Diarrhea in Multiple Myeloma:
A Review of the Literature

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Background: One of the most common and inadequately managed symptoms that patients with multiple myeloma (MM) experience as a result of cancer treatment is diarrhea. Diarrhea in patients with MM often is severe enough to warrant dose reduction, delays, or discontinuation of chemotherapy. Short-term diarrhea can occur as a side effect of drugs, such as bortezomib (Velcade®) or panobinostat (Farydak®). Late-onset diarrhea from lenalidomide (Revlimid®) can occur 17–24 months after the start of therapy. Treatment of diarrhea is often by dose reduction and discontinuation of the offending drug. However, the symptom fails to entirely resolve with these interventions and dose reductions place the individual at risk for disease progression. Best practices for diarrhea management in MM are poorly understood, but diarrhea symptoms impede patient adherence and undermine quality of life.

Objectives: The purpose of this article is to review the etiology of the symptom of diarrhea in people with cancer, specifically MM. Management strategies also are discussed.

Methods: A comprehensive review of CINAHL®, MEDLINE®, and PubMed databases was performed using the search terms diarrhea, chemotherapy, multiple myeloma, and cancer. Research studies, guidelines, and papers from peer-reviewed publications were considered.

Findings: Although general guidelines from the American Society of Clinical Oncology and Oncology Nursing Society exist that suggest best practices in the management of chemotherapy-induced diarrhea, best practices to identify and manage diarrhea symptoms in patients with MM are lacking.

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Diarrhea is an often neglected and undertreated source of symptom distress in patients with multiple myeloma (MM) (Hoff et al., 2014; Muehlbauer et al., 2009). Reasons for diarrhea are multifactorial and can be related to chemotherapy, a weakened immune system, medications, nutritional supplements, psychological stress, infection, graft-versus-host disease (GVHD), or the cancer itself (Benson et al., 2004). Best practices in the management of diarrhea in patients with MM are conspicuously absent, but ineffective diarrhea management can lead to altered physiologic and psychological processes.

Physiologic consequences of mild diarrhea include electrolyte abnormalities, malabsorption of oral medications, and impaired nutritional status, and more severe symptoms can cause death (Benson et al., 2004; Hoff et al., 2014; Maroun et al., 2007; Muchlbauer et al., 2009; Sun, Wang, & Hu, 2012). Psychological consequences include social isolation, low self-esteem, anxiety, and hopelessness (Smith, Bertolotti, Curran, & Jenkins, 2008). Ineffective management of diarrhea not only leads to poor clinical outcomes, but also has a negative impact on quality of life, including alteration of roles, responsibilities, and interpersonal relationships, and may cause social isolation (Muchlbauer et al., 2009).
Physiology of the Gastrointestinal Tract

The gastrointestinal (GI) tract is a complex system responsible for the disintegration of solid foods, bioavailability of nutrients, and excretion of unnecessary waste (Kong & Singh, 2008). The human gut microbial plays a central role in immune protection and contains cells from more than 1,000 different bacterial species. Disruption of the normal intestinal flora has been linked to GI illnesses (Nitzan, Eliaš, Chazan, Raz, & Saliba, 2013). The upper GI tract consists of the esophagus, stomach, and duodenum. The lower GI tract includes the small and large intestines. The motility of the GI tract allows food and excrement to be pushed through the tract and produce bowel movements.

The small intestines are further divided into the duodenum, jejunum, and ileum. Digestive juices from the gall bladder and pancreas mix in the duodenum to break down proteins and bile and facilitate digestion. Products of digestion are absorbed through intestinal villi, or fingerlike projections that protrude from the intestinal wall in the jejunum and release into the bloodstream. Additional villi are present in the ileum, where nutrients and vitamins, such as B12, are absorbed (DeSesso, Jacobson, & Williams, 2012).

Intestinal crypts are glands found within the small intestinal mucosa and intestinal villi. The crypts and intestinal villi are covered by epithelium, which contain the mucus-secreting goblet cells and enterocytes, and are responsible for water absorption and nutrient secretion. Pathologic processes, such as inflammatory bowel disease, colitis, or GVHD, can affect the crypt cells and lead to crypt cell loss (Lin, Fan, Zhao, Cummings, & Chen, 2013; Umar, 2010).

