Kent and Medway Cancer Collaborative

Guidance Document

Systemic Anti-cancer Therapy Care Pathway

Guidelines for the management of systemic anti cancer therapy induced diarrhoea

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Contents

1 MANAGEMENT OF SYSTEMIC ANTI CANCER THERAPY INDUCED DIARRHOEA

1.1 Background

Diarrhoea is a serious potential consequence of systemic anti-cancer therapy. It is often severe enough to require a dose reduction of, a delay in, or a discontinuation of systemic anti-cancer therapy.

Anti-cancer drugs are mostly anti-proliferative agents. These drugs however are also toxic to other normal proliferating tissues of the body such as the gut mucosa.

Systemic anti-cancer therapy induced diarrhoea occurs due to a combination of factors, including an imbalance between absorption and secretion in the small bowel.

Systemic anti-cancer therapy produces acute damage to the intestinal mucosa that is characterized by necrosis of the cells that line the intestinal crypt, resulting in extensive bowel wall inflammation. Without crypt cells, replacement of cells in the intestinal villi is hampered; the mucosa becomes oedematous resulting in a decreased absorption surface (Holmes 1990).

Some newer systemic anti-cancer therapies (such as the anti-CTLA4 immunotherapy ipilumumab, or the anti-PD-1 immunotherapies pembrolizumab or nivolumab) cause diarrhoea through an immune mediated adverse effect, which can be severe, and sometimes delayed. Specific management is required for these agents. See relevant section below, and guidelines within chemotherapy protocols and/or relevant oncological treatment guidelines.

The degree and duration of diarrhoea depends on the agent, dose, nadir and frequency of systemic anti-cancer therapy administration. It is not only an inconvenient side effect of cancer treatment, but can be life-threatening if not managed adequately.

Drug related side effects may also necessitate dosage reductions or treatment interruptions that may compromise treatment efficacy.

Proper attention to communication with patients regarding bowel symptoms during treatment and rapid treatment of appropriate supportive and dietary interventions are key factors in optimizing control of systemic anti-cancer therapy induced diarrhoea (Leonard 2003).

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. Diarrhoea may increase the risk of sepsis if the patient is neutropenic.

1.2 Prevention of SACT induced diarrhoea

Various therapies have been suggested for the treatment of chemotherapy induced diarrhoea, but evidence is lacking. No preventative treatments are therefore suggested.

1.3 Symptoms

Diarrhoea is an increase in stool volume and liquidity, resulting in more bowel movements per day, over and above the patients' normal pattern.

Patients may have abdominal pain, cramping, urgency of defecation, change of colour and smell of faeces, proctitis, and anal or perianal skin breakdown. Patients with a stoma may also need to change their appliances more frequently and skin excoriation may occur.

All these factors can lead to weight loss and malnutrition.

Severe or extended episodes of diarrhoea may result in dehydration, electrolyte imbalance and malnutrition. Symptoms of mild low sodium levels can include tiredness, disorientation, headache, muscle cramps and nausea. Severely low levels of potassium can cause abnormal heart function.

1.4 Initial assessment

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.
All patients who receive systemic anti-cancer therapy should be assessed at baseline for normal pattern, and at each treatment visit, using a standardised assessment tool such as the NCI Common Toxicity Criteria (see below), and the Bristol Stool Chart (Appendix A).

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea (without stoma)	None	Increase of <4 stools per day	Increase of <4-6 stools/day or nocturnal stools	Increase of >7 stools/day or incontinence +/- parenteral support	Requires intensive support or hemodynamic collapse
Diarrhoea (with stoma)	None (normal emptying times)	Mild increase in loose watery output (>1-2x)	Moderate increase in loose watery output (>3-4x)	Severe increase in output, interfering with ADL	Requires intensive support or hemodynamic collapse

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 and afebrile, has not yet had any antidiarrhoeal medication, and can be reviewed daily.

