ORAL ANTI-CANCER AGENTS:
“BRIDGING THE GAP”

Learning Module
Aimed to Provide Pharmacists with Necessary Tools to Care for the Cancer Patients
OBJECTIVES:

- To provide community pharmacists with the necessary tools for provision of pharmaceutical care to cancer patients, as it relates to drug distribution and patient education.
- To raise awareness about the supportive resources available to community pharmacists in the oncology field.
- To discuss the role that the community pharmacist plays in a cancer patient’s care.
- To provide practical advice regarding the specifics of caring for cancer patients.
- To identify the red flags in a patient’s condition, which require referral.

BASIC ONCOLOGY PRINCIPLES:

Cancer refers to any uncontrolled growth of malignant cells, which if left undetected can destroy the organs and their functions. Currently there are more than 200 distinct forms of cancers known and this number keeps on growing.

Despite the fact that many cancers are more prevalent in the elderly, no age group is immune to this disease. Although cancer originates in our own cells, there are both intrinsic and extrinsic factors that can increase one’s risk of developing cancer. The intrinsic factors include the age, hormonal status and genetic predisposition (family history). The extrinsic factors consist of the following: diet, lifestyle, smoking and alcohol use, exposure to toxic chemicals, radiations and even some infections. Asbestos, dyes, food additives, vehicular emission and many other chemicals are carcinogenic and increase the risk of cancer development, especially if an individual concurrently has positive intrinsic factors.

Once the malignant tumor has developed it will be progressing and eventually it may metastasize (i.e. spread to other organs and tissues in the body). This process depends on the metastatic changes that lead to invasion of local normal tissues, entry of the neoplastic cells into the blood and lymphatic systems and the resultant development of secondary tumors at distant sites.
PRESCRIPTION FOR ANTI-CANCER AGENT:

Why is this important to you?

▶ Despite the fact that these patients are taken care of by specialists with expertise at CancerCare Manitoba (CCMB):
  ▪ The doctors know that you will be involved in the patient’s care and rely on you for that final check
  ▪ No matter how specialized and expert in the area one is – every human has the potential of making errors. Being overly reliant on someone’s expertise opens more gaps in the system!

Critical incidents

▶ From the recent critical incidents it is evident that there are serious gaps in the system that guides the care of patients who are taking oral anti-cancer agents.

1. A patient with neutropenia was given a handwritten prescription for cyclosporine. Due to the “sound-alike” drug name and poor handwriting the patient had received cyclophosphamide instead of cyclosporine. After taking 8 doses the patient realized that a mistake was made and presented to the emergency department, from where he was discharged and started on the correct medication.

2. A patient was prescribed capecitabine 2000 mg BID for 14 days. It was discovered later that based on the patient’s creatinine clearance a dose reduction was indicated. The pharmacy where the prescription was taken was phoned and a dose reduction to 1500 mg BID was ordered. However, the patient received and took capecitabine 2000 mg.

3. A patient was prescribed tretinoin 40 mg (ATRA – all-trans retinoic acid → was indicated on the prescription). The prescription was filled for cis-retinoic acid (i.e.: isotretinoin or Accutane).

These critical incidents demonstrate the necessity to improve the care “bridge” between CCMB and community pharmacies.

The survey about oral anti-cancer agents that was sent out in November – December of 2011, revealed that of the pharmacists who responded, only 11-16% feel comfortable dispensing and counseling on oral anti-cancer agents. Therefore, providing pharmacists with relevant tools to increase their comfort level in dispensing and counseling on these medications is of key importance.

SPECIFIC STEPS IN ANTI-CANCER AGENT PRESCRIPTION APPROACH:

1. **Verify patient’s information**

   Although this step is critical in filling any prescription, the anti-cancer agents have a very narrow therapeutic window and it is important to appreciate the significance and the great extent of complications if a patient is misidentified.
   ▪ In addition to the patient’s full name, need at least 1 specific identifier out of these 2:
     ✔ PHIN
     ✔ DOB
     ‣ Note: address is not considered a specific identifier

2. **Confirm the appropriateness of the treatment**
If diagnosis, indication or protocol is indicated on the prescription, or if you know the diagnosis from the patient, then you can check the appropriateness using the sources we will be talking about further (BCCA website).

You can check the eligibility and contraindications based on the information you know, and if any concerns or doubts arise – do not hesitate to call the clinic!

Specific link: [http://www.bccancer.bc.ca/HPI/default.htm](http://www.bccancer.bc.ca/HPI/default.htm)
- Cancer management guidelines
- Chemotherapy protocols
  - **Important note re. eligibility: MB criteria for use may be different than in BC**

Intent of treatment is very important in treatment rationale and the protocols are categorized according to the one of the four intents of treatment:

- **Neo-adjuvant** – chemotherapy given before the surgical procedure in an attempt to shrink the cancer in order to have less extensive surgery.
- **Adjuvant** – chemotherapy aimed to destroy the left-over cancer cells after the visible tumor has been removed by surgery. The goal is the prevention of cancer reoccurrence.
- **Induction** – chemotherapy aimed to induce a remission (commonly used term in treatment of leukemias)
- **Consolidation** – chemotherapy given to sustain a remission once it has been achieved.
- **Maintenance** – chemotherapy given to assist in prolonging the remission (usually lower doses are used).
- **Palliative** – chemotherapy given to address particular cancer symptoms to improve the patient’s quality of life, without targeting or expecting to reduce the cancer.

Confirm that the dosing regimen matches the indication and the intent of treatment. This can be easily done once you access the protocol. Appendix 1 contains a table demonstrating the common indications and dosing regimens for most common oral anti-cancer agents.

Once you have identified the appropriate dosing regimen - check that the dose was calculated correctly. Anti-cancer agents may be dosed based on BSA (body surface area, mg/m²), weight (mg/kg), or sometimes the doses are fixed based on the indication.

- BSA can be calculated using a number of formulas, and unfortunately, just like with creatinine clearance the results may vary depending on the formula used. Therefore, it is important that during checking process same formula that was used to calculate the dose is used, in order to avoid unnecessary confusion.
- Currently CCMB uses the Mosteller formula, which is presented below:

\[
\text{BSA} (\text{m}^2) = \sqrt{(\text{Height(cm)} \times \text{Weight(kg)})/3600}
\]

\[ \text{e.g. BSA} = \sqrt{(\text{cm} \times \text{kg})/3600} \]

Once you know the BSA, you can divide the prescribed dose by BSA to ensure its accurateness according to the recommended dosing regimen.

- Often you may see that the dose used is not exactly the one recommended by the regimen, but close to it. This is done by the system to ensure that there is no need to split the tablets and the rounding is usually done based on the drug monograph recommendations.
- It is important to note that even though the BSA might be provided, it is best if the pharmacist calculates it based on the patient’s height and weight and using the formula provided above. That will eliminate the possibility of a computer-related error (e.g. data entry error). For the same reason, try to always confirm the height and weight with the patient first.

As it has been discussed above, kidney function is very important and often serves as the guide for dosing. Thus, creatinine clearance (Clcr) is a very important piece of information to be considered when checking the dose.
► Therefore, if the serum creatinine / Clcr is provided you should take that into account when checking the appropriateness of the treatment.
► Just like with the BSA, it is best to re-calculate the creatinine clearance based on the serum creatinine (if provided). Currently CCMB uses the Cockroft-Gault formula for calculating estimated Clcr:

\[
\text{Clcr} = \frac{(140 - \text{age}) \times \text{weight}}{\text{sCr} \times 1.2^*}
\]

*1.4 for female patients

► Other bloodwork may be indicated on the prescription, including: WBC, ANC, platelets, etc. If the relevant recommendations on dosing adjustments are included you can use that information as a general guide to gain a better understanding of the patient’s situation, and appreciate if the patient is in the risk range. That information can also be helpful in cases when the dose is being reduced as it will provide you with the reason for that dose reduction.

