Guidance on the management of diarrhoea during cancer chemotherapy

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Diarrhoea induced by chemotherapy in cancer patients is common, causes notable morbidity and mortality, and is managed inconsistently. Previous management guidelines were based on poor evidence and neglect physiological causes of chemotherapy-induced diarrhoea. In the absence of level 1 evidence from randomised controlled trials, we developed practical guidance for clinicians based on a literature review by a multidisciplinary team of clinical oncologists, dietitians, gastroenterologists, medical oncologists, nurses, pharmacist, and a surgeon. Education of patients and their carers about the risks associated with, and management of, chemotherapy-induced diarrhoea is the foundation for optimum treatment of toxic effects. Adequate—and, if necessary, repeated—assessment, appropriate use of loperamide, and knowledge of fluid resuscitation requirements of affected patients is the second crucial step. Use of octreotide and seeking specialist advice early for patients who do not respond to treatment will reduce morbidity and mortality. In view of the burden of chemotherapy-induced diarrhoea, appropriate multidisciplinary research to assess meaningful endpoints is urgently required.

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Introduction

Many chemotherapeutic agents used to treat cancer target rapidly dividing cells, and the effects on such cells in the epithelium of the gastrointestinal tract can lead to various gastrointestinal symptoms. Of particular clinical importance is chemotherapy-induced diarrhoea, which has been reported as a grade 3–4 serious adverse event with a frequency of 5–47% in randomised clinical trials (table 1). As well as regimens used to treat gastrointestinal cancers, those used in patients with tumours at other sites—eg, breast cancer treated with docetaxel and capecitabine or folinic acid antagonists (such as methotrexate)—also raise the risk of chemotherapy-induced diarrhoea. The introduction of tyrosine-kinase inhibitors (TKIs) and epidermal-growth-factor inhibitors has also been complicated by a high frequency of clinically important diarrhoea (ie, diarrhoea that requires intervention and affects the patient's quality of life so they stop taking treatment). Treatment, therefore, is frequently compromised, sometimes leads to hospital admission, and can be life threatening.

The true degree of clinically relevant chemotherapy-induced diarrhoea is unknown. In the UK, 75 000 people receive a regimen including fluorouracil every year, of whom 15% (950 patients per month) develop grade 3 or worse diarrhoea, most of whom will require hospital admission (Ferry D, personal communication). Death from fluorouracil-induced diarrhoea is reported in 1–5% of patients in clinical trials (8–42 patients per month, table 1). Although some of these patients also have neutropenia and the contribution of neutropenia-associated sepsis to diarrhoea and death is unknown, chemotherapy-induced diarrhoea remains an important complication.

Despite the effects that diarrhoea has on patients, carers, health professionals, and health-care resources, research and authoritative guidance on management are sparse and there is little agreement among clinicians about the optimum approach to treatment. Whilst several reviews or guidelines have been published,[8–12] most have been written from an oncological rather than a gastroenterological perspective and have concentrated on management of symptoms rather than the underlying pathophysiology.[13] Organic causes of diarrhoea, such as bacterial overgrowth, malabsorptive syndromes, and inflammatory or infectious enteritides, may all be treated very simply but are undoubtedly frequently missed.[13]

We have developed multidisciplinary guidance to facilitate clinical practice, based on an extensive literature search, which we present in this Review. We have defined principles of management where possible and outline research priorities for the future.

Methods

A multidisciplinary working group of five medical oncologists and one clinical oncologist, two gastroenterologists, a nurse consultant, a dietitian, a specialist pharmacist, and a gastrointestinal surgeon was established. Chemotherapy-induced diarrhoea was discussed in a 1 day meeting sponsored by Sanofi-Aventis. The concept development, literature review, and writing of the drafts, however, were done independently by the authors. All members of the working group were allocated topics to research and wrote the corresponding sections independently. These contributions were edited and the resulting paper was reviewed as a whole by all authors. There was no input from Sanofi-Aventis into the content or writing of this Review.

Chemotherapeutic agents frequently associated with diarrhoea

Specific causes for the type of gastrointestinal injury, with each specific agent as far as known, are shown in panel 1. The drugs most frequently associated with diarrhoea are fluorouracil (a thymidylate synthase inhibitor), and irinotecan (a topoisomerase I inhibitor).

	Regimen	Proportion with grade 3–4 diarrhoea (%)
Saltz et al, 2001[1]	Irinotecan	6%
	Irinotecan with infused fluorouracil or folinic acid	15%
O'Shaughnessy et al, 2002[2]	Docetaxel	5%
	Docetaxel with capecitabine	14%
Chau et al, 2005[3]	Bolus fluorouracil with folinic acid	16%
	Infused fluorouracil	5%
Falcone et al, 2007[4]	FOLFOXIRI	20%
	FOLFIRI	12%
Fuchs et al, 2007[5]	FOLFIRI	14%
	mIFL	19%
	capeIRI	47%
Van Cutsem et al, 2011[6]	FOLFIRI	11%
	FOLFIRI with cetuximab	16%
Tveit et al, 2012[7]	FLOX	10%
	FLOX with cetuximab	17%

FOLFOXIRI=oxaliplatin, irinotecan, fluorouracil, and folinic acid (leucovorin). FOLFIRI=folinic acid (leucovorin), fluorouracil, and irinotecan. mIFL=irinotecan with bolus fluorouracil. capeIRI=capecitabine and irinotecan. FLOX=folinic acid (leucovorin), oxaliplatin, and bolus fluorouracil.

Table 1: **Randomised trial data of the frequency of grade 3–4 diarrhoea with different chemotherapy regimens**

Fluorouracil-induced diarrhoea

The toxic effects caused by fluorouracil are dependent on the schedule and dose. Bolus regimens cause more myelosuppression and stomatitis than infused fluorouracil and, correspondingly, are more frequently associated with diarrhoea, especially grade 3–4 diarrhoea.[3] Prodrugs of fluorouracil, such as capecitabine, S-1, and oral tregafururacil, produce similar effects.[14] The risk of diarrhoea is increased by the addition of leucovorin.

