BC Cancer Clinical Pharmacy Guide

Supportive Care Medications

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Introduction

Many protocols include guidelines for medications that are not directly aimed at cancer treatment but are used for supportive care while a patient is undergoing cancer treatment. This section describes a number of these drugs; however, an extensive review of each agent is beyond the scope of this guide. By understanding the role of these agents in cancer treatment, pharmacists can play a key role in ensuring that these drugs are used appropriately. Pharmacists are in a position to counsel patients about why they are taking these drugs and what side effects they may experience. The Cancer Drug Manual Drug Index has patient counselling handouts for some of these supportive care medications.

Even though they are recommended in many of the BC Cancer treatment protocols, drugs used for supportive care are not considered benefit drugs, and BC Cancer will not reimburse the cost of these drugs. In these instances, it is the responsibility of the patient to obtain them from their local community retail pharmacy. Please note that some medications may be used for either treatment (benefit status) or supportive care (non-benefit status), depending on their intended use. Therefore, it is important to distinguish between these two classifications prior to requesting reimbursement. If in doubt, refer to the Benefit Drug List for approved indications for use. There are a few exceptions where BC Cancer has allowed the coverage of supportive medications: eg., mesna and leucovorin (folinic acid). Further information regarding alternate sources of supportive care medication funding is available on the Drug Funding web page.

Supportive Care Information in Protocols

Most cancer drug treatment protocols (Chemotherapy Protocols) include information about supportive care medications that are used to manage the more common adverse reactions caused by the drugs in the protocol. Where to find supportive care medication information in the protocol depends on how the medication is being used.

- Medications that must be started prior to cancer drug administration are listed in the *Premedication* section of the Protocol Summary. Usually, these medications are started on Day 1, the day of treatment. However, some protocols have premedications that must be started one or more days prior to treatment.
- Required medications that are given after cancer drug administration begins are

listed in the *Treatment Table* section of the Protocol Summary. They may be started on the day of treatment or one or more days after the treatment has been delivered.

- Some supportive care medications are only given if the patient experiences an adverse effect. If the tumour group who developed the treatment protocol provided specific recommendations for managing adverse effects, they are included in the *Precautions* section of the Protocol Summary. Otherwise, refer to the *Supportive Medications* part of the Protocol Summary, or the specific ***Drug Monographs*** and ***Patient Handouts*** [Drug Index].

The tables below provide examples of supportive care medications contained in BC Cancer protocols which may be used before, during and after treatment.

Table 1. Required Supportive Care Medications Started Before Treatment Begins	
Hypersensitivity or Infusion Reactions	Protocols containing drugs that have high incidences of allergic or infusion reactions require medications to prevent and manage these reactions. For example, **diphenhydramine** and **acetaminophen** are given prior to rituximab administration in rituximab-containing protocols such as LYFLUDR. These medications are repeated every 4 hours if the IV infusion exceeds four hours.
Tumour Lysis Syndrome (TLS)	TLS is a life threatening oncologic emergency that occurs when tumour cells die and release their intracellular contents. It causes electrolyte imbalances, such as an increase in levels of uric acid which may result in kidney damage. **Allopurinol** starting 72 hours prior to the first dose of venetoclax is required as an anti-hyperuricemic in low, medium and high tumour burden disease in LYVENETOR. See the Anti-hyperuricemic section below.
Docetaxel-induced Fluid Retention	**Dexamethasone** is used to reduce the frequency and severity of fluid retention in docetaxel-containing protocols such as BRAJDC. Dexamethasone is given orally twice daily for 3 days, starting one day prior to each docetaxel administration. The patient must receive a minimum of 3 doses pre-treatment.

Nausea and Vomiting	Some protocols, such as BRAJACT, specify **antiemetic** premedications that must be started prior to treatment and are continued post-treatment. The Antiemetic section below describes how BC Cancer uses emetogenicity to determine the antiemetic requirements for chemotherapy protocols.
Pemetrexed-induced adverse effects	Oral **folic acid** and intramuscular **vitamin B12** are used to prevent pemetrexed-induced adverse effects such as bone marrow suppression, diarrhea and mucositis. These vitamins must be started at least 7 days prior to the first cycle for pemetrexed-containing protocols such as LUAVPEM.
Renal Toxicity	**Prehydration** is used to help prevent renal toxicity in some protocols that contain nephrotoxic drugs like cisplatin. For example, the LUAVPG protocol specifies prehydration with 1 litre of normal saline in the treatment table. See the Hydration Section below for more information.

