Systemic anti-cancer therapy-induced diarrhoea

Diarrhoea is a common acute complication of many systemic anti-cancer treatments for solid tumours. It requires prompt recognition and effective management to prevent escalating severity and remains potentially life threatening, particularly in neutropenic patients. It is also an unpleasant side effect, which can significantly impact patients' quality of life and result in hospitalizations, delays, dose reductions and even discontinuation of patients' systemic anti-cancer treatment (Andreyev et al, 2014).

It is crucial that oncology teams carefully educate patients as they commence a new course of systemic anti-cancer treatment about the risk and importance of self-management of diarrhoea. Toxicities from treatment are reviewed at chemotherapy appointments but patients are strongly advised to promptly contact their oncology centre directly, often through a chemotherapy helpline, if they are experiencing troublesome side effects. Thorough and if necessary repeated assessments, appropriate use of antidiarrhoeals and adequate fluid resuscitation are all crucial components of optimal management (Andreyev et al, 2014).

Several consensus guidelines have been published to guide clinical practice and many UK cancer centres will also have local guidance that can be referred to (Benson et al, 2004; Andreyev et al, 2014). This article outlines a safe, pragmatic approach to the initial assessment and management of adult solid tumour patients with diarrhoea related to their systemic anti-cancer treatment. It should equip clinicians to initiate appropriate treatment but it is imperative for patients' individual management that local guidelines are consulted where available and that the treating oncologist or acute oncology team is liaised with promptly.

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Causative agents

A wide range of intravenous and oral anti-cancer agents for non-haematological malignancies can cause diarrhoea, including cytotoxic chemotherapy, oral targeted drugs and immunotherapy. Those most frequently associated include the fluoropyrimidines (fluorouracil (5FU), capecitabine), irinotecan, tyrosine kinase inhibitors (e.g. gefitinib, sunitinib) and small molecule monoclonal antibodies (e.g. ipilimumab, cetuximab) (Stein et al, 2010; Pender et al, 2014).

Risk factors

Apart from the specific anti-cancer agent, the treatment regimen, e.g. bolus rather than infusional chemotherapy, frequency of dosing and concomitant abdominal pelvic radiation can all increase the risk of systemic anti-cancer treatment-induced diarrhoea. Other risk factors include older age, female gender, poorer performance status (a measure of overall fitness), associated bowel pathology and the presence of other comorbidities (Stein et al, 2010).

Initial clinical evaluation

A detailed history should assess baseline bowel function, onset and duration of diarrhoea, and stool frequency and consistency. The presence of nocturnal diarrhoea, steatorrhoea, urgency of defecation and faecal incontinence should be checked for. If a jejunostomy, ileostomy or colostomy is present, determine the baseline colour, consistency and 24-hour volume of output and how this has altered. Determining how frequently bags are now being emptied and/or changed allows an estimate of current volumes.

Complicating symptoms which indicate potentially high risk patients who may require inpatient management must be carefully assessed for (*Table 1*). These include associated gastrointestinal symptoms such as abdominal pain, bleeding, vomiting or other worrying systemic symptoms such as fever, increasing fatigue, weakness or poor oral intake (Benson et al, 2004). Other contributing factors should also be reviewed, including medications, diet, recent travel and infectious contacts. Patients, in particular those with ileostomies, may already take regular antidiarrhoeals or patients may have commenced antidiarrhoeals at home. It is important that an accurate record of what the patient has been taking, including dose and frequency, is established and then considered when adjusting medications. Temperature, blood pressure and hydration status should be assessed. Physical examination should include looking for oral mucositis and abdominal, perianal or peristomal abnormalities, including abdominal distension, tenderness and abnormal bowel sounds (Thorpe and Byar, 2015).

Grading of diarrhoea

Diarrhoea can be carefully graded, according to the National Cancer Institute's common terminology criteria for adverse events (*Table 2*) (National Cancer Institute, 2010). Accurate grading is important, influencing initial management, as well as subsequent changes to patients' anti-cancer treatment by their oncology teams, e.g. reductions in drug doses.