Almost all the data on fluorouracil-associated diarrhoea come from studies done in patients with gastrointestinal malignancies, but there are no reasons to think that patients with other cancers are not affected. Clinical factors predictive for fluorouracil-induced diarrhoea include being female, increasing age (although the threshold is not known), normal body-mass index, white ethnic origin, and diabetes mellitus.[15–17] Genetics might also contribute to drug-specific toxic effects. For example, dihydropyrimidine dehydrogenase deficiency (caused by mutations in *DPYD*) is associated with reduced clearance of fluoropyrimidines and, therefore, prolonged exposure.[18] The most common genetic mutation seen in *DPYD* is the exon 14 skip mutation, which is a G→A change in the 5′ splicing recognition site of intron 14 and is seen in 1–2% of the population.[19] Homozygous mutations in *DPYD* are very rare, occurring in one per 5000–10 000 patients, but are associated with rapid and severe myelosuppression, toxic effects to the skin, mucositis, and diarrhoea. The risk of death is high after even brief exposure to fluoropyrimidines.[19] In the largest cohort of patients receiving fluorouracil monotherapy studied so far, 110 (16%) of 683 had grade 3–4 toxic effects, and of these 59 (54%) had grade 3–4 diarrhoea.[20] Of the whole cohort 13 (12%) had the exon 14 skip mutation and only six (5%) with grade 3–4 toxic effects had mutations affecting *DPYD*. In a multivariate analysis the presence of dihydropyrimidine dehydrogenase deficiency was predictive for mucositis and neutropenia but not diarrhoea.[20] As most patients with severe diarrhoea do not have this deficiency, sensitivity is too low to recommend routine testing. The polymorphisms that might contribute to the risk of diarrhoea are those that regulate thymidilate synthase, methylenetetrahydrofolate reductase, and cytidine deaminase.[21] Only very limited data on the role of these polymorphisms are so far available and definitive data are needed. However, for example, capecitabine, the prodrug of fluorouracil, is activated through a series of steps, including metabolism by the enzyme cytadine deaminase. Raised concentrations of this enzyme were reported in an individual who had no toxic effects when infused fluorouracil was given, but who developed severe gastrointestinal toxic effects when treated with capecitabine.[22] Variants in the cytadine deaminase promoter region have been suggested to increase expression of this enzyme, which has been reported to cause a doubling of the frequency of diarrhoea during the first four cycles of chemotherapy involving capecitabine.[23]

Irinotecan-induced diarrhoea

Irinotecan is associated with dose-limiting diarrhoea when given either as a 30 min bolus every 3 weeks[24] or as a continuous infusion over 7 days.[25] Acute diarrhoea occurs due to inhibition of acetylcholine esterase, which increases cholinergic transmission within minutes of administration and up to 24 h later but is easily controlled with atropine. In animals, after a few days, irinotecan causes villous atrophy and crypt damage in the small intestine and severe colonic mucosal damage with crypt hypoplasia and increased mucus secretion.[26]

One proposed mechanism for late-onset irinotecan-induced diarrhoea is that the active metabolite of the drug, SN-38, is 100–1000 times more cytotoxic than the parent compound. Animal models suggest that SN-38 is conjugated in the liver by glucuronyltransferase to SN-38 glucuronide (SN-38G), a much less toxic metabolite that is excreted into the gastrointestinal tract via bile. In stool, however, SN-38G can be hydrolysed by β-glucuronidases by gastrointestinal bacteria, which returns it to the form of SN-38 and causes damage to the mucosa as the drug is being excreted.[27,28] Whether this mechanism occurs in human beings is unknown, although strategies that might reduce the rate of conversion of SN-38G to SN-38, such as intestinal alkalinisation, anticyclo-oxygenase 2 therapy, probiotics, antibiotics, and absorbing agents, have shown no benefits.[29,30]

Increased risk of severe diarrhoea from irinotecan is seen in patients with Gilbert's syndrome, which is characterised by decreased bilirubin glucuronidation. Homozygosity for a *UGT1A1*28* allele leads to decreased expression of UGT1A1 and SN-38 glucuronidation and

increased risk of irinotecan-induced toxic effects.[31,32] Whether dose reduction is indicated in patients homozygous for the *UGT1A1*28* allele, however, remains unclear.

Investigations of other polymorphisms that affect expression of UGT1A1 and other related enzymes (ie, carboxyl esterases and CYP450 isoforms) and transmembrane transporters (ABCB1, ABCC1, ABCG2, and SLCO1B1) have suggested that the ABCC2 transmembrane transporter has a role in irinotecan-induced diarrhoea.[33] Nonetheless, the variability of response remains unexplained and prospective clinical studies demonstrating the reliability of those pharmacokinetic and pharmacogenetic markers are lacking.

Tyrosine-kinase inhibitors

The human genome contains around 20 000 genes, around 600 of which encode tyrosine kinases.[34] Kinases can be divided into at least ten families, and all kinase inhibitors discovered so far inhibit many kinases.[35] Although it was hoped these drugs would lessen toxic effects, they have frequently been as toxic as chemotherapy, which is important when they need to be given long-term. Diarrhoea is one of the most common adverse events recorded following treatment with TKIs.[36]

In patients treated with TKIs, diarrhoea is second only to rash as the most common adverse event, affecting up to 50% of patients. The occurrence of diarrhoea, however, has been suggested to predict tumour response.[37–39] Diarrhoea grade 3 or higher occurs in up to 28% of patients taking TKIs,[39] whereas with VEGF inhibitors (eg, pazopanib, sunitinib, sorafenib) up to 66% of patients develop diarrhoea.[37] Diarrhoea might start as early as 2–3 days after initiation of EGFR inhibitor therapy. With most TKIs, the severity of diarrhoea is dose dependent and can be modulated by a decrease in total dose. Third-generation EGFR inhibitors that irreversibly block EGFR, such as afatanib, are associated with dose-limiting diarrhoea; whether these drugs are clinically better than earlier-generation TKIs and, if so, how that balances against quality of life, remain to be seen.[40]

TKI-associated diarrhoea could be related to excess chloride secretion caused by dysregulated EGFR signalling. As EGFR is expressed by epithelial cells throughout the gastrointestinal tract, inhibition of EGFR might inhibit epithelial repair, but more than one mechanism for diarrhoea seems likely. Possibilities include altered gut motility, colonic crypt damage, changes to intestinal microflora, altered nutrient metabolism, absorption, and altered transport in the colon. The mechanism for VEGFR-inhibitor-induced diarrhoea is unexplained.

Small-molecule monoclonal antibodies

Agents that interfere with crucial regulatory biological molecules are increasingly being used to induce tumour regression. An example is ipilimumab, a fully human monoclonal antibody to CTLA-4 that prolongs the time to progression in patients with melanoma and ovarian, prostate, and renal-cell cancers. Immune-mediated side-effects include severe diarrhoea; this is associated with perforation in less than 1% of patients and with death in 5%. Endoscopic studies of the upper and lower gastrointestinal tracts show small-bowel and colonic inflammatory changes.[41] A diffuse, patchy or segmental non-specific colitis might be seen. Histological changes can also be non-specific and include acute and chronic inflammatory infiltrate, cryptitis, crypt abscess formation, and abundant T-cell infiltrate. Treatment is mainly supportive, although in severe cases high-dose corticosteroids should be started early. If steroids fail, infliximab has been advocated.[42] Colectomy is occasionally required. Secondary infections as a result of profound immunosuppression also needs to be considered.

