Gastrointestinal Side Effects Associated With Novel Therapies in Patients With Multiple Myeloma: Consensus Statement of the IMF Nurse Leadership Board

Lisa C. Smith, MSN, FNP, AOCN®, Page Bertolotti, RN, BSN, OCN®, Kathleen Curran, RN, MSN, CRNP, Bonnie Jenkins, RN, and the IMF Nurse Leadership Board

The novel immunomodulatory drugs lenalidomide and thalidomide and the novel proteasome inhibitor bortezomib can cause gastrointestinal side effects, including constipation, diarrhea, nausea, and vomiting, which can have a deleterious effect on quality of life and interfere with optimal therapy. The International Myeloma Foundation's Nurse Leadership Board developed this consensus statement for the management of gastrointestinal side effects associated with novel therapies to be used by healthcare providers in any medical setting. It includes grading criteria and general recommendations for assessing and managing the side effects. Although constipation, diarrhea, nausea, and vomiting are expected side effects associated with novel therapies for multiple myeloma, they are manageable with appropriate medical interventions.

Novel therapies for multiple myeloma include the immunomodulatory drugs lenalidomide (Revlimid®, Celgene Corporation) and thalidomide (Thalomid®, Celgene Corporation) and the proteasome inhibitor bortezomib (Velcade®, Millennium Pharmaceuticals, Inc.). The benefits of the agents for patients with multiple myeloma include increased response rates and survival times compared with conventional chemotherapy (e.g., melphalan plus prednisone; or vincristine, adriamycin, and dexamethasone) (Celgene Corporation, 2007a, 2007b; Ghobrial et al., 2007; Manochakian, Miller, & Chanan-Khan, 2007; Millennium Pharmaceuticals, Inc., 2007; Rajkumar et al., 2005; Richardson & Anderson, 2006; Richardson, Hideshima, Mitsiades, & Anderson, 2007).

Like conventional chemotherapeutic agents, the novel therapies can cause serious side effects. Among them are gastrointestinal side effects, including constipation, diarrhea, nausea, and vomiting, which, although predictable and manageable, can be life threatening and interfere with adherence to optimal therapy and quality of life (Celgene Corporation, 2007a, 2007b; Millennium Pharmaceuticals, Inc., 2007). The International Myeloma Foundation's Nurse Leadership Board, in recognition of the need for specific recommendations on managing key side effects of novel antimyeloma agents, developed this consensus statement for the management of constipation, diarrhea, nausea, and vomiting associated with lenalidomide, thalidomide, and bortezomib. The statement can be used by healthcare providers in any type of medical setting (Bertolotti et al., 2007, 2008). The recommendations, which were developed through evidence-based reviews and a consensus of the Nurse Leadership Board,

At a Glance

- Lenalidomide, thalidomide, and bortezomib can cause serious gastrointestinal side effects.
- Adequate management of the toxicities can increase adherence to treatment, decrease impairment, improve quality of life, and prevent serious adverse events leading to prolonged hospitalization and increased morbidity and mortality.
- This article provides recommendations to assist healthcare providers in any medical setting to manage the gastrointestinal side effects.

Lisa C. Smith, MSN, FNP, AOCN®, is a nurse practitioner at the Cancer Centers of the Carolinas in Greenville, SC; Page Bertolotti, RN, BSN, OCN®, is an oncology nurse at the Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute in Los Angeles, CA; Kathleen Curran, RN, MSN, CRNP, is a certified registered nurse practitioner at the University of Pittsburgh Medical Center–Shadyside Hospital in Pennsylvania; and Bonnie Jenkins, RN, is the director of program coordination at the Myeloma Institute for Research and Therapy at the University of Arkansas in Little Rock. Smith and Curran are members of the speakers bureaus for Celgene Corporation and Millennium Pharmaceuticals, Inc. Bertolotti is a member of the speakers bureaus for Celgene Corporation and Ortho Biotech Products, L.P. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Clinical Journal of Oncology Nursing* or the Oncology Nursing Society.
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Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Gastrointestinal Toxicity

ADVERSE EVENT	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)	GRADE 5 (DEATH)
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with activities of daily living; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per 24 hours over baseline; IV fluids indicated < 24 hours; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of 7 stools per 24 hours over baseline; incontinence; IV fluids 24 hours; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition indicated 24 hours	Life-threatening consequences	Death
Vomiting	1 episode in 24 hours	2–5 episodes in 24 hours; IV fluids indicated < 24 hours	6 episodes in 24 hours; IV fluids or total parenteral nutrition indicated 24 hours	Life-threatening consequences	Death

Note. Based on information from National Cancer Institute, 2006.

also are applicable for managing gastrointestinal side effects caused by any chemotherapeutic agent.

Issue Statement

Gastrointestinal toxicities are common sequelae of treatment with novel therapies, including lenalidomide, thalidomide, and bortezomib. Although they are addressed often, they may not be managed adequately. Inadequate management of constipation, diarrhea, nausea, or vomiting can affect patients in multiple ways. Physical effects can lead to decreased adherence to treatment regimens. Psychological effects include anxiety and depression. Patients may become socially isolated and experience decreased function and abilities. Adequate management of gastrointestinal toxicities increases patient adherence to treatment regimens, decreases physiologic impairment, improves quality of life for patients and their caregivers, and prevents serious adverse events that lead to prolonged hospitalization and increased morbidity and mortality.

Table 2. Incidence of Gastrointestinal Events in Patients With Multiple Myeloma Receiving Novel Therapies

	LENALIDOMIDE[a] (TWO STUDIES, N = 346)		THALIDOMIDE[a] (OPEN-LABEL STUDY, N = 102)		BORTEZOMIB (PHASE III TRIAL, N = 331)	
TOXICITY	ALL GRADES (%)	GRADE 3[b] (%)	ALL GRADES (%)	GRADE 3[b] (%)	ALL GRADES (%)	GRADE 3[b] (%)
Constipation	39	2	55	8	42	2
Diarrhea	29	2	12	1	57	7
Nausea	22	< 2[c]	28	5	57	2
Vomiting	10	< 2[c]	12	2	35	3

[a] Administered in combination with dexamethasone

[b] No grade 4 events were reported.

[c] Only grade 3 and 4 adverse events with an incidence of ≥ 2% were reported.

Note. Based on information from Celgene Corporation, 2007a, 2007b; Millennium Pharmaceuticals, Inc., 2007.

Table 3. Risk Factors for Gastrointestinal Toxicities Other Than Treatment With Novel Therapies

VARIABLE	CONSTIPATION	DIARRHEA	NAUSEA	VOMITING
Patient characteristics	Adults older than 65 years Sedentary or bedridden	Adults older than 65 years Recent stay in a hospital or nursing home.	Age younger than 50 Female Nausea and vomiting during previous anticancer treatments Sweating, dizziness, or warmth after last anticancer treatment	More likely in children than in adults Female History of motion sickness and anxiety History of emesis and dehydration caused by cancer therapy
Diet	Low-fiber diet Poor fluid intake	Herbal supplements, including milk thistle, aloe, cayenne, saw palmetto, and ginseng	Current or prior heavy alcohol use	Current or prior heavy alcohol use
Medications	Particularly opioids and dexamethasone; also antacids, antiemetics, antiseizure medications, and iron supplements	Laxatives, antibiotics, antacids containing magnesium, colchicine, propanolol, diuretics, angiotensin-converting enzyme inhibitors, and antidepressants	Chemotherapy, opioids, levodopa, digitalis, pilocarpine, nicotine, nonsteroidal anti-inflammatory agents, antibiotics, and iron supplements	Chemotherapy, opioids, levodopa, digitalis, pilocarpine, nicotine, and nonsteroidal anti-inflammatory agents
Comorbidities	Diabetes, hypertension, hypothyroidism, tumor pressing on spinal cord, bowel obstruction, and peripheral neuropathy	History of irritable bowel syndrome, colitis, or diverticulitis; and graft-versus-host disease following bone marrow transplantation	Older patients with declining organ function and multiple illnesses and conditions, bowel obstruction, brain metastases, or gastrointestinal infections or bleeding	Bowel obstruction; brain metastases; gastrointestinal infections or bleeding; electrolyte imbalance
Medical procedures	Surgery involving the intestinal tract	Surgery involving the intestinal tract or bone marrow transplantation	Radiation therapy	Radiation therapy

Note. Based on information from American Gastroenterological Association, 2000; American Society of Clinical Oncology, 2005a, 2005b, 2005c; Berger & Clark-Snow, 2005, 2007; Bush, 2004; Dalal et al., 2007; Engelking, 2004; Glare et al., 2004; Mercadante, 2007; National Comprehensive Cancer Network, 2007; National Comprehensive Cancer Network & American Cancer Society, 2007; Tipton et al., 2006.