Table 1. Complicating signs and symptoms indicating high risk diarrhoea requiring inpatient management

Fever
Nausea or vomiting
Increasing fatigue or weakness
Neutropenia
Gastrointestinal bleeding
Abdominal pain
Dehydration

Adapted from Benson et al (2004)

Table 2. Grading diarrhoea using the common terminology criteria for adverse events

Grade	Frequency of stools	Stoma output
Grade 1	Increase of <4 stools/day additional to number pre-treatment	Mild increase in stoma output compared to baseline
Grade 2	Increase of 4–6 stools/day additional to number pre-treatment. Moderate cramping, not interfering with normal activity	Moderate increase in stoma output compared to baseline
Grade 3	Increase of 7–9 stools/day additional to number pre-treatment. Incontinence as well as severe cramping or nocturnal stools that interfere with activities of daily living.* Hospitalization indicated	Severe increase in stoma output compared to baseline
Grade 4	Increase to more than 10 stools/day additional to number pre-treatment, grossly bloody diarrhoea or life-threatening consequences requiring urgent intervention including parenteral support or intensive care support	–
Grade 5	Death	Death

*Adapted from the National Cancer Institute (2010) common terminology criteria for adverse events. *Activities of daily living refers to bathing, dressing and undressing, feeding, using the toilet and taking medications.*

Differential diagnosis

It is important to also consider whether there may be other causes for the patient's diarrhoea apart from the systemic anti-cancer treatment, as detailed in *Table 3*.

Table 3. Differential diagnosis of diarrhoea in a patient receiving systemic anti-cancer treatment

Systemic anti-cancer therapy-induced diarrhoea
Infective episode including *Clostridium difficile*
Medications, e.g. antibiotics, laxatives, oral electrolyte replacement, metoclopramide, proton pump inhibitors
Constipation with overflow
Sub-acute obstruction, e.g. can occur if a colonic tumour is still in situ or if there are post-surgical adhesions present
Malabsorption in biliary and pancreatic malignancies
Hypersecretion of 5HIAA (5-hydroxyindoleacetic acid) in carcinoid tumours
Other comorbidities including hyperthyroidism and inflammatory bowel disease

Investigations

A range of investigations should be considered, guided by the history and examination, as found in *Table 4*.

Table 4. Investigations to consider in patients presenting with diarrhoea

Blood tests	Full blood picture including differential white cell count, renal function, electrolytes, liver function, C-reactive protein
Stool sample for microscopy, culture and toxins (including *Clostridium difficile*)	Urgent stool or stoma samples should be sent as soon as possible to exclude an infective cause but results are not needed before commencing antidiarrhoeals
Imaging	Abdominal X-ray to exclude bowel obstruction or faecal impaction. A computed tomography scan of the abdomen might be indicated if there are signs of peritonism (guarding, rebound tenderness) to assess for small or large bowel involvement, neutropenic enterocolitis (typhlitis) or complications such as a perforation or abscess
Endoscopy and biopsy	Endoscopy and biopsy are sometimes also considered. Colonoscopy is relatively contraindicated if there is a suggestion of neutropenic enterocolitis because of the risk of perforation but flexible sigmoidoscopy can be performed if required to assess for other causes
Additional investigations	Additional investigations are sometimes also performed in conjunction with specialist input if other causes are suspected, e.g. tests for pancreatic insufficiency, bile acid malabsorption or small bowel bacterial overgrowth

Management

General management

It is imperative that hydration status be paid careful attention to. All patients should be advised to increase their oral fluids (2–3 litres daily) if they develop diarrhoea. For patients with severe diarrhoea adequate intravenous fluids with electrolyte replacement should be prioritized, with careful monitoring of fluid balance, including stool or stoma volumes, urine output and renal function.