Warning signs associated with diarrhoea include:

- abdominal cramps not relieved by loperamide
- an inability to eat
- increasing fatigue
- increasing weakness
- chest pain
- nausea not controlled by antiemetic
- vomiting
- dehydration accompanied by reduced urine output
- fever (>/= 38.5^0c)
- gastrointestinal bleeding
- previous admission for diarrhoea

1.5 Patient education

Before starting any systemic anti cancer therapy that is known to have the potential to cause diarrhoea, patients must be informed of this risk, and what actions they should take if they experience diarrhoea. A discussion should take place with the patient to establish what each individual patient's normal bowel function was before treatment and discuss how function could change with treatment.
They should be encouraged to keep a record about the duration of diarrhoea, approximate stool volume and other co-existing symptoms which may increase their risk e.g. decreased oral intake, or blood in stool.
In addition patients should be asked to assess the impact of the episodes on their ability to carry on with normal activities.
Patients can be encouraged to self-medicate with anti-diarrhoeal mediation, but should keep a record of their drug use. The National Chemotherapy Advisory Group report states that health professionals should discuss

with patients when to start treatment and give instructions about continuation. Patients should telephone the 24 hours hotline for advice to confirm the severity and whether face-to-face assessment is required.
After starting loperamide, patients need to know when they must contact their chemotherapy unit (as a guide, if taking eight 2 mg tablets in 24 h has had no effect).

1.6 Management

The most important decision is whether the patient can be managed as an outpatient or needs admission for fluid resuscitation. 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 antidiarrheal medication, and can be reviewed daily.

Patients with acute grade 3–4 diarrhoea admitted to hospital should have the following investigations: stool culture for microscopy and testing for *Clostridium difficile*., FBC, U&E, LFTs, glucose and C-reactive protein (plus acid base balance and lactate concentrations if a patient is hypotensive or tachycardic), abdominal radiography where indicated, and frequency of defecation and type of stool passed recorded on a stool chart. If the patient shows signs of guarding or rebound tenderness, a CT scan should be considered
if symptoms have not settled within 24 h of intensive therapy with loperamide and octreotide, biochemistry and full blood count should be repeated and for consideration of endoscopy referral if indicated (including duodenal biopsy and aspirate).

All patients with diarrhoea should be started on loperamide 4mg initial dose followed by 2mg every 2 hours. If there is no improvement after 12 hours or after 8 doses of loperamide, patients should be referred for clinical assessment. High risk patients (dehydrated, vomiting, fever, neutropenic or with abdominal pain) should be admitted to hospital. Patients should receive fluid resuscitation and loperamide should be continued every 2 hours. Consideration should be given to prophylactic quinolones (in line with Trust policy) and consider adding octreotide.

Patients treated as an out-patient should be given appropriate dietary advice, including appropriate fluids to drink and advice on oral electrolyte re-hydration, if required. They should aim to drink between 2-3 litres of fluid per day, to avoid dehydration.
They should be encouraged to eat small frequent amounts of low fibre foods such as rice, pasta, white bread, chicken and white fish. **Greasy or fried foods, raw vegetable or fruit, granary breads, cereals, and spicy foods should be avoided. In addition lactose containing foods and excessive alcohol may exacerbate diarrhoea.** After 24 hours of treatment with loperamide (initial dose of 4mg, followed by 2mg after every unformed stool, up to a maximum of 16mgs in 24hrs) , if the diarrhoea has resolved, Loperamide should be stopped following a 12-hour diarrhoea-free interval, and dietary advice given.

After 48 hours of treatment with Loperamide, if diarrhoea remains unresolved, regardless of the CTC grade, patients should be assessed by a doctor and have FBC and U&E's checked and a stool specimen collected for blood/infection profile. Fluids and electrolytes should be replaced as necessary and medical management reviewed.

Codeine Phosphate 30mg QDS can be prescribed instead of Loperamide or added to Loperamide when control is not achieved with Loperamide alone.

Octreotide should be considered if diarrhoea is grade 1–2 and patient is high-risk or there is persistent diarrhoea despite loperamide, or for first line treatment of grade 3–4 diarrhoea. Usual starting dose 100µg tds given subcutaneously or intravenously.

Budesonide may be considered second-line for persistent grade 1–2 uncomplicated diarrhoea refractory to loperamide. Usual dose 9mg once daily for 3-5 days.

Antacids with Magnesium should be avoided as they can increase diarrhoea.

Metoclopramide has pro-motility qualities, so should be avoided in systemic anti cancer therapy induced diarrhoea. An alternative anti-emetic should be prescribed.

If a patient has suffered from diarrhoea in previous cycles, provide a supply of loperamide for self-medication.