Rituximab is an anti-CD20 monoclonal antibody that is used to treat B-cell lymphoma. Bowel perforation and

***Panel 1:* Categories of chemotherapy-induced gastrointestinal tract injuries**

Panenteritis, enterocolitis, or mucositis

Antimetabolites

Cytosine arabinoside, methotrexate, fluoropyrimidines (fluorouracil, capecitabine, tegafur–uracil), multitargeted folinic acid antagonists (pemetrexed, raltitrexed, gemcitabine)

Plant alkaloids

Vinca alkaloids (vincristine, vinorelbine), epipodophyllotoxins (etoposide), taxanes (paclitaxel, docetaxel), topoisomerase I inhibitors (irinotecan)

Cytotoxic antibiotics

Anthracyclines (doxorubicin, daunorubicin, idarubicin, aclarubicin, daunomycin with prednisone)

Alkylating agents

Cyclophosphamide, platinums (cisplatin, carboplatin, oxaliplatin, nedaplatin)

Abdominal pain

Antimetabolites

Gemcitabine

Autoimmune colitis

Monoclonal antibodies

Ipilumumab

Ischaemic colitis

Monoclonal antibodies

Antibodies against VEGF (bevacizumab)

Plant alkaloids

Taxanes (docetaxel, paclitaxel)

Gastrointestinal leucocytoclastic vasculitis

Miscellaneous

Sirolimus

new-onset ulcerative colitis or exacerbation of pre-existing colitis have been reported. Viral-induced colitis has also been described and might be an important problem.

Cetuximab and panitumumab are monoclonal antibodies to EGFR with activity in *KRAS* wild-type colorectal cancer that may be used alone or in combination with chemotherapy. These drugs have been associated with grade 3–4 diarrhoea in up to 30% of patients when combined with a fluoropyrimidine.[43] The licence for a capecitabine combination has been withdrawn. The cause for cetuximab-related diarrhoea is not known and is managed symptomatically.

See Online for appendix

Chemotherapy combined with other treatments

Overlapping, and hence worsened, toxic effects are important factors to take into account when making decisions about combined strategies, such as chemotherapy with cetuximab[43] or aflibercept.[44] Additionally, chemotherapy is increasingly combined with radiotherapy as a radiosensitiser, but can also sensitise normal tissues to toxic effects.[45] The severity of acute gastrointestinal symptoms during pelvic radiation depends partly on the dose given and volume of bowel treated. Other risk factors for toxic effects include diabetes, inflammatory bowel disease, collagen vascular disease, HIV, old age, smoking, and low body-mass index, but are poorly researched.[46]

Acute intestinal side-effects of radiation begin at approximately 10–20 Gy and peak between weeks 3 and 5 of treatment. Acute diarrhoea is an independent prognostic factor of outcome during treatment for colorectal cancer,[47] but more severe acute effects are also associated with long-term consequences of treatment.[38]

Prevention of treatment-induced diarrhoea

Glutamine, celecoxib, probiotics, activated charcoal, absorbents, and racecadotril have been suggested for the treatment or prophylaxis of chemotherapy-induced diarrhoea, but evidence of efficacy is lacking for all. The options are reviewed in guidelines published by the Multidisciplinary Association for Supportive Care in Cancer.[39] No pharmacological strategies effectively prevent radiotherapy-induced diarrhoea. Oral glutamine,[48] sucralfate, sulfasalazine, or subcutaneous and intramuscular octreotide[49] have been tested in randomised controlled trials but none decreased or prevented diarrhoea during therapeutic pelvic irradiation.

Mechanisms underlying diarrhoea

Although the risk factors contributing to direct toxic effects in the gastrointestinal tract are starting to be understood, why diarrhoea happens remains unclear. Many lesions might occur in the gastrointestinal tract without causing any unusual symptoms, but lesions become relevant when they lead to changes in normal gastrointestinal physiology.

Maintenance of the secretory, absorptive, and propulsive functions of the gastrointestinal tract relies on complex neurological, hormonal, muscular, immune, and enzyme systems. Additionally multiple specialised cells contribute diverse cellular and molecular mechanisms. Dysfunction of different regions of the gastrointestinal tract might cause completely different physiological effects in different patients despite symptoms being similar (appendix).[50]

The physiological mechanisms underlying chemotherapy-induced diarrhoea are likely sometimes to be drug dependent, but relevant clinical research is scarce. Identification of the physiological changes induced by chemotherapy is of fundamental importance to develop new treatments. Optimum treatment would reduce the symptom burden on the patient and lessen the disruption of adequate oncological treatment.[13]

The gut epithelium acts as a semipermeable membrane. Whether some specialist cells or enzyme systems in the gastrointestinal tract are more sensitive to chemotherapy than others is unknown. Diarrhoea with or without steatorrhoea occurs for three principle reasons: if the lumen contains hypertonic substances, such as incompletely metabolised components of normal diet (osmotic diarrhoea); if there is damage to molecular pumps that control fluid fluxes in and out of enterocytes or across tight junctions or in response to quantities of inadequately absorbed intraluminal bile (secretory diarrhoea); and if gastrointestinal motility is altered. The known physiological causes of treatment-induced diarrhoea and steatorrhoea are outlined in table 2.

Damage to the mucosa

Nutrients in the diet, such as carbohydrates and proteins, need to be hydrolysed before absorption and lipids or fats also require emulsification. Damage to the enzyme systems in the brush border of the gastrointestinal tract or within the specialist cells responsible for many of these metabolic processes might contribute to diarrhoea. Malabsorption of carbohydrate and fat are particularly important. Protein malabsorption might occur in patients undergoing chemotherapy for solid tumours but has never been described.

Carbohydrate malabsorption

Chemotherapy-induced lactose intolerance, which is due to decreased functional expression of the enzyme lactase in the brush border, is seen in 10% of patients receiving fluorouracil[52,53] and is described in children after various chemotherapy regimens.[54,55] Diarrhoea associated with lactase insufficiency is frequently accompanied by pain, bloating, and wind.

Other brush-border enzymes with roles in final hydrolysis of carbohydrates to monosaccharide units probably affect monosaccharide transport proteins on the luminal side of gut enterocytes. This mechanism has never been studied, but the D-xylose absorption test has been reported to be abnormal in various groups of patients receiving chemotherapy,[54,55] which implies that

proximal small bowel malabsorption had occurred. If disaccharides, such as fructose or sucrose, or more complex polysaccharides, for instance starches, are malabsorbed, treatment with a simple diet that excludes these disaccharides should abolish gastrointestinal symptoms, including diarrhoea.

Fat malabsorption

Steatorrhoea is excess fat (more than 6 g per day) in the stool. Clinicians and patients frequently mistakenly diagnose this disorder as diarrhoea. It may be constant or intermittent. In the UK measurement of stool fat cannot be requested and, unless microscopy is done and identifies the presence of fat globules, diagnosis relies on clinical expertise. Patients might report pale stools that splatter, are difficult to flush away, have an offensive smell, or, most usefully of all, are associated with an oily film in the lavatory water.