Table 2. Required Supportive Care Medications Started After Treatment Begins	
Bladder Toxicity	**Mesna** (sodium 2-mercaptoethane sulphonate) is used to prevent drug-induced hematuria in certain protocols that contain ifosfamide or high-dose cyclophosphamide. For example, see the ifosfamide-containing protocol SAAI and the cyclophosphamide-containing protocol SAVACM. See the Protectants section below for more information.
Methotrexate-induced adverse effects	For protocols containing high-dose methotrexate, such as LYHDMTXPRO **leucovorin** is used to reduce methotrexate-induced adverse effects by rescuing healthy cells from its effects. See the Protectants section below for more information.
Neutropenia	**Filgrastim** is used for neutropenia prophylaxis in some chemotherapy protocols that have a high risk for inducing neutropenia, such as the BRAJACTG protocol, which includes subcutaneous filgrastim given on days 3 to 10. See the Granulocyte

	Colony Stimulating Factors section below for more information.
Infections	Antibiotics may be included for infection prophylaxis in some chemotherapy protocols that can cause febrile neutropenia. For example, **cotrimoxazole DS** 1 tablet twice daily three times a week while on dexamethasone is included in the LYHDMRTEM protocol. See the Anti-infective Agents section below for more information.

Table 3: As Needed Supportive Care Medications	
Allergic or Infusion Reactions	Refer to SCDRUGRX for protocols with drugs that do not have a high enough incidence of allergic or infusion reactions to require routine prophylaxis.
Arthralgia/ Myalgia	**Gabapentin** or **prednisone** may be ordered to manage paclitaxel-induced arthralgias/myalgias in paclitaxel-containing protocols such as BRAJACT. See the Arthralgia/Myalgia Therapies section below for more information.
Diarrhea	**Loperamide** may be required to manage diarrhea, which commonly occurs with drugs such as fluorouracil, capecitabine and irinotecan. See the Antidiarrheals section below for more information on irinotecan-induced diarrhea including higher loperamide dosing requirements for late-onset irinotecan-induced diarrhea and recommendations for **atropine** in early-onset irinotecan-induced diarrhea.
Nausea and Vomiting	**Antiemetics** are generally ordered on an as needed basis for chemotherapy protocols that do not include antiemetic requirements such as BRAVCAP. However, the ordering physician may still choose to order antiemetics routinely. The Antiemetic section below describes how BC Cancer uses emetogenicity to determine the antiemetic requirements for chemotherapy protocols.
Neutropenia	**Filgrastim** may be used for secondary neutropenia prophylaxis after an occurrence of cancer drug treatment-induced neutropenia with a previous cycle. For example, see the filgrastim recommendations in

	the Dose Modification section of the LYABVD protocol. Refer also to the Granulocyte Colony Stimulating Factors section below.
Cytokine Release Syndrome (CRS)	CRS is an acute systemic inflammatory response caused by a large, rapid release of cytokines into the blood from immune cells following certain immunotherapy treatments. **Tocilizumab** is a monoclonal antibody which may help lower the body's immune response and reduce inflammation by blocking both plasma and cell membrane IL-6 receptors. IL-6 is a proinflammatory cytokine. More information on CRS management can be found in the supportive care protocol SCCRS, and in the Immunosuppressants section below.
Immune – Mediated Adverse Reactions	The immune system may become dysregulated during treatment with immunotherapy checkpoint inhibitors, leading to symptoms which mimic autoimmune disorders. Any organ system in the body is at risk of these immune-mediated adverse reactions (also known as immune-related adverse effects or irAEs). Management of immune-related toxicities, depending on the grade may require initiation of immunosuppressive agents such as **corticosteroids, infliximab or mycophenolate.** Refer to the SCIMMUNE protocol for management of irAEs, and the Immunosuppressants section below.

Antidiarrheals

Diarrhea is a common side effect of cancer treatment that can lead to dehydration and electrolyte imbalance, and require treatment delay, dose reduction or discontinuation. Severe cases of diarrhea will require hospital admission for supportive care. Diarrhea can also be caused by radiation to the pelvic region, or the cancer itself, such as with neuroendocrine, pancreatic or colon cancers.

Cytotoxic cancer drugs that act on rapidly dividing cells can have a direct toxic effect on the gastrointestinal epithelial lining resulting in secretory diarrhea. The fluoropyrimidines (fluorouracil and capecitabine) and irinotecan are associated with a high incidence of severe diarrhea. Capecitabine has higher rates of diarrhea than fluorouracil, with diarrhea reported in about half of all patients. Irinotecan is associated

with both early-onset diarrhea in about half of all patients, and late-onset diarrhea in most patients. Certain tyrosine kinase inhibitors (TKIs), such as those targeting the epidermal growth factor pathway, are also associated with high rates of diarrhea. Afatinib trials have reported the incidence of diarrhea in almost all patients. Immunotherapy drugs can also cause diarrhea, but may require immunosuppression in addition to supportive care, see the Immunosuppressants section.