This consensus statement and the tools provided address the gastrointestinal toxicities of constipation, diarrhea, nausea, and vomiting and will allow oncology nurses, as part of interdisciplinary teams, to be better prepared to manage toxicities associated with novel therapies.

Toxicity Tool for Grading

The severity of gastrointestinal adverse events can be quantified with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The NCI CTCAE are used for identifying treatment-related adverse events to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures. For most adverse events, the NCI CTCAE define grades 1–5 using unique clinical descriptions; each grade is assigned a severity: grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life threatening or disabling, and grade 5 defines death associated with the adverse event. The grades may be used for monitoring gastrointestinal side effects and determining the need for intervention and dosage modifications. Table 1 defines the NCI CTCAE version 3.0 toxicity grades for constipation, diarrhea, nausea, and vomiting (NCI, 2006).

Incidence, Risk Factors, and Assessments for Gastrointestinal Toxicities

Table 2 presents the incidence of gastrointestinal toxicities in patients with multiple myeloma receiving lenalidomide, thalidomide, or bortezomib in clinical trials. Table 3 lists risk factors other than treatment with novel therapies that may cause constipation, diarrhea, nausea, or vomiting in patients with multiple myeloma. Table 4 outlines risk assessments for gastrointestinal toxicities in patients receiving novel therapies for multiple myeloma based on clinical observations, patient history, and physical and laboratory examinations.

Recommendations for Constipation

Constipation is defined as decreased frequency of defecation, usually less than three bowel movements per week, with accompanying abdominal discomfort. It is a common issue in patients with cancer because of poor oral intake or because of drugs such as opioids or antiemetics, which slow intestinal transit time. Constipation can be a disabling toxicity and often is underassessed and undertreated in patients with cancer

Table 4. Risk Assessments for Gastrointestinal Toxicities

VARIABLE	CONSTIPATION	DIARRHEA	NAUSEA	VOMITING
Clinical assessment	Abdominal, liver, or retroperitoneal pain Abdominal distention Anorexia Nausea and vomiting Urinary retention Confusion Pseudodiarrhea	Evaluate onset.	Evaluate onset and triggers.	Assess circumstances surrounding episodes of vomiting (e.g., after eating, empty stomach, time of day, associated with certain smells) Assess for epigastric pain, pain on swallowing, hiccups, and heartburn; quantity and description of emesis; weight and skin turgor to monitor fluid volume deficit; postural hypotension; secondary effects from vomiting (e.g., dehydration, electrolyte imbalances, vertigo, sleep deprivation, fatigue, anorexia)
Patient history	Pattern of recent bowel movements: frequency and difficulty of defecation prior to illness Usual use of laxatives, stimulants, or enemas History of cancer and cancer treatment Use of constipating medications[a] Recent fluid and food intake Presence of comorbid conditions that can exacerbate constipation[a]	Determine normal bowel habits, diet, food intolerances, and fluid intake. Determine history of irritable bowel syndrome, colitis, or diverticulitis Medications[a]	Obtain history including patterns of nausea to include medications and effect; assess the dose of drugs, as high doses are more likely to cause nausea Determine when and how often the drug is given and how the drug is given (e.g. via IV or orally) Determine food intolerances and dietary-restriction history and reasons Determine the type of nausea: acute, delayed, anticipatory, breakthrough, refractory	Consider the emetogenic potential of the novel agent: high, moderate or low Medication history to include all over the counter, prescription, vitamins, and alternative medications; sudden cessation of opioid analgesics (vomiting often occurs with physical withdrawal)
Physical and laboratory examinations	Palpation of fecal masses Presence or absence of feces in rectum, if present, consistency of stool Presence of bowel sounds: quality and character Flat abdominal x-ray will assess amount of stool in the bowel as well as evaluate for mechanical bowel obstruction	Determine hydration status: dry mucous membrane and poor skin turgor. Assess bowel sounds (absent or hyperactive bowel sounds may indicate obstruction). Rectal examination to rule out fecal impaction Complete blood count, comprehensive metabolic panel, and stool culture if infection (e.g., *Clostridium difficile* is suspected)	Determine hydration status: dry mucous membranes, poor skin turgor, sunken eyes, tachycardia, orthostatic blood pressure changes, weight loss, fluctuation in mental status, and color of urine (dark color indicates dehydration).	Physical examination should include assessment of mouth for oral candidiasis, herpes, or other infections; tongue for increased furrows (smaller tongue with lack of moisture indicates dehydration); abdomen for distention; and bowel sounds for partial or total bowel obstruction.

[a] See Table 3.

Note. Based on information from American Gastroenterological Association, 2000; American Society of Clinical Oncology, 2005a, 2005b, 2005c; Berger & Clark-Snow, 2005, 2007; Bush, 2004; Dalal et al., 2007; Glare et al., 2004; Mercadante, 2007; National Comprehensive Cancer Network, 2007; National Comprehensive Cancer Network & American Cancer Society, 2007.

(American Society of Clinical Oncology [ASCO], 2005a; Mercadante, 2007; NCI, 2007a). Table 5 provides management strategies for constipation by CTCAE version 3.0 grades 1–4. Appendix A offers the Oncology Nursing Society Putting Evidence Into Practice® recommendations.

Recommendations for Diarrhea

Diarrhea is defined as an abnormal increase in the amount of fluid in stool. Severe and uncontrolled diarrhea can lead to dehydration and electrolyte imbalances, exacerbate underly-

Table 5. Management of Constipation, Diarrhea, Nausea, and Vomitting by the National Cancer Institute Common Terminology Criteria for Adverse Events

	RECOMMENDATIONS			
GRADE[a]	CONSTIPATION	DIARRHEA	NAUSEA	VOMITING
1	Increase fluid intake: warm or hot drink approximately half-hour before time of patient's usual defecation. Increase fiber intake (e.g., psyllium 10 gm PO daily). Provide comfort, privacy, and convenience during defecation (e.g., provide toilet, bedside commode, and appropriate assistive devices). Increase physical activity, if possible. Consider bowel regimen when constipating medications are prescribed (e.g., docusate 2–3 tablets per day, senna not to exceed 8 tablets a day).	Increase oral fluid intake (8–10 cups daily). Recommend water, electrolyte-replacement beverages, sports drinks, diluted fruit juices, and broth. Avoid caffeinated, carbonated, heavily sugared, and hyperosmotic beverages. Foods to avoid: alcohol, caffeine-containing products, carbonated and high-sugar beverages, fruit juices with pulp, high-fiber and high-fat foods, hot or heavily spiced foods, dairy products. Discontinue, if possible, any medications or herbal supplements that may cause diarrhea. Perineal care: Clean area using mild soap and water or wet wipes. Pat dry rather than rub dry; air dry when possible. Use skin barrier products, vitamin D ointment, diaper-rash cream, or other moisture-barrier products. Use skin-barrier products with caution as they may be difficult to remove, resulting in further skin impairment. Pharmacologic management for grade 1 diarrhea that persists for more than 12–24 hours Antidiarrheal agent: loperamide 4 mg followed by 2 mg every four hours or after each unformed stool (maximum 16 mg per day). May take 4 mg every four hours at night to allow sleep.	All of the recommendations for anticipatory nausea (see Figure 1) plus the following. Strive to prevent (not just control) nausea. Start mild antinausea medications the night before treatment. Select medications based on how strongly the novel agents stimulate nausea. Consider palonosetron, dolasetron, aprepitant, granisetron, or ondansetron.	May be self-limiting Offer PO antiemetic such as short-acting phenothiazines. Oral care after each emesis Cool, damp cloth to the forehead, neck, and wrists Decrease noxious stimuli. Restrict fluid with meals. Try peppermint or ginger tea, a sports beverage, ice chips, or popsicles. Eat small, frequent meals. Have others prepare meals. Eat bland, cold, or room temperature food such as crackers, toast, cereals, and ginger cookies. Chew food well; suck on mints or hard candy. Do not lie flat for two hours after eating. Wear loose-fitting clothes. Have fresh air with a fan or open window. Use relaxation techniques and guided imagery. Avoid favorite foods so that they will not be associated with vomiting later. Avoid sweet, salty, fatty, and spicy foods Avoid citrus and tomatoes; limit sights, sounds, and smells that precipitate vomiting. Suggest that patients discuss hypnosis and acupuncture with a doctor.
2	All of the grade 1 recommendations plus the following: Nutritional consultation Consider laxatives and stimulants: magnesium sulfate 15 g PO daily, magnesium citrate 200 ml PO daily, lactulose	All of the grade 1 recommendations plus the following: Consider atropine-diphenoxylate one or two tablets every six to eight hours. Correct electrolyte imbalance as needed.	All of the grade 1 recommendations plus the following: Increases in dosages of medications may be needed to maintain oral intake. IV fluids should be restricted to bolus amounts of fluids to	All of the grade 1 recommendations plus the following: Serotonin 5-HT_3 receptor antagonists if needed Consider benzodiazepines.

