Kent and Medway Cancer Collaborative

Systemic Anti-Cancer Therapy Care Pathway

Guidelines for the Management of Systemic Anti-Cancer Therapy Induced Diarrhoea

Pathway of Care

Publication date	April 2023
Expected review date	April 2025
Version number	7
Version status	Final

TABLE OF CONTENTS

1.0 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

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, thyroid function, 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 Fluoropyrimidine Induced Diarrhoea and 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 for >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).

All patients being considered for fluoropyrimidine (i.e. capecitabine, 5-fluorouracil) based therapy should undergo pre-treatment pharmacogenomic screening for the four variants of DPYD associated with severe toxicity.

Uridine triacetate (Vistoguard) is an antidote for management of early-onset severe or life-threatening toxicity, including diarrhoea, within 96 hours following 5FU or capecitabine administration. It is not licensed in the UK, but is available on an unlicensed basis via a 24/7 emergency ordering service, via tel 0207 8872235. Blueteq form required.

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 ipilimumab, or the anti-PD-1 immunotherapies pembrolizumab or nivolumab)

Some newer systemic anti-cancer therapies (such as ipilimumab, 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 and the ‘St Luke’s Cancer Alliance Guidelines for Management of Immunotherapy-Related Adverse Events’ for the management of immune-mediated diarrhoea, and initiate corticosteroids 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), funding can be applied for via Blueteq® and an MHRA yellow card should be completed to report the adverse event. Infliximab is contraindicated if there is perforation or sepsis.

NB: The KMCC Chemotherapy Group have reviewed the St Luke’s Cancer Alliance Guidelines for Management of Immunotherapy-Related Adverse Events and with the kind permission of St Luke’s Cancer Alliance, have agreed to adopt these for use within KMCC.

1.10 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 2016) 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%	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1 100%	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 treatment permanently	Not applicable

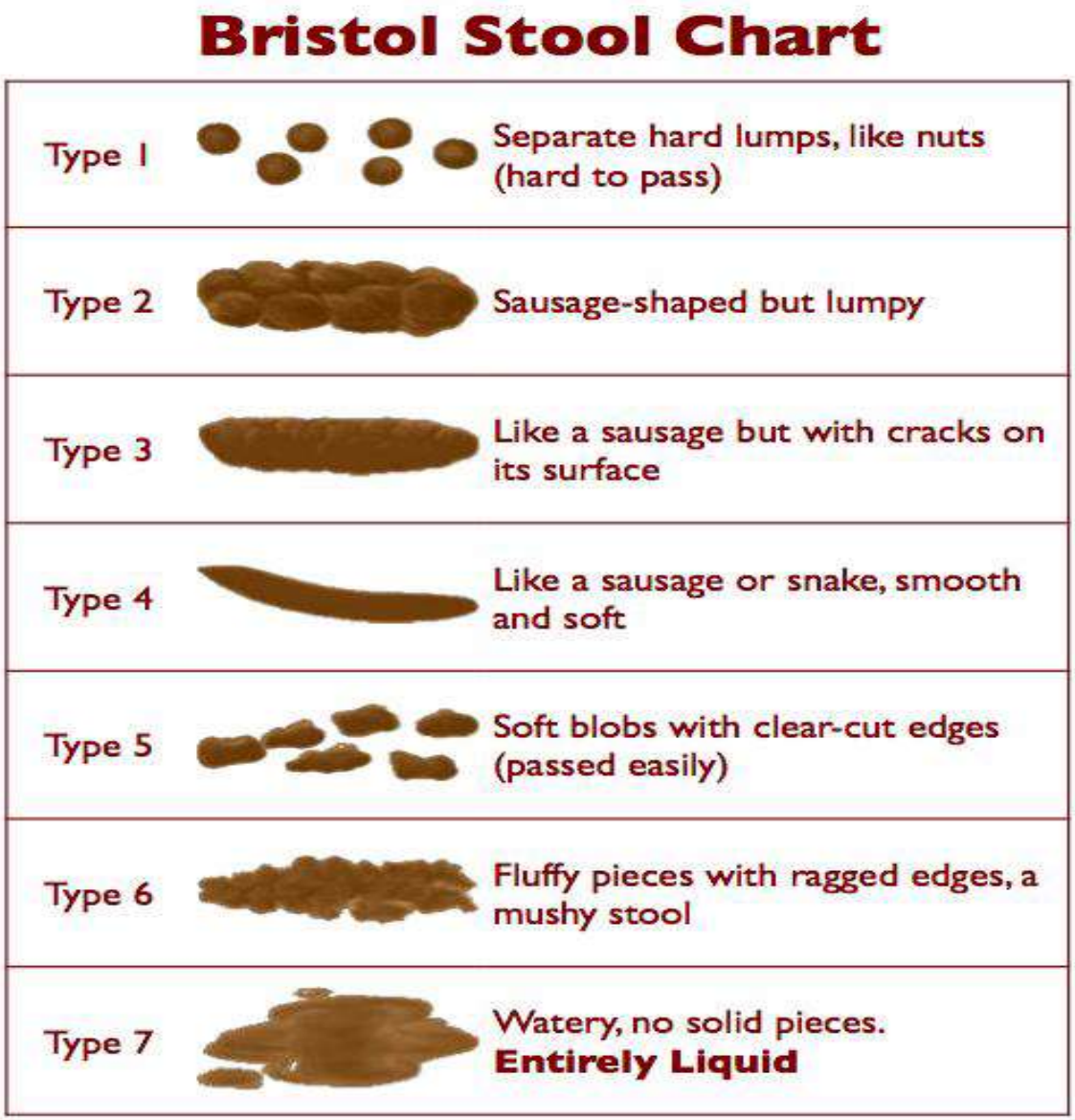
1.11 Management of Neratinib Induced Diarrhoea