Loperamide

Loperamide is used in the supportive treatment of Grade 1 or 2 diarrhea associated with cancer drug treatment. Loperamide slows intestinal motility and increases transit time by acting directly on the nerve endings and/or intramural ganglia of the intestinal wall. Loperamide can be used with drugs that have the common side effect of diarrhea, such as fluorouracil.

Irinotecan, however, presents a unique case with regards to loperamide use. Irinotecan can cause life-threatening diarrhea that requires prompt, aggressive treatment. When a group of patients were treated using irinotecan, fluorouracil, and leucovorin, 15.1% were reported to have severe diarrhea (grade 3) and 7.6% were reported to have life-threatening diarrhea (grade 4), requiring hospitalization.

When treatment is being considered for irinotecan-induced diarrhea, it is important to distinguish between early- and late-onset diarrhea, as both may occur and each has a different treatment regimen. Early diarrhea or abdominal cramping occurring within the first 24 hours with irinotecan is cholinergically mediated and is treated with atropine. Patients with a history of early-onset diarrhea may require atropine prophylactically for subsequent treatments. Late diarrhea has a median onset of 5 days and 11 days after the 3-weekly and weekly dosing schedules of irinotecan respectively and is treated with loperamide at doses greater than those usually recommended for diarrhea not associated with irinotecan. (See the GIIR protocol for an example of loperamide dosing in conjunction with irinotecan.) If diarrhea persists beyond 48 hours despite efforts to treat with high-dose loperamide, then the patient should be referred to hospital for assessment and rehydration.

Other antidiarrheal agents

Other opioid agents, such as diphenoxylate-atropine (Lomotil®), are considered less effective than loperamide for the treatment of acute chemotherapy-induced diarrhea. They are sometimes added to therapy for refractory Grade 1 or 2 diarrhea.

Octreotide is a somatostatin analogue recommended for the treatment of intractable Grade 1 or 2 chemotherapy-induced diarrhea despite treatment with high-dose loperamide, or severe Grade 3 or 4 chemotherapy-induced diarrhea. Short-acting octreotide can be given IV or SC three times a day. It decreases secretions of some GI hormones and facilitates the increased absorption of fluid and electrolytes by prolonging GI transit time.

Cholestryamine (bile salt sequestrant) and pancrelipase (pancreatic enzymes) may be helpful in treating diarrhea where bile salt malabsorption or pancreatic insufficiency is a contributing factor.

Antiemetics

Chemotherapy-induced nausea and vomiting (CINV) is an important adverse effect of many drugs used in cancer treatment. Since many cancer drugs act to inhibit rapidly dividing cells, and cells that line the gastrointestinal tract are dividing relatively rapidly, there can be considerable damage to the epithelial lining of the GI tract. This damage often manifests itself as nausea and vomiting (emesis), which can be mild to severe, depending on the agent(s) and dose(s) used. Cancer drugs are not equal in their emetogenic potential, as some drugs cause more nausea and vomiting than other drugs.

The goal of antiemetic therapy for patients who are undergoing cancer drug treatment is to achieve NO nausea or vomiting. For most antiemetic regimens, patients should be advised to take their antiemetic medication regularly, rather than on an “as needed” basis; it is easier to prevent the nausea and vomiting from starting, rather than trying to control it once it has begun. For regimens with low or rare emetogenic potential an “as needed” schedule may be considered.

Emetogenicity

BC Cancer has developed a protocol for the treatment of chemotherapy-induced nausea and vomiting: SCNAUSEA. The basis of this protocol is to determine the emetogenic potential of the chemotherapeutic agent. This can be determined by referring to the treatment protocol. If it is not listed in the protocol, refer to individual drug monograph(s). Refer to SCNAUSEA for the Hesketh Algorithm method of determining the combined emetogenicity of a combination of drugs, based on individual drug emetogenicity. The pharmacist can then ensure that the appropriate antiemetics have been prescribed for the patient.

The emetogenic potential of a cancer drug can be divided into four categories. The figures below represent the percentage of patients who will experience emesis if no antiemetic agent is used.

- High (HEC): greater than 90%
- Moderate (MEC): 30% to 90%
- Low: 10% to less than 30%
- Minimal (rare): less than 10%

Factors that can influence emetogenicity include:

- Infusion time - emetogenicity decreases if the infusion time increases
- Dose - emetogenicity increases as the dose increases
- Number of drugs - combination therapy can be more emetogenic than single agent therapy
- Nondrug factors that may also contribute to nausea and vomiting are outlined in the *Contributing Factors* section of ***Nausea and Vomiting*** [Symptom Management - Symptom Management Guidelines].