(Continued on next page)

[a] See Table 1.

[b] The incidence of severe nausea associated with novel agents is ≤ 5%. If grade 3 or 4 nausea occurs, consider gastroesophageal reflux disease or peptic ulcer disease.

[c] The incidence of severe vomiting associated with novel agents is ≤ 3%. If grade 3 or 4 vomiting occurs, consider gastroesophageal reflux disease or peptic ulcer disease.

Note. Based on information from American Gastroenterological Association, 2000; American Society of Clinical Oncology, 2005a, 2005b, 2005c; Basch & Ulbricht, 2005; Benson et al., 2004; Berger & Clark-Snow, 2005, 2007; Bisanz et al., 2007; Bush, 2004; Dalal et al., 2007; Engelking, 2004; Ernst & Pittler, 2000; Glare et al., 2004; Grunberg, 2007; Jordan et al., 2007; Kris et al., 2006; Mercadante, 2007; Molassiotis et al., 2002; National Comprehensive Cancer Network, 2007; National Comprehensive Cancer Network & American Cancer Society, 2007; Redd et al., 2001; San Miguel et al., 2006; Shen et al., 2000; Tipton et al., 2006.

Table 5. Management of Constipation, Diarrhea, Nausea, and Vomitting by the National Cancer Institute Common Terminology Criteria for Adverse Events *(Continued)*

	RECOMMENDATIONS			
GRADE[a]	CONSTIPATION	DIARRHEA	NAUSEA	VOMITING
2 *(continued)*	15–60 ml PO daily, bisacodyl 5–20 mg PO at night or 10–20 mg rectally after a meal	May manage on an outpatient basis until diarrhea resolves	maintain hydration and electrolyte balance. Use the lowest effective dose of the antinausea medication before novel therapy. Monitor how the individual responds to the antinausea treatment. Consider the side effects of the antinausea medications.	May require IV hydration or electrolyte replacement
3	All of the grade 2 recommendations plus the following: Initiate bowel regimen (call physician if no bowel movement in three days). Assess for bowel obstruction. Consider referral for disimpaction (following institutional guidelines). Consider IV hydration. If no response, consider referral to a gastroenterologist.	All of the grade 2 recommendations plus the following: Hospitalize for fluid replacement. Stool cultures and sensitivity: rule out *Clostridium difficile,* ova, cysts, and parasites. Consider empiric antibiotic, (e.g., metronidazole). Consider tincture of opium 0.6 ml PO every four to six hours. Consider sandostatin 100–150 mcg subcutaneously TID. Monitor continuously. Vigilant skin care and use of disposable pads or diapers Consider holding or adjusting cancer therapy (see Table 6).	All of the grade 2 recommendations plus the following[b]: Increase medications appropriate to the degree of incapacitation caused by nausea. Consider adding lorazepam, proclorperazine, dexamethasone, famotidine, promethazine, metoclopramine, or ranitidine. Assess for distention of abdomen and obstruction; monitor electrolytes and hydration. May require hospitalization	All of the grade 2 recommendations plus the following[c]: May require hospitalization Antiemetics around the clock IV hydration and electrolyte replacement May need total parenteral nutrition Assess for intestinal obstruction.
4	All of the grade 3 recommendations plus the following: Hospitalization Rule out perforation, particularly if patient is taking dexamethasone combination therapy.	Admit to hospital. Stabilize and monitor vital signs. Aggressive electrolyte and fluid replacement Dietary modifications: nothing by mouth; consider total parenteral nutrition. Follow previous guidelines as appropriate. Strict monitoring of fluid intake and output Discontinue any agent associated with diarrhea. Monitor continuously.	All of the grade 3 recommendations plus the following[b]: If nausea causes severe incapacitation, then total parental nutrition may be considered. Note that grade 4 nausea is unlikely without concommittant vomiting.	All of the grade 3 recommendations plus the following[c]: Hospitalization Referral to a gastroenterologist Total parenteral nutrition

[a] See Table 1.

[b] The incidence of severe nausea associated with novel agents is ≤ 5%. If grade 3 or 4 nausea occurs, consider gastroesophageal reflux disease or peptic ulcer disease.

[c] The incidence of severe vomiting associated with novel agents is ≤ 3%. If grade 3 or 4 vomiting occurs, consider gastroesophageal reflux disease or peptic ulcer disease.

Note. Based on information from American Gastroenterological Association, 2000; American Society of Clinical Oncology, 2005a, 2005b, 2005c; Basch & Ulbricht, 2005; Benson et al., 2004; Berger & Clark-Snow, 2005, 2007; Bisanz et al., 2007; Bush, 2004; Dalal et al., 2007; Engelking, 2004; Ernst & Pittler, 2000; Glare et al., 2004; Grunberg, 2007; Jordan et al., 2007; Kris et al., 2006; Mercadante, 2007; Molassiotis et al., 2002; National Comprehensive Cancer Network, 2007; National Comprehensive Cancer Network & American Cancer Society, 2007; Redd et al., 2001; San Miguel et al., 2006; Shen et al., 2000; Tipton et al., 2006.

ing renal dysfunction, decrease quality of life, and increase emotional distress. Nurses are in a pivotal position to evaluate patients' risk for diarrhea and implement the necessary steps to prevent and treat the potentially serious adverse event (ASCO, 2005b; Bush, 2004; Engelking, 2004; Mercadante, 2007).

- Eat small amounts of food throughout the day and eat before getting too hungry.
- Eat dry foods such as dry cereal, toast, or crackers without liquids, especially first thing in the morning.
- Avoid heavy, high-fat, and greasy meals before anticancer therapy.
- Consider avoiding favorite foods, as they may no longer be favorite foods if they become associated with nausea.
- Don't lie flat for at least two hours after eating.
- Fresh air and loose clothing may be helpful after eating.
- Exercising after eating may increase discomfort.
- Avoid strong odors.
- Distraction
- Suggest patients relax and try to keep their minds off therapy by using soothing music, relaxation tapes or CDs, progressive relaxation, guided imagery, or self-hypnosis.
- Acupuncture
- Biofeedback
- Systematic desensitization
- Consider how likely the therapy is to cause nausea in the absence of effective nausea treatment.

Figure 1. Recommendations for Anticipatory Nausea

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 it can cause social isolation. Many patients with diarrhea are acutely embarrassed and will not discuss the issue with healthcare providers. Some fear that disclosure will cause reductions or delays in treatment. Fear of incontinence and the possibility of embarrassment often leave patients "trapped" at home. Eventually, altered body image, low self-esteem, depression, anxiety, and hopelessness may occur (Engelking, 2004). Once a patient has been determined to be at risk for or is experiencing diarrhea, the Nurse Leadership Board recommends appropriate prophylactic and therapeutic interventions and an effective diarrhea management plan. Table 5 presents recommendations for management of diarrhea by CTCAE version 3.0 grades 1–4.