Sometimes the prescriber may choose to override the guidelines recommendations therefore, if you see that the dose does not correspond to the recommended dosing, and the intent to purposely override the recommendation is not mentioned, it is always best to discuss this fact with the prescriber.

**Take home message:**

**NEVER IGNORE ANY CONCERN YOU HAVE WITH THE PRESCRIPTION**
– better be safe than sorry!

- If the dosing guidelines are provided, and the dose seems incorrect, never adjust it without discussing the fact with the prescriber.
- If the dosing guidelines are not provided, you can check the relevant parameters guiding the dosing by accessing the BCCA website.

► Always check the allergies and potential drug interactions. If there is a concern with a drug interaction, ask the patient or their caregiver or contact CancerCare Manitoba first, as it may turn out that this drug interaction has been already dealt with at the time of prescribing. Efforts are being made right now to ensure that such information is documented on the prescription for your convenience, however, often times it may not be done. Therefore, do not assume – it is always best to check.

**3. Ensure that you have all the information you need about the regimen**

► Often the therapy is given in cycles with break periods in between. This is to ensure that the healthy cells that are undergoing cytotoxic damage have a chance to restore themselves. It is important that you have a clear understanding of the treatment plan in order to properly instruct the patient.
► Sometimes you may receive a treatment calendar along with the prescription, however, even if it not provided – always ask the question about the treatment plan. Often you may see the prescription indicating “No Refills Permitted”. This is done in an attempt to prevent the patient refilling their prescriptions when there should be a break period or assessment done before proceeding with the treatment.
► Ask the patient to assess how confident they are in how they are taking this medication (how long, is there a break period, when do they go for follow-up, etc.) and if you sense that the patient is not clear on what they should be doing and no detailed instructions were provided to you – do not hesitate to call the clinic to get that information. Do not let the patient leave your pharmacy without ensuring that they are certain on how the therapy should be taken correctly.
4. **Confirm the appropriateness of the supportive treatment**

- The toxicity of many chemotherapy drugs makes it necessary for preventative therapies to be in place even before the patient starts taking the drug. You can use the section on the side effect management of this learning module as a general guide for assessing the supportive treatment. A better tool is getting familiarized with the BCCA website and navigating the treatment protocols specific to the chemotherapy regimen to determine the necessary supportive treatment. Keep in mind that many of the side effects are too difficult and sometimes impossible to manage once they started occurring. On the side if they are prevented from the very beginning, that allows the patient to benefit more from the chemotherapy’s effects on the cancer, as there is less chance that the patient will require dose reductions or treatment discontinuation.

5. **Counsel the patient**

- It is often assumed that the patient coming from CancerCare Manitoba has already been extensively counseled by the experts in this area. Unfortunately, this is not always the case, and the counseling process is not standardized at this time. Not all patients will see a pharmacist at their visit, and you are the only healthcare provider in place to offer pharmaceutical care to the patient. Although the patient may not think that they need counseling, there is information that is absolutely necessary for the patient to know. Despite the fact that it might be a lot of information, very often the patient, or their caregiver will be interested to learn it, appreciating the seriousness of the condition and therapy.

- Since these drugs are relatively new, and the pertinent information is often very specific, you need to know the resources where you can find reliable information. Also you want to make sure that the information that you are providing is consistent with what the patient has been told in the clinic. Therefore, it is best if you can use the same information source for counseling as CCMB does: BCCA website - http://www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPt/default.htm

  - These patient monographs have been all written in patient-friendly language and contain specific information that all patients need to know. If the patient has additional questions you can find more detailed pharmaceutical information under the “Health Professional Info” section of the website.

- If the prescription is new for this patient – assess the patient’s level of knowledge. Even if the patient is counseled thoroughly at the clinic, they may have missed a lot of information or misinterpret what was being said due to a number of reasons: being overwhelmed by information, shocked by diagnosis, dealing with emotions, being physically tired / fatigue, etc. Due to these reasons, it is always best to have the patient’s caregiver present at the counseling and encouraging them to read over the material that has been provided by their clinic and by your pharmacy.

- If the patient is refilling the prescription – assess if they are experiencing any adverse effects and provide them with managing strategies or refer them to their clinic if necessary. Use the opportunity to remind them of important things they should keep in mind and summarize when and whom should they contact (as it relates to toxicities or red flags).

▶ **How should you approach these patients?**

- Many people feel extremely uncomfortable getting into discussions around such a sensitive topic like cancer. As health care providers who are always focusing on the patient we fear that this discussion may lead to patient breaking down into tears or anger, due to the tension that may be building up inside them. There are people who naturally have a tendency to deal with such situations better than others, yet others need to put in effort to learn how to approach these situations. As pharmacists, we need practical advice on this issue:
A very useful model was proposed by Harvey Chochino → the ABCDs of dignity in care

- **Attitude**: examine your personal attitudes and assumptions regarding your patients.
  - Know your subjective biases, and be ready to think out of the box.
  - Do not make assumptions!
- **Behavior**: once you are aware of your attitudes you can then manage your behavior towards others.
  - Simple gestures to make a patient feel like a person worthy of attention and respect and small acts of kindness may have a strong effect on the trust relationship.
  - In everything show professionalism, kindness and connectedness, especially when dealing with patients with advanced disease.
- **Ways to improve communication**:
  - Always aim for the discussions to be done in a private setting (patient counseling area)
  - Give the patient your full attention
  - Invite the caregiver to participate in the discussion as well
  - Sit at a comfortable distance and at the person's eye level
  - Try to understand the overwhelming situation your patient is going through and offer repeated explanations if necessary
  - Use patient-friendly language and tailor it to your specific patient
  - Ask if the patient or caregiver have any questions and reassure that they can ask them later as they arise

- **Compassion**: deep awareness of the suffering of another and strong wish to relieve it
  - Some people naturally have more compassion, while for others it comes with life experience, clinical practice and realization that no one living on earth is insured from suffering.
  - You cannot fake compassion: it shows in your look, manners, tone, etc.

- **Dialogue**: in order to understand you need to communicate
  - Safety and quality of patient care depends on the quality of information exchange.
  - You may need to ask the patient about the diagnosis and other specific information and to get the best response – foster a sense of trust, openness and honesty and approach the patient in this way.
  - To acknowledge the patient’s feelings use phrases, like:
    - This must be frightening for you.
    - I can only imagine what you must be going through.
    - It's natural to feel overwhelmed at times like this.

The job of a retail pharmacist is very busy and time constraints can easily prevent you from practically applying all the aspects of patient care you may want to provide. Due to this fact, the intended changes often stop at the stage of being just a wish. To avoid such situation – set a realistic goal for yourself and your team – start by making small changes to your practice and eventually develop a practical system that will work for you and your team.