1.7 DPD deficiency

5-FU and Capecitabine are pro-drugs, thus requiring intracellular conversion into cytotoxic metabolites for anti-tumour effects to take place.
Dihydropyrimidine dehydrogenase (DPD) is the enzyme responsible for catabolism of 5-FU in both oral and intravenous forms, and is responsible of >85% of 5-FU elimination (Milano 2000). DPD deficiency due to genetic defect gives rise to severe 5-FU toxicity from reduced catabolism, as this resulting reduced drug clearance results in markedly increased 5-FU exposure. This pharmacogenetic 'DPD syndrome' manifests typically as severe or fatal diarrhoea and mucositis/stomatitis and neutropenia/myelosupression. These side-effects are observed with the first or second dose of 5-FU (Lim, Wan-Teck 2004).

1.8 Irinotecan induced diarrhoea

Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of Irinotecan and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleukocytosis, those with WHO performance status ≥ 2 and women. If not properly treated, diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.

The currently recommended antidiarrheal treatment consists of high doses of Loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should Loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the antidiarrheal treatment, a prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea, in the following cases:

- Diarrhoea associated with fever
- Severe diarrhoea (requiring intravenous hydration)
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose Loperamide therapy

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles.

1.9 Management of Immune-mediated GI adverse reactions (e.g with the anti-CTLA4 immunotherapy ipilumumab, or the anti-PD-1 immunotherapies pembrolizumab or nivolumab)

Some newer systemic anti-cancer therapies (such as ipilumumab, pembrolizumab, nivolumab) cause diarrhoea through immune mediated side-effects such as colitis which can be severe, and sometimes delayed.

Patients should be issued with the appropriate Patient Alert Card and monitored closely for immune related adverse effects during treatment and following the end of treatment (as a delayed effect can occur). They should be advised to contact the oncology team or 24 hour chemotherapy hot-line immediately they experience any symptoms, as side effects can progress rapidly.
Reference should be made to the relevant chemotherapy protocol and/or oncological treatment guidelines for the management of immune-mediated diarrhoea and corticosteroids should be initiated as appropriate. The decision to use infliximab should only be made by the consultant (with an application made as necessary to the Trust Drugs and Therapeutics Committee), and a retrospective IFR should be completed. Infliximab is contraindicated if there is perforation or sepsis.

2.0 Management of capecitabine induced diarrhoea

Because of the nature of capecitabine treatment (oral and continuing either throughout or for a prolonged period of the treatment cycle), the following should be followed (SmPC accessed Sept 016) in relation to management of the capecitabine treatment:

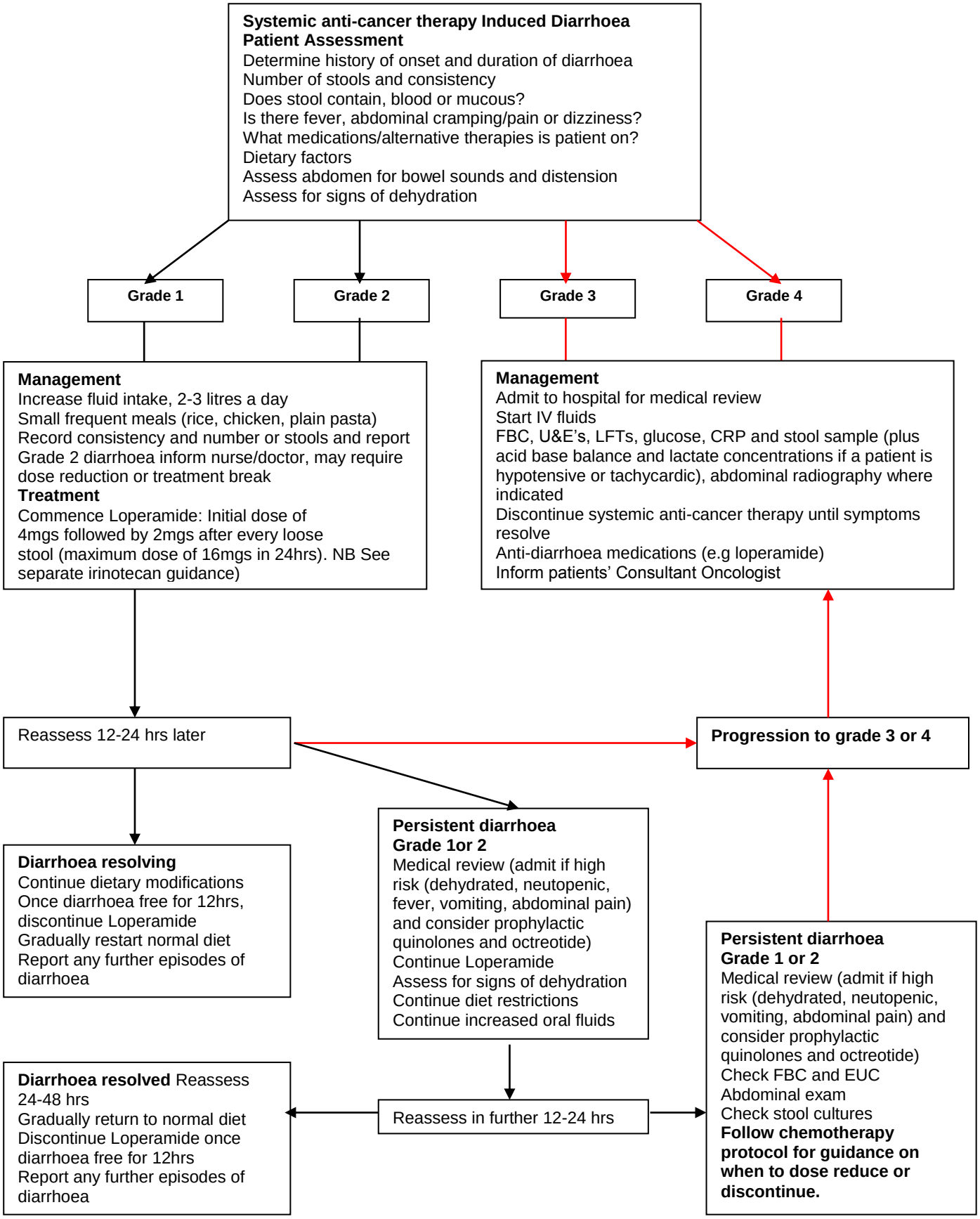
Toxicity grades	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of starting dose)**
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4*		
-1st appearance	Discontinue permanently *or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

