Cancer management from a chronic gastrointestinal function perspective

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ABSTRACT

Bowel dysfunction in cancer is a significant and challenging issue for both clinicians and patients. As cancer survival improves, the impact of gastrointestinal symptoms on quality of life is of ever-increasing relevance. This review aims to provide an overview of the common gastrointestinal complaints seen in cancer sufferers and discuss the principles of management and up to date treatment options available.

Introduction

As survival of patients with cancer improves, attention has necessarily turned to improving quality of life for patients living with cancer. In the last 40 years, all-type cancer 5-year survival in the UK has increased from 50% to 70%.[1] This improvement in outcomes means more patients than ever before are living, and living longer, with the consequences both of their disease and of the treatments they receive. This review will discuss the causes of bowel dysfunction in patients living with cancer and explore their management options.

Up to 58% of patients with advanced cancer will experience constipation during their illness, but many will also suffer symptoms such as abdominal bloating, pain, diarrhoea, vomiting and obstruction.[2,3] The causes for these symptoms are multifaceted and often co-exist. Understanding the processes behind these symptoms is key to providing effective targeted interventions for patients.

Constipation

Constipation is the most commonly occurring GI symptom reported in patients with advanced cancer and can lead to further symptoms such as nausea, vomiting, haemorrhoids and anal fissures, with a subsequent deterioration in performance status and quality of life.[4–6] The causes of constipation can be categorised as medication-related, neurogenic (upper (UMN) or lower (LMN) motor neuron), metabolic (hypercalcaemia, uraemia, hypokalaemia etc), anatomical (stricture, compression), or related to lifestyle factors.[5]

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Medication-related constipation

The commonest cause of constipation in patients with cancer is related to analgesia, and in particular opioids.[7,8] Opioids simultaneously disrupt multiple stages of bowel function: they delay gastric emptying, decrease peristalsis, increase sphincter tone, increase absorption and reduce enterocyte secretion.[9] It is therefore unsurprising that constipation occurs in a reported 59% of cancer patients receiving opioid analgesia.[7] Other examples of medications known to detrimentally effect bowel function in cancer are chemotherapy agents and anticholinergics.[5,10]

Neurological constipation

Neurogenic constipation can be caused either by the cancer itself (eg primary spinal tumours or metastases), or by cancer therapies such as chemo- and radiotherapy. UMN neurogenic bowel is characterised by colon spasticity, increased segmental peristalsis with decreased propulsive peristalsis leading to prolonged colon transit time.[5,11–13]

Key points

- Developments in cancer therapy are leading to both extended survival and increased gastrointestinal complications of that therapy, meaning that bowel dysfunction is an increasingly important consideration.
- Treatment plans should be individualised to the patient and tailored to the aetiology of their bowel dysfunction.
- Constipation is most often related to drug therapy rather than mechanical disturbance post cancer therapy; clinicians should seek to prevent constipation where possible through judicious use of opioids and lifestyle advice.
- Diarrhoea in patients following cancer therapy should be proactively investigated to identify one of a wide range of reversible causes.
- Bacterial overgrowth and bile acid malabsorption are important, but often overlooked, causes of diarrhoea in cancer patients and steatorrhoea features should be a prompt to consider the latter.

KEYWORDS: cancer therapy, constipation, diarrhoea, gastrointestinal

DOI: 10.7861/clinmed.2023-GA1

UMN deficits cause spasticity of the external anal sphincter leading to a hyperactive holding reflex.[14] LMN lesions deficits also slow peristalsis but have decreased anal tone due to a denervated external sphincter.[5] This results in a similarly prolonged colonic transit time, but instead there is a risk of faecal incontinence.[5]

Management

The key principle of managing constipation in cancer is to design an individualised bowel programme targeted for the patient.[15] This usually consists of therapies and lifestyle changes known to generally improve bowel function–for example, good oral/fluid intake, stool softeners and stimulant laxatives–alongside specific measures to target the patient-specific aetiology, such as digital rectal stimulation or enema for UMN neurogenic bowel.[16] Biofeedback is a well-recognised non-invasive treatment for constipation and incontinence. It uses bowel retraining/behaviour modification techniques to improve bowel dysfunction and has been shown to have a good effect in managing pelvic floor dysfunction, including low anterior resection syndrome (LARS).[17,18]