If you have only a small number of patients on oral anti-cancer agents – take some time and get yourself familiarized with the drug monographs, so that you have confidence that the prescription you dispensed is safe for your patient. Having the resources that have been provided added to the skills you have as the pharmacist you should look forward to continuously raising the bar of patient care and making that difference for your patient. Even if the patient does not appreciate it, it is ensuring their safety!
RESOURCES AVAILABLE FOR YOUR SUPPORT:

Useful and reliable oncology resources are readily available:

► **BCCA (BC Cancer Agency: [http://www.bccancer.bc.ca/default.htm](http://www.bccancer.bc.ca/default.htm))**
  - Agency of the Provincial Health Services Authority that provides a cancer control program for the residents of British Columbia and the Yukon.

The website is divided into different subsections, among which you can find the following: Patient/Public Info, Regional Services, Health Professionals Info and Research. Under Patient/Public Info you can find information that is written in patient-friendly language. This info includes information about the types of cancers, treatment options, prevention, coping with cancer, etc. Under “Health Professionals Info” you can find cancer management guidelines, chemotherapy protocols, cancer drug manual, etc.

What makes this source very valuable to you is the fact that all patients coming out of CancerCare Manitoba are counseled based on the patient counseling sheets from the “Patient/Public Info” section. This source is widely used across Canada. All the information is easily accessible and no charges apply.

► **Chemo Care (Chemotherapy Drugs and Side Effects Information: [http://chemocare.com/](http://chemocare.com/))**
  - This is a very useful website designed and maintained by The Cleveland Clinic Foundation. It contains information about chemotherapy drugs, side effects management and other information that can be very helpful for your patients. All the information is written in a patient-friendly language and is of high quality. It is a great resource for healthcare providers as well,
as it contains very detailed information pertinent to patient care, which is organized very neatly.

► **Cancer Glossary from the Canadian Cancer Society:**
  - Canadian source that provides information related to risks, signs/symptoms, diagnosis, pathology/staging, treatment, supportive care and other, specific to the type of cancer. It is very well organized and easy to navigate.

► **CAPhO (Canadian Association of Pharmacy in Oncology):** [http://www.capho.org/](http://www.capho.org/)
  - National forum for oncology pharmacy practitioners, where you can find online education programs ranging from oncology basics to sessions dealing with molecular biology of cancer.

  - Great resource for patients to learn about cancer, prevention, research and support that they can receive in such situation. Also you can use it for answering many patient’s questions about the cancer and to dissipate the common cancer myths.

**Other useful websites:**
- **National Cancer Institute:** [http://www.cancer.gov/](http://www.cancer.gov/)
- **CancerCare Nova Scotia:**
- **American Cancer Society:** [http://www.cancer.org/](http://www.cancer.org/)
- **Doctor-approved cancer information from ASCO:**
  [http://www.cancer.net/portal/site/patient](http://www.cancer.net/portal/site/patient)
POTENTIAL CANCER SYMPTOMS:

Early detection is the goal, since it offers a better prognosis of the disease; therefore, referring someone to get checked out early may guarantee a better chance for cure and remission. Many people ignore the symptoms for two reasons: either they do not consider the symptoms to be concerning, or they are afraid of discovering that they are seriously ill, meanwhile, this procrastination decreases their chances for cure.

The common problem with symptom analysis is that they are often very general and could be due to many other reasons. These include unexplained weight loss, fatigue, nausea, pain, fever, skin changes and others. Such non-specific symptoms can exist for a long time and the cancer might be developing while the person is being misdiagnosed and mistreated.

Since the pharmacist is the most accessible health care professional for many patients, we need to make sure we know when to refer and encourage our patients not to “wait it out”. For instance, the unexplained weight loss occurs in most cancer patients, and an unintentional loss of 10 pounds may be the first indicator of a gastrointestinal or lung cancer. Fever, being very common in some cancers, could be the first sign of leukemia or lymphoma. In leukemias, certain colon and stomach cancers, as well as other cancers that may lead to chronic blood loss, the most prominent sign of cancer is usually the fatigue. Pain can also be an early detectable symptom, especially in bone and testicular cancers, however, pain is rarely seen at the point of diagnosis, and rather appears as the cancer advances. Hyperpigmentation, jaundice, erythema, pruritis or excessive hair growth can be due to an internal cancer.

Specific symptoms include changes in bowel habits, bladder function, sores that do not heal, unusual bleeding / discharge, solid mass detection, dysphagia, indigestion, nagging cough and hoarseness. These may be due to a variety of reasons as well; however, it will be helpful to know which symptoms should make you uncomfortable and prompt you to refer the patient. These include the following:

- Chronic constipation, diarrhea or a change in the size of stool may indicate a colon cancer
- Pain with urination, hematuria, or any other functional change of the bladder could point towards a bladder or colon cancer
- Skin cancers may be suspected based on persistent sores that bleed and do not heal.
- Bleeding or discharge that is unusual includes blood in phlegm could be a sign of a lung cancer
- Blood in the stool or dark black stool could signify gastrointestinal cancer
- Unexpected vaginal bleeding often appears in cervix or endometrium cancers
- Bloody discharge from the nipple occasionally appears in breast cancers

It is important to note that these signs and symptoms are general and usually are not caused by a malignancy. However, a patient experiencing any of these should be referred for further investigation.

Other potentially alarming symptoms:

Some patients detect solid masses, and that is more commonly noted in breast, testicle, lymph nodes, as well as soft tissues of the body. Cancers that may cause indigestion include the cancer of esophagus, stomach or pharynx. Recent changes in a wart or mole appearance should also be seen as concerning until melanoma or other skin malignancy is ruled out. Persistent nagging cough may be a sign of lung cancer, while hoarseness can be due to the larynx or thyroid cancer. There are many more symptoms that upon detection should be referred for a detailed work-up, therefore, if one complains of major changes in their body function or the way they feel – the patient should be referred.

Unfortunately, many cancers go undetected and present asymptptomatically until the disease has advanced, therefore, screening programs offer a great help in detection and early cancer treatment. Patients should be encouraged to participate in these screening programs where available. Screening can help detect and treat some types of cancer early. The treatments available are more effective when the cancer is in its earlier stages and the prognosis continuously worsens as the stage
progresses. Screening tests are commonly used for cancers of the breast, cervix, colon and rectum. For breast cancer screening a mammogram is used and is usually recommended every 1-2 years to women > 40 years old. The Pap smear is used for cervix cancer screening and is recommended to all women every 3 years once they started having sexual intercourse. Colon and rectum cancers are screened via a variety of tests (fecal occult blood test – to detect cancer / polyps bleeds; sigmoidoscopy / colonoscopy – to detect abnormalities and remove polyps if necessary; double-contrast barium enema – to improve the x-ray images of the colon and rectum; digital rectal exam – to find abnormal areas at the lowest part of the rectum).

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SIDE EFFECT MANAGEMENT:

Supportive Therapy

Supportive therapy refers to any form of treatment that is intended to prevent, relieve or control the symptoms, complications and side effects with an ultimate goal of improving the patient’s comfort and quality of life. In this module we will cover the most common side effects. Additional information can be found at [http://www.bccancer.bc.ca/default.htm](http://www.bccancer.bc.ca/default.htm) and [http://chemocare.com/](http://chemocare.com/) (the latter is a website for patients mainly but contains very useful information).

→ Chemotherapy-Induced Nausea / Vomiting (CINV)

Nausea can be defined as the subjective urge to vomit, which is often accompanied by tachycardia and hypersalivation. It can be subjectively measured using a “0-10” scale or Visual Analog Scale. Emesis, on the other hand, can be objectively measured as the number of episodes in 24 hours. Emesis is categorized into three types, based on the onset time: acute (within the first 24 hours after chemotherapy administration; peaks at 4-6 hours), delayed (between 24 hours to 5 days post-chemotherapy; peaks at 2-3 days) and anticipatory (starts before chemotherapy and is psychologically induced by sights, smells or sounds secondary to inadequately controlled nausea and vomiting in the past). Therefore, the best way to treat CINV is primary prevention at the very initiation of the chemotherapy.

