



Acute Oncology Group
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**ACUTE MUCOSITIS AND
GASTROINTESTINAL
TOXICITY CAUSED BY
RADIOTHERAPY OR
SYSTEMIC ANTI-CANCER
TREATMENT
2019**

Version Control

This is a controlled document please destroy all previous versions on receipt of a new version

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Signature Sheet

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Guidelines for Management of Acute Mucositis caused by Radiotherapy and/or Chemotherapy

Introduction

The current guideline concisely addresses the main types of toxicity of systemic and radiation antineoplastic treatment involving the disruption of the mucosal lining of the gastrointestinal tract.

Mucositis

Mucositis is an acute injury to the mucosal lining of the gastrointestinal or the respiratory tract induced by radiotherapy and/or chemotherapy. Radiotherapy and chemotherapy affect the mucosa directly through the toxic effects on rapidly dividing epithelial stem cells and lead to the interruption of the integrity of the mucosal barrier. Mucositis, which reflects a short-term, self-limited adverse effect of treatment, can affect the entire alimentary tract.

Oropharyngeal mucositis affects on average 35% to 40% of patients receiving cytotoxic chemotherapy. Cytotoxic drugs most commonly associated with mucositis are shown in Table 1. The predilection of some agents such as 5-FU and irinotecan for intestinal, colonic mucositis should be noted.

Chemotherapy-induced mucositis is typically less severe and of shorter duration (3-12 days) than that associated with Radiotherapy or Chemo-radiotherapy.

Radiation induced acute mucositis usually begins in the 3rd or 4th week of radiotherapy when standard fractionation is used; it aggravates towards the end of the treatment and gradually subsides once radiation finishes. The severity of radiation induced mucositis is dose dependent and can last between 3-12 weeks.

The use of concurrent chemotherapy with RT accelerates the onset, exacerbates the severity and prolongs the duration of mucositis. When palliative radiotherapy regimens are employed, typically using lower radiation dosages, mucositis is expected to be less severe and usually begins after completion of the treatment course.

Grading system

Pharmaceutical or radiation injury to the mucosal lining of human organs results in the disruption of the normal function of mucosal cells. It presents with inflammation (pain, swelling, functional disruption) leading to necrosis of mucosal cells (ulceration) frequently aggravated by local infection and ultimately may result in the inflammation and necrosis of the organ wall leading to perforation. Common Terminology Criteria for Adverse Events (CTCAE v4.0) includes grading for oral, pharyngeal, laryngeal, tracheal, rectal, small intestinal, , and anal mucositis as well as for esophagitis, gastritis and colitis, conditions which refer to disruption of the mucosal lining and inflammation of the wall of the respective hollow organs.

The complete list and grading of GI toxicities can be found in: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Adverse Event	1	2	3	4	5
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicate	Life-threatening consequences; urgent operative intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicate	Death
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent operative intervention indicated	Death

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bed

In general, pain and functional disruption of the organ (i.e. difficulty in swallowing / dyspepsia / nausea / vomiting / diarrhoea) can gradually increase in severity. Ulceration may result in bleeding. Life-threatening consequences usually refer to perforation and sepsis. Consequent scarring, damage of adjacent organs (such as salivary glands) and vascular damage may lead to long-term symptoms (dry mouth, chronic diarrhoea, malabsorption, fistulae).

Oropharyngeal Mucositis and Oesophagitis

Table 1 Antineoplastic agents associated with oropharyngeal mucositis

Category	Specific Drugs
Alkylating agents	Busulphan, Carboplatin, Cisplatin, oxaliplatin, Cyclophosphamide, ifosfamide, melphalan, procarbazine, thiotepa.
Anthracyclines	Doxorubicin, Epirubicin, Liposomal doxorubicin, idarubicin, mitoxantrone
Antimetabolites	5-Fluorouracil, Methotrexate, Cytarabine, Capecitabine, Fludarabine, Gemcitabine, Pemetrexed, Hydroxyurea, 6-Mercaptopurine, 60thioguanine, Procarbazine
Antitumour antibiotics	Dactinomycin, Bleomycin, Mitomycin
Taxanes	Paclitaxel, Docetaxel, Cabazitaxel
Topoisomerase inhibitors	Etoposide, Teniposide, Irinotecan, Topotecan
Molecularly targeted agents	Everolimus, Temsirolimus, Sorafenib, Sunitinib, Regorafenib, Cetuximab, Erlotinib, Afatinib, Lapatinib, Palmocilib, Cabozantinib

Symptoms of oral / pharyngeal mucositis include erythema and ulceration (“mouth and throat sores”); difficulty swallowing; pain; lost or altered taste (dysgeusia); excessive secretions that may lead to gagging, nausea, and vomiting; loss of appetite; fatigue; weight loss; and aspiration excessive and viscid mucus in the mouth and throat at later stage.