As is often the case, however, prevention is better than cure, and many cancer care guidelines now stipulate monitoring for the development of constipation using patient-reported outcome measures (PROMs) such as the Bowel Function Index.[6,19–21] Judicious use of appropriate opioids is essential. More recently, advances have been made with the advent of peripherally activated mu-opioid receptor antagonists (PAMORAs). These drugs are specifically designed to reduce the effects of opioids in the GI tract and evidence for their efficacy is promising.[22,23]

Mechanical obstruction

Cancer patients can be affected by mechanical bowel obstruction, whereby a structural abnormality prevents the normal passage of gastrointestinal contents.[24] Symptoms can be wide-ranging and overlapping, from abdominal pain, bloating and progressive constipation to absolute constipation or, counter-intuitively, loose motions. These symptoms again may be directly linked to a patient's cancer or secondary to oncological treatment.[25] The commonest causes of bowel obstruction in cancer are malignant tumour infiltration into the bowel or external compression due to mass effect.[25] Radiotherapy is an important tool in the management of cancers in particular GI, urological and gynaecological cancers.[26] However, its use can lead to chronic bowel inflammation with subsequent stricturing and obstructive dysfunction.[26]

Management

Conservative measures are usually trialled first, depending on the nature of the blockage and the stability of the patient, the mainstays of treatment being nasogastric decompression, fluid resuscitation and bowel rest with or without steroids.[27] Other possible interventions include radiotherapy (for obstruction due to tumour effects), endoscopic stenting/dilatation and/or surgical resection or bypass.[28] Stoma formation is a commonly performed procedure in obstructing cancer but stomas themselves can be a cause of dysfunction and impaired quality of life. Medical symptomatic management should not be overlooked to control symptoms such as pain and vomiting. Options include somatostatin analogues (eg octreotide) to reduce bowel motility and gastrointestinal secretions, opioids to directly relieve pain and reduce painful bowel contractions and antiemetic therapy (eg haloperidol or prochlorperazine).[28]

Diarrhoea

Diarrhoea is a common symptom that has a large impact on patient quality of life. There are many causes seen in people living with cancer; most attention is paid to side effects of oncological therapies, but increasingly we are gaining an understanding of the role of the gut biome and altered gut physiology in this cohort of patients.

Diarrhoea caused by anti-cancer therapies

Diarrhoea is a well-recognised side effect of many anti-cancer therapies. This has an impact on quality of life and on clinical outcome, as it may lead to dose reductions or changes in treatment.[29,30] The causative agents and underlying aetiologies of diarrhoea-causing therapies are outlined in Table 1. Indirectly, diarrhoea is a symptom of neutropenic enterocolitis, an acute life-threatening complication of anti-cancer therapies.[31] Diarrhoea is seen in patients who develop ischaemic colitis after chemotherapy or graft versus host disease in stem cell patients. These are acute causes of diarrhoea and usually need acute hospital care.[32]

Cancer-related diarrhoea

Diarrhoea is a common presentation in many types of cancer, particularly colorectal cancer (where it is often combined with constipation) and neuroendocrine tumours.[31,33] It is a common presentation in other cancers including lymphoma, medullary cancers, pheochromocytoma and pancreatic cancer. In pancreatic cancers, the cause of diarrhoea is usually related to bile salt malabsorption.[31]

Diarrhoea resulting from bile acid malabsorption

Bile acid malabsorption can result in bowel frequency, diarrhoea and steathorrhea.[34] This can be the result of high dose chemotherapy, ileal disease/resection, upper GI resection surgery, cholecystectomy, pancreatic disease, pelvic radiotherapy or idiopathic.[35] Diagnosis of the condition can be difficult and is through SeChat studies or C4 blood tests.[34] Treatment is by diet (cutting back on fatty food), anti-diarrhoeal medication or a trial of bile-sequestering medication, which can be diagnostic.