CINV Prophylaxis

All chemotherapy agents may cause CINV, and they are categorized into four groups based on the particular agent’s emetogenicity (capability to induce emesis): high (>90% incidence), moderate (30-90%), low (10-30%) and minimal (<10%). There are guidelines that have been developed to direct the approach to prophylaxis, depending on the agent’s emetogenicity. However, it is important to note that the emetogenicity rating is based on the single-agent treatment, while many patients are treated with a combination therapy, which may increase the CINV risk. There are also patient-related risk factors, which include: young age, female sex, poor control in previous cycles, history of morning sickness with pregnancies, history of motion sickness and various psychosocial factors. Thus, although the chemotherapy’s emetogenicity may be rated as “low”, the patient might need to be placed on a more aggressive CINV prophylaxis than the guidelines recommend. However, the guidelines help us in the general approach, upon which we can build the CINV prophylaxis regimen, taking into consideration all the contributing factors. Table # 1 shows the chemotherapy agents based on their emetogenicity, route of administration, and prophylaxis suggested by guidelines.
Table # 1: Emetogenicity and corresponding prophylaxis based on the route of administration:

Note: These are very general guidelines and the chosen therapy will depend on many patient-specific factors.

<table>
<thead>
<tr>
<th>Emetogenicity</th>
<th>Oral agents</th>
<th>IV agents</th>
<th>Pre-chemotherapy prophylaxis</th>
<th>Post-chemotherapy prophylaxis</th>
</tr>
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<tbody>
<tr>
<td><strong>High (&gt;90% incidence)</strong></td>
<td>hexamethylmelamine, procarbazine</td>
<td>cisplatin, mechloretamine, streptozocin, cyclophosphamide (&gt; or = 1500mg/m2), carmustine, dacarbazine</td>
<td>Day 1: ondansetron 16-24mg PO + dexamethasone 12mg PO + Aprepitant 125mg PO +/- lorazepam 0.5-2mg PO or SL q4-6h +/- H2 blocker or PPI (some of these can be IV)</td>
<td>dexamethasone 8mg/day PO (days 2-4) + aprepitant 80mg PO (days 2-3) +/- lorazepam 0.5-2mg PO or SL q4-6h +/- H2 blocker or PPI (one anti-emetic should be prn for breakthrough therapy)</td>
</tr>
<tr>
<td><strong>Moderate (30-90% incidence)</strong></td>
<td>cyclophosphamide, temozolomide, vinorelbine, imatinib</td>
<td>oxaliplatin, cytarabine (&gt; 1000mg/m2), carboplatin, ifosfamide, cyclophosphamide (&lt; 1500mg/m2), azacitidine, alemtuzumab, doxorubicin, daunorubicin, epirubicin, idarubicin, irinotecan, bendamustine, clofarabine</td>
<td>Day 1: ondansetron 16-24mg PO + dexamethasone 12mg PO +/- lorazepam 0.5-2mg PO or SL q4-6h +/- H2 blocker or PPI (some of these can be IV)</td>
<td>dexamethasone 8mg/day PO (days 2-3) +/- lorazepam 0.5-2mg PO or SL q4-6h +/- H2 blocker or PPI (one anti-emetic should be prn for breakthrough therapy)</td>
</tr>
<tr>
<td><strong>Low (10-30% incidence)</strong></td>
<td>capecitabine, tegafur uracil, etoposide, sunitinib, fludarabine, everolimus, lapatinib, lenalidomide, thalidomide</td>
<td>paclitaxel, docetaxel, mitoxantrone, topotecan, etoposide, premetrexed, methotrexate, doxorubicin liposome injection, temsirolimus, ixabepilone, mitomycin, gemcitabine, cytarabine (&lt; or = 1000mg/m2), 5-fluorouracil, bortezomib, cetuximab, trastuzumab, catumaxomab, panitumumab</td>
<td>Day 1: dexamethasone 4-12mg PO or metclopropamide 10-40mg PO and then q4-6h prn or prochlorperazine 10mg PO and then q4-6h prn +/- lorazepam 0.5-2mg PO or SL q4-6h +/- H2 blocker or PPI (some of these can be IV)</td>
<td>no routine treatment; optional: one anti-emetic prn for breakthrough therapy</td>
</tr>
<tr>
<td><strong>Minimal (&lt;10% incidence)</strong></td>
<td>chlorambucil, hydroxyurea, melphalan, methotrexate, 6-thioguanine, gefitinib, sorafenib, erlotinib</td>
<td>bleomycin, busulfan, cladribine, fludarabine, vinblastine, vincristine, vinorelbine, bevacizumab</td>
<td>no routine treatment</td>
<td>no routine treatment</td>
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**CINV Treatment**

Although aggressive prophylaxis is the main strategy in dealing with CINV, this side effect remains one of the most feared chemotherapy-associated side effects, due to incidence of refractory and breakthrough CINV. Similar classes of agents are used in treatment of CINV as in prevention. Below are the most common drug classes used for refractory and breakthrough CINV treatment:

**Serotonin (5-HT3) antagonists** are considered the most effective antiemetics. The examples include: ondansetron (Zofran®), dolasetron (Anzemet®), granisetron (Kytril®), palonosetron (Aloxi®). All of these agents have similar efficacy and safety. The most common side effects include: headache, ECG interval abnormalities (asymptomatic and transient), drowsiness, dizziness, constipation / diarrhea, liver transaminases elevation. Typical dosing regimens are as follows: ondansetron 16-24 mg/day PO, granisetron 1-2mg/day PO or 1mg PO bid and dolasetron 100mg/day PO. Palonosetron currently is not available in Canada (as of December 5, 2011).

**Neurokinin – 1 (NK-1) receptor antagonists** are indicated for prevention of acute and delayed nausea / vomiting. The most common example seen in community setting is aprepitant (Emend®). Aprepitant’s approved dosing regimen is as follows:125mg on day 1 and 80mg on days 2 and 3 (administered independently of food). It is important to note that it crosses the blood-brain barrier and placenta. On the positive side, no dosage adjustments are required for patients with ESRD (end-stage renal disease) or severe renal insufficiency. Most common side effects include: fatigue, dizziness, hiccups, gastritis, heartburn, diarrhea, elevated liver transaminases. There were case reports of urticaria, angioedema and Stevens-Johnson syndrome with aprepitant.

**Corticosteroids** are commonly used as antiemetic, despite the fact that they are not approved for this indication. Dexamethasone and methylprednisolone are effective for both acute and delayed nausea / vomiting. They are often used in combination with other classes of antiemetics. Although the exact mechanism of action is unknown, it is thought that corticosteroids antiemetic effects have to do with the inhibition of prostaglandin synthesis in the cortex and subsequent decrease in CNS serotonin turnover, which ultimately results in modulation of higher cortical pathways leading to the emetic center.

The general rationale for managing breakthrough CINV is to add one antiemetic drug from a different class than is already being used. If the CINV remains uncontrolled, the treatment strategy should be re-evaluated and adjustments may be necessary.