The patient should also start to monitor the frequency and consistency of stools or stoma bag emptying and their own temperature to monitor for any fever. Medications should be reviewed and dietary advice discussed. This includes small, frequent meals as tolerated, encouraging a 'BRAT' diet of bananas, rice, apples, toast, and plain pasta. Any laxatives or high osmolar supplements, e.g. Ensure Plus, should be stopped. It is sensible to avoid spicy, high fibre or high fat foods, as well as fruit, vegetables, caffeine, carbonated drinks and alcohol. Some patients with severe diarrhoea may try limiting milk and milk products temporarily to see if this improves

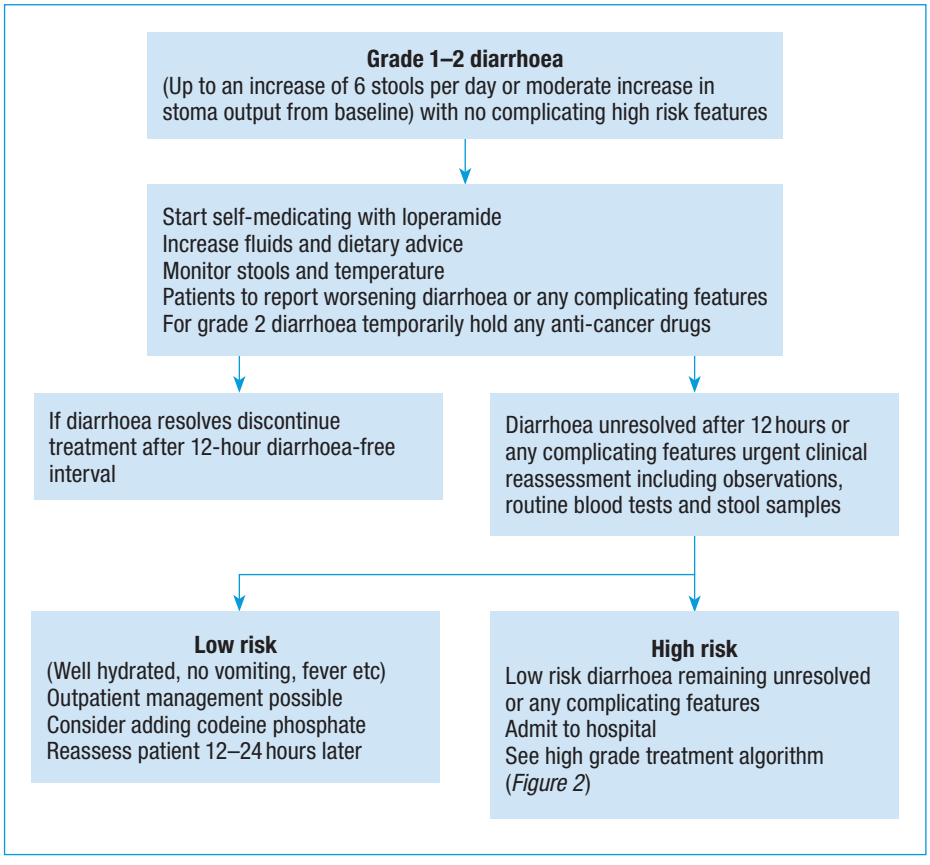
symptoms, as the bowel may become temporarily lactose intolerant (Bisanz et al, 2010; Thorpe and Byar, 2015).

Careful attention must be given to patients with stomas, especially jejunostomies or ileostomies, where the impact of systemic anti-cancer treatment-induced diarrhoea can be more severe. Advice should be sought early from gastroenterology or nutrition support colleagues, to optimize oral fluid and electrolyte management plans (Nightingale and Woodward, 2006).

Systemic anti-cancer therapy, including oral drugs, should be interrupted for grade 2 diarrhoea or above until diarrhoea resolves. A dose delay or reduction may be required for subsequent cycles (Wilkes and Barton-Burke, 2016).

