Management of Chemotherapy-Induced Diarrhea

Clinical Significance

Diarrhea is a common side effect of chemotherapy, especially for patients with advanced cancer. The incidence of chemotherapy-induced diarrhea (CID) has been reported as 50-80% of treated patients (Stein, Voigt & Jordan, 2010). The consequences of uncontrolled CID can be physically, psychologically and economically devastating. Diarrhea may lead to dehydration, electrolyte imbalance, renal insufficiency, immune dysfunction and, in extreme cases possibly even death (Cherney, 2008). The psychological effects of diarrhea include: anxiety, depression, social isolation, low self-esteem and caregiver strain (Viele, 2003). Tong, Isenring and Yates (2009) found diarrhea to be one of the most distressing nutritional symptoms affecting medical oncology patients. Those suffering from CID often require additional healthcare resources, which raises costs for the patient and the health care system (Dranitsaris, Maroun, & Shah, 2005). Of those who require hospitalization, the median length of stay is eight days (Dranitsaris, Maroun, & Shah, 2005).

Chemotherapeutic regimens containing 5-fluorouracil (5-FU) and irinotecan are associated with an 80% rate of CID (Robinson & Dobish, 2007). Of those experiencing CID, greater than 30% will experience interference in their daily activities, require hospitalization and risk cardiovascular compromise (Stein, Voigt & Jordan, 2010). Other agents known to cause CID are: capecitabine, cisplatin, cyclophosphamide, cytarabine arabinoside, daunorubicin, doxorubicin, docetaxel, methotrexate, oxaliplatin, and paclitaxel. (Richardson & Dobish, 2007). Targeted therapies such as, erlotinib, sorafenib, and cetuximab, may also cause significant CID.

CID may result in a deviation from the planned chemotherapy schedule, leading to suboptimal cell kill and, ultimately, a worse outcome (Arnold et al., 2007). In order to prevent complications and develop an appropriate treatment plan, a careful assessment of CID and identification of the causative agent is paramount (Stein, Voigt & Jordan, 2010). Dose reductions, treatment delays, and discontinuation of therapy, particularly in the curative adjuvant setting, may have direct adverse effects on patient outcomes (Maroun et al., 2007). Reduced dose intensity (the amount of drug administered per unit of time) has been associated with a decreased overall and disease–free survival (Arnold et al., 2005). In a retrospective study of 378 cancer patients with CID, Arnold et al. (2005) found that nearly 65% of patients experienced a reduction in dose intensity at some point in their chemotherapy course. Within the same study, 45% required a dose reduction, 71% experienced a delay in treatment and 3% required a discontinuation of therapy (Arnold et al., 2005).

Pathophysiology

Normal function in the gastrointestinal tract (GIT) is a balance between metabolism, secretion, oral intake, and fluid absorption (Stringer et al., 2007). The main function of the small intestine is digestion. The luminal surface is arranged in crypts, villi and brush boarder enzymes, which aid in digestion, metabolism and absorption (Stringer et al., 2007). The primary function of the
large intestine is the re-absorption of water through a highly regulated process involving electrolytes and solutes (Stringer et al., 2007). The epithelial cells absorb sodium and chloride and, as a result, water follows due to the osmotic gradient (Stringer et al., 2007).

The pathophysiology of CID is multifaceted, complex and still under investigation (Stein, Voigt & Jordan, 2010). The rapidly dividing crypt cells throughout the intestinal epithelium are damaged by chemotherapy, altering the absorptive and secretory capacity within the gut (Robinson & Dobish, 2007). When chemotherapy affects the absorptive capacity, there is an increase of solutes in the intestinal lumen. This causes an osmotic shift of water into the lumen, resulting in diarrhea (Robinson & Dobish, 2007; Stringer et al., 2007). A disruption in the intestinal epithelium may also cause exudative diarrhea that results from the leakage of water, electrolytes, mucus, proteins, and red and white blood cells into the intestinal lumen (Robinson & Dobish, 2007). The direct toxicity of chemotherapy on colonic crypt cells sets off a cascade of events that contribute to CID. The remaining immature crypt cells attempt to compensate by releasing more secretory compounds (Gibson & Keefe, 2006). Damaged villi and brush border enzymes within the small intestine cause improper fluid absorption and increased gut wall secretions. Mechanical changes within the GIT are associated with inflammation, inducing the release of prostaglandins and cytokines (Gibson & Keefe, 2006). Damaged crypt cells lead to an increased risk of opportunistic infections. The enterotoxins produced by bacteria lead to a direct secretory effect on the intestinal mucosa (Gibson & Keefe, 2006).