Types of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting is classified by onset:

- Anticipatory: prior to chemotherapy
- Acute: in the first 24 hours after receiving chemotherapy
- Delayed: after 24 hours, with the maximum intensity 2 to 3 days after receiving chemotherapy

Additionally, chemotherapy may be a contributing factor in the development of chronic nausea and vomiting in patients with advanced cancer.

Classifications of Antiemetics

Serotonin (5-HT_3) antagonists

Ondansetron, granisetron and palonosetron are the 5-HT_3 antagonists included in the

SCNAUSEA protocol summary. First generation 5-HT_3 antagonists (ondansetron, granisetron) are considered interchangeable in terms of their ability to treat chemotherapy induced nausea and vomiting, and choice of agent is generally based on availability and cost. The second generation 5-HT_3 antagonist, palonosetron, has a longer duration of action compared to first generation 5-HT_3 antagonists. It is now covered in combination with netupitant by PharmaCare under a new Pharmacare Collaborative Prescribing Agreement (CPA). These agents are used to prevent nausea and vomiting in high to moderate emetogenic chemotherapy. However, they lose their effectiveness within several days after treatment ends, presumably because recently released serotonin is eliminated and is no longer the source of nausea and vomiting. For this reason, there is usually no need for patients to continue using 5-HT_3 antagonists longer than 24 hours post-chemotherapy. Serotonin antagonists are not recommended for delayed nausea and vomiting, as they have been shown to have no effect in this setting. Common adverse effects include headache and constipation. These agents are also associated with increased risk of QT prolongation per the Credible Meds QT Drugs Lists.

Corticosteroids

Dexamethasone has been shown to enhance the effectiveness of 5-HT_3 antagonists for prophylactic management of acute nausea and vomiting associated with moderately emetogenic chemotherapy. Dexamethasone alone is also considered the backbone for the prophylactic management of delayed nausea and vomiting.

Neurokinin 1 (NK_1) Receptor Antagonists

The SCNAUSEA protocol summary includes the NK_1 receptor antagonists: aprepitant, fosaprepitant and netupitant (available as a combination product with the 5-HT_3 antagonist palonosetron). They are all considered equally effective. Netupitant/palonosetron is now covered by PharmaCare. Aprepitant has been shown to improve the prevention of acute and delayed chemotherapy-induced emesis (CIE) in highly emetogenic chemotherapy regimens. It can be used in a triplet or quadruplet antiemetic drug regimen with dexamethasone, a 5-HT_3 antagonist, and as required olanzapine. Aprepitant can also be used for CIE prophylaxis for less emetogenic chemotherapy regimens if there is a treatment failure using dexamethasone and a 5-HT_3 antagonist. Intravenous fosaprepitant is available as an alternative to oral aprepitant.

Antipsychotics

The antipsychotic medication olanzapine has been shown to have antiemetic activity when used in combination with other antiemetics for highly and moderately emetogenic regimens. A common adverse effect is sedation. It is most notable on day two, but usually resolves thereafter despite continued use. Olanzapine use is also associated with increased mortality in elderly patients with dementia, QT prolongation, extrapyramidal symptoms and fall risk.

Benzodiazepines

Lorazepam can be useful in decreasing anticipatory nausea and vomiting due to its anti-anxiety effect. Note the caution with concomitant administration of benzodiazepine and olanzapine (especially via the parenteral route), due to increased toxicity (e.g., excessive sedation and cardiorespiratory depression).

Dopamine Antagonists

The SCNAUSEA protocol summary includes the dopamine antagonists metoclopramide, prochlorperazine, and haloperidol, which act on the chemoreceptor trigger zone for antiemetic effect. Dopamine antagonists can be used as single agents for low-emetogenic regimens or as needed for moderate- to high-emetogenic regimens, for breakthrough control of emesis. The side effects of these agents (e.g., sedation, extrapyramidal effects such as drowsiness, restlessness, and dry mouth) can often limit their use. The addition of metoclopramide to dexamethasone in delayed nausea is more effective than dexamethasone alone.

Antihistamines

Dimenhydrinate is an antihistamine that is included in the SCNAUSEA protocol summary. It can be added to an antiemetic regimen if a patient is experiencing delayed nausea and vomiting and has failed on other prophylactic treatment. It can also be considered if there is a vestibular component to the patient's nausea and vomiting.

Other Antiemetic Therapies

Behaviour modifications (such as relaxation techniques) and dietary modifications can also help control emesis. The patient handout ***Practical Tips to Help Manage Nausea*** [Nutrition Handouts - Managing Eating Difficulties – Nausea] has many useful

suggestions.

Emesis can be a debilitating adverse effect of chemotherapy. Pharmacists can support patients by providing valuable medication information and ensuring that prescribed antiemetic agents are used appropriately.

