Management of Radiotherapy- and Chemotherapy-Induced Diarrhoea

The Oncology Team must be informed if patients are admitted with diarrhoea whilst on chemotherapy or radiotherapy.

Diarrhoea is classified as an increase of at least 2 to 3 stools per day or causing waking at night or an increase in loose watery stoma output compared with before treatment. If not properly treated, diarrhoea can be life-threatening, especially in a patient who is also neutropenic.

Cytotoxic agents causing diarrhoea
Nearly all cytotoxics have the potential to induce diarrhoea.

Drugs which commonly cause diarrhoea and require specific management are:

- **Capecitabine and 5-FU**
  For patients on continuous 5-FU or capecitabine, chemotherapy must be interrupted for Grade 2 or above diarrhoea. Severe diarrhoea and/or mucositis in the first cycle may be due to DPD deficiency*, in which case severe neutropenia can quickly follow.
  (*A genetic disorder in which there is significantly decreased activity of dihydropyrimidine dehydrogenase, an enzyme involved in the metabolism of active 5FU to inactive metabolites)

- **Idelalisib** – see specific management details in the R-IDelalisib protocol

- **Ipilimumab, Nivolumab and Pembrolizumab**
  This guideline does not apply for these agents - any diarrhoea related to ipilimumab, nivolumab or pembrolizumab requires specialist management by an oncologist experienced in their use, in line with the Alliance ipilimumab, nivolumab and pembrolizumab protocols, and the treating Oncologist must be notified.

- **Irinotecan** - see separate section below

- **Radiotherapy** to the abdomen or pelvis is also associated with treatment-related diarrhoea.

Differential Diagnosis
It is important to exclude other causes of diarrhoea in these patients:

- Infection
- Subacute obstruction, or constipation with overflow (abdominal X-ray if suspicious)
- Steatorrhoea in pancreatic or biliary malignancy
- Hypersecretion of 5-HIAA (carcinoid tumours)
- Previous GI surgery
- Other medicines, e.g. laxatives, bulk agents, prokinetics
- Other co-morbidities, e.g. diverticulitis, Crohn’s disease
- Note that diarrhoea in neutropenic patients may indicate *C. difficile* infection requiring urgent antibiotic treatment.

Grading of Chemotherapy-Induced Diarrhoea

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea (without stoma)</td>
<td>Increase of &lt; 4 stools/day over baseline</td>
<td>Increase of 4-6 stools/day over baseline, or nocturnal stools. Not interfering with daily living activities.</td>
<td>Increase of ≥ 7 stools/day over baseline. Interfering with daily living. Incontinence Hospitalisation</td>
</tr>
<tr>
<td>Diarrhoea (with stoma)</td>
<td>Mild increase in stoma output compared to baseline</td>
<td>Moderate increase in stoma output compared to baseline. Not interfering with daily living activities.</td>
<td>Severe increase in stoma output over baseline, interfering with daily living.</td>
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</tbody>
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Reason for Update: adapted in line with AOS requirements
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Checked by: C Tucker
First Report of Diarrhoea
For patient receiving chemotherapy and /or pelvic or abdominal radiotherapy

Evaluation of the Condition
Onset and duration of diarrhoea: duration > 12 hours take stool sample (exclude C diff)
Number of stools and stool composition (watery, blood)
Assess patient for fever, neutropenic sepsis, abdominal pain, weakness
Assess for evidence of dehydration
Medication history (laxatives, bulking agents, softeners, prokinetics)

General Management
- Stop all lactose-containing products, alcohol and high osmolar supplements
- Eat frequent small meals (bananas, rice, apple sauce, toast, plain pasta)
- Drink 8-10 large glasses of clear fluids a day (e.g. water, clear soup, non-fizzy soft drinks)
- Keep a record of number of stools
- REPORT ANY NEW SYMPTOMS of life threatening potential e.g. fever, dizziness on standing
- For Grade 2+ diarrhoea, withhold cytotoxic chemotherapy and refer to relevant chemotherapy protocol

Grade 1-2 diarrhoea with no complicating signs
Consider investigations, as Grade 3 - 4
Initiate loperamide 4mg, followed by 2mg after every loose stool, up to 16mg daily (N.B. for irinotecan see **) or Codeine phosphate 30-60mg QDS
For patients with an ileostomy, loperamide often needs to be taken routinely before meals;
- contact stoma nurse for specialist advice and management
- loperamide tablets or syrup may be more effective than capsules.