Fat malabsorption triggered by chemotherapy has two likely causes: small bowel bacterial overgrowth and bile acid malabsorption. Small bowel bacterial overgrowth is difficult to diagnose definitively,[56] but immunosuppressed patients are at higher risk of developing pathological levels of colonic bacteria growing in the small bowel than are non-immunocompromised patients. The rates of bacterial overgrowth have not been systematically studied, but clinical experience and animal data suggest that it is a frequent problem in patients undergoing chemotherapy.[57–60] Appropriate antibiotic therapy given for a few days should be curative.[61]

No data are available on chemotherapy-induced bile acid malabsorption. Clinical experience suggests that this effect is common. It sometimes causes severe symptoms and is generally responsive to treatment with bile acid sequestrants, dietary fat reduction, or both. That bile acid malabsorption causes a substantial proportion of chemotherapy-induced secretory diarrhoea, steatorrhoea, or both, would not be surprising. The definitive diagnostic test for bile acid malabsorption is the 23-seleno-25-homo-tauro-cholic acid (SeHCAT) scan, but is available in only eight European countries, Canada, and Australia. Consequently, this disorder is seldom considered. An alternative test is the C4 (7α-hydroxy-4-cholesten-3-one) blood test. Although slightly less sensitive than the SeHCAT scan, it is a useful way to screen for bile acid malabsorption.

Less frequently, fat malabsorption occurs for other reasons. Pancreatic insufficiency is described after conditioning regimens that precede stem cell transplantation.[62–64] Whether other chemotherapy regimens predispose to pancreatic insufficiency is unknown. Intestinal lymphatic obstruction from tumour infiltration, previous small bowel resection causing malabsorption of free fatty acids, radiotherapy-induced intestinal lymphangiectasia, excessive use of somatostatin analogues, or hormone secretion from tumours (usually when a previously non-functioning neuroendocrine tumour dedifferentiates into a functioning tumour) might all result in diarrhoea or steatorrhoea of varying severity.

	Chemotherapy	Radiotherapy*
Lactose intolerance	10–50%	50%
Malabsorption of non-lactose disaccharides	?	?
Bile acid malabsorption	?	50%
Small bowel bacterial overgrowth	?	25%
Reduced transit time	?	100%
Viral infection (eg, cytomegalovirus)	?	?
Bacterial infection (eg, *Clostridium difficile*)	?	?
Parasitic or opportunistic infection	?	?
Pancreatic insufficiency	?	?
Drug related (non-chemotherapy)	?	?
Other (eg, hormone secretion, changes in neural pathway signalling, stress)	?	?

*Pelvic radiotherapy.[13,51]

Table 2: **Acute physiological changes in normal gastrointestinal function that cause diarrhoea**

Effects on delivery of cancer treatments

Whether dose reduction because of toxic effects leads to adverse outcomes is controversial. Early data suggested no benefit from maintaining the dose intensity of fluoropyrimidine,[65,66] but the importance of dose intensity and optimum management of toxic effects has been emphasised as a guiding principle for the delivery of adjuvant therapies.[67] Circumstantial data indicate that dose reductions lead to more severe toxic effects than no dose reductions, but are likely to improve outcomes.[67] The guidelines of the American Society of Clinical Oncology favour maintaining dose intensity.[68] A randomised study that included 280 patients with metastatic colorectal cancer showed significantly improved response rates (33% *vs* 18%, p=0·0004) and non-significant improvement in overall survival (median 22 months *vs* 16 months) with pharmacokinetically guided fluorouracil dosing compared with standard dosing.[69] Furthermore, the frequency of toxic effects, particularly grade 1–4 diarrhoea, was reduced from 60% to 16% and grade 3–4 from 18% to 4%. Therefore every effort should be made to manage toxic effects without compromising clinical efficacy.

Effects of diarrhoea on patients

Diarrhoea can have a notable effect on performance status and the ability to perform daily activities. Patients may become housebound because of embarrassment, fatigue, dehydration, and abdominal, rectal, and perianal pain, excoriation or discomfort, and the fear of needing to defecate suddenly. Thus, chemotherapy-induced diarrhoea can result in social isolation, time off work, relationship difficulties, and psychological distress. Some individuals doubt their ability to complete treatment.[70]

The role of patients in management

If patients do not present in a timely manner with potentially serious symptoms, optimum management might not be possible. The National Confidential Enquiry into Perioperative Death audit into deaths within 30 days of receiving systemic anticancer therapy[71] confirmed that substantial numbers of patients did not recognise toxic effects or seek advice appropriately. Additionally, the audit noted that patients do not want to bother health professionals. Therefore, clinicians delivering chemotherapy must educate patients and carers about the optimum management of potentially life-threatening effects before chemotherapy is started. The information should be reiterated at every clinical meeting throughout treatment.

All patients must be given a regimen-based information sheet outlining potential side-effects, written in simple language. The use of visual aids, such as the Bristol stool chart (appendix), might improve understanding. Self-assessment tools to assess bowel function might also give patients the confidence to seek help.

Before chemotherapy is started, clinicians must establish what each individual patient's normal bowel function was before and whether it changed after their cancer was diagnosed, and discuss how function could change in the future with treatment. Patients can be encouraged to self-medicate but should keep a record of their drug use. Antidiarrhoeal tablets should be provided for patients to keep at home and carry with them if they go out should diarrhoea start. The National Chemotherapy Advisory Group report[72] states that health professionals should rehearse with patients when to start treatment and give instructions about continuation. If an acute oncology helpline is available, patients should be encouraged to telephone for advice after starting antidiarrhoeal medication to confirm the severity and whether face-to-face assessment is required. Alternatively, patients should speak to their oncology team or covering staff immediately.

Many studies have indicated that patients are reluctant to take medicines. For chemotherapy-induced diarrhoea the most important drug is loperamide. Patients should be told that this drug is not absorbed into the body and is excreted in the faeces and, in contrast to the commonly accepted advice associated with this drug's use for travellers' diarrhoea, risk of overdose in this clinical setting is unlikely. How much to take, how often, and when in relation to meals patients can take antidiarrhoeal medication must be made clear. Importantly, if the first doses of loperamide do not work, patients should be informed that it is likely that they have not taken enough. After starting loperamide, patients need to know when they must contact their chemotherapy unit and when they can delay contact; generally, patients should make contact if taking eight 2 mg tablets in 24 h has had no effect. The possible need for intravenous fluids and other treatments because of diarrhoea must be explained.