Anti-infective Agents

Antibiotics

One of the major dose-limiting side effects of cancer drug treatment is neutropenia. When the white blood cell count decreases, patients are at risk for developing a bacterial infection. Antibiotics are used in two different ways in the oncology setting:

- As prophylaxis in patients receiving specific protocols documented to have a high risk of febrile neutropenia
- As active treatment in infections secondary to neutropenia

An example of a BC Cancer protocol in which prophylactic dosing of antibiotics is used:

- LYHDMRTEM
    - Cotrimoxazole DS 1 tablet PO BID three times a week while on dexamethasone. Discontinue cotrimoxazole 48 hours prior to beginning treatment and resume when the plasma methotrexate is, or is projected to be, less than 0.1×10^{-6} molar (note: µmoles/L = 10^{-6} molar). If allergic to cotrimoxazole, do not use any antibiotic prophylaxis.

Antivirals

Cancer patients with chronic or prior infection of hepatitis B virus (HBV) are at risk of reactivation following immunosuppressive therapy. BC Cancer recommends routine screening for all patients with lymphoma and myeloma as they are at a particularly high risk for reactivation due to the immunosuppressive effects of both the cancer drug treatment and their disease. Patients who test positive for either Hepatitis B surface Antigen (HBsAg) or Hepatitis B core antibody (HBcoreAb) are at risk for HBV reactivation and depending on the specific treatment regimen risk, will be treated with hepatitis B

prophylaxis and/or monitored according to current guidelines prior to immunosuppressive or cytotoxic therapy.

These patients should also be monitored with frequent liver function tests and Hepatitis B virus DNA at least every 3 months. See SCHBV protocol for Hepatitis B Reactivation prophylaxis summary.

Protocols containing proteasome inhibitors (bortezomib, daratumumab and carfilzomib) and immunomodulators (lenalidomide, pomalidomide) are associated with a significant risk of reactivation of varicella-zoster virus (VZV) caused by Herpes zoster (shingles). It is recommended that patients take valacyclovir 500 mg PO daily while receiving these cancer drugs. An example is the protocol MYMPBOR.

Refer to individual Lymphoma and Myeloma protocols for required screening tests and antiviral prophylaxis information.

Anti-hyperuricemics

Tumour lysis syndrome (TLS) is a life-threatening oncologic emergency which can occur spontaneously or after chemotherapy treatment. TLS occurs with certain leukemias, lymphomas and solid tumours. Risk factors that can increase the incidence of TLS include tumours with a high rate of proliferation or high sensitivity to chemotherapy, large tumour burden and pre-existing renal dysfunction.

As tumour cells die, they break apart and rapidly release their contents into the blood. This causes an increase in levels of potassium, phosphorous and uric acid (from nucleic acid breakdown), beyond the capacity of the body to clear. The emerging hyperuricemia, hyperkalemia, hyperphosphatemia, and associated hypocalcemia can cause damage to organs, including the kidneys, heart, and liver. Uric acid is water insoluble, and can precipitate in the renal tubules. Patients on drugs such as venetoclax are at risk for TLS and require close monitoring, hydration and prompt electrolyte correction.

Allopurinol is useful in preventing the development of TLS by inhibiting the enzyme xanthine oxidase which converts hypoxanthine to uric acid. It is required as a prophylactic anti-hyperuricemic in low, medium and high tumour burden disease in LYVENETOR to prevent kidney injury.

Higher risk patients with elevated baseline uric acid levels should receive prophylaxis with rasburicase instead of allopurinol. Rasburicase is a uricolytic agent that catalyzes the oxidation of existing uric acid. Additionally, it does not increase xanthine levels like allopurinol, and so avoids causing xanthine precipitation in the renal tubules.

Arthralgia/Myalgia Therapies

Taxanes have the potential to cause severe neuropathic pain in the form of myalgias and arthralgias, which can limit their use in the treatment of various tumours. Arthralgias and/or myalgias can start 24–48 hours after paclitaxel infusion and can last for 3–5 days. No consistent correlation has been established between cumulative doses or infusion duration and the frequency or severity of the arthralgia/myalgia. Non-steroidal anti-inflammatory drugs or acetaminophen with codeine have generally been used to treat arthralgias and/or myalgias associated with paclitaxel. If these drugs do not relieve a grade 2 (moderate) or higher level pain, then prednisone or gabapentin may provide possible therapeutic benefit.

Gabapentin

Gabapentin was initially marketed as an anti-seizure medication and is now commonly prescribed to treat neuropathic pain. Gabapentin's exact mechanism of action is unknown; however researchers know that gabapentin freely passes the blood-brain barrier and acts on neurotransmitters. A limited number of studies report a possible therapeutic benefit in the treatment of neuropathic pain. The majority of studies examining this type of pain have focused on the use of tricyclic antidepressants. However, gabapentin has a more favourable side effect profile, is easily titratable and has a more rapid onset of action than tricyclic antidepressants in neuropathic pain relief.