Recommendations for Nausea

Nausea is defined as an uncomfortable, unpleasant feeling in the back of the throat or in the stomach that may or may not result in vomiting. Other common terms used to describe nausea are "sick to my stomach" and "queasy." Increased saliva, dizziness, light-headedness, difficulty swallowing, changes in skin temperature, and fast heart rate are other symptoms that may occur as a result of nausea. Although nausea and vomiting are separate phenomena, risk factors and assessments are similar. Treatment-related nausea may be a difficult symptom to manage in patients with advanced cancer (ASCO, 2005c; Berger & Clark-Snow, 2005, 2007; Dalal, Palat, & Bruera, 2007; Grunberg, 2007; NCI, 2007b). Many patients worry that nausea is inevitable after treatment with anticancer agents, and it is second only to fatigue as an expected side effect (Hofman et al., 2004). The expectation of nausea has been shown to be correlated with its development during treatment (Hofman et al.). With antiemetic therapy and appropriate care and advice, the incidence and severity of nausea can be reduced (Berger & Clark-Snow, 2007). Antiemetic therapies, which also may be helpful for nausea, are listed in Appendix B. Antiemetics for older patients should have the following characteristics.

- A low risk of drug-drug interactions
- No cardiovascular side effects
- A simple, convenient dosing regimen
- No dose adjustments in patients with impaired kidney or liver function

Once a patient has been determined to have or to be at risk for nausea, the IMF Nurse Leadership Board recommends appropriate prophylactic and therapeutic interventions and an effective nausea management plan. Acute nausea usually occurs within a few minutes to several hours after administration of anticancer agents and often resolves in the first 24 hours. Delayed nausea occurs more than 24 hours after administration of anticancer agents. It often peaks 48–72 hours after treatment and can last six or seven days. Patients also may experience anticipatory nausea, which occurs before they receive anticancer treatment. Anticipatory nausea is a conditioned response and can occur before a subsequent treatment with an anticancer agent that previously caused nausea (Tipton et al., 2006). Although anticipatory nausea has no CTCAE category or grade, it requires management

Table 6. Dosing Guidelines for Novel Therapies in Patients With Gastrointestinal Toxicities

TOXICITY	THERAPY	RECOMMENDATION
Grade 3 or 4 toxicities judged to be related to lenalidomide therapy	Lenalidomide	Hold treatment and restart at next lower dose level when toxicity has resolved to < grade 2. Do not dose below 5 mg daily.
Grade 3 or 4 constipation	Thalidomide	Patients who develop side effects such as constipation may benefit by either temporarily discontinuing the drug or continuing at a lower dose. With the abatement of these side effects, the drug may be started at a lower dose or at the previous dose based on clinical judgment.
Any grade 3 nonhematologic toxicity	Bortezomib	Hold bortezomib until toxicity resolves, then reinstate therapy at a 25% reduced dose (1.3 mg/m^2 dose reduced to 1 mg/m^2; 1 mg/m^2 dose reduced to 0.7 mg/m^2).

Note. Based on information from Celgene Corporation, 2007a, 2007b; Millennium Pharmaceuticals, Inc., 2007.

with preventive strategies (see Figure 1). Such strategies also form the basis of management of therapy-associated nausea; see Table 5 for recommendations for management of nausea by CTCAE version 3.0 grades 1–4.

Recommendations for Vomiting

Vomiting often is confused with nausea but is, in fact, a separate phenomenon that may or may not occur in conjunction with nausea. It is a self-protective mechanism by which the body attempts to expel toxins. Vomiting involves the expulsion of gastric contents through the mouth. The action is caused by the forceful and spasmodic contraction of the abdominal muscles and diaphragm (ASCO, 2005c; Berger & Clark-Snow 2005, 2007; Dalal et al., 2007; Glare, Pereira, Kristjanson, Stockler, & Tattersall, 2004). Like nausea, vomiting can be anticipatory, acute, or delayed (Tipton et al., 2006).

Vomiting, along with nausea, is considered one of the most disturbing and feared side effects of cancer treatment (ASCO, 2005c). The Nurse Leadership Board believes that ineffective management of vomiting has a negative effect on quality of life, often leading to anxiety and depression, delayed recovery, poor clinical outcomes, anticipatory vomiting, and aversion to future treatments. Many patients even consider stopping treatments to avoid vomiting. However, vomiting can be one of the most manageable side effects of cancer treatment. Table 5 presents recommendations for management of vomiting by CTCAE version 3.0 grades 1–4.

Dose Modification of Novel Therapies

In addition to using the general strategic recommendations for management of gastrointestinal toxicities associated with novel agents for multiple myeloma, healthcare professionals may consider dose modifications, particularly when symptoms are severe. The labeling for lenalidomide describes dose modification recommendations for grade 3 and 4 toxicities judged to be related to lenalidomide therapy. The labeling for thalidomide describes dose modification recommendations for constipation. The labeling for bortezomib describes dose modifications for any grade 3 nonhematologic toxicity. They are summarized in Table 6.

Therapies for multiple myeloma, including the newer therapies, can cause gastrointestinal side effects, including constipation, diarrhea, nausea, and vomiting, which can have a deleterious effect on quality of life, lead to or prolong hospitalization, and interfere with optimal therapy. However, with appropriate medical interventions, the side effects are manageable, and their impact on patient quality of life and adherence to therapy can be minimized.

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Author Contact: Lisa C. Smith, MSN, FNP, AOCN®, can be reached at lcsmith65@hotmail.com, with copy to editor at CJONEditor@ons.org.

References

American Gastroenterological Association. (2000). AGA guideline: Constipation. *Gastroenterology, 119,* 1761–1778.

American Society of Clinical Oncology. (2005a). Constipation. Retrieved October 18, 2007, from http://www.asco.org/portal/site/patient/menuitem.169f5d85214941ccfd748f68ee37a01d/?vgnextoid=d9f041eca8daa010VgnVCM100000ed730ad1RCRD

American Society of Clinical Oncology. (2005b). Diarrhea. Retrieved October 18, 2007, from http://www.asco.org/portal/site/patient/menuitem.169f5d85214941ccfd748f68ee37a01d/?vgnextoid=def041eca8daa010VgnVCM100000ed730ad1RCRD

American Society of Clinical Oncology. (2005c). Nausea and vomiting. Retrieved October 18, 2007, from http://www.asco.org/portal/site/patient/menuitem.169f5d85214941ccfd748f68ee37a01d/?vgnextoid=2f0141eca8daa010VgnVCM100000ed730ad1RCRD&cpsextcurrchannel=1

Basch, E.M., & Ulbricht, C.E. (2004). Complementary, alternative, and integrative therapies in cancer care. In V.T. DeVita, S. Hellman, & S.A. Rosenberg (Eds.), *Cancer: Principles and practice of oncology* (7th ed.). Philadelphia: Lippincott Williams and Wilkins.

Benson, A.B., Ajani, J.A., Catalano, R.B., Engelking, C., Kornblau, S.M., Martenson, J.A., et al. (2004). Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *Journal of Clinical Oncology, 22*(14), 2918–2926.

Berger, A.M., & Clark-Snow, R.A. (2005). Nausea and vomiting. In V.T. DeVita, S. Hellman, & S.A. Rosenberg (Eds.), *Cancer: Principles and practice of oncology* (7th ed.). Philadelphia: Lippincott Williams and Wilkins.

Berger, A.M., & Clark-Snow, R.A. (2007). Chemotherapy-related nausea and vomiting. In A.M. Berger, J.L. Shuster, & J.H. Von Roenn (Eds.), *Principles and practice of palliative care and supportive oncology* (3rd ed.). Philadelphia: Lippincott Williams and Wilkins.

Bertolotti, P., Bilotti, E., Colson, K., Curran, K., Doss, D., Faiman, B., et al. (2007). Nursing guidelines for enhanced patient care. *Haematologica, 92*(Suppl. 2), 211.

Bertolotti, P., Bilotti, E., Colson, K., Curran, K., Doss, D., Faiman, B., et al. (2008). Management of side effects of novel therapies for multiple myeloma: Consensus statements developed by the International Myeloma Foundation's Nurse Leadership Board. *Clinical Journal of Oncology Nursing, 12*(3, Suppl.), 9–12.

Bisanz, A., Woolery, M., Lyons, H.F, Gaido, L., Yenulevich, M.C., & Fulton, S. (2007). Putting Evidence Into Practice®: Constipation. Retrieved October 29, 2007, from http://www.ons.org/outcomes/volume2/constipation.shtml

Bush, N. (2004). Chemotherapy-induced diarrhea. *Oncology Nursing Forum, 31*(5), 889–892.