Panel 2: **Common Terminology Criteria for Adverse Events grades of diarrhoea[73]**

- Grade 1: increase to two to three bowel movements per day additional to number before treatment or mild increase in stoma output
- Grade 2: increase to four to six bowel movements per day additional to number before treatment, moderate increase in stoma output, as well as moderate cramping or nocturnal stools
- Grade 3: increase of seven to nine bowel movements per day additional to number before treatment, incontinence, or severe increase in stoma output, as well as severe cramping or nocturnal stools, that interfere with activities of daily living
- Grade 4: increase to more than ten bowel movements per day additional to number before treatment, grossly bloody diarrhoea, need for parenteral support, or a combination of these features
- Grade 5: death

Clinical assessment

Patients with early signs of acute toxic effects might need adjustment or even discontinuation of chemotherapy or breaks in radiotherapy. The seriousness of diarrhoea is frequently defined with the Common Terminology Criteria for Adverse Events (panel 2).[73] The most important decision is whether the patient can be managed as an outpatient or needs admission for fluid resuscitation, and is dependent on the risk of adverse outcomes. Patients with grade 1–2 diarrhoea without worrying clinical features and test results can usually be managed at home. Those with grade 3–4 diarrhoea generally need immediate admission unless clinical review suggests the patient is well hydrated, has not yet had any antidiarrhoeal medication, and can be reviewed daily (figure).

Warning signs

Several features should alert clinicians to the fact that diarrhoea is clinically worrying. These include abdominal cramps not relieved by loperamide, an inability to eat, increasing fatigue, increasing weakness, chest pain, nausea not controlled by antiemetics, vomiting, dehydration accompanied by reduced urine output, fever (temperature higher than 38·5°C), gastrointestinal bleeding, and previous admission for diarrhoea.

History taking

Gastrointestinal symptoms are frequently manifestations of pathologies outside the gastrointestinal tract, such as chest or urinary sepsis. Reviewing systems in detail, therefore, is always required. If a patient is taking unfamiliar drugs, especially biological agents, urgent review of the drug information sheets is mandatory.

What constituted normal bowel function before the onset of diarrhoea must be established before any new

treatment is started, to understand how much bowel function has really changed. Guidance in the UK on the management of gastrointestinal side-effects of cancer therapies emphasises three crucial factors: whether the patient is being woken from sleep to defecate; whether there is any steatorrhoea; and whether there is urgency of defecation or any faecal incontinence. If any of these factors is present, an urgent gastroenterological assessment is mandated. If the first two are present, an organic cause is always indicated that should, if identified, be treatable. A positive answer to the third question means the presence of symptoms that are particularly disabling for patients.

Five other important factors to consider are the degree of fatigue, changes in medication, diet, other chemotherapy-induced toxic effects, and whether the patient is presenting with overflow diarrhoea.

The intensity of fatigue correlates with the severity of diarrhoea at 3 weeks.[74,75] Fatigue can also be associated with a significant decrease in albumin concentrations in serum ($p<0\cdot001$).[75] Recent changes to medication (within the previous 10–14 days) should be taken into account, as the introduction of proton-pump inhibitors, non-steroidal anti-inflammatory drugs, laxatives, or antibiotics particularly can lead to diarrhoea. When assessing diet, it should be established whether patients are eating very little or excessive amounts of fibre. Foods containing lactose might trigger diarrhoea and should be suspected, especially if the diarrhoea is accompanied by marked bloating. Other causes to consider are excessive alcohol intake and an inability to eat and drink normally. Other chemotherapy-related toxic effects, such as nausea, vomiting, or both, odynophagia, mouth ulceration, red hands or feet, and rashes can be useful indicators of the cause of diarrhoea. Finally, if the patient has loss of appetite, abdominal pain, bloating, increased frequency of soft or loose stool rather than profuse watery diarrhoea, overflow diarrhoea should be suspected.

Physical assessment

Physical assessment must include the standard observations of temperature, pulse, blood pressure (lying and standing), respiratory rate, oxygen saturation, peripheral perfusion, capillary refill, urine analysis, and full physical examination. If the patient has neutropenia, avoidance of rectal examination was suggested in previous guidelines, but there is almost no evidence to support this recommendation. Unless rectal examination causes severe anal pain, it should be done together with gentle perianal palpation to exclude the possibility of a local sepsis as the cause for diarrhoea.

Investigations

If the patient is tachycardic or dehydrated or if sepsis is suspected, fluid resuscitation should be started and 4 mg loperamide given before investigations are done. Investigations should be done early to rule out causes of diarrhoea not associated with chemotherapy. Diarrhoea is so common with chemotherapy that all patients should be provided with stool-culture bottles before the start of treatment to enable collection of a sample as soon as they feel changes in bowel function. This approach avoids delays in obtaining samples if admission to hospital is required.

Evidence from oncological studies to guide the choice of investigations is limited. Therefore, the suggestions we make here are based on the best available alternative sources, which, notwithstanding differences in pathophysiology, are three peer-reviewed UK guidance documents: the UK Inflammatory Bowel Disease guidelines,[76] the British Society of Gastroenterology guidelines on the management of chronic diarrhoea,[77] and guidance on managing acute and chronic gastrointestinal symptoms in cancer treatments.[13]

Immediate laboratory investigations

Patients with acute grade 3–4 diarrhoea admitted to hospital require urgent stool culture for microscopy

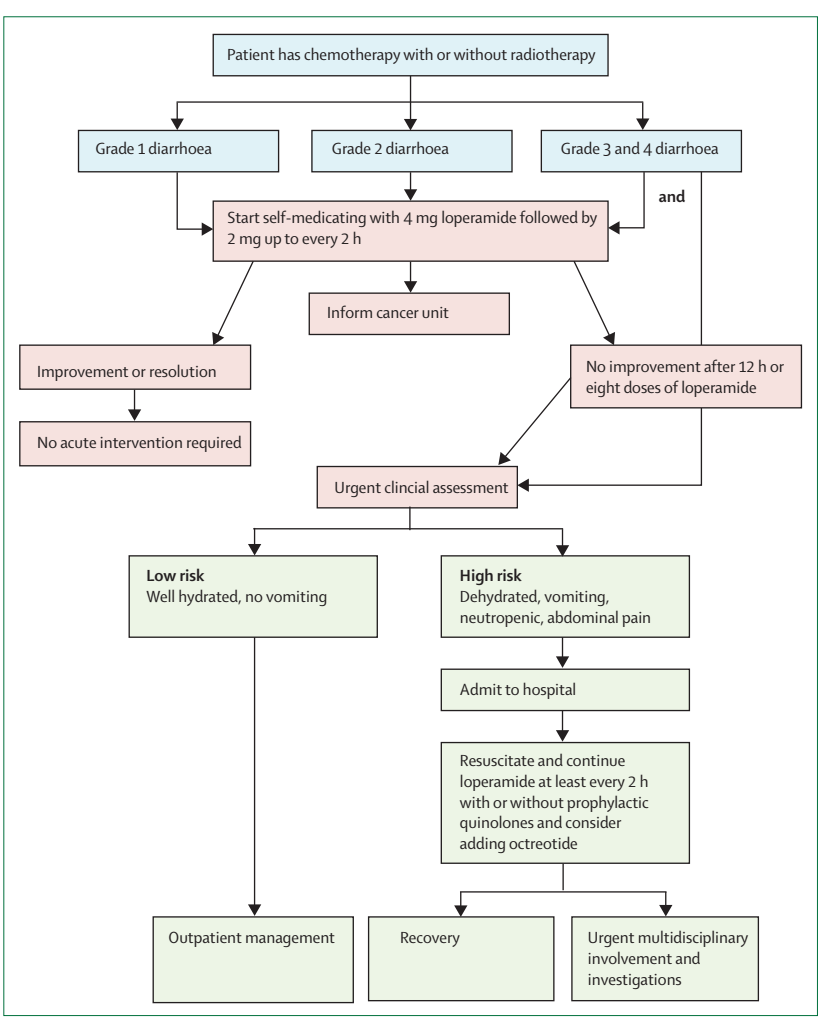

Figure: **Flow diagram of action required for managing chemotherapy-induced diarrhoea**