On examination mild erythema is usually present at the onset of mucositis and is subsequently followed by patchy mucositis which may produce an inflammatory serosanguine discharge and

later confluent fibrinous mucositis. Ulceration, haemorrhage or necrosis is typical for grade 4 mucositis. Oropharyngeal mucositis can be complicated by oral candidiasis and HSV infections.

Mucositis causes a systemic release of cytokines which may lead to fevers and rigors that may be difficult to differentiate from neutropenic fever or sepsis. It should be a consideration that if fever persists despite antibiotics it may be the ongoing mucositis leading to this rather than an infective cause.

Symptoms of acute radiation oesophagitis include pain and difficulty in swallowing (dysphagia, odynophagia) and chest pain (substernal discomfort/pain). Symptoms usually occur within two to three weeks of initiation of RT. Patients may describe a sudden, sharp, severe chest pain radiating to the back. Acute toxicity rarely causes oesophageal perforation or bleeding.

Oesophagitis in the context of high-dose chemotherapy may be more severe as it affected with the concurrent deep immunosuppression and can be complicated by HSV or CMV infection.

Oesophageal perforation may result in mediastinal chemical and/or microbial inflammation (mediastinitis).

Investigations

Clinical and symptomatic assessment including assessment of oral intake and nutritional status

Body weigh assessment with BMI calculation.

Full blood count and biochemical profile.

CRP and viral swabs for HSV and candida for all severe persisting mucositis.

Body weight / fluid balance

Management

The treatment strategy in management of acute oropharyngeal mucositis caused by radiotherapy and/or chemotherapy is based on symptom control as there is no proven treatment effective in management of this toxicity besides Palifermin (keratinocyte growth factor) which is licenced for use in patients undergoing high-dose chemotherapy with stem cell support but not widely available outside clinical trials in the NHS.

Basic oral care

- Good Oral Hygiene is highly recommended
- Pre-treatment dental assessment with extractions when required is mandatory for all patients having radical radiotherapy when high dose is delivered to oral cavity and/or oropharynx.
- Frequent rinsing with bland solutions such as normal saline with sodium bicarbonate (1 L water with 1/2 teaspoon baking soda and 1/2 teaspoon salt) and use of soft toothbrush.
- The oral cavity should be rinsed after meals, and dentures cleaned and brushed often to remove plaque. Rinsing with artificial saliva may lessen the duration and severity of mucositis.

Nutrition / Fluids

- All patients with severe mucositis should be monitored for Body weight and Fluid balance
- Diet should be limited to foods that do not require significant chewing; acidic, salty, or dry foods should be avoided.
- Enteric (i.e. with naso-gastric or naso-jejunal tube) or parenteral nutrition (TPN) should be considered in appropriate patients with severe oropharyngeal mucositis / oesophagitis especially when it is expected to have a long course. Please consult managing Oncology / Haematology team and consult specialist Dietetic service as required.

Mouth washes with local analgesics, coating agents or anti-inflammatories:

Barrier / coating agents

Gelclair Gel (glycyrrhetic acid / povidone / sodium hyaluronate)

Mucilage (Carboxymethylcellulose suspension)

Sucralfate

MuGard

Local Anaesthetics /Analgesic / Anti-inflammatory

Diffiam (Benzydamine hydrochloride)

Saltwater mouthwash

Prophylaxis in chemotherapy patients

Corsodyl (chlorhexidine)

Artificial saliva/biotene

Glandosane, Caphosol or similar.

Topical steroids (rinse)

Specifically, useful for stomatitis caused by everolimus.

Systemic pain relief:

Adequate analgesia is extremely important in the management of oropharyngeal mucositis. Treatment should be arranged according to WHO ladder and pain killers should be given in liquid or transdermal form as swallowing is usually severely altered.

Initial Paracetamol soluble tablets 500-1000mg QDS at G1 is usually followed by soluble (codeine and paracetamol) 8/500 or 30/500 1-2 tablets QDS when G2.

At G3 and G4 usually strong opioid analgesia is required.

Modified release morphine suspension 12 hourly preparations or fentanyl patches in increasing doses are used with the choice based on the patient's preference and tolerance. Morphine sulphate oral solution (Oramorph) is used for breakthrough pain.

