

# Gastrointestinal side effects of cancer treatments

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**Abstract:** Cancer survival rates have significantly improved over the last number of years due to advancements in cancer therapies. Unfortunately this has come at a cost. Therapeutic side effects are feared complications of therapy that may result in decreased quality of life and early cessation of the therapy, which can have knock-on effects on outcomes. This article outlines the main gastrointestinal side effects seen with radiation therapy, chemotherapy and immunotherapy, and discusses appropriate investigation and management.

**Keywords:** Cancer, Radiotherapy, Chemotherapy, Immunotherapy, Enteritis, Colitis, Proctitis, Typhilitis, Hepatitis, Gastrointestinal side effects

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## Introduction

Advances in multidisciplinary, multimodality cancer therapies over the years have led to greatly increased survival rates. Many of the therapies however come with significant adverse effects for survivors of cancer and 25% report impaired quality of life due to chronic physical problems following treatment, of which gastrointestinal (GI) symptoms are the most common and most associated with decreased quality of life.<sup>1,2</sup> They may also result in premature discontinuation of the therapy which has consequences for efficacy and survival. This article will review the GI side effects following treatments of radiation therapy, chemotherapy and immunotherapy.

## Radiotherapy-related enteritis

It is estimated that by 2025, 4 million patients per year in Europe will require radiotherapy for cancer.<sup>3</sup> Radiation therapy causes ionisation within tissues that absorb the high-frequency X/γ rays used. Reactive oxygen species are produced which cause apoptosis and necrosis within all cells; both benign and malignant. These toxic compounds acutely damage the gut and subsequently persistent cytokine activation in the sub-mucosa leads to ischaemia and fibrosis. Irreparable damage to DNA results in a loss of stem cells.<sup>4</sup> There are a number of risk factors that increase

the risk of radiation toxicity: higher radiation dose, longer treatment duration, increased area of bowel involved and concurrent chemotherapy increase the likelihood of developing toxicity. In the context of multimodality cancer treatments, chemotherapy increases the sensitivity of noncancerous tissues to damage from radiotherapy. Those receiving radiation to a pelvic/abdominal/thoracic malignancy commonly experience GI side effects if the GI structures are located within the radiation field resulting in a range of injuries, including radiation colitis, radiation mucositis and pelvic radiation disease. The most common malignancies treated with radiation therapy leading to radiation enteritis are cervical and prostate cancer.<sup>5</sup> The epithelium of the GI tract has a high rate of turnover without a developed process for cell salvation and DNA repair, which makes it vulnerable to damage. When mucosal stem cells within the crypts of Lieberkuhn are injured by free radicals produced by radiation it leads to intestinal inflammation, shortened villi and oedema. Histologically there are similarities between the damage caused by radiation and the appearance of the gut mucosa in inflammatory bowel disease. Leucocyte infiltration with evidence of crypt abscesses and occasionally ulcers are seen within the first month post radiation. Ulcerations can lead to abscesses, perforation and fistulae. As ulcers heal the process can lead to fibrosis of the tissue

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with stricture formation, which can cause obstruction and perforation of the viscus.

After the acute injury gradual fibrotic changes occur over months to years within the submucosal layer with collagen deposition: an occlusive vasculitis is seen with foam cell invasion of the tunica intima and hyaline thickening of the arteriolar walls. Injury to the small bowel causes it to become thickened. These chronic changes lead to decreased absorption of nutrients. Flatulence, abdominal discomfort and diarrhoea are seen secondary to impaired fat absorption and degradation of lactose, which may also be accompanied by bacterial overgrowth. Radiation damage to the large intestine can cause a pancolitis which mimics ulcerative colitis, though this is less common than segmental colitis to the areas directly radiated. The timing of GI symptoms may vary with some occurring acutely and others not arising for years or even decades, which limits the recognition of these late side effects in the published literature.<sup>6</sup>

Clinical presentation will depend on the area of the digestive tract affected but a range of symptoms exist including abdominal pain, diarrhoea, rectal bleeding, bloating and weight loss. Choice of modality for investigation will be guided by the symptoms. In abdominal pain or in cases of systemic toxicity, cross-sectional radiological assessment with computed tomography or magnetic resonance imaging should be performed to ensure the patient does not have an acute intra-abdominal pathology, such as an abscess or perforation that needs emergency intervention. Endoscopic procedures to assess the structure of the GI mucosa (including colonoscopy, capsule endoscopy or double-balloon enteroscopy, depending on the site of damage) are also a mainstay of investigation, especially when symptoms like diarrhoea, bleeding or tenesmus are present.