The large intestines are comprised of the cecum and colon. The main function of the large intestines is to absorb water and facilitate excretion of stool. The four parts of the colon are the ascending, transverse, descending, and sigmoid segments. The colon connects to the rectum and then the anal canal. The GI tract terminates with the anus. Crypt goblet cells have the ability to regenerate the mucus layer throughout the GI tract by secretion; mucus plays an essential role in GI immune protection (Johansson, Sjövall, & Hansson, 2013).

Pathobiology of Diarrhea

Four basic pathophysiologic mechanisms are involved in the production of diarrhea: (a) abnormal intestinal motility, (b) increased vascular or fluid permeability, (c) impaired intestinal absorption, and (d) intraluminal absorbable solutes. Diarrhea is further characterized as acute or chronic. Acute diarrhea usually is transient and may be of infectious, toxic, or dietary causes. Chronic diarrhea may be secondary to functional bowel disorders, colonic disease, diseases of the small intestine, or drugs (Friedman, 2000). Once an individual with MM develops chronic diarrhea, the etiology must be determined.

Etiology of Diarrhea

Diarrhea is a GI manifestation of illness and can be classified as being one of the following four factors: infection, inflammation, malignancy, or an autoimmune phenomenon.

Infection: More than 200 million cases of enteric illness occur in the United States per year (Guerrant et al., 2001). Transmission of viral illness occurs from person to person, water, or food. Infectious diarrhea often is acute and transient but can be life-threatening even in healthy individuals (Surawicz et al., 2013). The most common type of intestinal infection in patients with MM is Clostridium difficile (Kinnbrew et al., 2014; Nucci & Anaissie, 2009a, 2009b; Tam, Viviani, Rodrigues, & O’Brien, 2013). Infectious diarrheal illnesses are diagnosed based on the history of symptoms and stool culture (Hong & Rhee, 2014; Kinnbrew et al., 2014; Surawicz et al., 2013).

Inflammation: Intestinal inflammatory disorders will predispose patients to developing diarrhea (Abraham & Cho, 2009; Nitzan et al., 2013). The two main types of inflammatory disorders are Crohn’s disease (CD) and ulcerative colitis (UC) (Baumgart & Sandborn, 2012; Danese & Fiocchi, 2011; Moris, 2014). CD and UC can be confirmed by a structural abnormality. UC is a disease of the colonic mucosa and can be cured by colectomy (Danese & Fiocchi, 2011; Moris, 2014). CD affects the entire GI tract, from the mouth to the anus (Baumgart & Sandborn, 2012), and usually requires immunotherapy and autoimmune therapies to reduce diarrhea and abdominal symptoms.

Irritable bowel syndrome (IBS) is a common and potentially disabling functional GI inflammatory disorder characterized by abdominal pain, bloating, and erratic bowel habits. Irritable bowel syndrome is based on patient history and symptom assessment (Lee & Park, 2014). Unlike UC and CD, symptoms of IBS cannot be confirmed by a structural abnormality; rather, the syndrome likely is related to a multitude of disorders. Current research into IBS includes possible etiologies, such as low-grade inflammation, altered intestinal flora, and/or infection (Dai, Zheng, Ma, & Jiang, 2013; Hong & Rhee, 2014; König & Brummer, 2014). One psychological component of IBS, brain–gut interaction, has been attributed to a high prevalence of psychiatric disorders in patients with IBS (Hong & Rhee, 2014; Lee & Park, 2014).

No biochemical, histopathologic, or radiologic diagnostic test to diagnose IBS currently exists, and the diagnosis of IBS is based on patient history and symptom assessment (El-Salhy, 2012). Treatments for IBS, such as probiotics (Dai et al., 2013), 5-HT₃ receptor antagonists (Itagaki et al., 2014), melatonin (Siah, Wong, & Ho, 2014), and alternative therapies (e.g., hypnosis, cognitive therapy, acupuncture), have been studied (Grundmann & Yoon, 2014) with varying effectiveness.

Drugs used to treat MM can cause diarrhea. These include lenalidomide (Revlimid®), bortezomib (Velcade®), and panobinostat (Farydak®). In clinical trials of bortezomib and panobinostat, diarrhea was one of the most commonly reported side effects and often managed by loperamide (Imodium®) (Celgene Corporation, 2015; Millennium Pharmaceuticals, 2014). However, how effective loperamide is in treating diarrhea in MM is unclear. Moderate to severe diarrhea in patients on chronic lenalidomide therapy can occur and may lead patients to withdraw from treatment because of poor or ineffective management of symptoms. No guidelines have
been established to manage lenalidomide-related diarrhea in MM, and existing guidelines to manage diarrhea are outdated (Benson et al., 2004).