**Other classes and dosing regimens that may be used in CINV management:**

- **Antipsychotics / Dopamine receptor antagonist:** haloperidol 1-2mg PO q4-6h prn, olanzapine 2.5-5mg PO bid, metoclopramide 10-40mg PO q4-6h
- **Benzodiazepine:** lorazepam 0.5-2mg PO or SL q4-6h
- **Cannabinoid:** dronabinol 5-10mg PO q3-6h, nabilone 1-2mg PO bid
- **Phenothiazine:** prochlorperazine 10mg PO then q4-6h prn, promethazine 12.5-25mg PO q4h

**Constipation**

Constipation in cancer patients can be caused by variety of reasons, including: malignancy, neurologic (depression, autonomic neuropathy), gastrointestinal (nutrition-related, decreased abdominal muscle tone), metabolic/endocrine and/or it could be therapy-related (radiation, postsurgical, chemotherapy with thalidomide, arsenic trioxide and vinca alkaloids, especially vincristine)*. Vincristine: constipation might be the first sign of neurotoxicity, and can progress to ileus if left untreated.
Signs and symptoms of constipation vary, but commonly include the following: abdominal pain/distension, anorexia, confusion, liver or retroperitoneal pain, nausea/vomiting, urinary retention, pseudo-diarrhea (severe cases).

Management

Management starts with careful assessment of the patient and the constipation episode. Onset of constipation, normal bowel habits, use of laxatives, dietary modifications, activity level are all necessary facts that should be assessed prior to recommending a laxative to rule out impaction before using an oral laxative.

A variety of options are available for constipation management. Some of them include:

- **Stimulant laxatives** (bisacodyl, senna) - can be used for either one-time relief, or as chronic constipation prevention / management. It is seen especially in therapies involving vinca alkaloids and/or opioids. These agents are dosed to the desired effect of minimum one bowel movement in 48 hours.

- **Stool softeners** (docusate sodium/calcium) - can be combined with stimulant laxatives, however, should not be used alone for constipation caused by therapy with either vinca alkaloids or opioids.

- **Mineral oil** - can be helpful for one-time relief, however, is not recommended for chronic phophylaxis. In addition its unpalatability can be problematic in patients who are already feeling nauseated. Mineral oil also decreases the absorption of fat-soluble vitamins, which is highly undesirable in cancer patients, who often have appetite problems.

- **Saline laxatives** (magnesium citrate, magnesium hydroxide, sodium phosphate, sodium biphosphonate) - can also be used as a one-time relief, with the exception of magnesium hydroxide, which can be used for prophylaxis in the patients who find it palatable.

- **Hyperosmotic laxatives** (lactulose, sorbitol, PEG-electrolyte solution, glycerin suppositories) - can be used as preventative for vinca- and opioid-induced constipation and are just like stimulant laxatives are also dosed to the desired effect of minimum one bowel movement in 48 hours. They can be use as a one-time relief (q2h until a bowel movement occurs). The most common problem with this class of agents is their unpalatability, a factor which is especially problematic in patients who are already nauseated.

- **Prokinetic agents** (domperidone, metoclopramide) - are often used in patient on enteral feeding to reduce gastric emptying time. In addition they are also effective in mild-moderate nausea/vomiting. Their main role is in prevention of opioid-induced constipation.

**Diarrhea**

Diarrhea is a potential side effect of any chemotherapeutic agent, however, it is most commonly seen with irinotecan (unique: has 2 components: early and late onset), fluorouracil, methotrexate, cytarabine and in stem cell transplant conditioning (busulfan). There are also patient-associated risk factors that make one more predisposed to experiencing this side effect. These include: age (older than 65 y.o.) female sex, ECOG performance status > 2 (Eastern Cooperative Oncology Group; performance status from 0 – fully active to 5 – dead), tumor’s location (i.e.: bowel), bowel pathologies: inflammation, malabsorption, biliary obstruction as well as genetic factors that influence the metabolism and distribution.
Each patient that presents with diarrhea should be assessed regarding fever, hydration status, stool consistency, stool volume, stool frequency, duration of diarrhea and other contributing factors. This assessment is very important, since the management of diarrhea depends on the graded criteria (Common Toxicity Criteria, CTC, and graded 1-4).

Uncomplicated mild-moderate diarrhea (can be generally managed in the community):
- **Grade 1 (no colostomy):** increase by less than 4 stools/day compared to pretreatment
- **Grade 2 (no colostomy):** increase of 4-6 stools/day or nocturnal stools present
- **Grade 1 (colostomy):** mild increase in loose watery colostomy output
- **Grade 2 (colostomy):** moderate increase in loose watery colostomy output that does not interfere with normal activity

**Note:** If one of the following is present, the diarrhea cannot be rated as mild-moderate: moderate-severe cramping, moderate nausea/vomiting, decreased ECOG performance status, fever, sepsis, neutropenia, flank bleeding, dehydration.

Complicated moderate-severe diarrhea: refer to Emergency!
- **Grade 3 (no colostomy)** - >7 stools/day or incontinence (need parenteral support for dehydration)
- **Grade 4 (no colostomy)** – hemodynamic collapse requiring ICU (possible symptoms: shortness of breath, bradycardia, lightheadedness and signs of hypoxia)
- **Grade 3 (colostomy)** – severe increase in loose watery colostomy output that interferes with normal activity
- **Grade 4 (no colostomy)** – same as grade 4 without colostomy

Management:

**Non-pharmacological:**

Although non-pharmacological interventions may not be sufficient on their own, they should never be ignored in diarrhea management. First of all, the patient should avoid alcohol, caffeine, fruit juices and lactose ingestion (eliminate all products containing lactose), and rather eat frequent small meals and drink 8-10 glasses of clear fluids with electrolytes (Gatorade®, clear juices, decarbonated soft drinks, decaffeinated tea). Suggestions regarding nutrition can be summarized in short mnemonic - BRAT diet (bananas, rice, applesauce and toast). Psyllium fiber is also useful in mild diarrhea. If diarrhea is very severe, patient may require parenteral nutrition in order for GI tract mucosa to heal. Self-monitoring (recording the number of stools in 24 hours and other symptoms) of the diarrhea should be suggested to all patients.

**Pharmacological:**

Loperamide is the most commonly used remedy in diarrhea, and in certain situations the dosing regimen may be slightly different from the standard dosing of 4mg at first sign of diarrhea, then 2mg q4h or after each loose bowel movement, with a daily maximum of 16mg. This is particularly true for those patients whose grade 1 or 2 diarrhea persists longer than 24 hours after starting standard loperamide therapy, and also those who are on chemotherapy regimens involving irinotecan. In these two situations the recommended loperamide dosing instructions is 4mg at first sign of diarrhea, then 2mg q2h (4mg q4h while asleep) until 12-hour diarrhea-free. In this situation the daily maximum may exceed 16mg. Patients experiencing radiation-induced diarrhea should continue taking loperamide for the duration of the radiation therapy.

- If diarrhea persists longer than 24 hours after starting high-dose loperamide therapy, the patient should be referred, as antibiotic prophylaxis may be necessary. When diarrhea lasts longer than 48 hours, loperamide may be discontinued and patient could be started on either octreotide (Sandostatin®) 100mg subcutaneously, tincture of opium or budesonide 9mg daily for 2-3 days (studied in fluorouracil- and irinotecan-induced diarrhea refractory to loperamide...
- Annals of Oncology: “Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment” by B.H.M. Lenfers et al. [http://annonc.oxfordjournals.org/content/10/10/1251.full.pdf+html](http://annonc.oxfordjournals.org/content/10/10/1251.full.pdf+html). Table #2 summarizes typical anti-diarrheals and highlights most important features of each therapy.

