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Recommendations for the Management of Constipation in Cancer Patients

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Abstract

Constipation is a common condition that is often overlooked among cancer patients particularly those with advanced disease. It is often associated with distressing or debilitating symptoms that adversely impact the quality of life of these patients. Hence, it is imperative that practicing clinicians are cognizant of the various etiologies of constipation especially those that are secondary to both cancer therapies and supportive care. Since discontinuation of the offending drug(s) may not be a viable option in the hematology/oncology setting, patient counseling and initiation of preventative measures which include scheduled bowel regimens for therapies known to cause constipation are central to optimal management. As constipation goes unresolved or becomes more severe laxative therapy should be optimized to achieve resolution of symptoms. In severe and refractory cases of constipation consulting a gastrointestinal specialist may be prudent. Herein, we highlight the most common laxative therapies that may be considered in adult cancer patients experiencing initial and refractory constipation as well as provide practical considerations and a management algorithm that can be easily applied or implemented in clinical practice.

Keywords: Cancer; Gastrointestinal; Patients; Management

Introduction

Constipation is the most common gastrointestinal disorder accounting for over 2 million clinic visits annually. The prevalence of constipation ranges from 2-27% among the US population [1,2]. This condition causes very distressing symptoms that may compound the symptoms of cancer and its treatment; thereby affecting the quality of life of these patients. If left untreated, constipation may cause abdominal pain, distention, urinary retention, nausea, vomiting, anorexia, development of hemorrhoids, anal fissures, perianal abscesses, and intestinal obstruction which could be life-threatening.

The term constipation is associated with infrequent bowel movements, and often equated with straining, hard stool or abdominal discomfort.3 The ROME III criteria were developed to standardize the definition of constipation and provide a comprehensive approach to its diagnosis. Based on these criteria, the diagnosis of constipation requires the presence of at least two of the following symptoms for the past three months or 12 weeks (with symptom onset at least 6 months prior to diagnosis) [3].

a) Straining during at least 25% of defecations

b) Lumpy or hard stools in at least 25% of defecations

c) Sensation of incomplete evacuation for at least 25% of defecations

d) Sensation of anorectal obstruction for at least 25% of defecations

e) Manual maneuvers to facilitate at least 25% of defecations

f) Fewer than three defecations per week

g) Loose stools are rarely present without the use of laxatives and there are insufficient criteria for diagnosis of irritable bowel syndrome

The diagnosis of constipation includes conducting a careful physical exam (abdominal and rectal examination, signs of anemia, weight loss, and liver enlargement) and obtaining a thorough patient history (duration, stool frequency, straining, and medication history and comorbidities) for the purposes of ruling out secondary causes of constipation [4]. Other studies or further work up including colonoscopy is generally not warranted unless patients present with alarming symptoms [4].

The etiology of constipation is multifactorial, though can be simplistically classified into primary (idiopathic) or secondary constipation [5,6]. Primary constipation arises from colonic or

anorectal dysfunction (due to intrinsic causes), and secondary constipation is attributed to an underlying disease state or use of certain medications [6] (Table 1) lists the major drug classes known to contribute to the development of constipation. If a medication or medical condition is the cause of constipation, eliminating the offending medication or treating the underlying medical condition may lead to its resolution. Since drug discontinuation may not be a viable option in the hematology/oncology setting, patient counseling and initiation of preventative measures are central to optimal management. For example, opiates are commonly used to manage cancer-associated pain, and almost always cause some degree of constipation. This complication can be mitigated if a proper bowel regimen is considered when prescribing chronic opioid therapy.

Table 1: Drug classes associated with constipation [6,7,10,11].