Celgene Corporation. (2007a). Revlimid® (lenalidomide) [Package insert]. Summit, NJ: Author.

Celgene Corporation. (2007b). Thalomid® (thalidomide) [Package insert]. Summit, NJ: Author.

Dalal, S., Palat, G., & Bruera, E. (2007). Chronic nausea and vomiting. In A.M. Berger, J.L. Shuster, & J.H. Von Roenn (Eds.), *Principles and practice of palliative care and supportive oncology* (3rd ed.). Philadelphia: Lippincott Williams and Wilkins.

Engelking, C. (2004). Diarrhea. In C.H. Yarbro, M.H. Frogge, & M. Goodman (Eds.), *Cancer symptom management* (3rd ed., pp. 528–556). Sudbury, MA: Jones and Bartlett.

Ernst, E., & Pittler, M.H. (2000). Efficacy of ginger for nausea and vomiting: A systematic review of randomized clinical trials. *British Journal of Anaesthesia, 84*(3), 367–371.

Ghobrial, J., Ghobrial, I.M., Mitsiades, C., Leleu, X., Hatjiharissi, E., Moreau, A.S., et al. (2007). Novel therapeutic avenues in myeloma: Changing the treatment paradigm. *Oncology, 21*(7), 785–792.

Glare, P., Pereira, G., Kristjanson, L.J., Stockler, M., & Tattersall, M. (2004). Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far-advanced cancer. *Supportive Care in Cancer*, *12*(6), 432–440.

Grunberg, S.M. (2007). Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: Dosing, efficacy and tolerability analysis. *Annals of Oncology, 18*(2), 233–240.

Hofman, M., Morrow, G.R., Roscoe, J.A., Hickok, J.T., Mustian, K.M., Moore, D.F., et al. (2004). Cancer patient's expectations of experiencing treatment-related side effects: A University of Rochester Cancer Center—Community Clinical Oncology Program study of 938 patients from community practices. *Cancer, 101*(4), 851–857.

Jordan, K., Sippel, C., & Schmoll, H.J. (2007). Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: Past, present, and future recommendations. *Oncologist, 12*(9), 1143–1150.

Kris, M.G., Hesketh, P.J., Somerfield, M.R., Feyer, P., Clark-Snow, R., Koeller, J.M., et al. (2006). American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. *Journal of Clinical Oncology, 24*(18), 2932–2947.

Manochakian, R., Miller, K.C., & Chanan-Khan, A.A. (2007). Clinical impact of bortezomib in frontline regimens for patients with multiple myeloma. *Oncologist, 12*(8), 978–990.

Mercadante, S. (2007). Diarrhea, malabsorption, and constipation. In A.M. Berger, J.L. Shuster, & J.H. Von Roenn (Eds.), *Principles and practice of palliative care and supportive oncology* (3rd ed.). Philadelphia: Lippincott Williams and Wilkins.

Millennium Pharmaceuticals, Inc. (2007). Velcade® (bortezomib) [Package insert]. Cambridge, MA: Author.

Molassiotis, A., Yung, H.P., Yam, B.M., Chan, F.Y., & Mok, T.S. (2002). The effectiveness of progressive muscle relaxation training in managing chemotherapy-induced nausea and vomiting in Chinese breast cancer patients: A randomized controlled trial. *Supportive Care in Cancer*, *10*(3), 237–246.

National Cancer Institute. (2006). *Common Terminology Criteria for Adverse Events v.3.0.* Retrieved December 28, 2007, from http://ctep.cancer.gov/forms/CTCAEv3.pdf

National Cancer Institute. (2007a). Gastrointestinal complications (PDQ®). Retrieved October 29, 2007, from http://www.cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessional

National Cancer Institute. (2007b). Nausea and vomiting (PDQ®) Retrieved October 29, 2007, from http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/healthprofessional/allpages

National Comprehensive Cancer Network. (2007). *NCCN Clinical Practice Guidelines in Oncology™: Antiemesis* [v.3.2008]. Retrieved September 10, 2007, from http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

National Comprehensive Cancer Network & American Cancer Society. (2007). *Nausea and vomiting: Treatment guidelines for patients with cancer.* Retrieved September 10, 2007, from http://www.nccn.org/patients/patient_gls/_english/pdf/NCCN%20Nausea%20Guidelines.pdf

Rajkumar, S.V., Hayman, S.R., Lacy, M.Q., Dispenzieri, A., Geyer, S.M., Kabat, B., et al. (2005). Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood, 106*(13), 4050–4053.

Redd, W.H., Montgomery, G.H., & DuHamel, K.N. (2001). Behavioral intervention for cancer treatment. *Journal of the National Cancer Institute, 93*(11), 810–823.

Richardson, P.G., & Anderson, K. (2006). Thalidomide and dexamethasone: A new standard of care for initial therapy in multiple myeloma. *Journal of Clinical Oncology, 24*(3), 334–336.

Richardson, P.G., Hideshima, T., Mitsiades, C., & Anderson, K.C. (2007). The emerging role of novel therapies for the treatment of relapsed myeloma. *Journal of the National Comprehensive Cancer Network, 5*(2), 149–162.

San Miguel, J., Blade, J., Boccadoro, M., Cavenagh, J., Glassmacher, A., Jagannath, S., et al. (2006). A practical update on the use of bortezomib in the management of multiple myeloma. *Oncologist, 11*(1), 51–61.

Shen, J., Wenger, N., Glaspy, J., Hays, R.D., Albert, P.S., Choi, C., et al. (2000). Electroacupuncture for control of myeloablative chemotherapy-induced emesis: A randomized controlled trial. *JAMA, 284*(21), 2755–2761.

Tipton, J., McDaniel, R., Barbour, L., Johnston, M.P., LeRoy, P., Kayne, M., et al. (2006). Putting Evidence into Practice®: Chemotherapy-induced nausea and vomiting. Retrieved October 29, 2007, from http://www.ons.org/outcomes/volume1/nausea.shtml

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Appendix A. Putting Evidence Into Practice® Card on Constipation in Patients With Cancer

What interventions are effective for preventing and treating constipation in patients with cancer?

RECOMMENDED FOR PRACTICE

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits

No intervention can be recommended for nursing practice as of September 30, 2006.

LIKELY TO BE EFFECTIVE

Interventions for which effectiveness has been demonstrated by supportive evidence from a single rigorously conducted controlled trial, consistent supportive evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion

Opioid-Induced Constipation: Prophylactic Regimen

A proactive approach, including initiation of a prophylactic regimen, is needed to prevent constipation when taking opioids. However, not enough evidence exists to identify the most effective regimen (see Expert Opinion section).

Opioid-Induced Constipation: Opioid Rotation

Research has demonstrated that some opioids have less constipating effect than others, and rotating opioids would decrease the associated side effects.

- Switching opioids from sustained-release oral morphine to transdermal fentanyl patches may decrease constipation.
- Switching opioids to methadone may result in a reduction in laxative use.

Refractory Constipation in Adults

The National Comprehensive Cancer Network recommends the use of polyethylene glycol (PEG) as a treatment alternative for patients with cancer with persistent constipation. Standard-dose PEG with electrolytes in the United States is known as Golytely® (Braintree Laboratories) and Colyte® (Schwarz Pharma). Low-dose PEG, referred to as PEG 3350, is available without electrolytes in the United States and is marketed as Miralax® (Schering-Plough). Stimulant or osmotic laxatives are effective in improving bowel function in patients with cancer with persistent constipation and/or at the end of life, and some patients may need both types of laxatives to achieve optimal results.

BENEFITS BALANCED WITH HARMS

Interventions for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities

Opioid-Induced Constipation: Oral Naloxone

Oral naloxone, an opioid receptor antagonist, has shown mixed results for managing opioid-induced constipation, potentially causing adverse reactions, including loss of analgesia and withdrawal symptoms.

EFFECTIVENESS NOT ESTABLISHED

Interventions for which there are currently insufficient or conflicting data or data of inadequate quality, with no clear indication of harm

Pharmacologic Interventions for Constipation in Adults

These interventions are based on high-level evidence in nononcology populations and need to be studied in the oncology population.