Prednisone

It has been hypothesized that an inflammatory process is involved in paclitaxel-induced arthralgia and/or myalgia. Low-dose prednisone may provide possible therapeutic benefit. If arthralgia and/or myalgia persist after trying prednisone and/or gabapentin, a reduction in the subsequent paclitaxel dose may be required.

Examples of BC Cancer protocols recommending the use of prednisone or gabapentin for supportive care purposes include BRAVTAX and GOOVCATM.

Granulocyte Colony Stimulating Factors

Granulocyte Colony Stimulating Factors (GCSFs), such as filgrastim and pegfilgrastim, regulate the production and function of neutrophils by controlling proliferation of committed progenitor cells, influencing their maturation into neutrophils, and stimulating the release of neutrophils from bone marrow storage pools. This results in an acceleration of the neutrophil recovery time, which may be of benefit to patients receiving potentially curative regimens.

In situations where treatment is potentially curative, a delay in receiving cancer drug treatment due to neutropenia in the patient might compromise the outcome to that patient. The use of a GCSF in a neutropenic patient increases the neutrophil count enough to allow the patient to receive treatment on schedule. Since BC Cancer protocols are established using evidence-based treatment, it is important in potentially curative situations that treatments remain on schedule as much as possible.

GCSFs are not used routinely for patients admitted to hospital with febrile neutropenia, as they have not been shown to reduce mortality or length of hospital stay; however they may be used in cases of prolonged neutropenia. GCSFs are not routinely used in the palliative setting; dose delays and/or reductions are usually preferred.

The safety and efficacy of GCSFs given simultaneously with cytotoxic chemotherapy has not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, GCSFs should not be used in the period beginning 24 hours preceding treatment until 24 hours after the treatment.

Filgrastim

Filgrastim (NEUPOGEN®) is the reference biologic GCSF developed for neutropenia management. There are three formulations of filgrastim available: NEUPOGEN®, the reference biologic, GRASTOFIL® and NIVESTYM® the biosimilars to NEUPOGEN®. Filgrastim has a relatively short half-life, so it is given for multiple days per cycle, starting at least 24 hours after treatment.

Filgrastim is a Limited Coverage Drug through the BC PharmaCare Special Authority program and the indications for coverage are outlined in the Filgrastim Special Authority Request Form. BC Cancer provides coverage for **inpatients** that require filgrastim and aligns coverage with the criteria outlined by the BC PharmaCare program. Inpatients that require filgrastim, and meet the criteria, may have the cost of the drug reimbursed

through the usual BC Cancer procedures. Outpatients must fill their prescriptions at a community retail pharmacy and are responsible for the cost of the drug.

Filgrastim may be used in the following ways to manage cancer drug treatment-induced **neutropenia:**

1. **Primary Prophylaxis** involves the use of filgrastim, starting with cycle one, to prevent cancer drug treatment-induced neutropenia. Filgrastim is included in the *Treatment Table* section of the protocol when it is used for primary prophylaxis. See the *Treatment Table* of the BRAJACTG protocol as an example.
2. **Secondary prophylaxis** involves the use of filgrastim, starting after neutropenia (without fever) has occurred, to prevent its recurrence in subsequent cycles. This means that filgrastim is not started until after cycle one. Filgrastim for secondary prophylaxis is usually included in the *Dose Modifications* section of the protocol, such as in LYABVD.
3. **Therapeutic use** involves the use of a GCSF, starting after febrile neutropenia develops. Antibiotics, not GCSF, are the treatment of choice for this medical emergency.

See Febrile Neutropenia and/or Febrile Neutropenia Assessment and Treatment for Adults with Solid Tumour and Lymphoma.

Filgrastim **may** be considered in addition to antibiotics for patients with high risk factors for infection-associated complications, such as:

- Neutropenia is expected to be prolonged (greater than 10 days) and profound (less than $0.1x10^9$/L)
- Age greater than 65 years
- Uncontrolled primary disease
- Pneumonia
- Sepsis syndrome (hypotension, multi-organ dysfunction)
- Invasive fungal infection
- Fever develops while hospitalized

PegFilgrastim

Pegfilgrastim (NEULASTA®) is a pegylated form of filgrastim, which means a polyethylene glycol (PEG) molecule has been added to it, creating a larger molecule with reduced renal clearance and a longer half-life. Pegfilgrastim is administered once per treatment cycle.