It is particularly important in patients with presumed systemic anti-cancer treatment-induced diarrhoea not to wait for stool cultures before commencing antidiarrhoeals, and antidiarrhoeals do not need to be stopped even if sepsis is suspected. The probability of infection in patients receiving systemic anti-cancer treatment remains low, although *Clostridium difficile* should be excluded quickly. It is essential that the patient's diarrhoea is actively treated as quickly as possible alongside any suspected infection (Andreyev et al, 2014).

Figure 1. Management of uncomplicated grade 1–2 diarrhoea. Adapted from Benson et al (2004), Andreyev et al (2014).



Uncomplicated grade 1–2 diarrhoea

If patients are well hydrated with no complicating signs or symptoms outpatient management is feasible but regular follow up is imperative to ensure improvement (*Figure 1*). There should be a low threshold for clinical assessment, including bloods and stool samples being sent.

Patients should start self-medicating with loperamide, for example 4 mg initially, followed by 2 mg 4-hourly or after each loose stool, to a maximum of 16 mg per 24 hours. Loperamide is an anticholinergic, causing a reduction in peristalsis and gut secretions. It is generally well tolerated but can cause abdominal cramps, bloating, urinary retention and dry mouth. It is normally discontinued after the patient has been diarrhoea free for 12 hours. If diarrhoea persists after 12 hours of loperamide treatment, the addition of codeine phosphate can be considered, for example 30–60 mg four times daily to a maximum of 240 mg per 24 hours. Codeine works on opioid receptors in the gut wall to increase intestinal smooth muscle tone and suppress peristalsis but can cause drowsiness and nausea. If diarrhoea fails to settle or the patient develops any complicating features the patient should be urgently assessed and admitted to hospital (Benson et al, 2004; Shaw and Taylor, 2012; Andreyev et al, 2014).