Most of the current literature focuses on the pathophysiologic mechanism of CID with irinotecan. Irinotecan is unique because it's associated with early and delayed phase diarrhea. Early onset diarrhea occurs within 24 hours of irinotecan administration, while delayed onset diarrhea develops after 24 hours or more (Robinson & Dobish, 2007). Acute, early onset, irinotecan-induced diarrhea is caused by cholinergic properties that may be accompanied by cramping, rhinitis, lacrimation, and salivation (Stein, Voigt & Jordan, 2010). The mechanism of delayed-type diarrhea is still a matter of debate (Stein, Voigt & Jordan, 2010). One proposed explanation is the direct mucosal damage from the active metabolite of irinotecan, SN38, resulting in water and electrolyte malabsorption and mucous hypersecretion (Stein, Voigt & Jordan, 2010). Another possible mechanism is severe colonic damage, resulting in increased apoptosis, crypt hypoplasia and goblet cell changes, which affect the absorptive capacity (Stein, Voigt & Jordan, 2010).

Clinical Presentation/Risk Factors

Although the occurrence of chemotherapy-induced diarrhea may be unpredictable, several treatment- and patient-related risk factors may be associated with an increased incidence. Patient-associated risk factors are: age >65 years, female, low performance status, associated bowel pathology such as inflammatory or mal-absorption processes, bowel tumor, genetic polymorphisms affecting drug metabolism and distribution, and biliary obstruction (Richardson & Dobish, 2007). As mentioned above, certain chemotherapy agents increase the risk of CID, especially regimens which contain 5-FU, irinotecan, or capecitabine. Therapy-related risk factors include: weekly chemotherapy schedule, infusional chemotherapy, bolus 5-FU, prior history of CID, and prior or concurrent abdominal-pelvic radiation (Richardson & Dobish, 2007). Davila & Bresalier (2008) state that the addition of leucovorin to 5-FU increased both the severity and prevalence of CID. Regimens that contain 5FU in combination with oxaliplatin or irinotecan have become the standard of care for patients with advanced colorectal cancer, but have also increased the risk of CID (Dranitsaris, Maroun & Shah, 2005).

The National Cancer Institute (2009) defines diarrhea as a disorder characterized by frequent and watery bowel movements. Cherney (2008) objectively defines diarrhea as the passage of 3 or more unformed stools in 24 hours. Muehlbauer et al. (2009) defines diarrhea as an abnormal increase in stool frequency (four to six times or more per day over the baseline) and stool liquidity, with or without nocturnal bowel movements or moderate abdominal cramping. Grading CID in a standard, consistent manner may be challenging when the definition varies.
The most commonly used scale for rating CID is the National Cancer Institute’s (2009) Common Terminology Criteria for Adverse Events (CTCAE) (see Table 1). The CTCAE system classifies the grade of diarrhea on a scale from one (mild) to five (death) according to the number of stools per day. A major limitation of the CTCAE is the failure to address stool volume, which is a major consideration for severity and for determining the risk of complications (Muehlbauer, 2009). Despite the limitations, Cirillo et al. (2009) demonstrated validity of the CTCAE nurse toxicity reporting, showing that there was strong agreement between the nurse and patient ratings. In order to properly use this scale, the practitioner must first assess the patients’ baseline stool frequency, continence status, and ability to perform activities of daily living. When assessing CID, the practitioner should inquire about the onset and duration of the bowel change, frequency of bowel movements, incontinence, nocturnal bowel movements, color, consistency, and the presence of blood or mucus (Gibson & Keefe, 2006).