When small bowel overgrowth (SIBO) is suspected breath testing may be performed prior to antibiotic treatment: where this is not available and a high suspicion of SIBO persists empiric antibiotic therapy may be considered. The single most appropriate antibiotic is debated; rifaximin is commonly used as it has a low side-effect profile and low levels of resistance.<sup>7</sup>

The protective role of antioxidants on the gut has been hypothesised. A well-balanced diet with physiological quantities of antioxidants such as

vitamin C and vitamin E is believed to be important. There is no concrete evidence to suggest that higher quantities of antioxidants are beneficial.<sup>8</sup>

Treatment depends on the pattern of the symptoms involved. Controlling diarrhoea involves use of anti-diarrhoeal agents such as loperamide<sup>9</sup> and, if ongoing, the addition of bile acid sequestrants can be helpful.<sup>10</sup> Hyperbaric oxygen therapy has been postulated to improve outcomes. It is an expensive, specialised resource and the results from the literature are not conclusive; it may be reserved for refractory patients who fail conservative management.<sup>11</sup> Surgery is a last resort for radiation enteritis as it is technically difficult with a high rate of postoperative complications.

Rectal bleeding occurs with radiotherapy delivered to the anterior rectal wall resulting in some bleeding from telangiectasia in 50% of patients after pelvic radiotherapy, but impairs quality of life requiring intervention in fewer than 6%.<sup>12</sup> Randomised trials support four separate treatment options namely sucralfate enemas,<sup>13</sup> 4 weeks of treatment with metronidazole,<sup>14</sup> vitamin A<sup>15</sup> and hyperbaric oxygen therapy.<sup>16</sup>

The role of anti-inflammatory agents like corticosteroids and sulphasalazine has been hypothesised in case series, but there are no large-scale randomised studies proving their effect.<sup>17</sup> Similarly, probiotic use has been successful in animal models in reducing the gut inflammation associated with radiation, but this has not been confirmed in a large randomised study.<sup>18</sup>

Argon plasma coagulation is still widely used in practice to treat vascular ectasia caused by radiotherapy. This should be used carefully as the rate of serious complications including deep ulceration, fistulation, stricturing, perforation and chronic pain may occur in as many as one in four patients.<sup>19-23</sup>

### **Chemotherapy-induced nausea and vomiting**

Nausea and vomiting is a well-known and widely feared side effect of chemotherapy. The literature shows that between 60% and 80% of patients with cancer suffer from chemotherapy-induced nausea and vomiting if untreated.<sup>24</sup> There are a number of non-modifiable risk factors that increase the risk of developing emesis including female sex and younger age.<sup>25</sup> Modifiable risk factors include chemotherapeutic agent along with rate and dose.<sup>26</sup>

The pathogenesis of chemotherapy-induced emesis is complicated. It is believed that there are a few interconnected neuronal areas within the medulla which make up the vomiting centre. Enteroendocrine cells in the GI mucosa are stimulated by the chemotherapeutic agent to release mediators such as prostaglandins, 5-hydroxytryptamine (5-HT), cholecystikinin and substance P that stimulate vagal afferents and trigger the emetic reflex.<sup>27</sup>

The stimulation of the 5-HT<sub>3</sub> receptor by release of 5-HT from cells in the GI tract in response to chemotherapeutic agents appears to be the major contributor to acute onset nausea and vomiting. These 5-HT<sub>3</sub> receptors are present centrally and peripherally. Drugs which block these receptors are very effective in preventing chemotherapy-induced nausea and vomiting.<sup>28</sup>

Substance P is another mediator that is believed to trigger the emetic reflex when it binds to the neurokinin-1 receptor.<sup>29</sup> Aprepitant, which is a neurokinin-1 antagonist, is part of the standard protocol used when patients are receiving high emetogenic agents.<sup>30</sup>

Dexamethasone is a corticosteroid with anti-inflammatory and anti-emetic properties. Corticosteroids have been used in the oncological setting to prevent nausea and vomiting for decades. Their mechanism of action is not fully comprehended, but is thought to be secondary to the inhibition of prostaglandin synthesis.<sup>31</sup>