Adjuvants / treatment of complications

Oropharyngeal candidiasis: nystatin oral.susp. 100,000U/ml, 4-6 ml QDS, fluconazole oral suspension 50mg OD

Herpes simplex (HSV) oesophagitis: aciclovir tab. or oral suspension 200 mg five times daily; in immunocompromised patients or patients with suspected severe HSV infection; IV infusion of aciclovir 5-10mg/kg every 8 hours can be considered. Please refer to the SPC for the agent.

Severe periodontitis, abscess formation: antibiotics (co-amoxiclav + metronidazole).

CMV oesophagitis: ganciclovir, valganciclovir, foscarnet

Culture and sensitivity evaluation is recommended when feasible to provide patient with targeted antibiotic therapy.

Some systemic agents will require treatment interruption and re-institution as per specific guidance available in their SPC. Generally, radical radiotherapy and chemo-radiotherapy should not be interrupted for oropharyngeal mucositis / oesophagitis. Treatment interruption is a specialist medical decision and the treating Oncologist needs to be consulted as soon as possible to give guidance.

Radiotherapy specific considerations: Maintain adequate hydration and nutrition:

All patients having radical radiotherapy to the Head and Neck should be routinely provided with dietician support from the beginning of irradiation. For palliative radiotherapy and chemotherapy patients this should be provided with support on an as needed basis since radiation doses are generally lower and severe complications rarer.

Radiotherapy specific considerations: Prophylactic Radiologically Inserted Gastrostomy (RIG) or Percutaneous Endoscopic Gastrostomy (PEG)

Prophylactic RIG (radiologically inserted gastrostomy) or PEG (percutaneous endoscopic gastrostomy) is placed in anticipation of problems expected in maintaining adequate and safe oral nutritional intake during and after the radiotherapy treatment for head and neck patients.

A patient having a prophylactic gastrostomy may be managing adequate oral nutrition at the time of placement.

Prophylactic RIG or PEG prior to radiotherapy should routinely be requested for all patients planned for radical chemo-radiotherapy to the neck bilaterally.

For other patients planned for radical radiotherapy to a large volume of the head and neck e.g. nearly total mucosal irradiation and/or planned for radical radiotherapy to a large volume of oral cavity and/or oropharynx gastrostomy, the request is to be based on individual case discussion between assigned the clinical oncology consultant and the rest of the treatment head and neck team.

Prophylactic feeding tube placement through the speech valve fistula for post laryngectomy patients to be considered as alternative to RIG or PEG.

The remaining group of patients having radiotherapy for head and neck cancer when prophylactic gastrostomy is not indicated or refused by patient or having chemotherapy related mucositis are to be managed as follows:

1. Diet modification e.g. soft food, semi liquid food etc. along with adequate analgesia.
2. Oral nutritional supplements.

NG (nasogastric) tube placement and feeding should be considered when 1 and 2 fail to maintain adequate and safe oral nutrition and hydration. If acute problems with dehydration, IV fluids with serum electrolyte correction to be considered.

If there is prolonged use of NG tube post treatment, use of therapeutic RIG or PEG to be considered.

Outcome

Treatment usually gives useful symptomatic relief and enables continuation of radiotherapy and/or chemotherapy to prescribed doses. When radiation induced mucositis reaches G4, discontinuation of radiotherapy is recommended, however this decision should be only taken by the assigned Clinical Oncology Consultant. When G3 or G4 chemotherapy induced mucositis develops, chemotherapy should be withheld until symptoms resolve to grade 1 or less and dose reduction may need to be considered especially in the palliative setting according to local chemotherapy guidelines.

Radiation Gastritis, Enteritis, Proctitis.

Gastritis

Irradiation of the stomach as a consequence of treatment of a range of tumours can cause early and/or delayed toxicity.

Risk factors for gastritis include the radiation dose and use of concurrent chemotherapy.

Acute symptoms

Nausea and vomiting may occur within 24 hours after the start of treatment. Approximately one-half of patients receiving upper abdominal irradiation will experience emesis within two to three weeks of the start of treatment. Other early effects of gastric irradiation include dyspepsia, anorexia, abdominal pain and malaise. Symptoms generally resolve within one to two weeks following completion of RT. These symptoms may be accompanied by development of acute ulceration, occurring shortly after completion of RT

Management

Nausea and vomiting are generally managed with antiemetics (ondansetron 8mg bd plus dexamethasone 4mg bd or 2mg tds). Patients with abdominal pain and dyspepsia should be treated with antisecretory medications, including a proton pump inhibitor (i.e. omeprazole, lansoprazole).