Bulk Laxatives (Psyllium)

Psyllium is recommended for patients with a good functional status, including the ability to tolerate adequate fluids for the prevention and treatment of constipation. Most bulk laxatives need to be taken with at least 200–300 ml of water. Psyllium should be avoided in patients who do not have adequate physical activity or fluid intake and/or who have severe constipation, as it may worsen manifestations of constipation. Psyllium administered in large amounts has been associated with increased flatulence, abdominal distension and bloating, mechanical obstruction of the esophagus and colon, and anaphylactic reactions.

Osmotic Laxatives (Sorbitol, Lactulose)

Osmotic laxatives such as sorbitol or lactulose are associated with significant improvements in stool consistency, fecal impaction, and other symptoms of chronic constipation, such as straining of stool. Adverse effects include abdominal cramping, flatulence, bowel distension, an unpleasant sweet taste, and diarrhea. In many cases, osmotic laxatives were no better than other laxatives such as senna. Lactulose often is used in combination with a stimulant laxative in difficult-to-treat constipation.

Polyethylene Glycol With or Without Electrolytes

A high level of evidence was found in the nononcology population regarding the safety and efficacy of PEG with or without electrolytes. Caution: Do not administer electrolytes when kidney function is compromised.

Tegaserod

The effectiveness of tegaserod, a 5-HT_3 agonist, in patients with cancer has not been established because this population was excluded from published premarketing studies. However, in nononcology patients, tegaserod has been shown to be effective and safe in relieving symptoms of chronic constipation, with a recommended dosage of 6 mg orally twice a day.

Interventions for Constipation Where Data Are Insufficient

The effectiveness of the interventions described below has not been established because they are based on studies that are inadequately powered, have limited sample sizes, or have flaws in study design or in study procedures. The majority of the research is in nononcology patients who have chronic constipation. Further study using randomized controlled trials is needed.

Pharmacologic Interventions (Adults)

- Laxatives
  - Bulk-forming laxatives
    - Methylcellulose

  - Lubricants
    - Glycerin suppositories
    - Mineral oil
  - Osmotic laxatives (saline)
    - Magnesium salts
    - Magnesium hydroxide (Phillips' Milk of Magnesia®, Bayer Consumer Care)
  - Stimulant laxatives
    - Bisacodyl
    - Senna
  - Non-bulk-forming fiber laxatives
  - Stool softeners: Systematic reviews of the chronic constipation population found insufficient data to make a recommendation, and the consensus was that stool softeners are minimally effective in improving symptoms of constipation.
    - Docusate sodium and docusate calcium
- Prokinetic agent: Erythromycin
- Enemas: Phosphate enema and sodium citrate enema
- Chloride channel activator: Amitiza® (lubiprostone, Sucampo Pharmaceuticals and Takeda Pharmaceuticals America)

For information on investigational drugs used in preventing and treating constipation, see the detailed ONS PEP card at www.ons.org/outcomes.

Nonpharmacologic Interventions (Adults)

- Activity/increased mobility
- Aromatherapy, massage therapy, and aromatherapy massage
- Biofeedback: Many studies excluded patients with cancer. Of the studies found, the data were inadequate to support its efficacy in treating chronic constipation.
- Dietary fiber: A relatively large body of mixed-quality evidence indicates positive effects of dietary fiber on bowel function in oncology and nononcology populations. Note: Fiber is not recommended in patients with inadequate fluid intake, such as patients with advanced disease.
- Fresh baker's yeast
- Herbal supplements

NOT RECOMMENDED FOR PRACTICE

Interventions for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews or interventions for which the costs, burdens, or harms associated with the intervention exceed anticipated benefit

- Cisapride: A prokinetic drug that is known to increase gastrointestinal motility (Caution: Restricted access exists in some countries because of adverse cardiac effects. Cisapride was taken off the market in the United States in 2000 by the U.S. Food and Drug Administration [FDA].)
- Corn syrup: No longer recommended as a stool softener because it is not sterilized when packaged and may be a source of *Clostridium botulinum* spores
- Dantron™ (Hexal Pharma): This drug has not been approved by the FDA for use in the United States because it has been associated with rodent cancer.
- Nalmefene: Limited studies of the efficacy of oral nalmefene in humans are available because of its propensity to reverse analgesia or to induce withdrawal.
- Naltrexone: A lipid soluble drug that crosses the blood-brain barrier and may negatively affect the analgesic effects of opioids. It has been associated with dose-related elevations in serum transaminase levels, resulting in the discontinuation of the drug. (Note: This is different from methylnaltrexone.)

EXPERT OPINION

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual who has authored articles published in a peer-reviewed journal in the domain of interest.

Special Note: Myelosuppressed Patients

Avoid rectal agents and/or manipulation (i.e., rectal examinations, suppositories, and enemas) in myelosuppressed patients. These actions can lead to development of bleeding, anal fissures, or abscesses. In addition, avoid manipulation of the stoma of neutropenic patients.

General Constipation

Prevention

- Take preventive measures in anticipation of constipation for those receiving medications, such as vincristine or other chemotherapies, that slow colonic transit times.

Assessment

- Perform a thorough history and physical examination in evaluation of constipation before determining the treatment plan, including assessment of individual risk factors.
- Obtain a nutritional consult.
- Consider in-depth diagnostic workup for constipation after patient fails initial treatment.

Interventions

- Teach the patient about bowel function.
- Provide a comfortable, quiet, private environment for defecating.
- Provide a toilet, bedside commode, and any necessary assistive devices. Avoid the use of a bedpan when possible.
- Minimize use of constipating medications whenever possible.
- Involve the patient in development of a bowel regimen.
- Encourage the intake of warm or hot liquids.
- Castor oil: Not recommended secondary to severe cramping

Opioid-Induced Constipation

Stimulant Laxatives Plus Stool Softener

This combination is recommended when initiating opioid therapy. A useful bowel regimen includes docusate sodium (100–300 mg per day) along with senna (two to six tablets twice a day). Bulk laxatives are not recommended for opioid-induced constipation because of the risk of bowel impaction in poorly hydrated patients.

- The laxative dose should be individually titrated for effectiveness according to bowel function, not opioid dosing.

Pharmacologic Interventions

- Prokinetic medication (i.e., metoclopramide) should be reserved for use in individuals with severe constipation and those resistant to bowel programs. Caution: Avoid in patients with large abdominal tumors or bowel obstruction.
- Oral mineral oil is effective for hard stool but should not be used for routine prevention of constipation because it may interfere with absorption of some nutrients.
- Expert opinion supports the use of a stimulant laxative plus a stool softener in preventing and managing constipation in patients at the end of life.

Nonpharmacologic Interventions

- Recommended fluid intake per day is eight 8-oz glasses in adults.
- Treat high and low impactions differently.
  - High impactions: These are comfortably relieved with low-volume (< 300 ml) milk and molasses enemas up to four times per day along with an oral laxative. For enema recipe, see definition table at www.ons.org/outcomes.
  - Low impactions: Oil-retention enemas soften hard stool. In nonmyelosuppressed patients, stool can be manually disimpacted followed by enemas of choice.

Individualized Bowel Management Program

- After three days without a bowel movement, initiate a bowel management program.
- A good program includes fluids, fiber, and a decrease in constipating medications or provision of medications to offset constipating side effects of medications.

Note. From "Putting Evidence Into Practice®: Evidence-Based Interventions for the Prevention and Management of Constipation in Patients With Cancer," 2008, by M. Woolery, A. Bisanz, H.F. Lyons, L. Gaido, M. Yenulevich, S. Fulton, et al., *Clinical Journal of Oncology Nursing, 12*(2), pp. 334–337. Copyright 2008 by Oncology Nursing Society. Adapted with permission.

Appendix B. Putting Evidence Into Practice® Card on Preventing and Treating Chemotherapy-Induced Nausea and Vomiting

What interventions are effective in preventing and treating chemotherapy-induced nausea and vomiting?

RECOMMENDED FOR PRACTICE

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews and for which the expectation of harms is small compared to the benefits

Anticipatory nausea and/or vomiting

Nausea and/or vomiting that occurs before patients receive their next chemotherapy treatment. It is a conditioned response and can occur after a negative past experience with chemotherapy. Prevention is key, especially early in therapy.