Treatment should be tailored to patients based on the emetic risk anticipated with the treatment.<sup>32</sup> Where the risk of emesis is high, for example when agents such as anthracycline are used, treatments such as a combination of aprepitant, a 5-HT<sub>3</sub> receptor antagonist, dexamethasone and olanzapine may be used on day 1 of the cycle with metoclopramide added on days 2–4.<sup>33</sup> The intensity of the anti-emetic treatment needed can be reduced as the level of emetogenicity of the chemotherapy decreases.<sup>34</sup> Patients with a moderate risk of emesis (30–90%), such as may be expected with an agent like vinorelbine, could receive a 5-HT<sub>3</sub> receptor antagonist on day 1 and dexamethasone on days 1–3. When the risk of emesis is relatively low (10–30%), such as when capecitabine is used, patients may only require a 5-HT<sub>3</sub> receptor antagonist or dexamethasone on day 1.<sup>30</sup>

### Chemotherapy-induced diarrhoea

Diarrhoea is a common and well-known side effect of many chemotherapy regimens. It is estimated that 50–80% of patients develop chemotherapy-induced diarrhoea<sup>35</sup> with 30% of patients developing a grade 3 [common terminology criteria for adverse events (CTCAE)] diarrhoea.<sup>36</sup> Regimens including 5-fluorouracil and irinotecan are especially likely to cause diarrhoea.<sup>37</sup> Prompt recognition and treatment are crucial to improve quality of life, limit chemotherapy dose reductions and deferrals, and to limit morbidity and mortality secondary to dehydration.

Loperamide is an opioid-receptor agonist and acts on the  $\mu$ -receptors in the myenteric plexus of the colon. Its use is recommended for grade 1–2 diarrhoea, with it being less effective in more severe diarrhoea. For grade 3–4 diarrhoea the general consensus is use of octreotide, a potent synthetic somatostatin analogue. Often patients will need to be admitted to hospital for intravenous rehydration with electrolyte replacement as needed.<sup>38</sup>

The use of treatments such as budesonide, probiotics or antibiotics has not been shown to be of benefit in preventing or ameliorating chemotherapy-induced diarrhoea.<sup>39</sup>

### Immunotherapy-related colitis

Immune check point inhibitors (ICIs) have revolutionised cancer treatment over the past decade. Some cancers have mechanisms to evade recognition by T cells, which allow the cancer cells to avoid recognition by the immune system.<sup>40</sup> ICIs are monoclonal antibodies that counteract these mechanisms and stimulate the immune response against the cancer cells. There are three targets for the ICIs. Anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) drugs are less cancer cell specific than anti-programmed cell death-1 receptor (PD-1) and its ligand PD-L1 drugs and therefore cause more autoimmune-like side effects.

The side-effect profile of ICIs is related to sustained T-cell activation. The side effects generally occur within 6 weeks of commencing immunotherapy but can occur up to 4 months after discontinuing the therapy.<sup>41</sup>

The most common adverse effect related to immunotherapy is diarrhoea. The frequency is reported to be between 19% and 50% depending

on the agent,<sup>42,43</sup> but is usually reported to occur in a third of patients.<sup>42</sup> The anti-CTLA-4 drugs have a reported incidence of diarrhoea of between 31% and 49% with the anti-PD-1 and PD-L1 drugs having a reported incidence of between 3% and 23%.<sup>44</sup> Around 3% of immunotherapy-related diarrhoea is grade 3 or higher (CTCAE grading), requiring hospitalisation.<sup>41</sup> Intestinal perforation and death have been reported, but occur in less than 1% of patients.<sup>45,46</sup>

Colitis secondary to immunotherapy has a reported incidence of 2%,<sup>47</sup> which increases to 12% as therapies are combined.<sup>48</sup> Colitis symptoms include diarrhoea, abdominal pain, nausea and vomiting.<sup>49</sup> Colitis should be diagnosed by endoscopic evaluation with biopsies. Endoscopically the pattern of inflammation is heterogeneous without a single defined appearance. There is usually a picture of an acute colitis with erosions, ulcerations and erythema of the mucosa. Histologically neutrophil and eosinophil infiltration is observed. Given the rectum and sigmoid colon are involved in the majority of cases flexible sigmoidoscopy often is sufficient to make the diagnosis but may miss some cases where inflammation is seen to affect the right colon only.<sup>50,51</sup> There is an increased risk in the order of 10 times of developing severe colitis (CTCAE grade 3 or higher) with use of anti-CTLA-4 compared with PD-1/PD-L1.<sup>52</sup> Combination therapies which merge anti-CTLA-4 and anti-PD-1 agents lead to increased severity of diarrhoea and frequency of colitis compared with the use of either agent in isolation.<sup>48</sup> Those with severe colitis are at risk of developing potentially fatal complications such as bowel necrosis, perforation and toxic megacolon.<sup>53</sup>

The main differential diagnosis of ICI colitis is GI infections and symptoms caused by the malignancy. The incidence of infective colitis in patients receiving ICIs is not well documented in the literature. Absence of infection needs to be confirmed with stool culture and analysis for *Clostridium difficile* toxin in all patients with significant diarrhoea before the colitis can be treated.