Pegfilgrastim may be prescribed as an alternative to filgrastim. Pegfilgrastim does not qualify for reimbursement through BC PharmaCare. For this reason, it is not included in the BC Cancer protocols.

For more information on GCSFs, see:

- Filgrastim / Pegfilgrastim (GCSF) Coverage
- Filgrastim Monograph and Patient Handout
- ***Neutropenia*** [Symptom and Side Effect Management Resource Guide]

Hydration

The primary goal of hydration during cancer drug treatment is to prevent complications from dehydration such as nephrotoxicity. The risk of developing nephrotoxicity increases with a decreased ability to eliminate certain drugs. Intravenous hydration, forced diuresis, and alkalinization of the urine are some methods used to assist with the excretion of potentially nephrotoxic drugs.

Methotrexate, ifosfamide, cyclophosphamide, and high-dose cisplatin can cause various forms of renal toxicity. Intravenous fluids can be used as either pre- or post-hydration to maintain renal blood flow and urine output, which enhances elimination of a potentially nephrotoxic drug. Oral hydration may also be encouraged to enhance this effect. The use of antiemetics also helps maintain adequate hydration by preventing fluid loss due to vomiting when highly emetogenic drugs are administered.

There is a variance in hydration guidelines among many BC Cancer protocols. Some protocols, such as LUAVPG or GUBEP, give very specific guidelines. In many cases, BC Cancer protocols have been adopted from original studies, and specific hydration guidelines from these studies have been incorporated into the protocol. Other protocols, such as GOCXCRT, suggest optional IV hydration at the physician's discretion. Many protocols containing drugs with the potential for renal toxicity recommend

encouraging oral hydration under the *Precautions* section.

Potassium chloride and magnesium sulphate are often added to hydration orders, e.g., HNLAPRT. Potassium chloride is used to maintain adequate electrolyte balance and prevent adverse effects from hypokalemia. Cisplatin has been shown to cause hypomagnesemia. Magnesium sulphate is often added to pre and post hydration fluids when higher doses of cisplatin are administered. Magnesium also protects the kidneys during cisplatin treatment without interfering with chemotherapy.

Forced Diuresis

The principle of forced diuresis is to enhance IV hydration and expedite the movement of drug and fluid through the kidneys. The use of mannitol with high-dose cisplatin is one such example of this. Cisplatin, which is an alkylating agent, is used in a variety of BC Cancer protocols, and can cause toxic nephropathy via tubular necrosis of both the proximal and distal renal tubules. It has been demonstrated that IV hydration and forced diuresis can greatly minimize this adverse effect.

Mannitol is an osmotic diuretic, which acts in the proximal tubule of the kidneys. The osmotic pressure that mannitol generates prevents the reabsorption of water and sodium, thereby increasing urine flow. When used with high-dose cisplatin (i.e., 40–120 mg/m^2), the mannitol-induced diuresis prevents the cisplatin concentration from reaching nephrotoxic levels in the urine. Mannitol (30 grams) is usually added to the IV solution containing cisplatin, as illustrated in LUAJNP and GOCXCRT.

Urine Alkalinization

Acidity of the urine may cause renal precipitation of a drug. This effect can be prevented by using sodium bicarbonate to alkalinize the urine. This strategy is used with high-dose methotrexate, an anti-metabolite which is associated with renal toxicity at doses of 100 mg/m^2 and greater. Nephrotoxicity is secondary to tubular precipitation of methotrexate, which is poorly soluble at a pH of less than 7. A combination of aggressive diuresis and alkalinization of the urine prevents this toxicity. In theory, the aggressive hydration maintains good renal flow, and a relatively low urinary concentration of methotrexate. The sodium bicarbonate maintains a urinary pH greater than 7, preventing methotrexate precipitation in the renal tubules and collecting ducts.

Examples of BC Cancer protocols using this process include LYHDMTXPRO and LYCHOPRMTX.

Immunosuppressants

More effective cancer immunotherapies are a growing field in cancer treatment. They help the immune system better detect and fight cancer cells. However, an overactivated immune system can cause adverse reactions and immune-related adverse effects that may require immunosuppression.

Cytokine release syndrome

Cytokine release syndrome (CRS) is an acute systemic inflammatory response that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies, bispecfic T cell engaging (BiTE) antibodies and chimeric antigen receptor (CAR) T cell therapy. Cytokine release syndrome is sometimes called Cytokine Storm.

CRS is caused by a large, rapid release of cytokines, such as IL-6, into the blood from immune cells affected by the immunotherapy. IL-6 is a proinflammatory cytokine. Cytokines are immune substances that have many different actions in the body, including activating coagulation cascades and causing capillary leakage. Signs and symptoms of cytokine release syndrome may include fever, nausea, headache, rash, rapid heartbeat, hypotension, and trouble breathing. Most patients have a mild reaction, but sometimes, the reaction may be severe or life threatening. Patients with severe CRS may have high fever and hypotension and will need hospitalization to avoid deterioration into circulatory shock and multi-organ failure.