- Benzodiazepines
  - Alprazolam 0.5–2 mg PO TID, beginning the night before treatment, or
  - Lorazepam 0.5–2 mg PO on the night before and the morning of treatment
- Using treatments for acute and delayed nausea and vomiting

Acute and delayed nausea and/or vomiting: Highly emetogenic chemotherapy

Acute nausea and/or vomiting usually occurs within a few minutes to several hours after chemotherapy administration and often resolves within the first 24 hours. Delayed nausea and/or vomiting occurs more than 24 hours after chemotherapy administration. It often peaks 48–72 hours after chemotherapy and can last 6–7 days.

- 5-HT_3 receptor antagonists
  - Palonosetron 0.25 mg IV on day 1, or
  - Granisetron 2 mg PO, 1 mg PO BID, or 1 mg IV on day 1, or
  - Ondansetron 16–24 mg PO or 8–32 mg IV on day 1, or
  - Dolasetron 100 mg PO or IV on day 1, and
- Corticosteroid
  - Dexamethasone 12 mg PO or IV on day 1, 8 mg PO or IV daily on days 2–4, and
- NK1 receptor antagonist
  - Aprepitant 125 mg PO on day 1, 80 mg PO daily on days 2 and 3, and
- Benzodiazepine (may or may not be given with other antiemetics because of sedating effects)
  - Lorazepam 0.5–2 mg PO, IV, or SL every 4–6 hours on days 1–4

Acute and delayed nausea and/or vomiting: Moderately emetogenic chemotherapy

- 5-HT_3 receptor antagonists
  - Palonosetron 0.25 mg IV on day 1, or
  - Granisetron 1–2 mg PO, 1 mg PO BID, or 1 mg IV on day 1, or
  - Ondansetron 16–24 mg PO or 8–32 mg IV on day 1, or
  - Dolasetron 100 mg PO or IV on day 1, and
- Corticosteroid
  - Dexamethasone 12 mg PO or IV on day 1, and
- Benzodiazepine (may or may not be given with other antiemetics because of sedating effects)
  - Lorazepam 0.5–2 mg PO, IV, or SL every 4–6 hours, and
- Aprepitant 125 mg PO on day 1, 80 mg PO on days 2 and 3

On days 2–4, consider:

- Corticosteroid
  - Dexamethasone 8 mg PO or IV daily, or
- 5-HT_3 receptor antagonists
  - Ondansetron 8 mg PO BID, 16 mg PO daily, or 8 mg IV, or
  - Granisetron 1–2 mg PO daily, 1 mg PO BID, or 1 mg IV, or
  - Dolasetron 100 mg PO or IV
- Substituted benzamide
  - Metoclopramide 0.5 mg/kg PO or IV every 6 hours or 20 mg PO qid ± diphenhydramine 25–50 mg PO or IV every 4–6 hours prn

Acute and delayed nausea and/or vomiting: Low emetogenic chemotherapy

- No antiemetic agent, or
- Corticosteroid
  - Dexamethasone 12 mg PO or IV on day of treatment, or
- Phenothiazine
  - Prochlorperazine 10 mg PO or IV every 4–6 hours, or
- Substituted benzamide
  - Metoclopramide 20–40 mg PO every 4–6 hours or 1–2 mg/kg every 3–4 hours ± diphenhydramine 25–50 mg PO or IV every 4–6 hours, or
- Benzodiazepine (may or may not be given with other antiemetics because of sedating effects)
  - Lorazepam 0.5–2 mg PO or IV every 4–6 hours

Breakthrough nausea and/or vomiting

Nausea and/or vomiting that occurs despite prophylactic antiemetics and requires "rescue" antiemetic therapy.[1]

Consider using a drug from a class not previously used.

- Corticosteroid
  - Dexamethasone 12 mg PO or IV daily, if not previously given, or
- 5-HT_3 receptor antagonists
  - Granisetron 1–2 mg PO daily, 1 mg PO BID, or 1 mg IV, or
  - Ondansetron 8 mg PO or IV daily, or
  - Dolasetron 100 mg PO or IV daily, or
- Phenothiazine
  - Prochlorperazine 25 mg suppository every 12 hours, or 10 mg PO or IV every 4–6 hours, or
- Substituted benzamide
  - Metoclopramide 20–40 mg PO every 4–6 hours or 1–2 mg/kg IV every 3–4 hours ± diphenhydramine 25–50 mg PO or IV every 4–6 hours, or
- Butyrophenones
  - Haloperidol 1–2 mg PO every 4–6 hours or 1–3 mg IV every 4–6 hours, or
- Benzodiazepine
  - Lorazepam 0.5–2 mg PO every 4–6 hours, or
- Cannabinoid
  - Dronabinol 5–10 mg PO every 3–6 hours, or
- Olanzapine 2.5–5 mg PO BID prn

LIKELY TO BE EFFECTIVE

Interventions for which the evidence is less well established than for those listed under "Recommended for Practice"

Nonpharmacologic interventions are to be used in conjunction with pharmacologic interventions.
Provide referral to appropriate practitioners as needed.

Acupuncture

A method of producing analgesia or altering the function of a body system by inserting fine, wire-thin needles (about the diameter of a strand of hair) into acupoints along a specific meridian on the body. The insertion of the needles may cause momentary discomfort. The needles are twirled or energized electronically or are warmed and left in place for approximately 20–30 minutes. The acupuncture point P6 is most commonly used for treatment of nausea and vomiting.

- Study populations: People with various carcinomas; women with high-risk breast cancer receiving myeloablative chemotherapy; and patients with mixed cancer types

Acupressure

A therapeutic technique of applying digital pressure or acustimulation bands in a specified way on designated points on the body. By applying pressure to one or more acupoints, practitioners can correct imbalances by stimulating or easing energy flow. The acupoint most commonly investigated and accessible is P6, which is located on the anterior surface of the forearm, approximately three finger-widths from the wrist crease.

- Study populations: Women undergoing adjuvant chemotherapy for breast cancer, receiving CMF (cyclophosphamide, methotrexate, 5-fluorouracil) or a doxorubicin-containing regimen; postoperative patients with gastric cancer receiving their first cycle of chemotherapy with cisplatin and fluorouracil; and patients with other mixed cancer types

Guided imagery

Forming a relaxing, pleasing mental image, often preceded by relaxation techniques and/or music

Music therapy

The application of music to influence physiologic, psychological, and emotional functioning during chemotherapy. It often is used with other behavioral techniques, such as relaxation.

Progressive muscle relaxation

Focusing on and isolating various muscle groups while moving progressively up or down the body to establish a state of deep relaxation. Focused breathing, with all attention centered on the sensations of breathing, including the rhythm and rise and fall of the chest, often is used along with progressive muscle relaxation.

- Study populations: Patients with mixed cancer types; women with breast cancer receiving doxorubicin and cyclophosphamide; bone marrow transplant recipients with leukemia, lymphoma, and other solid tumors; and patients receiving cisplatin-based chemotherapy, some of whom were chemotherapy-naive, whereas others had previously received chemotherapy

Psychoeducational support and information

The use of counseling, support, and structured educational interventions, through the use of interactive media (audiotapes, computer-assisted, telephone, video) to provide specific information on self-care measures for patients with chemotherapy-induced nausea and vomiting

- Study populations: Women receiving cisplatin-based chemotherapy for ovarian cancer; and women receiving chemotherapy for breast cancer

BENEFITS BALANCED WITH HARMS

Interventions for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities

Nonpharmacologic interventions are to be used in conjunction with pharmacologic interventions.
Provide referral to appropriate practitioners as needed.

Virtual reality

A computer-simulated technique that allows individuals to hear and feel stimuli that correspond with a visual image. Individuals wear a headset that projects an image with an accompanying sound. Virtual reality is interactive, and it engages the senses simultaneously.

- Study populations: Patients with mixed cancers, primarily women with breast and ovarian cancers

EFFECTIVENESS NOT ESTABLISHED

Interventions for which insufficient data or data of inadequate quality currently exist

Nonpharmacologic interventions are to be used in conjunction with pharmacologic interventions.
Provide referral to appropriate practitioners as needed.

Exercise

Any planned, structured, and repetitive bodily movement performed that incorporates cardiovascular, strength, and/or flexibility conditioning of any intensity with the intent of improving or maintaining one or more components of physical fitness, performance, or health.