**Malignancy** Diarrhea can occur as a result of malignancy. Types of cancers associated with the development of diarrhea include colon, endometrial, ovarian, and sarcomed cancers, as well as T-cell lymphoma (Cho, Kim, Cho, Bae, & Kim, 2002; Kim et al., 2013).

**Immunodeficiency and the role of immunoglobulin A in the intestines:** Various forms of immune regulation occur along the length of the intestine, depending on the site of the challenge, such as food in the small bowel or changes to the intestinal flora (Agarwal & Mayer, 2013). The intestines play a central role in maintaining homeostasis within the immune system (Lamm & Phillips-Quagliata, 2002). Two main cells within the intestines are essential to immune function: gut-associated lymphoid tissue (GALT) and mucosal-associated lymphoid tissue (Weiner, 2000).

The bulk of the body’s immunoglobulin-producing cells reside within the intestinal tract. An estimated 80% of plasma cells with immunoglobulin A (IgA) predominance reside within GALT (Vigli, Marcucci, Sensi, Di Cara, & Frati, 2008). IgA triggers immune response and effectively binds to proteins, toxins, and foreign invaders against environmental antigens and local microbial flora to maintain homeostasis and provide protective immunity against viruses (Blutt & Conner, 2013). IgA antibodies represent the first line of immune defense against the external environment (Lamm & Phillips-Quagliata, 2002). In primary immune IgA deficiency, decreased IgA levels (less than 7 mg/dl, with normal or increased levels of other immunoglobulins) may be the result of immune dysfunction in the regulation of terminal maturation of B cells into IgA-secreting plasma cells (Agarwal & Mayer, 2013). Why individuals with low serum IgA levels develop diarrhea is unclear. One theory is that because IgA antibodies are transported in secretions to mucosal surfaces (e.g., mouth, esophagus, other membranes), a lack of IgA antibodies may lead to diarrhea in some individuals.

**Diarrhea related to graft-versus-host disease:** GVHD is immune-related and the most frequent complication after donor allogeneic hematopoietic cell transplantation (HCT) in patients with MM (Deeg, 2007; Lokhorst et al., 2010). The pathogenesis of allogeneic GVHD is complex, attributable to immune cell injury induced by chemotherapy prior to HCT (Hou et al., 2013). In GVHD, antigenic presentation from the donor (graft) to the host (patient) leads to donor T-cell lymphocyte activation and immune system stimulation (Cogbill, Drobsy, & Komorowski, 2011).

Intestinal GVHD has been reported after non-donor autologous HCT, and GVHD plays a role in MM disease-free survival (Melson, Jakate, Fung, Arai, & Keshavarzian, 2007). Histopathologic findings of crypt mucosal cell loss or abnormalities are evident on colonic biopsy. Crypt loss is a hallmark of GVHD and a marker of GVHD severity (Melson et al., 2007). Colon biopsy specimens are graded on a severity scale. Grade 1 shows isolated crypt apoptosis of epithelial cells, and grade 4 shows extensive crypt loss (Cogbill et al., 2011; Sale, Lerner, Barker, Shulman, & Thomas, 1977).

**Measurement of Diarrhea** Diarrhea is measured according to national guidelines and patient self-report. In randomized, controlled prospective trials, the Infectious Diseases Society of America (IDSA) or National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading scale (version 4) may be used. IDSA defines diarrhea as three or more loose stools per day, and the NCI CTCAE considers the severity of one’s diarrhea (Guerrant et al., 2001). The NCI CTCAE is a standardized grading system to report treatment-related adverse events. Diarrhea episodes are graded in severity from 1 (mild) to 5 (death-associated event). For example, patients are classified as having grade 1 diarrhea if they experience an increase of less than four stools daily from baseline, but the diarrhea does not interfere with activities of daily living.

**Characteristics of lenalidomide-related diarrhea:** Little is known about the characteristics of lenalidomide-related diarrhea because the concept has not been extensively studied. One review reported the onset of moderate to severe diarrhea in long-term lenalidomide therapy to occur at 19 months (Simpson et al., 2008). Similarly, the authors’ center reported onset of diarrhea on lenalidomide to occur at a median of 17.7 months (Faiman et al., 2013). The diarrhea observed in each retrospective analysis was classified as chronic with an increase in stool output. No other specific measures of diarrhea (e.g., number of stools per day) were mentioned.