Enteritis

The gastrointestinal epithelium has a high proliferative rate, making it susceptible to injury from both radiation and chemotherapy. Enteritis involves damage to mucosal stem cells as well as damage to small vessels. Inflammation, denudation, vasculitis, oedema (swelling) of the intestinal wall are initial findings and may be complicated with ulceration, fibrosis, atrophy but also perforation, fistulas and abscess formation. Chronic persistent changes will result in malabsorption.

Risk factors include the dose and schedule of radiotherapy, and the concurrent use of chemotherapy especially 5-FU or capecitabine. Additional risk factors are age, prior surgery, prior pelvic inflammatory disease, diabetes, atherosclerosis, collagen vascular disorders, and inflammatory bowel disease.

Acute symptoms

Symptoms of acute radiation enteritis include Diarrhoea, abdominal pain, nausea and vomiting, anorexia and malaise. Radiation-induced Diarrhoea often appears during the third week of treatment, with reports of frequency ranging from 20 to 70 percent. Diarrhoea may occur after doses of 18 to 22 Gy delivered using conventional fractionation and will occur in most patients who receive doses of 40 Gy. The symptoms subside as the acute pathologic effects resolve and typically disappear two to six weeks after the completion of RT.

Management

Stool culture may be required to rule out infectious gastroenteritis. Enteritis may be prevented to some extent by appropriate radiotherapy planning to prevent excessive dose to the intestine. Mild symptomatic enteritis can be managed with dietary advice (low-fibre), anti-Diarrhoeals (loperamide, codeine) and anti-spasmodic medications (hyoscine butylbromide).

For the general principles for the management of radiation-related and chemotherapy -related Diarrhoea please refer to subsequent sections.

Proctitis

Acute radiation proctitis is usually encountered following treatment of cancers of the anus, rectum, cervix, uterus, prostate, urinary bladder and testes.

Risk factors for radiation proctitis include the dose of radiation, area of exposure and method of delivery. Other potential risk factors include inflammatory bowel disease and HIV/AIDS.

Doses of radiation <45 Gy are associated with few long-term radiation side effects. In contrast, doses between 45 and 70 Gy cause more complications and doses above 70 Gy cause significant and longstanding injury to the surrounding area.

External beam radiation, typically administered by a linear accelerator, results in significantly greater exposure to surrounding organs as compared with brachytherapy, where radiation is administered via radioactive implants. Newer modalities of external beam radiation delivery, including three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, and the use of heavy particles including protons and neutrons, may be associated with a reduced risk of radiation toxicity. Chronic sequelae include progressive epithelial atrophy and fibrosis associated with obliterative endarteritis and chronic mucosal ischaemia.

Acute Symptoms

Acute radiation proctitis should be suspected in patients with Diarrhoea, mucous discharge, urgency, tenesmus, or bleeding during or within six weeks of radiation therapy.

Management

Stool studies to rule out infective proctitis including C.Difficile. Diagnosis may require endoscopy if there is a differential diagnostic problem. MRI may reveal complications such as fistulas.

In the majority of cases radiation proctitis is self-limiting. Hydration, anti-Diarrhoeals and pain relief (codeine, loperamide) can be used as appropriate. Withholding of radiation treatment requires specialist Clinical Oncology decision and may be needed for up to 20% of patients. In severe cases including severe / persistent tenesmus and / or bleeding and / or severe pain, specialist gastroenterology advice may be sought for the use of topical (enema) corticosteroids or sucralfate or sulphasalazine. Chronic complications may require endoscopic or surgical treatments.

For the general principles for the management of radiation-related and chemotherapy -related diarrhoea please refer to subsequent sections.

Chemotherapy-related diarrhoea

Chemotherapy-induced diarrhoea is most commonly described with fluoropyrimidines (particularly fluorouracil [FU] and capecitabine) and irinotecan. Diarrhoea is the dose-limiting and major toxicity of regimens containing a fluoropyrimidine with or without irinotecan. Both FU and irinotecan cause acute damage to the intestinal mucosa, leading to loss of epithelium. With irinotecan, early onset diarrhoea occurs during or within several hours of drug infusion in 45 to 50% of patients and is cholinergically mediated. Late irinotecan-associated diarrhoea is not cholinergically mediated. The pathophysiology of late diarrhoea appears to be multifactorial, including toxicity to the intestinal mucosa. Severe toxicity has been described with irinotecan in patients with Gilbert's syndrome.