Assessment of the patient with CID should include a detailed medical history, dietary history, medication review, description of stool and a thorough physical exam (Cherny, 2008). Other symptoms such as fever, chills, weight loss, bloating, nausea, vomiting, and decreased oral intake should be noted (Gibson and Keefe, 2006). Physical examination should assess for signs and symptoms of dehydration, and abnormalities in the abdominal and rectal areas (Cherny, 2008). Laboratory data should be assessed for evidence of dehydration, electrolyte abnormalities and renal dysfunction (Cherny, 2008).

Chemotherapy-induced diarrhea may be categorized into uncomplicated and complicated. Uncomplicated diarrhea is comprised of grades 1 and 2 toxicity without complicating signs or symptoms (Richardson & Dobish, 2007). Complicating signs and symptoms 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 are also considered complicated (Cherny, 2008; Richardson & Dobish, 2007). Differentiating between complicated and uncomplicated may help to determine the appropriate interventions.

Differential Diagnosis

Before treating for chemotherapy-induced diarrhea, other common causes of diarrhea should be considered. Diarrhea may be present secondary to a viral illness, medications, dietary habits or co-morbid conditions such as hyperthyroidism or inflammatory bowel disease. Diarrhea can also be a consequence of fecal impaction or partial bowel obstruction. This often manifests as a pattern of alternating constipation and diarrhea (Cherny, 2008). With fecal impactions, liquid stool may leak around the mass and cause incontinence (Cherny, 2008). An infectious process should be ruled out with stool cultures prior to giving anti-diarrheal agents to prevent prolonging the mucosal exposure to toxins (Yarbro, Frogge & Goodman, 2005). Clostridium difficile may be seen in patients receiving chemotherapy who have had previous antibiotic therapy (Yarbro, Frogge & Goodman, 2005). When diarrhea is characterized by increased fecal fat, a mal-absorption syndrome should be considered. This may be present in tumors with an obstructed pancreatic duct or biliary obstruction (Cherny, 2008). Post-surgical complications or side effects should be considered in appropriate patients. Patients who have undergone a Whipple procedure, resection of more than 100cm of ileum or a colectomy are at risk for malabsorption (Cherny, 2008). Alternative causes of secretory diarrhea include, pancreatic islet cell tumors, vasoactive intestinal protein-secreting tumors, and carcinoid syndrome, all of which may include severe, life-threatening diarrhea (Cherny, 2008).

Management Strategies

Currently, the National Comprehensive Cancer Network, the American Society of Clinical Oncology and the Multinational Association of Supportive Care in Cancer, all lack published guidelines for the management of CID. The guidelines published by Benson et al. (2004), address the classification of CID into complicated and uncomplicated subtypes, antibiotic use,
pharmacologic and non-pharmacologic interventions, and antibiotic use. Muehlbauer et al. (2009), though more recent, only addresses pharmacologic interventions.

Non-Pharmacologic Interventions

The initial treatment for mild to moderate diarrhea includes non-pharmacological interventions. Dietary modifications such as eliminating all lactose-containing products, alcohol and high osmolar dietary supplements may help decrease CID. Sorbitol-containing products, such as sugar-free gum and candy, should be eliminated, as they can cause diarrhea (Muehlbauer et al., 2009). Any medications or foods that may enhance the diarrhea should be discontinued. The patient should be instructed to document stool frequency and promptly report symptoms of fever or dizziness upon standing (Benson et al., 2004; Cherny, 2008). Other non-pharmalogical interventions include: hydriating with 8-10 glasses of clear liquids per day, implementing the BRAT diet (Bananas, rice, applesauce, toast), and eating small frequent meals (Benson, 2004). Oral rehydration with fluids that contain water, sugar and salt will help prevent hyponatremia and hypokalemia (Benson et al., 2004; Richardson & Dobish, 2007). Examples of such fluids are sports drinks, broth, gelatin and decaffeinated, decarbonated soft drinks (Benson et al., 2004; Richardson & Dobish, 2007).