Drug class	Examples
Cancer Therapies	
Alkylating agents	Cisplatin, carboplatin, temozolamide
Microtubule inhibitors	Vincristine, vinorelbine, vinblastine
Topoisomerase II inhibitors	Liposomal doxorubicin
Proteasome inhibitors	Bortezomib, carfilzomib
Immunomodulatory agents	Lenalidomide, pomalidomide, thalidomide
Aromatase inhibitors	Letrozole, anastrazole
Antiandrogens	Bicalutamide
Common Supportive Therapies	
Opioid analgesics	Morphine, oxycodone, fentanyl, hydrocodone
Antidepressants (tricyclics)	Amitriptyline, nortriptyline
5-HT3 receptor antagonists	Ondansetron, granisetron
Antispasmodics	Mebeverine, dicyclomine
Antipsychotics	Chlorpromazine, clozapine, haloperidol
Antihistamines	Diphenhydramine, promethazine
Antiepileptics	Carbamazepine, phenytoin
Supplements	Calcium, iron salts
Antidiarrheal agents	Loperamide
Antiresorptive agents	Zoledronic acid, denosumab
Bile acid sequestrants	Cholestyramine

When no secondary cause of constipation is identified, empiric treatment should be initiated. Non-pharmacologic methods (bowel training, increasing fiber intake thru diet or bulk agents, fluid intake, and exercise) should be considered first to improve bowel regularity prior to proceeding to the use of laxatives [6] Because of the progressive nature of the disease, it may not be feasible to optimize these strategies in cancer patients, and subsequently pharmacologic interventions may be required to prevent or treat constipation (Table 2).

Table 2: Drug classes associated with constipation [6,7,10,11].

Medication	Onset of Action	Onset of Action	Comments
Docusate sodium Docusate calcium	50-300mg daily orally in 1-2 doses 240mg daily orally	12-72 hours (oral)	Recommend adequate hydration
Bisacodyl	5-15mg orally daily 10 mg per rectum daily*	6-12 hours (oral)	Avoid within an hour of antacids or milk
Senna	8.6 mg sennosides orally 1 twice to 2 four times daily times daily 5-15 ml daily oral solution	6-24 hours	Maximum at 8 tablets (30 ml of liquid) daily
Magnesium hydroxide Magnesium citrate	Suspension (400mg/5ml) PO 30-60ml daily Solution (1.75g/30ml) PO 5-10 floz daily	30 minutes to 6 hours	Consider chilling magnesium citrate prior to administration
PEG without electrolytes PEG with electrolytes	17g orally 1-2 times daily in 8 fl oz 200-500ml orally daily	24 to 96 hours 1 hour	PEG with electrolyte: dosage for bowel cleansing 240 ml every 10 min until diarrhea fluid is clear or until 4-5 L consumed

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Lactulose	15-45 ml solution orally 1-4 times daily 300 ml solution in 700 ml of water or normal saline retained for 30-60 minutes*	(for constipation): 24-48 hours to normal bowel movement;2-4 administrations with aggressive dosing Enema may be repeated in 4-6 hours	Hourly or every other hour doses of 20-45 ml may be used to induce rapid laxation (20 ml every 2 hours is a common consideration) If enema is evacuated too quickly consider redosing immediately
Sorbitol	30 ml oral solution daily 20 ml 25-30% solution per rectum*	~1 hour	Hourly doses of 30 ml may be used to induce rapid laxation
Methylnaltrexone bromide	Weight-based subcutaneous injection: <38 kg, 0.15 mg/kg 38-61 Kg, 8mg 62-114 kg, 12mg >114 kg, 0.15 mg/kg 450mg once daily orally	(In responding patients) 30 to 60 minutes 1 to 3 days	Contraindicated in known or suspected gastrointestinal obstruction 50% dose reduction in patients with creatinine clearance <30 ml/ min Discontinue maintenance laxatives prior to initiation of oral therapy; reinitiate laxative therapy after 3 days of poor response for oral administration, absorption/distribution may be reduced when taken with high fat meals
Naloxegol	25mg orally once daily	Less than 2 hours	Decrease dose to 12.5mg when used concomitantly with moderate CYP3A4 inhibitors; contraindicated with strong CYP3A4 inhibitors Decrease dose to 12.5mg in patients with creatinine clearance <60 ml/min Contraindicated with known or suspected gastrointestinal obstruction
Lubiprostone	24mcg orally twice daily with food and water	Within 24-48 hours	Take with food to reduce nausea
Metoclopramide	10mg orally/intravenously four times daily	Oral: 30 - 60 minutes; Intravenous: 1-3 minutes; Intramuscular: 10 to 15 minutes	Extrapyramidal effects may occur at higher doses and is more likely in younger patients, diphenhydramine may temper
Erythromycin	250 to 500mg (base) orally 3 times daily before meals	Limit duration of therapy, tachyphylaxis may occur after 4 weeks	Consider in patients refractory/intolerant to other prokinetic agents (e.g metoclopramide, domperidone)