Diarrhoea related to antineoplastic treatment can be severe, debilitating and potentially lethal therefore it requires prompt evaluation and treatment and good monitoring. Elderly patients and patients in poor performance status as well as immunocompromised patients are at higher risk for severe diarrhoea and complications and thus require additional attention to prevent and promptly treat this toxicity.

Patients with symptoms of diarrhoea on treatment with immune checkpoint inhibitors (i.e. ipilimumab, nivolumab, pembrolizumab etc.) require immediate treatment for suspected immune colitis and should be managed as per specific guidelines for these agents).

General Principles for the Management of Diarrhoea related to antineoplastic treatments (chemotherapy – radiotherapy).

CTCAE ver. 4.03 criteria for diarrhoea

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Uncomplicated Diarrhoea (CTCAE grade 1-2 without complicating signs or symptoms)

: Non-specific management (see below)

Complicated Diarrhoea: Admit to hospital (see below)

- CTCAE grade 3-4
- CTCAE grade 1-2 with one or more of the following signs and symptoms:
 - Cramping
 - Nausea/vomiting worse than grade 1
 - Decreased performance status
 - Fever
 - Sepsis
 - Neutropenia
 - Frank bleeding
 - Dehydration

Management of uncomplicated diarrhoea (reassess after 12-24 hrs)

- General measures:
 - Avoid lactose-containing food, alcohol, high-osmolar supplements
 - 8-10 glasses of clear liquids per day, oral electrolyte solutions.
 - Frequent small meals-low residue (bananas, apple sauce, toast, plain pasta)
 - Record number and consistency of stool
 - Withhold chemotherapy for persisting grade 2 diarrhoea. Dose reduction may need to be considered.
- Specific treatment
 - Loperamide 4mg after diarrhoea followed by 2mg every 4 hrs until resolution can be escalated to 2mg every 2 hrs.
 - Loperamide can be stopped for chemotherapy-induced diarrhoea after resolution of symptoms but should continue for RT-related diarrhoea
 - For persistent diarrhoea, medical review will be required for further evaluation / work-up (stool, FBC, electrolytes, renal function) and possible second-line medication.

Management of complicated diarrhoea

- Thorough clinical assessment.
- FBC/BCP/CRP, Stool work-up. C.diff. testing if clinically relevant
- Aggressive IV fluid / electrolytes / glucose supplementation or resuscitation.
- Dietary measures as above. Guidelines used for infectious diarrhoeal syndromes can be utilised. Nil by mouth in very severe cases.
- Loperamide or other opioids if no infective cause is suspected.
- Second line adjunct: Octreotide sc (100-150 mcg TDS, higher doses can be used after titration and continuous sc infusion can be considered) for fluoropyrimidine or irinotecan-related persistent severe diarrhoea.
- Antibiotics (oral or IV antibiotics with wide spectrum and good gram (-)ve cover may be required in septic conditions or neutropenic severe diarrhoea suggesting extensive breakdown of the mucosal barrier alongside systemic immunosuppression; oral ciprofloxacin in milder cases, IV piperacillin-tazobactam with or without metronidazole are reasonable options. The use of antibiotics generally requires senior input but should be immediate in septic and / or severely neutropenic patients)
- Discontinue chemotherapy until symptoms resolve. If necessary to restart after resolution, reduce dose as per agent specific guidance. Radiotherapy should be interrupted for complicated severe diarrhoea after consultation with treating Oncologist.

Antineoplastic drugs causing diarrhoea and specific considerations

Agent	Specific Characteristics	Specific management considerations
Fluoropyrimidines (5-FU, capecitabine, UFT)	Worse with bolus 5-FU compared with infusional 5-FU Leucovorin increases rate of diarrhoea DPD deficiency and Thymidilate synthase gene polymorphisms may result in threatening diarrhoea and other FP-related toxicities	Octreotide can be useful for persistent severe Diarrhoea. Withhold and reassess dosage if diarrhoea grade ≥ 2 . If DPD deficiency suspected consider alternative (i.e. raltitrexed)
Irinotecan (CPT11)	Acute (cholinergic) and late (multifactorial). UGT1A1 polymorphisms result in increased CPT11-related toxicities (Gilbert syndrome is homozygous UGT1A1*28 and results in reduced clearance of the active metabolite of CPT11)	Atropine SC 300-600mcg is indicated for the management of acute CPT11-related diarrhoea and prophylaxis in subsequent cycles. Octreotide can be useful for persistent severe diarrhoea. Withhold and reassess dosage if diarrhoea grade ≥ 2 .
Pemetrexed		Withhold treatment for diarrhoea \geq grade 2. Re-introduction and dose
Cabazitaxel		
Bortezomib and other proteasome inhibitors		
Vorinostat, belinostat, and panobinostat		