Severe diarrhoea and associated dehydration during treatment with neratinib has been reported. Patients must commence prophylactic anti-diarrhoeal medication prior to treatment and continue regularly throughout the first 1-2 months. Dosing should be titrated to achieve 1-2 bowel movements per day. If despite prophylactic therapy and dietary management diarrhoea persists, increase loperamide to a maximum of 16mg per day, or consider the use of budesonide (9mg PO OD for 3-5 days) or octreotide (starting dose 100mcg SC/IV TDS). See chemotherapy protocol for further information.

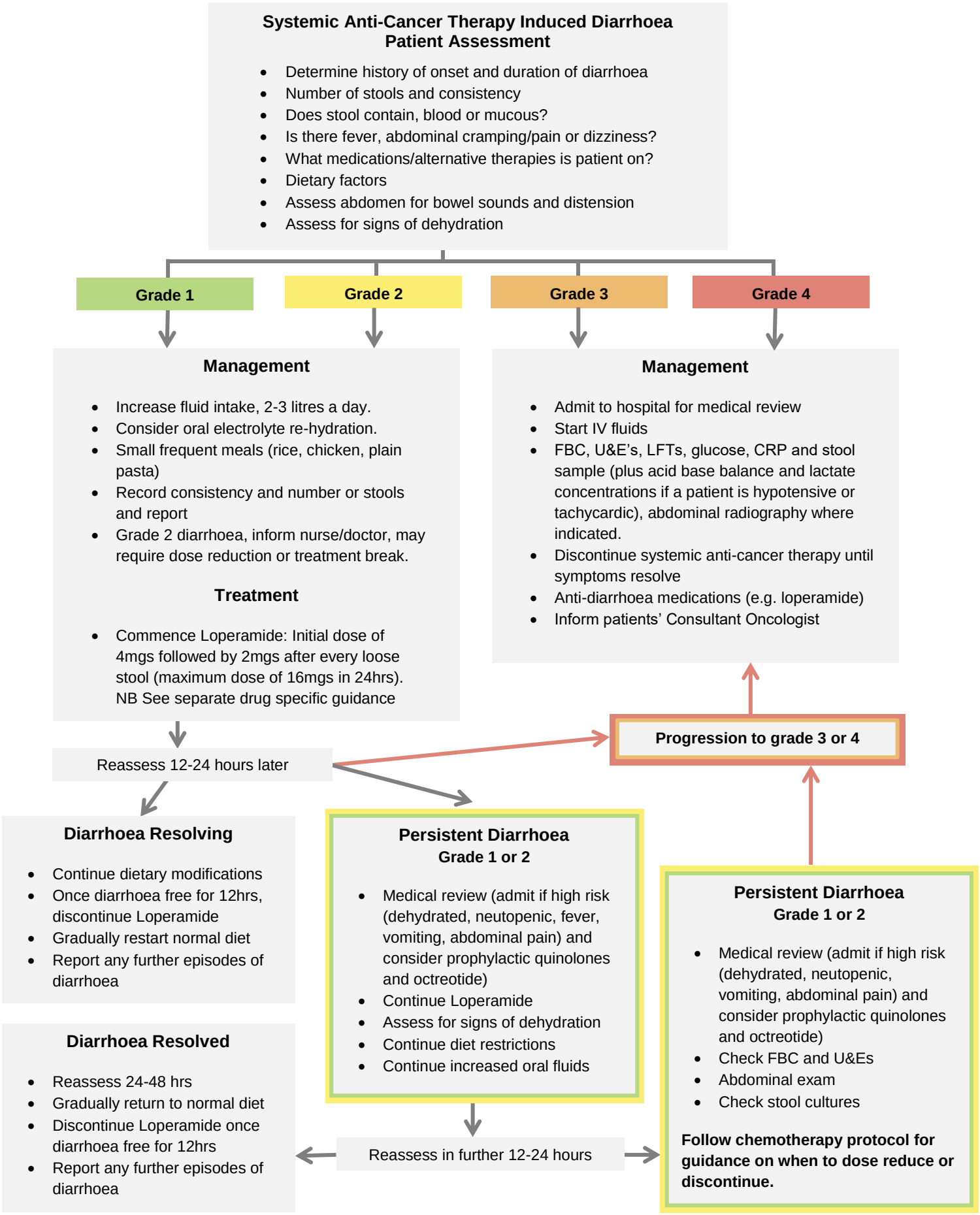
Anti-diarrhoeal prophylaxis:

Duration on treatment	Dose of loperamide	Administration
Week 1-2 (days 1-14)	4mg	Three times a day
Week 3-8 (days 15-56)	4mg	Twice a day
Week 9-52 (days 57-365)	4mg	As needed (not to exceed 16mg per day)

2.0 APPENDIX A: BRISTOL STOOL CHART



3.0 APPENDIX B: MANAGEMENT OF DIARRHOEA FLOW CHART



4.0 REFERENCES

- Can dihydropyrimidine dehydrogenase impact 5-fluoracil-based treatment? **Milano G, McLeod HL** (2000) Eur J Cancer;36:37-42
- Guidance on the management of diarrhoea during cancer chemotherapy Lancet Oncol 2014 **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 (2004)**; 15: e447–60
- J Support Oncol **Saltz, Leonard B** (May/June 2003):1:35-46
- **National Cancer Institute** (NCI) 1998 Common Toxicity Criteria Version 2
- **NHSE: Clinical Commissioning Urgent Policy Statement:** Uridine triacetate for the treatment of patients exhibiting early-onset severe toxicities following 5-fluorouracil or capecitabine administration (all ages) [URN: 1929] (2020)
- Should Screening for DPD Deficiency Be Mandatory before 5-Exposure? **Lim Wan-Teck, McLeod, HL** (2004) Onkologie; 27:531-533
- Stool form scale as a useful guide to intestinal transit time. **Lewis SJ, Heaton KW** (1997) Scand. J. Gastroenterol **32** (9): 920–4
- The Oral Complications of Specific Anticancer Therapy. **Homes S** (1990) International Journal of Nursing Studies 28(4) 343-360
- UK Chemotherapy Board: Personalised Medicine Approach For Fluoropyrimidine-based Therapies

5.0 GLOSSARY

BNF	British National Formulary
BOPA	British Oncology Pharmacist Association
CNB	Cancer Network Board
COSHH	Control of substances hazardous to health regulations.
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
DGT	Dartford and Gravesham NHS Trust
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
EPS	Electronic Prescribing System
FP10(HNC)	Prescriptions issued by hospital doctors for dispensing in the community
GP	General Practitioner
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
IV	Intravenous
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCC	Kent & Medway Cancer Collaborative
KMCRN	Kent & Medway Cancer Research Network
KOMS	Kent Oncology Management System
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NHS	National Health Service
NMP	Non-medical prescriber
NPSA	National Patient Safety agency
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
QSIS	Quality service information system
QST	Quality Surveillance Team
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
SACT	Systemic Anti-Cancer therapy
SACT regimen	Systemic Anti-cancer prescription on the electronic prescribing system
SACT protocol	Systemic Anti-cancer protocol on KMCC website
TTO	Treatment to take home
QVH	Queen Victoria Foundation Trust Hospital East Grinstead

UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

6.0 DOCUMENT ADMINISTRATION

The document is located in electronic format at www.kmcc.nhs.uk/kent-and-medway-cancer-collaborative-kmcc/	
Enquiries:	Caroline Waters. Lead Oncology Pharmacist, Kent ad Medway Cancer Collaborative
Date of Next Review:	April 2025

Revision History			
Date of revision	New Version Number	Nature of Revision	Author
01/04/09	V0.1	Words ' systemic anti-cancer therapy, cytotoxic and monoclonal' replaced by 'systemic anti-cancer therapy' to reflect NCEPOD report	Bryony Neame
11/05/09	V2.2	Alterations made to flow chart re stopping systemic anti-cancer therapy if Grade 2 diarrhoea persists as suggested by Dr. Waters	Bryony Neame
16/07/2012	V3.1	Addition of Ipilimumab guidance	Bryony Neame
13/09/12	V3.2	Addition of Irinotecan SPC guidance as requested by CW	Bryony Neame
24/03/16	V4.1	Extensive review and update to all sections.	C Waters
04/05/16	V4.2	Changes made following KMCC chemotherapy group	C Waters, NCCAG
14/09/16	V4.3	Changes made following distribution to acuteoncology group (addition of section on capecitabine)	C Waters
Sept 2016	V5	Final	
August 2020	V.5.1-5.4	Addition of sections: 1.11 Amendment of sections: 1.7, 1.4 Correction of spelling and grammatical errors Update references	C Waters
October 2020	V6	Reformatted	R Patel
Jan 2023	V6.1-6.2	Draft created MA Section 1.9 updated Reviewed at CGG and approved	C.Waters

April 2023	V7	FINAL	C.Waters CGG