Table #2: Anti-diarrheals, their role and dosing regimens in cancer patients:

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication name</th>
<th>Dosing regimen</th>
<th>Role in therapy</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorbent anti-diarrheals</td>
<td>Attapulgite (Diasorb®)</td>
<td>15-30 ml up to 8 times / day</td>
<td>safe to use in C. diff. infection since no effects on GI motility; not effective in moderate-severe diarrhea; unpalatable taste</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kaolin/pectin (Kaopectate®)</td>
<td>60-120 ml after each loose bowel movement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid anti-diarrheals</td>
<td>Loperamide (Imodium®)</td>
<td>4mg at first sign of diarrhea, then 2mg q4h or after each loose bowel movement, with a daily maximum of 16mg (see above for exceptions) 10-15 drops in water q3-4h</td>
<td>effective for some chemotherapy- and radiation-induced diarrhea; contraindicated in suspected C. diff. infection due to slowing of GI motility; loperamide is more potent than diphenoxylate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Opium tincture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diphenoxylate/atropine (Lomotil®)</td>
<td>2.5mg/0.025mg - 1-2 tabs q6h or after each loose bowel movement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mucositis**

Mucositis refers to inflammation of the mucosa lining of the GI tract, which presents itself as mouth sores and esophagitis. This is a very common side effect, due to the fact that the turnover of GI epithelial lining occurs every 7-14 days, which makes these cells very vulnerable to cytotoxic damage induced by chemotherapy. The severity of mucositis may vary from mild inflammation to bleeding ulcerations. Most commonly affected area is the oral mucosa due to lack of keratin protection.

Mucositis progresses in the following manner:

- 0-5 days after therapy: asymptomatic redness
- 0-7 days after therapy: desquamation with white patches
- 6-12 days after therapy: contiguous pseudomembranes (painful lesions) associated with dysphagia and decreased oral intake
- 12-16 days after therapy: painful lesion (ulceration may be present)

Many chemotherapy agents are responsible for this side effect, which includes cyclophosphamide, fluorouracil, anthracyclines, vinca alkaloids, methotrexate, mercaptopurine and a variety of biologic agents.
Mucositis can also be caused by radiation, and its severity depends on the daily radiation dose, total dose and the tissue size being irradiated. Other factors may also contribute pre-disposing one to a higher risk of developing mucositis. These include: alcohol, tobacco, xerostomia, infection, pre-existing oral lesions, poor dental hygiene, ill-fitting dentures and Caucasian race. When radiation is combined with chemotherapy the risk and severity of mucositis is combined also, thus making it a very significant problem for patients who are treated with both therapies.

Management:

Non-pharmacological:

Dietary recommendations are very important in both prevention and treatment of the mucositis. The key highlights of dietary modifications include: avoiding rough foods (chips, toast), spices, salt and acidic fruits. Smoking and alcohol consumption should also be avoided, in order to prevent additional irritants to mucosal cells. The patient should rather eat soft, pureed foods, non acidic fruits, soft cheeses and eggs.

Pharmacological:

- **Topical antibacterials** (i.e.: chlorhexidine mouthwash) is commonly used and although it is found to be more effective than good basic mouth care, the systematic review does not support its use in prophylaxis of oral mucositis. Chlorhexidine acts against gram-positive colonization, however, established infections require systemic antibiotics.

- **Topical antifungals** (nystatin mouthwash, clotrimazole troches) are used in treatment of mild candidiasis and in prophylaxis in patients receiving remission-induction chemotherapy for solid tumors, lymphomas or leukemias.

- **Antiviral prophylaxis** may be necessary, since immunocompromised patients commonly undergo herpes simplex/zoster virus reactivation. Oral acyclovir or valacyclovir are equally beneficial and recommended patients receiving standard-dose chemotherapy. Acyclovir-resistant cases will require IV foscarnet.

- **Allopurinol mouthwash** (1-16mg/ml) is used as a preventative from epithelial damage in patients treated with fluorouracil. Allopurinol inhibits orotidylate decarboxylase enzyme, increasing orotic acid levels, which binds to fluorouracil, thus preventing epithelial damage. This strategy has not become the standard of practice, since the benefit has not been seen consistently.

- **Benzydamine rinse** is a non-steroidal analgesic / anesthetic / anti-inflammatory that is used for prevention of radiation-induced mucositis (mostly in head-neck cancers). Evidence suggests that this therapy is effective in improving the mucositis symptoms in these patients, however, more research is required in order to investigate this therapy’s effectiveness.

- **Sucralfate solution** is also used as a mucosal protectant as it increases the prostaglandin E2 production, thus forming a protective barrier. It is commonly dosed at 1g po qid for both chemotherapy- and/or radiation-induced mucositis. Unfortunately, as many other oral liquid medications, the texture can be too nauseating for some patients. The current evidence does not support its use, due to inconsistency in efficacy.

- **Normal saline solution, sodium bicarbonate homemade solution** (½ teaspoon baking soda or salt in 1 cup warm water and rinse several times a day) are also very useful and effective preventative and management measures. It should be emphasized to the patient that this measure should be used early as a prevention, rather than waiting until problems arise.

Other useful recommendations:
- Use a soft toothbrush that is replaced regularly
Multidisciplinary approach: include dental professionals in management
Morphine (topical spray) is the analgesia of choice in patients undergoing hematopoietic stem cell transplantation
During 5-fluorouracil administration cryotherapy is often used (ice chips constrict the blood vessels decreasing the distribution of the drug to oral mucosa)

➔ Xerostomia

Xerostomia (dry mouth) presents with the following signs and symptoms: difficulty chewing, tasting, swallowing and talking (in severe cases), dry/cracked lips and oral mucosa. Patients will often complain of inability to get a good night’s sleep due to necessity to continuously wake up to moisten the mouth or to relieve polyuria secondary to increased water consumption. Secondary candida infections and dental caries (as result of alterations in normal oral flora) may develop.

Management:

Saliva substitutes, such as Mouth Kote®, Moi-Stir® are widely used and provide some relief. Pilocarpine 5mg tid or qid is sometimes used in prevention of radiation-induced xerostomia, however, there is not enough evidence to date to recommend this strategy as standard of practice. In addition, the extensive list of side effects (nausea/vomiting, cramps, diarrhea, CNS / CV / GU effects) makes this even less attractive prophylaxis option.

Key Counseling Points:

- Keep mouth / lips moist by rinsing mouth with water q2h, using saliva substitutes, applying lip moisturizer, sucking on hard candies and using cool mist room humidifiers.
- Keep mouth and teeth clean by using soft toothbrush; cleaning dentures / bridge(s) after eating; flossing with unwaxed floss and avoiding mouthwashes with alcohol base.
- Increase fluids by drinking at least 8-12 glasses of fluid/day; carrying a water bottle with you and limit coffee, tea and alcohol.
- Dietary changes: eat a soft, high protein and moist diet; serve food lukewarm, avoid dry foods that can scrape the mouth, yogurt, fruit slushies, avoid frizzy sodas

➔ Anemia

Anemia can be caused by a multitude of reasons, such as: tumor’s effects on bone marrow, renal dysfunction and subsequent reduction in erythropoietin production, radiation/chemotherapy side effect, deficiency in vitamin B12, iron or folic acid and also blood loss. Currently patients rate fatigue as worse than nausea, vomiting or pain (>75% of patients experience it monthly and 30% suffer from fatigue on daily basis). Therefore, adequate management of this side effect is highly necessary in order to improve patient’s quality of life.