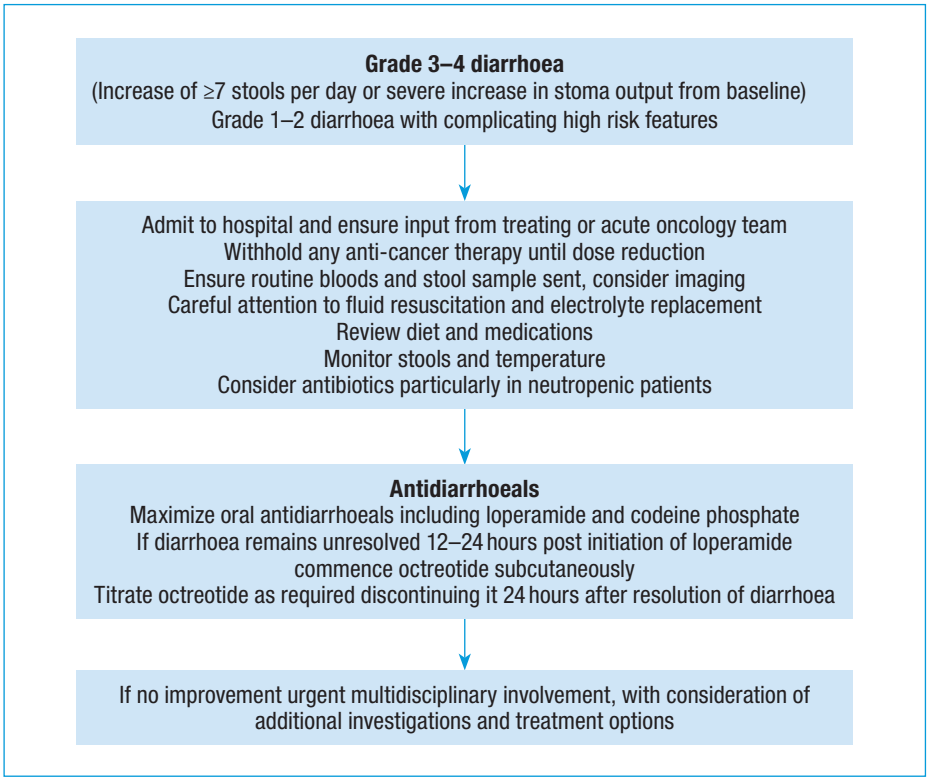
Grade 3–4 diarrhoea

These patients require urgent assessment and admission (*Figure 2*). Loperamide should be maximized as detailed above and consideration given to adding in codeine phosphate. If diarrhoea remains unresolved 12–24 hours post initiation of loperamide, octreotide should be commenced. Octreotide is a somatostatin analogue, reducing small bowel secretions and promoting resorption of fluids and electrolytes. Initial options include 150 µg subcutaneously three times daily or 300 µg over 24 hours via a syringe driver. Octreotide can be uptitrated, for example in a syringe driver, in 300 µg increments to 1500 µg per 24 hours, and is normally discontinued 24 hours after resolution of diarrhoea (Benson et al, 2004; Shaw and Taylor, 2012; Andreyev et al, 2014).

Antibiotics, e.g. ciprofloxacin or metronidazole, may be considered in grade 3–4 diarrhoea, particularly in neutropenic patients. It is important to remember that antibiotics might worsen diarrhoea and the risk of developing *C. difficile* colitis, and therefore advice should be taken from microbiology colleagues (Benson et al, 2004). Any positive stool cultures should guide antibiotic treatment. If patients are neutropenic with any signs or symptoms of sepsis they must be urgently commenced on empirical broad spectrum intravenous antibiotics for presumed neutropenic sepsis as per local hospital antibiotic guidelines.

If diarrhoea fails to improve urgent multidisciplinary involvement and further investigations are required. Additional options may include budesonide controlled release, for example 9 mg orally once daily for 3–5 days (Andreyev et al, 2014). If other underlying causes are felt to be contributing treatment should be tailored accordingly, for example exogenous pancreatic enzymes like Creon for pancreatic insufficiency, oral antibiotics and prokinetics for small bowel bacterial overgrowth (Quigley and Quera,

Figure 2. Management of grade 3–4 diarrhoea. Adapted from Benson et al (2004), Andreyev et al (2014).



2006), and bile acid sequestrants like cholestyramine for bile acid malabsorption (Walters and Pattni, 2010). Surgery for any associated complications is high risk and should only be performed in exceptional circumstances, with careful senior clinical input to guide decision making.

Neutropenic enterocolitis

Neutropenic enterocolitis (also referred to as necrotizing enterocolitis or typhlitis) is a potentially life-threatening complication of chemotherapy, particularly docetaxel and paclitaxel, normally occurring when the neutrophil count falls to less than $0.5x10^9$/litre. Patients typically present with fever, diffuse or right lower quadrant abdominal pain, nausea, vomiting, watery or bloody diarrhoea and signs of sepsis. Abdominal pain may be absent, particularly if patients are receiving steroids. Microbial infection causes bowel wall necrosis, most commonly affecting the caecum but can extend into the ascending colon and terminal ileum. Abdominal X-rays may demonstrate fluid-filled, thickened bowel loops but computed tomography is preferred and will identify complicating perforations or abscesses. Initially conservative medical management is encouraged with broad spectrum intravenous antibiotics, bowel rest, nasogastric suction and fluid resuscitation. Blood product and granulocyte colony-stimulating factor support should be considered. Antidiarrhoeals are often avoided as they may worsen ileus. Surgical intervention is occasionally considered in those failing to respond but there is a significant risk of death (Cherny, 2008).

Specific considerations

Fluoropyrimidines

Severe diarrhoea, often with mucositis and pancytopenia, early in the treatment with a fluoropyrimidine (capecitabine or 5FU) can be the result of a complete or partial deficiency in the enzyme dihydropyrimidine dehydrogenase which plays a central role in 5FU metabolism (Thorpe and Byar, 2015). Patients often require aggressive management and if suspected blood should be sent for dihydropyrimidine dehydrogenase genotyping. No further fluoropyrimidines should be administered to patients with a complete dihydropyrimidine dehydrogenase deficiency. For patients with a partial but clinically significant dihydropyrimidine dehydrogenase deficiency, significant dose reductions or cessation of treatment should be considered (Caudle et al, 2013).