The grading and management of CRS is specific to the type of immunotherapy and cancer. It involves frequent monitoring of vital signs and symptomatic treatment, and may require treatment interruption along with the initiation of glucocorticoid steroids and/or tocilizumab for more severe cases. Tocilizumab is an anti-IL-6 monoclonal antibody which can help lower the body's immune response and reduce inflammation by blocking both plasma and cell membrane IL-6 receptors.

More information on CRS management due to bispecific antibodies can be found in the supportive care protocol SCCRS.

Immune-related Adverse Effects

Immune checkpoints are a normal part of the immune system. Checkpoint proteins, such as PD-L1, PD-1 and CTLA-4 help keep immune responses in check. Immunotherapy with immune checkpoint inhibitors (ICIs), such as ipilimumab or nivolumab, block these checkpoint proteins allowing T cells to kill the cancer cells more effectively. The immune system may become dysregulated during immunotherapy, leading to symptoms which mimic autoimmune disorders (immune-related adverse effects or irAEs). Any organ system in the body is at risk. Adverse events can occur during or after treatment has been completed and can be life threatening.

Management of immune-related toxicities, depending on the grade may require initiation with corticosteroids. Doses of 1 to 2 mg/kg of prednisone are recommended for many Grade 2 or higher immune-mediated adverse reactions. If severe symptoms persist or worsen, treatment with immunosuppressive agents such as infliximab or mycophenolate may be recommended. Refer to the SCIMMUNE protocol for management of irAEs.

Protectants

Leucovorin (Folinic Acid)

Leucovorin is a reduced form of folic acid that acts as a cofactor in the biosynthesis of purines and pyrimidines in nucleic acids. Folic acid must be reduced to tetrahydrofolic acid, via dihydrofolate reductase, in order for DNA synthesis and cellular replication to occur. Methotrexate and its active metabolite compete for the folate binding site of this enzyme, thus inhibiting DNA and cellular replication. Because of its ready conversion to other forms of tetrahydrofolic acid, leucovorin is a potent antidote of folic acid antagonists such as methotrexate. It has been suggested that because of leucovorin's difference in membrane transport mechanisms, it has a preference for normal cells over certain tumour cells, and therefore has the ability to "rescue" normal cells from the toxic effects of folic acid antagonists.

Leucovorin is rarely used with doses of methotrexate that are less than 100 mg/m^2. It is required for methotrexate doses that are greater than 500 mg/m^{2}and may be considered for methotrexate doses ranging from 100–500 mg/m^2. Leucovorin must be administered 6–24 hours after the end of a high-dose methotrexate infusion. The effectiveness of leucovorin rescue diminishes as the time increases between the end of

the methotrexate infusion and the start of leucovorin rescue. Leucovorin should not be administered concurrently with methotrexate, as there is some concern that the antidote effect of leucovorin may reduce the effectiveness of methotrexate.

High-dose methotrexate must be administered in a hospital where rapid reporting of methotrexate levels is available. Please see the LYHDMTXPRO and LYHDMRTEM protocols as an example for details on timing of methotrexate levels and leucovorin dosing.

The use of leucovorin for methotrexate rescue needs to be distinguished from the use of leucovorin for fluorouracil (5-FU) efficacy enhancement. In this setting, leucovorin stabilizes the bond between the active 5-FU metabolite and thymidylate synthetase. Examples of BC Cancer protocols using combination leucovorin and fluorouracil therapy include GIAJFFOX and HNNAVFUFA.

Mesna

Mesna (sodium 2-mercaptoethane sulphonate) is a uroprotectant that protects the bladder from unwanted urotoxic effects of high-dose cyclophosphamide and ifosfamide. These two drugs form an oxazaphosphorine metabolite, acrolein, that has the potential to cause hemorrhagic cystitis (HC), which is characterized by hematuria that may be accompanied by dysuria, frequency, and urgency, and may lead to bladder fibrosis and obstructive renal failure. Mesna passes unchanged through the liver and binds to acrolein in the bladder, producing an inactive compound that is rapidly eliminated by the kidneys. The combination of diuresis and mesna reduces the incidence of HC. The goal of treatment is to keep sufficient mesna levels within the urinary tract beyond the time of administration of ifosfamide or cyclophosphamide, to allow for its uroprotectant effect. Because the half-life of mesna is shorter than that of ifosfamide or cyclophosphamide, either continuous infusion or multiple doses of mesna are required.

Examples of BC Cancer protocols using mesna include GUVEIP, GUVIP2 and SAIME.