Those with mild symptoms (lower than grade 2 CTCAE) are advised to continue the ICI and to use anti-diarrhoeal agents and fluid and electrolyte supplementation as needed. Those with more severe symptoms (grade 3 CTCAE or higher) should cease the ICI treatment and be commenced on intravenous corticosteroids (1–2 mg/kg/day); in steroid-responsive patients this should

be changed to a tapering course of oral prednisolone over 6–8 weeks.<sup>54</sup> Those who do not respond to systemic steroids within 5 days should be commenced on infliximab; usually a single dose (5 mg/kg) is enough.<sup>55</sup> Early studies on vedolizumab, which is an intestine-specific monoclonal antibody used in treatment of inflammatory bowel disease which binds to the integrin  $\alpha 4\beta 7$ , shows potential as an alternative to infliximab in steroid-dependent or partially steroid refractory colitis'.<sup>56</sup>

### Typhlitis and neutropenic enterocolitis

Typhlitis is a rare yet significant consequence of chemotherapy-induced neutropenia and is characterised by inflammation localised to the caecal wall, possibly caused by bacterial invasion.<sup>12</sup> Patients experience rapid progression to ischaemia, necrosis, haemorrhage, perforation and multi-organ failure. When the ileum is involved as well, the term neutropenic enterocolitis is used. Patients will usually present with systemic toxicity with GI symptoms and when the condition is suspected diagnosis should be based on cross-sectional imaging. Colonoscopy should never be attempted due to the high probability of inducing iatrogenic perforation. Treatment is supportive with gut rest, fluids and broad-spectrum antibiotics. Close contact with surgeons is recommended due to the risk of abscess or perforation which requires emergency intervention and may present in atypical ways in a neutropenic patient.

### Immunotherapy-related hepatitis

Hepatitis is commonly seen in patients on immunotherapy. The incidence is between 5% and 10% with 1–2% being a CTCAE grade 3 hepatitis.<sup>48</sup> Anti-CTLA-4 drugs have an incidence of 3–9% and anti-PD-1 and anti-PDL-1 drugs have an incidence of 1–7%.<sup>44</sup> This incidence increases threefold when patients are on a combination of immunotherapies.<sup>57</sup> The majority of treatment-induced hepatitis is picked up incidentally on routine blood monitoring in an asymptomatic patient as a mixed cholestatic and hepatocellular injury. Onset usually occurs 4–12 weeks after initiation.<sup>58</sup> Diagnosis is one of exclusion, without specific radiological features, but can be used to rule out differentials such as vascular/malignancy related. A thorough history should be obtained to elicit any concomitant chemical causes (including alcohol/herbal medicines/antibiotics) or infection as a differential cause of the hepatitis. In severe cases of hepatitis consultation with a hepatologist

and a liver biopsy may be performed. The histological findings in immunotherapy-induced hepatitis are identical to those seen in autoimmune hepatitis.<sup>59</sup> Immunotherapy can be safely continued in CTCAE grade 1 hepatitis.<sup>60</sup> ICI therapy should be held and liver function biochemically checked biweekly in grade 2 hepatitis.

Grade 3/4 hepatitis should be treated with high-dose intravenous systemic glucocorticoids for 24–48 h followed by a slow oral steroid taper (starting at 1–2 mg/kg of prednisolone) over at least 30 days.<sup>61</sup> The immunotherapy should be permanently discontinued. If no improvement in liver function is seen within 3 days mycophenolate mofetil should be commenced at 1000 mg twice daily.<sup>62</sup> Third-line immunosuppressive options include tacrolimus but there is no consensus in the literature on the best way to proceed.

### Summary

Cancer therapies have a number of different GI side effects which are managed differently depending on the cause and symptom. Adequately managing symptoms and the inflammatory activity is crucial to improve quality of life and improve compliance with cancer therapies. Cross-disciplinary working groups involving medical oncology, radiation oncology, gastroenterology, surgery and general practice should be established to share knowledge and expertise.

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