Lenalidomide	modification as per individual drug SPC
Small molecule EGFR inhibitors (erlotinib, gefitinib, afatinib)	
Small molecule inhibitors of VEGFR (Sorafenib, sunitinib, axitinib, regorafenib, ponatinib, pazopanib, cabozantinib, lenvatinib)	
Bcr-Abl tyrosine kinase inhibitors (imatinib, dasatinib, bosutinib)	
Lapatinib and pertuzumab (HER2 targeting agents)	
Temsirolimus and everolimus	
Anti-EGFR monoclonal antibodies (cetuximab, panitumumab)	
ALK inhibitors (crizotinib, ceritinib)	
MEK inhibitors (trametinib, cobimetinib)	
Ibrutinib, Idelalisib	

DIARRHOEA AND ABDOMINAL PAIN ASSOCIATED WITH THE USE OF CHECKPOINT INHIBITORS (i.e. immunotherapy agents such as ipilimumab, nivolumab, pembrolizumab) REQUIRE SPECIAL ATTENTION AND SPECIFIC MANAGEMENT WHICH IS ADDRESSED IN A SEPARATE DOCUMENT.

Chemotherapy-related colitis and intestinal perforation

Adverse Event	1	2	3	4	5
Colitis	Asymptomatic, clinical or diagnostic observations only, intervention not indicated	Abdominal pain, mucus or blood in stool	Severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs	Life-threatening consequences, urgent intervention indicated	Death
Enterocolitis	Asymptomatic, clinical or diagnostic observations only, intervention not indicated	Abdominal pain, mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences, urgent intervention indicated	Death
Perforation	-	Symptomatic,	Severe	Life-threatening	Death

(colonic, duodenal, ileal. etc)		medical intervention indicated	symptoms, elective operative intervention required	consequences, urgent operative intervention indicated	
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Colitis

Three types of colitis have been described in association with chemotherapy: neutropenic enterocolitis, ischemic colitis, and C. difficile-associated colitis. In addition, an immune-mediated colitis has been reported in patients treated with anti-CTLA-4 antibody therapy.

Neutropenic enterocolitis

Neutropenic enterocolitis (a form of necrotizing enterocolitis or typhlitis) is one of the most common GI complications in leukaemic patients who are undergoing induction therapy, and can occur in other malignancies and following stem-cell supported high dose chemotherapy. Management requires prompt suspicion and specialist /surgical opinion.

Ischemic colitis

Ischaemic colitis has been reported with docetaxel. The typical onset is four to ten days following administration. The clinical manifestations are similar to neutropenic enterocolitis but not all patients are neutropenic at presentation.

Clostridium difficile-associated colitis

Clostridium difficile colitis is a common problem in patients with cancer, mostly due to the high rate of oral antibiotic use and hospitalisation. However, several reports have described this complication in patients without any prior antibiotic use following chemotherapy. The proposed mechanism is chemotherapy-induced intestinal damage that facilitates the proliferation of C. difficile.

All patients with severe diarrhoea and /or symptoms of pseudomembranous colitis require stool tests for Clostridium difficile and management as per local guidelines.

Checkpoint inhibitor immunotherapy

As mentioned above, patients with symptoms of diarrhoea on treatment with immune checkpoint inhibitors (i.e. ipilimumab, nivolumab, pembrolizumab etc.) require immediate treatment for suspected immune colitis and should be managed as per specific guidelines for these agents).

Intestinal perforation

Bowel perforation is an uncommonly encountered complication that seems to be associated with antiangiogenic agents, particularly bevacizumab. Bowel perforation is also seen with tumours involving the GI tract that respond rapidly to conventional cytotoxic chemotherapy (e.g., GI tract lymphomas, ovarian cancer) or patients with symptomatic diverticular disease.

Although several risk factors have been described for gastrointestinal perforation during bevacizumab treatment, bowel perforation may occur even in the absence of predisposing risk factors, and it remains difficult to predict which patients will develop this complication.

Clinicians should maintain a high index of suspicion for perforation in patients who develop acute abdominal pain while receiving bevacizumab, even if they have no apparent risk factors.

Cases of fatal GI perforation have been reported with erlotinib and idelasib.