**Prevention and Treatment of Diarrhea** Few prevention or treatment strategies are effective for lenalidomide-related diarrhea in patients with MM. In addition, current management strategies fail to resolve the diarrhea symptom in a majority of cases. Nurses should begin assessment of diarrhea by asking the patient about the color and consistency of the stools, as well as the number of stools per day from baseline. Dietary and lifestyle modifications are important for all grades of diarrhea from moderate to severe. Dietary modifications include advising the patient to eliminate fiber and lactose from the diet; avoid greasy, fried, and acidic foods; abstain from alcohol and caffeine; and discontinue high-osmolar food supplements (e.g., Ensure®) if they are taking them (Benson et al., 2004). Guidelines exist to prevent and treat chemotherapy- and radiotherapy-related diarrhea in cancers other than MM (Benson et al., 2004; Maroun et al., 2007; Muehlbauer et al., 2009). Research into best practices for diarrhea management in MM is conspicuously absent. Loperamide, over-the-counter glutamine, octreotide (Somatostatin®), and budesonide (Entocort®) are four commonly cited drugs used to control chemotherapy-induced diarrhea. Cholestyramine (Questran®) has also been used to treat diarrhea because of malabsorption and can be useful in diarrhea related to novel agents (Lee, 2015). Management of chemotherapy- and radiation-induced diarrhea has been reported in the Oncology Nursing Society Putting Evidence Into Practice resources (Thorpe et al., 2016), but management of diarrhea related to the use of novel agents (e.g., lenalidomide, panobinostat) is not captured in these guidelines and requires further investigation.
Loperamide is an over-the-counter antidiarrheal agent that has been studied extensively, and it is considered to be the gold standard and most effective first treatment for chemotherapy-induced diarrhea in patients with MM (Maroun et al., 2007). Another treatment, glutamine, is the most abundant amino acid in the body and responsible for cellular growth of rapidly dividing cells, such as in the gastric mucosa. The effect of glutamine on chemotherapy-induced diarrhea has been studied in multiple randomized, controlled trials but with varying results (Bozzetti et al., 1997; Heyns, Walker, Smith, & Eremin, 1999; Sornsuvit et al., 2008). Another medication, somatostatin, reduces the secretions of pancreatic and GI hormones, reducing gut transit time (Martenson et al., 2008). Somatostatin is fairly effective in treating patients with chemotherapy-induced diarrhea (Hoff et al., 2014; Martenson et al., 2008).

Budesonide, a drug that acts directly on the intestinal mucosa, is a glucocorticoid with high local activity but much lower systemic availability than other corticosteroids, such as prednisone (Deltasone®) (Edsbäcker & Andersson, 2004; Tromm et al., 2011). Clinical trials have demonstrated that budesonide is an effective treatment for irritable bowel disease and disorders of the microscopic colitis spectrum, which includes collagenous, lymphocytic-immune, and lymphocytic colitis (Baert et al., 2002; Bonderup et al., 2003; Bonderup, Hansen, Teglbjaerg, Christensen, & fallingborg, 2009; Greenberg et al., 1996; Miehlke et al., 2008, 2009; Van Gossuin, Schmit, & Peny, 1998).

Lastly, live Lactobacillus acidophilus and probiotics have been shown to prevent chemotherapy- and radiotherapy-induced diarrhea in cervical cancer (Chitapanarux et al., 2010; Salminen, Elomaa, Minkkinen, Vapaatalo, & Salminen, 1988; Siitonen et al., 1990; Van Neil, Feudtner, Garrison, & Christakis, 2002).

Implications for Nursing

Immediate implications of diarrhea exist because the consequences of diarrhea can be significant and life-threatening. Symptoms of severe diarrhea can lead to physiologic and psychological complications, withdrawal from treatment because of poor or ineffective management of the symptoms, and poor quality of life. Nurses can help patients by assessing diarrhea severity, assessing for concurrent medications that may be contributing to diarrhea, and recommending over-the-counter agents to treat noninfectious causes of diarrhea.

Conclusion

Research into the symptom of diarrhea is evident in other cancers and disease states but is conspicuously absent in patients with MM. High-quality studies that investigate the etiology of diarrhea and the patient symptom experience are desperately needed because of the major adverse impact that this poorly understood complication has on quality of life and control of disease. Short-term diarrhea occurs in patients on bortezomib and in those with MM who receive long-term lenalidomide. Causes of diarrhea, such as infection, inflammation, IgA, and other immune factors must be considered. Strategies to prevent the development of diarrhea in patients with MM are unknown. High-quality studies are needed to provide insight into the diarrhea phenomena.

References