By correcting anemia there is no guarantee that the fatigue will be gone, since the cancer-related fatigue is the most common side effect of the cancer itself and of the treatment. Patients often describe it as “paralyzing”. It typically comes on suddenly, not as a result of activity or exertion, and is not relieved by the rest or sleep. It may continue even after the treatment has been stopped.
Management:

ESA (erythropoetin stimulating agents) are indicated for patients receiving chemotherapy. In patients who are not receiving radiation or chemotherapy, these agents actually increase the risk of death.

- **Epoetin alpha (Eprex®)** binds to erythropoetin receptors on bone marrow cells stimulating the proliferation of erythroid colony-forming units and blast forming units. Its half-life is around 4 hours, and increases up to 13 hours in chronic renal failure. Subcutaneous administration is preferred over intravenous due to the prolonged half-life, which is desirable for better effect. The onset of action is approximately 7 days. Eprex is contraindicated in uncontrolled hypertension, hypertension to albumin or mammalian cell-derived products and should be used with caution in dialysis patients due to seizures risk. Side effects commonly seen in cancer patients include: fever, diarrhea, edema, injection-site reactions, hypertension and thrombotic events. Although this is a very effective agent in anemia management, lately concerns regarding possible reduction of time to tumor progression started arising. There are studies that have reported undesirable effects on proliferation, decrease in chemotherapy efficacy and increased resistance to selective therapies (Clin Cancer Res. 2011 Oct 15;17(20):6373-80. Epub 2011 Jul 12. The role of erythropoietin and erythropoiesis-stimulating agents in tumor progression. Hedley BD et al.). Other studies have found no such effects; therefore, this issue needs to be investigated further until reliable conclusions can be made. Risks and benefits should be carefully weighed before starting a patient on this therapy.

- **Darbepoetin alfa (Aranesp®)** is very similar as epoetin alpha, except for the addition of sialic acid that prolongs the half-life by 2-3 times, reducing the administration frequency, while not compromising the efficacy. Steady state concentration is reached at around 4 weeks, and hemoglobin levels start increasing at 2-6 weeks after initiation of therapy. This agent is contraindicated in uncontrolled hypertension, hypersensitivity to epoetin alpha. Iron supplementation (IV route more commonly) is often used as a response enhancer. All patients prescribed ESA will have baseline iron assessment (serum ferritin, iron, TSAT and TIBC) and will be prescribed iron therapy accordingly.

Sometimes hemoglobin needs to be raised rapidly and blood transfusion is the only answer. The safety of blood transfusion has significantly improved over the years, however, the following risks cannot be fully eliminated: transfusion reactions, congestive heart failure, virus transmission, bacterial contamination and iron overload.

**Key counseling points:**

- Discuss risk versus benefits of using ESA (risk = risk of hypertension and blood clots + possibility of enhancing effects on tumor progression; benefits = alleviate the fatigue and ability to continue cancer treatment without requiring blood transfusions)

**Febrile Neutropenia (FN)**

Neutropenia refers to bone marrow suppression, which is the leading toxicity requiring dose reductions. The normal WBC (white blood cells) range is between 4.8 to 10.8 x 10^9 / L. The lowest value of the neutrophils during a cycle of chemotherapy (nadir) occurs approximately 10-14 days after the first dose of chemotherapy and they normally recover by 3-4 weeks after chemotherapy is stopped. Neutropenia is defined as Absolute Neutrophil Count (ANC) < 0.5 x 10^9 / L or < 1 x 10^9 / L with a predicted decrease to < 0.5 x 10^9 / L over the next 48 hours. The importance of this is in the fact that the lower the ANC the greater the risk of developing serious infections. Febrile neutropenia means that in addition to neutropenic ANC the patient also develops a fever (sign of infection). This is
considered a medical emergency, and is a common cause of mortality and morbidity in cancer patients.

Since it is impossible to know the patient’s ANC at every instance,

**Any cancer patient with a fever of 38°C (or >100°F) or greater must be immediately referred to an Emergency Department or to their treating doctor.**

Therefore, febrile neutropenia = neutropenia + single oral temperature ≥ or > 38.3°C.

It is important to note that other symptoms of infection can be absent.

As soon as a patient is started on chemotherapy, he/she should be strongly advised to purchase a thermometer, if they do not have one yet. Also extensive counseling should be done regarding proper and frequent hand washing, proper oral care, avoiding crowds and being around sick people.

Infections associated with neutropenia are often polymicrobial, resulting in higher mortality rates than the infections caused by a single organism.

**Management:**

Colony-stimulating growth factors (CSFs) are known to reduce the incidence of febrile neutropenia, length of hospitalizations, incidence of confirmed infections, duration of infection treatment, without established effect on mortality, tumor response rate or overall survival. The main benefit of prophylaxis with CSFs is the ability to treat the cancer more aggressively.

CSFs are indicated for neutropenia prophylaxis in patients undergoing chemotherapy regimens that are known to cause >20% incidence of febrile neutropenia, patients diagnosed with acute leukemia and myelodysplastic syndromes, as well as those with patient-related risks, listed below:

- age > 65 y.o., poor performance status, previous febrile neutropenia episode, extensive prior treatment, combined radiation and chemotherapy, tumors involving bone marrow, poor nutrition habits, presence of open wounds/active infections, advanced cancers, as well as other serious immunocompromising comorbidities.

**Table #3: Indications, dosing and contraindications of CSF:**

<table>
<thead>
<tr>
<th>Agent * Filgrastim (Neupogen®)</th>
<th>Indication</th>
<th>Dosing</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After myelosuppressive chemotherapy</td>
<td>5 mcg/kg/day starting 1-3 days after chemotherapy completion</td>
<td>Hypersensitivity to hematopoietic growth factors or E.coli - derived products</td>
</tr>
<tr>
<td></td>
<td>Following BMT</td>
<td>5-10 mcg/kg/day subcut or IV infusion</td>
<td>Caution in patients with hairy cell leukemia, gout, psoriasis and pre-existing heart conditions</td>
</tr>
<tr>
<td></td>
<td>PBSC (peripheral blood stem cell) mobilization</td>
<td>5-10 mcg/kg/day 4 days before first leukapheresis procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe chronic neutropenia</td>
<td>6 mcg/kg BID</td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>Indication</td>
<td>Dose</td>
<td>Side Effects</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>------</td>
<td>--------------</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta®) – pegylated filgrastim (prolonged half-life = 15-80 hours)</td>
<td>Decrease FN incidence in patients with non-myeloid malignancies receiving chemotherapy with a FN risk of 17% or more after chemotherapy completion, given that there is an interval of at least 14 days between Neulasta injection and next chemotherapy</td>
<td>6 mg starting 1-3 days</td>
<td>Hypersensitivity to hematopoietic growth factors or yeast–derived products</td>
</tr>
<tr>
<td>Sargramostim (Leukine®) – currently not available in Canada</td>
<td>Following BMT</td>
<td>250 mcg/m2/day subcut bolus or IV infusion</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>PBSC (peripheral blood stem cell) mobilization</td>
<td>250 mcg/m2/day subcut bolus or IV infusion continued through leukapheresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Induction therapy for AML in elderly</td>
<td>250 mcg/m2/day</td>
<td></td>
</tr>
</tbody>
</table>

* All three agents can be administered subcutaneously.

**Important note:** These agents should not be administered within 24 hours of chemotherapy due to the high risk of hematologic toxicity.