and testing for *Clostridium difficile*. Blood samples should be tested for full blood count, urea and electrolytes, liver function, glucose, thyroid function, and C-reactive protein. If a patient is hypotensive or tachycardic, acid base balance and lactate concentrations should also be measured in blood. Abdominal radiography should be done and frequency of defecation and type of stool passed should be recorded on a stool chart.

If at any time a patient shows signs of peritonism (guarding, rebound tenderness), CT of the abdomen is required to assess the extent of involvement of the small and large bowel, exclude the possibility of neutropenic enterocolitis, and detect complications (eg, perforation, abscess, and pancreatitis). Surgery for these complications carries a high risk and should be performed only in exceptional cases when there is no alternative. Patients should, however, be reviewed by an experienced gastrointestinal surgeon at the earliest opportunity.

If symptoms have not settled within 24 h of intensive therapy with loperamide and octreotide,[47] biochemistry and full blood count should be repeated and endoscopy should be done that includes duodenal biopsy and aspirate. Biopsy should be done of any small ulcers or erosions seen in the upper gastrointestinal tract, as these might indicate viral infection, especially cytomegalovirus infection.[13] Aspirate should be assessed to exclude small bowel bacterial overgrowth and parasite infection. Platelet infusion should be available for patients with platelet counts lower than 50–80 000 cells per µL in case of severe bleeding from biopsy sites. Endoscopy of the lower gastrointestinal tract is contraindicated if there is any suggestion of neutropenic enterocolitis (also known

	Indication	Mode of action	Dosing	Administration	Caution
Loperamide [89]	First-line treatment of diarrhoea	A synthetic opiate that has direct effects on smooth muscle, which decreases motility and increases anal sphincter tone; minimum absorption and no central activity	In patients with diarrhoea, initial 4 mg dose followed by 2 mg every 2–4 h (higher frequency for persistent diarrhoea) or after every loose stool (maximum 16 mg per day); for increased physiological benefit take 30 min before eating four times daily to slow the gastrocolic reflex (no maximum dose but >16 mg per day might not add benefit)	Oral tablets or liquid preparation; the latter might have faster onset of action and allows finer dose adjustment than tablet; effectiveness is increased substantially if taken 30 min before food	No systemic effects but aggressive dosing risks paralytic ileus
Codeine	Alternative to loperamide, no evidence for its use in chemotherapy-induced diarrhoea	Opiod that works through possibly a central and a local mechanism to delay transit through the small and large bowel	15–60 mg maximum four times per day	Oral	Can cause dose-limiting nausea, flatulence, and sedation
Octreotide [86,90–92]	Grade 1–2 high-risk or persistent diarrhoea despite loperamide, or first line in grade 3–4 diarrhoea	Somatostatin analogue that decreases hormone secretion (eg, vasoactive intestinal polypeptide), reduces motility and pancreatic secretions and promotes absorption	100 µg three times daily; increase if no improvement after 24 h (maximum 500 µg per day) for intractable diarrhoea; in severely ill patients start at 500 µg three times daily	Subcutaneous injection (preferred) or intravenous injection or infusion (25–50 µg/h)	May reduce insulin requirements in patients with type 1 diabetes and might precipitate steatorrhoea
Budesonide [93–95]	Second-line therapy for persistent grade 1–2 uncomplicated diarrhoea refractory to loperamide	Topically active corticosteroid that might restore mucosal function and fluid absorption; a 90% first-pass effect in the liver results in low systemic availability	9 mg once daily for 3–5 days	Oral	Systemic effects are possible, risk of infection might be increased, and viral or bacterial infections might be exacerbated
Atropine [96]	Acute diarrhoea starting <24 h after irinotecan administration caused by inhibition of acetylcholinesterase	Competitive inhibition of acetylcholine at the muscarinic receptors	0·25 mg for prophylaxis or treatment of cholinergic effects of irinotecan	Subcutaneous or intravenous injection	Caution required in elderly patients and those with Down's syndrome; contraindicated in patients with glaucoma
Antibiotics [8,97–100]	Grade 3–4 diarrhoea associated with neutropenia in outpatients	Broad spectrum antibiotic that targets small intestinal bacterial overgrowth of aerobic and anaerobic organisms	Prophylactically, eg, oral ciprofloxacin 250–500 mg twice daily; as treatment, eg, 400 mg norfloxacin twice daily, 600 mg rifaximin daily, 100–200 mg doxycycline daily, or 400 mg metronidazole three times daily for 7–14 days	Oral*	Might cause diarrhoea and increase risk of *Clostridium difficile* colitis; choice should be based on patients' allergies and resistance patterns
Bile acid sequestrants [13,51]	Diarrhoea or steatorrhoea caused by bile acid malabsorption	Prevent water secretion into the colon induced by non-sequestered bile acids	Colestyramine initially 2–4 g per day taken with food (maximum dose 24 mg per day) or colesevelam up to 6 × 625 mg three times daily with food; accompany with low-fat diet	Oral	Ideally, start after SeHCAT scan or C4 blood test; risk of drug interaction with other orally administered medication; colestyramine often poorly tolerated

(Table 3 continues on next page)

as typhlitis).[13] In these patients CT scanning should be done instead. If there is no typhlitis, flexible sigmoidoscopy should be done at the same time as the upper-gastrointestinal endoscopy. The pathologist should be asked to comment specifically on the biopsy samples taken with reference to the possibility of infection with cytomegalovirus and *C difficile*. *C difficile*-toxin-negative colitis might be difficult to detect as neutrophils are needed to produce typical pseudomembranes, and numbers of neutrophils are low in neutropenic paients.[13] If ulceration is substantial, PCR for cytomegalovirus could be requested or empirical anticytomegalovirus therapy could be started.[76]

If symptoms have not settled within 48 h, CT scanning of the abdomen is required, after which the patient requires review by a gastroenterologist. Additional investigations, such as amylase concentrations in serum or pancreatic elastase-1 in the stool, should be considered to exclude pancreatic insufficiency, particularly if the patient has had previous radiotherapy or surgery to the pancreas or has a history of excessive alcohol intake. A SeHCAT scan will exclude bile acid malabsorption. Alternatively, a bile acid sequestrant can be tried empirically. Small bowel bacterial overgrowth should be investigated, for instance with a glucose hydrogen methane breath test, or empirical antibiotics and a trial of lactose-free diet considered.