- Study population: Women with breast cancer receiving chemotherapy (not doxorubicin) who had received at least three treatments prior to study

Hypnosis

A behavioral intervention process whereby patients learn to focus attention on thoughts or images unrelated to a source of distress (i.e., nausea or vomiting). The patient is relaxed through a meditation-like excursion to pleasant locations and/or activities while a clinician introduces suggestions of calmness and well-being.

- Study population: Patients who had received at least four cycles of chemotherapy combined with a 5-HT_3 receptor antagonist who developed nausea and vomiting within the first six hours prior to receiving chemotherapy (drugs included cisplatin, carboplatin, cyclophosphamide, dacarbazine, doxorubicin, and epirubicin)

Massage/aromatherapy

An ancient form of healing that involves the therapeutic manipulation of soft tissues of the body by various hand movements (e.g., rubbing, kneading, pressing, rolling, slapping, tapping). Massage therapy can elicit the relaxation response as measured by decreases in heart rate, blood pressure, and respiratory rate. Often, massage is complemented by the use of aromatherapy, which is the use of essential oils that are combined with a carrier cream or oil to manipulate the soft tissues.

- Study populations: Autologous bone marrow transplant recipients; hospital inpatients

Acustimulation with wristband device

Stimulation of the P6 point by transcutaneous electrical stimulation through a wristband device. A wristband device currently available is the ReliefBand®, a class-2 device approved by the U.S. Food and Drug Administration for the treatment of CINV. The device delivers slow, weak, electrical pulses to the P6 point via two metallic electrodes. Patients can adjust the electrical output to deliver 10–35 mAmps/pulse.

- Study populations: Women with breast cancer receiving their second course of chemotherapy (doxorubicin-based); chemotherapy-naive patients with mixed cancers receiving cisplatin or doxorubicin; and those with mixed cancers receiving moderately high to highly emetogenic chemotherapy

Ginger

A plant herb used in traditional Chinese and Indian medicine for the treatment of nausea and vomiting. Ginger has aromatic, spasmolytic, carminative, and absorbent properties that suggest direct effects on the gastrointestinal tract.

- Study populations: Patients with leukemia; patients with gynecologic cancers receiving cisplatin

EXPERT OPINION

Consensus exists recognizing the growing evidence that the following interventions may be effective in the prevention and management of CINV.

- Prevention of nausea and vomiting is the goal.
- Oral and IV antiemetics have equivalent effectiveness.
- The period of expected nausea and vomiting should be covered with appropriate antiemetics (anticipatory, acute, and delayed period for at least four days).
- The lowest efficacious dose of antiemetics should be used.
- Clinicians should base selection of antiemetics on the emetic potential of the chemotherapy agent(s), as well as on patient factors.
- Healthcare providers need to consider the many potential causes of nausea and emesis in patients with cancer that may be contributing factors.

Limited evidence exists, but experts recommend the following dietary interventions in patients receiving chemotherapy to minimize nausea and vomiting.

- Eat smaller, more frequent meals.
- Reduce food aromas and other stimuli with strong odors.
- Avoid foods that are spicy, fatty, and highly salty.
- Take antiemetics prior to meals so that the effect is present during and after meals.
- Repeat previous measures, and consume foods that minimize nausea and that are "comfort foods."

Note. From "Putting Evidence Into Practice®: Evidence-Based Interventions to Prevent, Manage, and Treat Chemotherapy-Induced Nausea and Vomiting," 2007, by J.M. Tipton, R.W. McDaniel, L. Barbour, M.P. Johnston, M. Kayne, P. LeRoy, et al., *Clinical Journal of Oncology Nursing, 11*(1), pp. 75–78. Copyright 2007 by Oncology Nursing Society. Adapted with permission.

Patient Education Sheet: Managing Gastrointestinal Side Effects of Novel Agents for Multiple Myeloma

KEY POINTS

Novel therapies used to treat multiple myeloma include thalidomide, lenalidomide, and bortezomib. Each of the drugs, alone or in combination, may be associated with gastrointestinal side effects, including nausea, vomiting, diarrhea, and constipation. Managing the side effects can reduce your discomfort and can allow you to receive the best treatment for your myeloma. Your healthcare provider may change your dose or schedule of medication to help manage your symptoms. Do not stop or adjust medications without discussing it with your healthcare provider.

TYPES OF GASTROINTESTINAL SYMPTOMS

- Nausea: an unpleasant feeling in the throat and stomach
- Vomiting: a forceful emptying of the stomach contents
- Constipation: decreased frequency of defecation accompanied by discomfort and difficulty
- Diarrhea: an abnormal increase in the frequency and the amount of fluid in the stool
- Always report symptoms early to your healthcare team.

MANAGEMENT OF NAUSEA

- You may be asked about the circumstances surrounding episodes, upper abdominal pain, pain when swallowing, hiccups or heartburn, weight loss, dizziness on standing up, and your medication history.
- General nausea: Eat small, frequent meals; do not eat fatty or fried foods; avoid strong odors; do not exercise after eating; wear loose clothing; begin appropriate medications before chemotherapy; use relaxation, acupuncture, biofeedback, and guided imagery.
- Loss of appetite, still able to eat normally: Adjust dosages of medications, drink enough water and other fluids, and keep track of effects of medications in a daily diary.
- Decreased ability to eat or drink: Consider asking for increased or different medications and see your physician for physical examination and evaluation.
- Inability to eat or drink: You may need hospitalization or medications through a vein. Call a physician immediately.
- Medications that may be ordered by your healthcare team: lorazepam, prochlorperazine, promethazine, metoclopramide, ranitidine, famotidine, and dexamethasone

MANAGEMENT OF VOMITING

- You will be asked about the appearance of the fluid, whether digested or undigested, whether a "trigger" was involved, whether it was new or different from other times.
- One episode in 24 hours: This is usually self-limiting; continue medications for nausea.
- Two to five episodes in 24 hours: New medications, oral or through a vein, may be needed. Contact a physician immediately.
- Six or more episodes in 24 hours: This may require hospitalization to assess fluid status and rule out bowel obstruction. Contact a physician immediately.
- Medications that may be ordered by your healthcare team: aprepitant, ondansetron, and granisetron

MANAGEMENT OF CONSTIPATION

- You will be asked about any abdominal pain, bloating, nausea and vomiting, inability to urinate, confusion, and diarrhea alternating with constipation.
- Mild: Increase fluid and fiber intake, increase physical activity, and start stool softeners
- Moderate: You may need to speak with a dietician about your food intake; consider laxatives and stimulants.
- Severe: Bowel obstruction should be assessed by a physician; dehydration may require fluids through a vein; treatment for an impacted colon may be discussed; medication changes may be ordered by physician; referral to a gastrointestinal specialist may be arranged by a physician.
- Medications that may be ordered by your healthcare team: docusate, senna, magnesium sulfate, magnesium citrate, lactulose, and bisacodyl

MANAGEMENT OF DIARRHEA

- You will be asked about any history of irritable bowel syndrome, colitis, diverticulitis, and medications other than routine chemotherapy. The physician will want to know whether you have "gas" and whether the diarrhea is a "leakage" or sudden.
- Fewer than four stools a day: Drink more liquids; avoid caffeinated, carbonated, heavily sugared beverages; dietary changes may be needed; discontinue any medications that cause diarrhea; keep the rectal area clean.
- Four to six stools per day: Medications may be considered, and you may need fluids and salts. A physician must be notified if you have more than four to six stools per day for more than 24 hours.
- Seven to nine stools per day: Hospitalization may be considered for fluid replacement, a stool culture will be ordered to see whether the diarrhea is the result of an infection, and medications will be given to control frequency. You should take very good care of your skin and use disposable pads or diapers. Cancer therapy may be stopped for a period of time, or the dose may be lowered.
- Medications that may be ordered by your healthcare team: imodium, diphenoxylate, and octreotide

Note. For more information, please contact the International Myeloma Foundation (1-800-452-CURE; www.myeloma.org). The foundation offers the Myeloma Manager™ Personal Care Assistant™ computer program to help patients and healthcare providers keep track of information and treatments. Visit http://manager.myeloma.org to download the free software.

Note. Patient education sheets were developed in June 2008 based on the International Myeloma Foundation Nurse Leadership Board's consensus guidelines. They may be reproduced for noncommercial use.