 2001), may be effective in reducing irinotecan-related diarrhea.

**Effectiveness not established:** This category lists medications that may work, but not enough research has been done to establish adequate scientific evidence. Medications under this category for irinotecan-related diarrhea include oral alkali- zation, budesonide, charcoal, and cholestyramine plus levofloxacin. Vitamins E and C may help to treat radiation-induced diarrhea, but more research is needed. Glutamine’s effectiveness has not been established (Kozelsky et al., 2003).

**Effectiveness unlikely:** Sulfasalazine, selenium, and pentosan polysulfate have no proven effect on the prevention or treatment of radiation-induced diarrhea.

**Not recommended for practice:** Sucralfate is not recommended for prevention of radiation-induced diarrhea.

**Implications for Practice**

Diarrhea can be an ongoing challenge for patients receiving chemotherapy or radiation and can be a life-threatening condition if left untreated. By obtaining a detailed history and physical assessment and communicating the results within the healthcare team, oncology nurses have the opportunity to optimize the prevention and management of cancer treatment-related diarrhea.

Bowel assessments should be performed at the start of treatment and continued until the completion of treatment. Accurate assessment, including dietary intake, is the first step in choosing appropriate management of diarrhea at various stages of treatment. Nutritional management incorporated with bowel assessment and pharmacologic measures may decrease the rate and frequency of diarrhea episodes. Available evidence-based guidelines synthesize current scientific literature and can guide the oncology provider in choosing appropriate prevention and treatment strategies. Oncology professionals must be aware not only of the evidence-based practice guidelines for the prevention and treatment of cancer treatment-related diarrhea, but also consistently incorporate these guidelines into their practice. With the appropriate evidence-based practice and multidisciplinary approach, diarrhea in patients with cancer can be managed effectively. ONS PEP resources provide evidence-based oncology nursing interventions for diarrhea that can be used in the clinical setting. Visit www.ons.org/Research/PEP/Diarrhea for more information.

**References**


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