Management

Acute fluid resuscitation

Patients frequently become dehydrated because of diarrhoea with or without vomiting. Assessment of fluid balance is crucial, but is often done poorly. Physiological requirements must be established before and reviewed regularly after replacement of fluids is started. Patients with severe chemotherapy-induced diarrhoea can lose up to 4–6 L of diarrhoea per day. Consequently, patients might be severely hypovolaemic, which can make exclusion or differentiation from sepsis difficult (they might coincide).

	Indication	Mode of action	Dosing	Administration	Caution
(Continued from previous page)					
Oral rehydration therapy	Grade 1–2 diarrhoea	Increases sodium and water absorption in small intestine	Five sachets in 1 L water†, but consider 8–10 sachets in 1 L is for replacing electrolye deficits	Oral	Rehydration should occur slowly (over 12 h) in patients with hypernatraemic dehydration
Electrolytes					
Magnesium	Magnesium concentration <0·4 mmol/L or, in symptomatic patients, magnesium 0·4–0·7 mmol/L	Electrolyte supplementation	If serum electrolyte concentrations suggest deficiency of at least 160 mmol/L, give 24 mmol oral magnesium in divided doses; for severe symptomatic hypomagnesaemia give 5 g magnesium sulphate (equivalent to 20 mmol magnesium) in 1 L 0·9% saline or glucose (5%) intravenous infusion over 3 h‡	Oral (preferred) as 50% of an intravenous dose is lost in urine (the rapid rise in magnesium concentration reduces renal retention)	No oral preparation of magnesium is licensed in the UK; monitor cardiac function during intravenous infusions; patients with impaired renal function are at increased risk of hypermagnesaemia; successful magnesium replacement requires normal calcium concentrations; concentrations in serum might not reflect total body stores; oral magnesium frequently causes diarrhoea (magnesium oxide or magnesium aspartate are tolerated best); oral magnesium has multiple interactions
Calcium	Adjusted calcium concentration <2·20 mmol/L	Electrolyte supplementation	10–50 mmol calcium daily; for severe acute hypocalcaemia 2·2–4·5 mmol calcium as a slow intravenous injection over 5–10 min into a large vein, followed by intravenous infusion to prevent recurrence, and oral calcium thereafter as appropriate; check for correction of magnesium if secondary to hypomagnesaemia	Oral preferred in asymptomatic patients; if intravenous, monitor with electrocardiogram; correct calcium and magnesium together	Risk of cardiac arrhythmias; existing hyperphosphataemia may result in calcium precipitation; if the patient is septic or has renal failure, metabolic acidosis might be present and calcium should be replaced to the normal range before the acidosis corrects, as failure to do this might result in convulsion or cardiac arrest; causes of hypocalcaemia include septic shock, hypomagnesaemia, and use of diuretics or bisphosphonates
Phosphates	If severe (<0·3 mmol/L) or moderate (0·3–0·6 mmol/L), consider treatment; hypomagnesaemia and hypocalcaemia might predispose patients to hypophosphataemia	Electrolyte supplementation	0·2–0·5 mmol/kg per day (maximum 50·0 mmol in 24 h)	Consider oral administration if phosphate 0·3–0·6 mmol/L and patient asymptomatic	Risk of severe renal impairment in patients with hypocalcaemia; oral supplementation can cause diarrhoea, nausea, and vomiting; oral supplements should not be used with aluminium, calcium, or magnesium salts
Probiotics[46]	Prevention of diarrhoea	Unknown	Various *Lactobacillus* spp	Oral	Risk of invasive potential in the profoundly immunosuppressed

SeHCAT=23-seleno-25-homo-tauro-cholic acid. C4=7-α-hydroxy-4-cholesten-3-one. *Intravenous administration is rarely required for prophylaxis. †Licenced dose. ‡Avoid use of 5% dextrose in hypovolaemic patients.

Table 3: **Review of potential antidiarrhoeal interventions**

Panel 3: Recommendations for assessment and management of patients with chemotherapy-induced diarrhoea

Recommendation 1: assessment of patients

- All units with potential to be involved in the management of chemotherapy-induced diarrhoea (eg, oncology, gastroenterology, intensive care) should agree a robust pretreatment strategy for patients at high risk of toxic effects and provide rapid access to appropriate investigations and opinions if toxic effects develop
- Create a risk assessment checklist for use before chemotherapy is started
- Check that high-risk patients understand the risk and their responsibilities clearly
- In patients with pre-existing bowel dysfunction (eg, irritable bowel syndrome, bile acid malabsorption, coeliac disease, or inflammatory bowel disease), consider pretreatment reassessment of bowel function and diagnoses by a gastroenterologist
- In patients who have undergone previous colorectal surgery resulting in bowel dysfunction, consider pretreatment assessment of bowel function by a gastroenterologist
- If the patient is malnourished or at nutritional risk before the start of treatment (body-mass index <18 kg/m² or >5% weight loss in previous 3 months), arrange a dietetic review before starting chemotherapy
- If the patient has a stoma, ensure he or she can assess changes in output and education is given about possible actions if output does change

Recommendation 2: requirements for urgent referral of patients with diarrhoea

Before chemotherapy

- Specialist nurse for patients at high risk of chemotherapy-induced diarrhoea
- Dietitian for patients with body-mass index <18 kg/m² or >5% weight loss in previous 3 months
- Stoma nurse for patients at risk of high output from a stoma
- Gastroenterologist for bowel dysfunction affecting quality of life

During chemotherapy

- Gastrointestinal surgeon if the patient shows signs of guarding, rebound or peritonism or if imaging suggests neutropenic enterocolitis or perforation
- Gastroenterologist for patients with steatorrhoea, nocturnal waking for defecation, urgency of defecation or faecal incontinence, or two or more episodes of diarrhoea and no response to treatment after 3 days
- Intensivists (possibly with nephrologists) for patients with a high lactate concentrations, hypotension, and tachycardia, and no or poor response to fluid loading or who have possible acute kidney injury and oliguria

Recommendation 3: research priorities for the future

- Develop definitions of grades of diarrhoea, which are rooted in clinical outcomes
- Identify the gastrointestinal physiological abnormalities induced by different chemotherapy agents
- Enrol patients in randomised trials of antidiarrhoeal regimens to explore the benefits of different doses
- Investigate the role of antibiotics
- Develop the use of other antidiarrhoeal strategies (eg, use of clays or prebiotics)
- Investigate the impact on patients

If hypovolaemia is unclear, the response to a 500 mL bolus (250 mL in patients with a history of cardiac failure) of a balanced crystalloid (0·9% saline is preferred if potassium concentrations are higher than 5·5 mmol/L or if oliguric acute kidney injury is possible) or colloid (eg, gelatine or hydroxyethyl starch) should be assessed to see if blood plasma volume increases. Hypotonic fluids such as 4% dextrose/0·18% saline or 5% dextrose are never appropriate for fluid resuscitation. If 0·9% saline is used initially, patients should be switched to a balanced salt solution, such as Ringer's lactate and acetate or Hartmann's solution, once potassium concentrations are known and good urine output is established.