Pharmacologic Interventions

Loperamide, an opioid that decreases intestinal motility, is the standard first line therapy for CID (Stein, Voigt & Jordan, 2010). Loperamide may be given as a loading dose of 4mg followed by 2mg every 4 hours (Benson, 2004; Cherney, 2008; Richardson & Dobish, 2007). The loperamide can be discontinued when the patient is diarrhea free for 12 hours (Benson, 2004). If the mild to moderate diarrhea persists for greater than 24 hours, high dose loperamide may be given, increasing to 2mg every 2 hours, and oral antibiotics should be initiated as prophylaxis for infection (Benson et al., 2004; Cherny, 2008). If mild to moderate CID persists for greater than 48 hours while on high-dose loperamide, it should be discontinued and a second line anti-diarrheal agent should be started, such as octreotide (starting at 100-150?g SC) (Benson et al., 2004; Muehlbauer et al., 2009). At this point, the patient should be assessed by a practitioner and a complete work-up should be performed, including stool cultures for infection and blood work to evaluate for neutropenia and electrolyte imbalances (Benson, 2004; Cherny, 2008). Fluid and electrolytes should be repleted as needed.

Complicated cases of CID require aggressive treatment, involving hospitalization and intravenous fluids (Cherny, 2008). This aggressive approach is due to evidence that suggests these patients are at high risk for dehydration, infection and other potentially life-threatening complications (Benson et al. 2004). Loperamide, even at higher doses, may be less effective for grade 3 to 4 CID. Initial therapy should include octreotide 100-150?g (SC or IV) with a dose escalation up to 500?g until diarrhea is controlled (Benson et al., 2004). A fluoroquinolone should also be administered as the prophylactic antibiotic of choice (Benson et al., 2004). A full work up should include a complete blood count, electrolyte profile and stool studies for fecal blood, leukocytes, C. difficile, Salmonella, E. coli, Campylobacter, and infectious colitis (Benson et al., 2004; Cherny, 2008). Medications such as atropine, deodorized tincture of opium, and long-acting octreotide, lack supportive literature and are not included within the guidelines (Stein, Voigt & Jordan, 2010).

Conclusion

Up to 30% of cancer patients will experience severe or life-threatening CID (Stein, Voigt & Jordan, 2010). Presently, despite the high incidence and potential severity of CID, it is often under recognized, poorly understood and improperly managed (Richardson & Dobish, 2007). The prompt assessment, diagnosis and implementation of appropriate management strategies are key to the prevention of potentially fatal complications. Nurses play a vital role in recognizing patients who are at risk for CID and implementing early interventions.

OncoLink is designed for educational purposes only and is not engaged in rendering medical advice or professional services. The information provided through OncoLink should not be used for diagnosing or treating a health problem or a disease. It is not a substitute for professional care. If you have or suspect you may have a health problem or have questions or concerns about the medication that you have been prescribed, you should consult your health care provider.

Information Provided By: www.oncolink.org | © 2017 Trustees of The University of Pennsylvania
The current research focuses on establishing predictive factors for CID, such as polymorphisms, to help identify those at risk for toxicity and to optimize the efficacy of anticancer treatments (Vincenzi, Shiavon, Pantano, Santini & Tonini, 2008). The lack of current, comprehensive guidelines may be a reflection upon the uncertain pathophysiology that surrounds CID. Presently, the management strategies for CID include supportive care (such as intravenous fluids), dietary modifications, loperamide and octreotide. With the emergence of new therapies that cause CID and an aging population, the incidence of CID will surely increase. Nurses are at the forefront of patient care and play a vital role in the assessment and management of CID.

### Table 1: Common Terminology Criteria for Diarrhea

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>Increase of &lt; 4 stools per day over baseline. Ostomy: Mild increase output compared to baseline</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increase of 4-6 stools per day over baseline. Ostomy: Moderate increase in output compared to baseline</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increase of ≥ 7 stools per day over baseline. Incontinence. Hospitalization indicated. Ostomy: Severe increase in ostomy output compared to baseline. Limited self care ADL</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life-threatening consequences. Urgent intervention indicated</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>