APPENDIX A: BRISTOL STOOL CHART

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

APPENDIX B: MANAGEMENT OF DIARRHOEA FLOW CHART



References

Homes S 1990 The Oral Complications of Specific Anticancer Therapy. International Journal of Nursing Studies 28(4) 343-360

Lewis SJ, Heaton KW (1997) Stool form scale as a useful guide to intestinal transit time. Scand. J. Gastroenterol **32** (9): 920–4

Lim Wan-Teck, McLeod, HL, Should Screening for DPD Deficiency Be Mandatory before 5-Exposure? Onkologie 2004;27:531-533

Milano G, McLeod HL; Can dihydropyrimidine dehydrogenase impact 5-fluoracil-based treatment? Eur J Cancer 2000;36:37-42

National Cancer Institute (NCI) 1998 Common Toxicity Criteria Version 2

Saltz, Leonard B May/June 2003 J Support Oncol 2003:1:35-46

Andreyev J, Ross P, Donnellan C, Lennan E, Leonard P, Waters C, Wedlake L, Bridgewater J, Glynne-Jones R, Allum W, Chau I, Wilson R, Ferry D (2014) Guidance on the management of diarrhoea during cancer chemotherapy Lancet Oncol 2014; 15: e447–60

Document Administration

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The document is located in the Kent and Medway Cancer Collaborative office, in hardcopy and in electronic format at www.kentmedwaycancernetwork.nhs.uk

DATE OF NEXT REVIEW

This item is next to be reviewed in September 2018

Revision History

Date	Version	Status	Author	Summary of Changes
1/04/09	V0.1	Draft	Bryony Neame	Words ' systemic anti cancer therapy, cytotoxic and monoclonal' replaced by 'systemic anti-cancer therapy' to reflect NCEPOD report
11/05/09	V2.2	Draft	Bryony Neame	Alterations made to flow chart re stopping systemic anti-cancer therapy if Grade 2 diarrhoea persists as suggested by Dr. Waters
16/07/2012	V3.1	Update	Bryony Neame	Addition of Ipilimumab guidance,
13/09/12	V3.2	Update	Bryony Neame	Addition of Irinotecan SPC guidance as requested by CW
24/3/16	V4.1	Draft	C Waters	Extensive review and update to all sections.
4/5/16	V4.2	Draft	C Waters	Changes made following KMCC chemotherapy group
14/9/16	V4.3	Draft	C Waters	Changes made following distribution to acute oncology group (addition of section on capecitabine)