In severely ill patients who are hypotensive, tachycardic, and potentially septic and have high lactate concentrations, an initial fluid bolus of 20 mL/kg should be given.[78] A balanced salt solution should be used instead of 0·9% saline to lessen the risk of inducing hyperchloraemic acidosis, except in patients who are hypochloraemic, for instance due to vomiting. Several litres of fluid might be required over the first 3–4 h. If after fluid loading there is no haemodynamic improvement, help should be urgently sought (figure). Consideration can be given to the insertion of a central venous pressure line and urinary catheter to aid monitoring, after assessment for the risks of infection and bleeding from thrombocytopenia versus the benefits of objective fluid replacement.[78,79] Fluid balance requires close monitoring, but provided central venous pressure is satisfactory, urine output is consistently more than 0·5 mL/kg per h, and lactate concentration is not rising, the rate of fluid resuscitation should be tailored to avoid fluid overload.

If at any time a patient develops oliguric acute kidney injury (less than 0·5 mL/kg per h) despite adequate volume resuscitation, as judged by central venous pressure, further fluid resuscitation might result in pulmonary oedema. In such cases the urgent advice of intensive-care experts or nephrologists must be sought.

If a patient shows a good clinical response, fluids may be continued until he or she returns to normal blood volume and circulation, when an appropriate regimen to replace ongoing fluid losses should be started.

Medications

Loperamide was designed as an antidiarrhoeal with minimum systemic absorption. Systemic bioavailability when taken orally is 0·3% because it is charged at physiological pH and, therefore, more than 90% leaves the stomach within 1 h and is excreted unchanged in faeces.[80] The small amount of absorbed loperamide is prevented by P-glycoprotein from crossing the blood–brain barrier.[81] Loperamide inhibits contraction of the gastrointestinal longitudinal smooth muscle activated by the myenteric plexus, which uses actylcholine as the main neurotransmitter. Loperamide binds with high affinity and is an agonist at μ2 opiate receptors, and its effects are reversed by naloxone.

Although loperamide is frequently effective, much of the evidence on how best to use it is weak and, frequently, pragmatic decisions about interventions are made. A starting dose of 4 mg followed by 2 mg every 2 h after an episode of diarrhoea are often recommended. If the patient can still eat, however, this treatment might be more effective if taken 30 min before food.[82,83]

The second main therapeutic option is octreotide. How this drug works physiologically is not clearly understood. Decreased mesenteric blood flow might be involved.[84] A phase 1 dose-finding study explored doses of 50–2500 µg three times daily and found that doses of 500 µg or higher correlated with more than 75% of patients having complete resolution of chemotherapy-induced diarrhoea.[85] Octreotide was compared with loperamide in patients with fluorouracil-induced diarrhoea. 41 patients received 4 mg loperamide, followed by 2 mg four times daily and 20 received 100 µg octreotide twice daily. Diarrhoea resolved in 19 (95%) patients in the octreotide group, compared with only three (7%) in the loperamide group.[86] In 42 patients receiving pelvic radiation and fluorouracil, patients refractory to 4 mg loperamide four times per day were treated with 150 µg octreotide three times per day, and 34 (81%) improved within 3 days and avoided hospital admission and treatment delays.[87]Although the starting dose tested was 100 µg twice daily, guidelines recommend the use of 500 µg twice daily in severely dehydrated patients.[8] Prophylactic long-acting octreotide analogues were not helpful in a randomised trial in a similar group of 215 patients.[88]

Patients who are not hypotensive may be managed less intensively. If the patient has already self-medicated intensively with loperamide without success, octreotide could be considered even in the ambulatory setting. Information on other potential medications and previous guidelines are provided (table 3, appendix).

Conclusions

In view of the frequency of diarrhoea induced by cancer treatment, the dearth of clinically relevant studies is worrying. Diarrhoea due to chemotherapy, radiotherapy, and biological therapy is frequently progressive and, therefore, requires prompt and effective management to prevent escalating severity. Crucial to this process are the patients and their families. Patients must be given the confidence to self-medicate with loperamide and, if this treatment fails, to contact their cancer team or visit an emergency department. Doctors need to understand how to rapidly assess and, if necessary, resuscitate patients and escalate management.

Clinicians must not stop antidiarrhoeals even if sepsis is suspected. Although infectious agents can cause diarrhoea in patients receiving chemotherapy, the probability of enteric infection seems to be low, although *C difficile* should be excluded quickly. Suspected possible infections can be treated as long as the diarrhoea is also treated actively. Octreotide, which is probably underused, should be considered as part of the acute management strategy despite little systematic research of this drug having been done in the past 20 years. For patients who do not improve, expert gastroenterological advice is needed early and we encourage medical oncology units to develop fast track pathways with specific gastroenterologists so that they can build expertise in the management of these patients (panel 3). In immunosuppressed patients other causes of diarrhoea must be considered, and few patients might need rapid access to appropriate invasive tests. A cohesive, uniform approach will almost certainly improve patients' care and would set a foundation on which to do clinical trials (panel 3).

Search strategy and selection criteria

Searches were done in Medline, Embase, Web of Science, the Cochrane library, and major conference reports and supplemented with wider internet searches. No date restrictions were applied, but we limited search results to abstracts and articles published in English. The search terms included free-text words and combinations of the following terms "chemotherapy", "cancer", "diarrhoea", "guidelines", "steatorrhoea", "biological agent", "tyrosine kinase inhibitor", "monoclonal antibody", "toxicity", "loperamide", "octreotide", "antibiotics", and "corticosteroids". Animal and paediatric studies were excluded other than for background information. The abstracts of identified articles were reviewed for relevance and full articles were retrieved for those judged appropriate. Reference lists of retrieved articles were reviewed for additional citations. Retrieved articles were classified by level of evidence: level A, randomised controlled trials; level B, outcomes research; level C, case series; and level D, expert opinion and physiological and laboratory studies. Recommendations were developed on the basis of evidence from randomised controlled trials where possible and otherwise on that from non-randomised studies or expert opinion.

Contributors

All authors except WA were present at a 1 day meeting during which the need for new guidance on chemotherapy-induced diarrhoea was established and draft headings for this Review were agreed. All authors contributed to the literature search and writing of the paper by allocation of topics. JA prepared the drafts, which were reviewed by all of the authors.

Declaration of interests

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