*Avoid rectal administration in neutropenic patients

Our strategy for prevention or early management of constipation begins with utilizing various agents notably over-the-counter medications. Stimulant laxatives include products containing Senna or bisacodyl. These laxatives increase intestinal motility and the secretion of water into the bowel.6,7 They generally produce bowel movements within hours, but may cause abdominal cramping. Stimulant laxatives should not be used in patients with suspected intestinal obstruction. Emollient laxatives or stool softeners, (e.g. docusates), act by lowering surface tension, allowing water to enter the bowel more readily

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[6,7]. They are generally well tolerated and may be particularly useful for patients with anal fissures or hemorrhoids that cause painful defecation. A common "mush and push" regimen to start with agents that are highly associated with constipation is the scheduled combination of Senna and docusate starting concomitantly with therapy and titrated to affect.

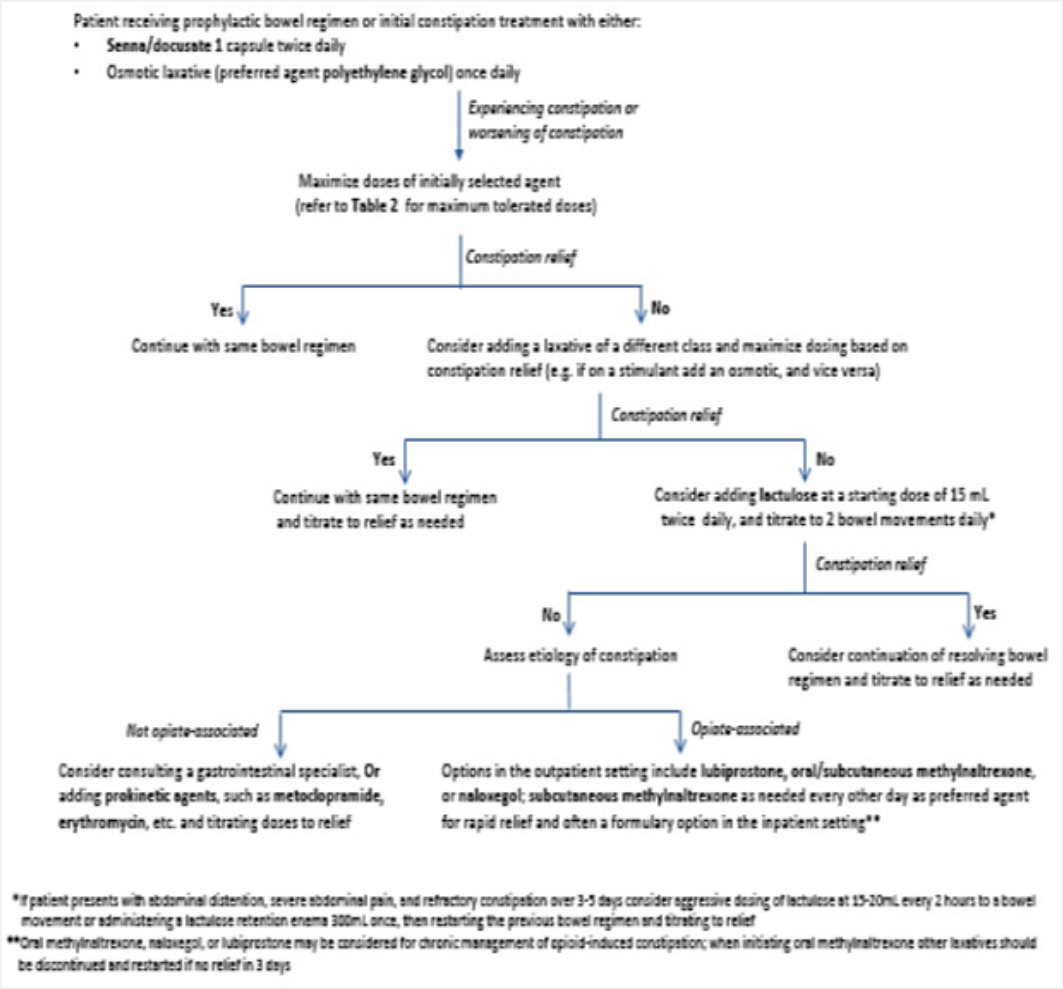

Figure 1: algorithm for the management of constipation in adult cancer patients.

Saline/osmotic laxatives are hyperosmolar agents that cause secretion of water into the intestinal lumen by osmotic activity [6,7]. The most commonly used osmotic saline laxatives are oral magnesium hydroxide or oral magnesium citrate. These agents are considered relatively safe because they work within the colonic lumen without systemic effects. Saline laxatives have been associated with electrolyte imbalance within the colonic lumen and may precipitate hypokalemia, fluid and salt overload, and diarrhea. Hence, caution is warranted particularly in patients with congestive heart failure and chronic renal insufficiency. Osmotic laxatives such as sorbitol, lactulose, and polyethylene glycol (PEG) 3350 with or without electrolytes are often considered as alternatives to stimulants (Senna and docusate, or bisacodyl). Furthermore, they may also be used in conjunction with stimulant laxatives (Figure 1) for refractory constipation.

Several prokinetic agents have been studied for the treatment of constipation (erythromycin for example may commonly be applied to therapy) [8] Notably, metoclopramide may be effective for delayed gastric emptying when used prior to meals and at bedtime. Extrapyramidal symptoms are a common concern and occur more often at higher doses (1 to 2 mg/kg), at which point diphenhydramine may be administered to reduce this risk [8]. Each of these agents accelerates colonic transit time and increase stool frequency in patients with constipation.