Irinotecan

Irinotecan can cause an early (less than 24 hours after irinotecan) or delayed (over 24 hours) diarrhoea. Early diarrhoea is caused by an acute cholinergic syndrome, normally starting within a few hours of treatment, with other symptoms of cholinergic excess such as sweating, blurred vision, lacrimation, rhinitis, abdominal cramping and dizziness. Symptoms can be quickly controlled with subcutaneous atropine (250 µg) and prevented by atropine being given before future doses of irinotecan (Stein et al, 2010).

Delayed onset diarrhoea as a result of mucosal damage can be severe and even life threatening, particularly in combination with bolus intravenous 5FU and folinic acid (Wilkes and Barton-Burke, 2016). Initial aggressive loperamide management is encouraged (e.g. 4 mg stat then 2 mg 2-hourly, ignoring the 16 mg daily maximum and continuing until 12 hours after the last loose stool), with a low threshold for hospitalization. Loperamide is normally not administered for more than 48 hours because of the risk of ileus and additional measures such as octreotide are often required.

Immunotherapy

A range of immunotherapy drugs such as ipilimumab, pembrolizumab and nivolumab are being increasingly used across different tumour sites including melanoma, lung and genitourinary cancers. Patients can develop severe diarrhoea secondary to an immune-mediated colitis, which if not proactively treated can result in bowel perforation and be potentially fatal. They should be commenced on antidiarrhoeal medications such as loperamide and codeine phosphate but high dose steroids are often also required. Oral prednisolone, for example 1 mg/kg, is commenced for grade 2 diarrhoea, with proton pump inhibitor cover. If symptoms fail to improve over a few days or worsen patients are admitted and treated as grade 3 diarrhoea. Grade 3 diarrhoea requires high dose intravenous methylprednisolone, for example 2 mg/kg increased to 4 mg/kg if required. If high grade diarrhoea does not respond quickly to steroids urgent assessment by gastroenterology is encouraged. Endoscopy and anti-tumour necrosis factor alpha therapy, such as infliximab at 5 mg/kg, may be indicated (Bristol Myers Squibb, 2013).

Conclusions

Diarrhoea remains a common systemic anti-cancer treatment toxicity with the potential to cause significant morbidity and even mortality. Fundamental to minimizing its impact is empowering patients to confidently self-manage diarrhoea with loperamide and make timely contact with their chemotherapy unit. Clinicians must be confident optimizing treatment including antidiarrhoeals, fluid resuscitation and seeking specialist advice early for those not responding quickly.

A range of prophylactic pharmacological strategies have been explored but with no successes to date (Benson et al, 2004; Andreyev et al, 2014). Antidiarrhoeal regimens are effective but there is surprisingly little high quality evidence to guide clinical decision making. Further randomized clinical trials are required to define the optimal antidiarrhoeal regimens and the role of antibiotics and other agents such as prebiotics (Andreyev et al, 2014). **BJHM**

Conflict of interest: none.

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KEY POINTS

- For patients receiving systemic anti-cancer therapy who report diarrhoea ascertain the grade of symptoms to help guide management. Use local cancer centre protocols if available and get advice from the patient's treating oncology team or local acute oncology team.
- Any patient with grade 3 diarrhoea or grade 1–2 diarrhoea with any complicating signs or symptoms requires admission to hospital to optimize management.
- Do not wait for stool cultures before commencing antidiarrhoeals.
- Regular loperamide and codeine phosphate are first-line antidiarrhoeal agents, with octreotide subcutaneously if diarrhoea remains inadequately controlled.
- Systemic anti-cancer therapy including oral drugs should be interrupted for grade 2 diarrhoea or above until resolution.
- If patients are also neutropenic with any signs or symptoms of sepsis they must be urgently commenced on empirical broad spectrum intravenous antibiotics for presumed neutropenic sepsis. Neutropenic enterocolitis (typhlitis) should be considered, with computed tomography imaging if suspected.