Surgical procedures

Bowel resections may lead to diarrhoea of varying severity depending on the procedure performed. If the small intestine is extensively resected, then short bowel syndrome (SBS) may develop, a condition where the lack of small intestine results in rapid transit of incompletely digested food, the volume of material then entering the colon exceeds its capacity to absorb, leading to diarrhoea.[36,37] Where a stoma is formed, high output stoma may develop due to SBS, as well as bile acid deficiencies, diabetes mellitus, and treatment side effects.[37]

Infections and overgrowth

When patients present with diarrhoea it is important to rule out infection. Mucosal, bacterial or viral infections commonly cause secretory diarrhoea in cancer patients, and immunosuppression makes them more at risk of developing pathological levels of

Table 1. Anti-cancer therapy causes of diarrhoea: agents, aetiology and severity[31]

Anti-cancer therapy	Causative agents	Underlying aetiology	Diarrhoea severity
Chemotherapy	5-Fluorouracil Irinotecan Capecitabine Taxanes (eg cabazitaxel, docetaxel) Anthracyclines Platinum salts (eg cisplatin)	Multifactorial process causing imbalances in absorptive and secretory functions of small bowel	Usually not severe, but may be dose-limiting or life-threatening
Targeted therapy	Tyrosine kinase inhibitors VEGFR inhibitors EGFR inhibitors mTOR inhibitors CDK inhibitors PARP inhibitors	Multifactorial process involving secretory, ischaemic, and autoimmune mechanisms	May cause high-grade diarrhoea, particularly severe when combined with chemotherapy
Immunotherapy	Immune-checkpoint inhibitors, particularly anti-cytotoxic T-lymphocyte antigen-4	Shares characteristics with inflammatory bowel disease and enterocolitis	Severe, may lead to colon perforation
Radiotherapy	Pelvic radiotherapy Abdominal radiotherapy	Energy absorption or free radical release causing damage to intestinal villi and loss of mucosal integrity	Often mild, but combination with chemotherapy may increase severity
Hormone therapy	Androgen synthesis inhibitors Antiandrogens Antioestrogens		Mild intensity

these organisms.[38] The integrity of the gastrointestinal tract can be disrupted by all forms of cancer therapy, which predisposes the patient to bacterial overgrowth and occasionally fungal overgrowth. *Clostridium difficile* flourishes when the intestinal flora has been altered, which may be triggered by the cancer itself or by therapies offered.[31] Other important infections to eliminate in these patients are *Salmonella*, *Escherichia coli* and *Campylobacter*.[38] Small bowel bacterial overgrowth is a common cause of chronic diarrhoea in cancer patients.[39] 15% of those who have received radiotherapy will suffer with bacterial overgrowth.[40] Besides causing diarrhoea it can be associated with malnutrition, osteoporosis and weight loss.[39]

Management

Managing diarrhoea in this patient cohort depends on the severity of the diarrhoea and any complications present and requires an MDT approach. Conservative methods such as oral rehydration and selective use of loperamide can be utilised in uncomplicated patients.[31] It may be beneficial to modify dietary intake, eliminating foods that are difficult to digest, adopting a low-fat diet to minimise unabsorbed bile salts, and some studies have recommended the use of probiotics.[41] Patients with moderate to severe diarrhoea that is complicated by other symptoms should be hospitalised for both close monitoring and treatment. Hospital management should focus on fluid resuscitation and balance, octreotide, antibiotics if indicated, and potential nasogastric decompression for bowel rest. If the diarrhoea is severe and within 96 hours of treatment with 5-FU or capecitabine, then the pharmacological antidote uridine triacetate can be used.[31]

Conclusion

Bowel dysfunction is an increasingly important consideration for patients as cancer survival improves, with both medication and cancer therapies being major causes of bowel-related morbidity, as well the cancer itself. Treatment plans for diarrhoea and constipation should be individualised to the patient and tailored to the aetiology of their bowel dysfunction. If symptoms are intractable and causing significant problems for the patient, seek advice from the gastroenterology team or consider a referral. ■

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