In patients experiencing severe or refractory constipation due to the chronic use of opioids, there are novel options to consider. Methylnaltrexone bromide is a peripherally acting μ-opioid receptor antagonist that is administered via subcutaneous injection every other day as needed [9]. The average time to laxation after the first dose was 6.3 hours with no evidence of withdrawal symptoms or reversal of analgesia. Lubiprostone is a locally acting chloride channel activator that increases intestinal fluid secretion without altering serum sodium or potassium levels [9]. The increased fluid secretion in the intestines serves to improve intestinal motility, allowing easier passage of stool.

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Naloxegol is a derivative of the μ-opioid receptor antagonist naloxone and has a pegylated chemical structure that prohibits crossing of the blood-brain barrier so that it maintains a solely peripheral mechanism [9]. It is recommended to discontinue other laxatives when starting naloxegol, however, other laxatives may be restarted if the patient does not produce a bowel movement within 72 hours after initiation. Linaclotide is a potent guanylate cyclase-C agonist that acts peripherally to increase the production of cyclic guanosine monophosphate in human colon cells, leading to eventual activation of the CFTR to increase chloride, bicarbonate, and water secretion into the colon [9]. When considering the prolonged use of any of these agents consulting gastrointestinal specialists may be prudent to help weigh the cost benefit as well as these compared with other options. While not all of these agents are indicated for constipation in cancer patients, they are valuable considerations in our supportive care arsenal [10].

Despite the availability of various classes of laxatives, constipation remains quite common among cancer patients. This may be attributed to failure to initiate laxatives in a timely manner i.e. before this condition arises in addition to the lack of guidelines to help select the most appropriate agents. Hence, the primary objective of this review is to provide clinicians with a practical or a real-world approach for managing constipation which is essential or pivotal for the care of patients with cancer [11].

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