Grade 3-4 diarrhoea or Grade 1-2, with one or more of cramping, fever, sepsis, neutropenia, frank bleeding, dehydration, nausea/vomiting, decreased PS

Investigations
FBC, U&Es, LFTs, Mg
Stool culture, C. difficile
Blood cultures (if neutropenic sepsis suspected)

Consider other causes (see above)

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** Persistent Grade 1 - 2 (no fever, neutropenia, dehydration, melaena)
- Evaluate as outpatient
- Stool culture, C. difficile, FBC, U&E
- Examine abdomen
- Fluids/electrolytes as appropriate
- Stop loperamide and consider initiating budesonide CR capsule 9mg po OD until diarrhoea resolved* (RT induced: continue loperamide for duration of RT***)
- If dietary intake is inadequate for more than 5 days, refer to dietician

** Severe (Grade 3 – 4) or complicated G1-2 (fever, dehydration, neutropenia, melaena)
- Admit the patient to hospital:
  - Consider budesonide CR capsules 9mg po OD until diarrhoea resolved*
  - or initiate octreotide as below
  - IV fluids, and antibiotics as appropriate

Diarrhoea resolved
- Stop loperamide / budesonide after 12 hour diarrhoea-free interval.
  - (RT-induced: continue loperamide for duration of RT***)

Diarrhoea unresolved
- Take stool sample if not previously done

12 – 24 hours later
- Diarrhoea resolved
- Persistent Grade 1 - 2
  - Increase loperamide dose to 2mg every 2 hours.
  - Start prophylactic oral antibiotics as appropriate.
  - N.B. for irinotecan see **

48 hours later

Diarrhoea unresolved
- Octreotide 300mcg/24 hr s/c for 5 days, increased to 600mcg/24 hr if not sufficiently effective.
- Continue IV fluids, review antibiotics and continue as necessary (seek microbiology advice)

Progression to Severe (Grades 3 – 4)
- Admit the patient to hospital
* Patients who achieve a positive response to budesonide may be considered for prophylactic budesonide (9mg po OD for 3 to 5 days) with subsequent chemotherapy cycles. However, this is **not** an alternative to appropriate dose reduction of chemotherapy, according to relevant protocol.

** Irinotecan-induced diarrhoea**

Following treatment with irinotecan, onset of diarrhoea may be acute (< 24 hours after administration) or delayed (> 24 hours after administration).

**Acute onset diarrhoea**

**Cholinergic syndrome** occurs during administration of irinotecan and can be controlled by giving **atropine 0.25mg** subcutaneously at the time of irinotecan administration. Should the syndrome develop a further dose of atropine may be given.

**Delayed onset diarrhoea**

Patients must be made aware of the risks of delayed diarrhoea which can occur more than 24 hours after the administration of irinotecan and at any stage before the next administration.

The risk of diarrhoea is increased in
- Previous abdominal / pelvic radiotherapy
- Patients also receiving 5-FU or capecitabine
- Performance status > 2

As soon as the **first** liquid stool occurs, the patient should:
- Start drinking large volumes of water / electrolytes
- Take **loperamide 4mg** (2 tablets) immediately, followed by **loperamide 2mg** (1 tablet) **every 2 hours** for at least 12 hours and continuing for 12 hours following the last liquid stool.

After **24 hours** of persistent diarrhoea, if no other symptoms or signs of infection:
- Start prophylactic course of **ciprofloxacin 250mg po bd** for 7 days as an out-patient

Patients must be **admitted** if they have
- persistent diarrhoea, > 48 hours, despite loperamide
- severe diarrhoea requiring intravenous hydration
- diarrhoea with fever
- concomitant vomiting

*** Radiotherapy-induced diarrhoea***

- Symptoms typically occur during the third week of radiotherapy (RT). They may then gradually increase in severity, with the peak reaction normally 7-10 days after the end of radiotherapy.
- Anti-motility agents should be continued until the end of treatment and should be tailed off gradually (do not stop abruptly).
- If the lower pelvis is treated (e.g. prostate only fields), patients may experience more of a sensation of tenesmus rather than a change in stool calibre. Fybogel (one sachet daily) may help to bulk the stool and improve symptoms.

**References:**

Benson et al; JCO 2004; 22: 2918 - 2926

Wadler et al; JCO 1998; 16: 3169 – 3178

Lenfers et al; Annals of Oncology 1999; 10: 1251 – 1253

RMH Policy “Management of Chemotherapy Induced Diarrhoea” kindly supplied in 2011

NCI (National Cancer Institute) Common Toxicity Criteria version 4