There are a number of prominent side effects that are common to all three CSF agents, which include:
- Bone pain (occasionally requiring analgesia with NSAIDs and sometimes opioids)
- Injection-site reactions
- Skin rashes

In addition, filgrastim and sargramostim also may cause: bruising, diarrhea, edema, flu-like symptoms and myalgias (sargramostim). Sargramostim has a higher incidence of these side effects than filgrastim.

**Less common side effects for each agent are listed below:**

- **Filgrastim (Neupogen®):** transient neutropenia with IV infusions, dyspnea in patients with underlying lung disease, anemia, thrombocytopenia, rheumatoid arthritis flare in patients with Felty's syndrome, sickle cell crisis.
- **Pegfilgrastim (Neulasta®):** adult respiratory distress syndrome in patients with sepsis, splenic rupture, anemia, thrombocytopenia, sickle cell crisis, allergic reactions.
- **Sargramostim (Leukine®):** dyspnea in patients with underlying lung disease, peripheral edema, capillary leak syndrome, pleural/pericardial effusion (patients with pre-existing fluid retention, pulmonary infiltrates, congestive heart failure).

**Prophylaxis:**

Antimicrobial prophylaxis with fluoroquinolones may be done if required, in which case fluoroquinolone would not remain a treatment option later. Prophylaxis is mandatory in certain cases, particularly the ones that involve the following: alemtuzumab, temozolamide + radiotherapy,
fludarabine, certain HSCT (Hematopoietic Stem Cell Transplant) recipients, solid organ transplant patients, acute lymphocytic leukemia patients, prednisone ≥ 20mg for 1 month. *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) is an opportunistic pathogen, and prophylaxis is required in immunocompromised patients (see list of criteria above). The following may be used for prophylaxis:

- *sulfamethoxazole / trimethoprim* two or three times a week
- *dapsone* daily
- *pentamidine inhalations*

Antifungal prophylaxis with *fluconazole* is sometimes necessary in bone marrow transplant patients.

Antiviral prophylaxis is necessary for shingle prevention purpose in HSV-seropositive patients on chemotherapy for acute leukemia and those who have received hematopoetic stem cell transplant.

**Vaccinations:**

All individuals at risk of immunosuppression, as well as their household contacts should be strongly encouraged to receive annual influenza vaccine. However, there are precautions with certain vaccines and it is important to note these when answering questions from your patients regarding vaccination. Live attenuated vaccines (MMR, FluMist®, chicken-pox vaccine, yellow fever vaccine, certain rabies vaccines, BCG, typhoid vaccine) may put radiation/chemotherapy patients at risk, and should be done only three months after the therapy has been completed. Thus FluMist® intranasal, being a live attenuated vaccine is contraindicated in immunosuppressed patients and neither should it be offered to household contact of the immunosuppressed patient due to lack of data regarding person-to-person transmission.

In addition, patients should not receive pneumococcal, meningococcal and Hib vaccines within two weeks before elective splenectomy. It is important to investigate the patient’s treatment modalities before offering vaccines and always checking the appropriate timing of these vaccines, in order to not compromise your patient’s safety.

**Key Counseling Points:**

- Immediately contact your doctor or report to an Emergency Department if you have fever of 38.3°C or greater. Make sure you have a thermometer at home.
- CSF: explain injection instructions, side effects and monitoring (bone pain, hypertension, blood clot, skin rash)

**Thrombocytopenia**

Thrombocytopenia is defined as platelets count of < 100,000/mm3. If platelet count is < 20,000/mm3 the patient is at increased risk of bleeding and platelet transfusion may be required.

**Management**

Although currently not available in Canada, oprelvekin – interleukin 11 (Neumega®) is used for prevention of severe chemotherapy-induced thrombocytopenia in non-myeloid cancers. It acts by supporting the proliferation of hematopoietic progenitor cells. It is usually doses at 50mcg/kg subcutaneously daily (dose should not be rounded up), starting 6-24 hours after chemotherapy completion and continuing for 2-3 weeks (until platelet count increases to >50,000 cells/mm3). Neumega should not be used within 48 hours before chemotherapy.
Most common side effects include: edema, decreased salt intake, shortness of breath, tachycardia, conjunctival redness, atrial arrhythmias, peripheral edema, headache, arthralgia, myalgia, dizziness, thrombosis of indwelling catheter and cerebral infarction. It should be used with caution in patients with the following comorbidities: left ventricular dysfunction, history of arrhythmias, respiratory disease, history of thromboembolic disorders and hepatic / renal dysfunction, hypertension.

Myalgia / arthralgia

This is a common side effect of the following: aminoglutethimide, anastrozole, letrozole, exemestane, tamoxifen, bleomycin, decitabine, docetaxel and paclitaxel. The symptoms are described as achining or deep pain in the muscles and/or joints that can also be radiating, shooting, stabbing or pulsating. This usually lasts for 3-7 days and may involve a variety of sites, such as: back, hips, shoulders, thighs, legs and feet. One of the theories of this symptom is that it is caused by hyperalgesic dysfunction of the nociceptive receptors, fibers and spinothalamic system.

Patients who are taking aromatase inhibitors (especially exemestane) have a risk of experiencing this side effect, and if patient happens to be developing osteoporosis he/she also will be at a higher risk of development myalgias and bone fractures. Bisphosphonates and calcium can help reduce these risks.

Management

If necessary, prevention can be done using prednisone 10mg BID for 5 days starting 24 hours after completion of chemotherapy. If the myalgia/arthralgia is present, there are a number of treatment options available to the patients: acetaminophen, NSAIDs (ibuprofen 400-800mg q6-8h or naproxen 500-750mg/day), prednisone (20mg daily for 2-5 days), tramadol, opioids, glucosamine/chondroitin, topical capsaicin and methylsalicylate may be used. Sometimes the patient can be managed with one of the following: amitriptyline 25mg HS, gabapentin 300-400mg BID-TID, calcitonin 200 IU HS or fexofenadine 60mg BID. If, despite trying all these options, the pain has not resolved or a new joint became involved then the patient should be referred to a rheumatologist. Ultimately, it may be necessary to modify the therapy (i.e.: switch to a different aromatic inhibitor). Non-pharmacological options include: using a heating pad, massage therapy or transcutaneous electrical nerve stimulation.

Hemorrhagic Cystitis

Cyclophosphamide and ifosfamide may cause hemorrhagic cystitis in a non-dose-dependent fashion. This happens due to the active metabolite, called acrolein, which in alkaline environment can irritate the bladder lining. Intravesicular chemotherapy administration may also lead to bladder irritation. The danger that comes with hemorrhagic cystitis is an increased risk for development of bladder cancer later in life. The symptoms include red or pink urine, pain during urination, urinary frequency, and an increased urge to urinate.

Management

This risk can be managed with prevention using aggressive hydration resulting in frequent voiding minimizes this risk, as well as intravenous administration of mesna (sodium-2- mercaptoethanesulfonate), which prevents hemorrhagic cystitis by binding to acrolein metabolite. For a patient that already has hemorrhagic cystitis, mesna can be used to treat this complication. The most common side effects include: fatigue, headache, diarrhea, hypotension, limb pain in high doses, and positive urine dipstick ketone test.
**Cardiac Toxicity**

There are many chemotherapy drugs that may cause various cardiotoxicity. The cardiotoxicity may present as the following: angina, arrhythmias, cardiogenic shock, cardiomyopathy, chronic heart failure, DVT, edema, effusion, endomyocardial fibrosis, heart block, hypertension, hypotension, ischemia, left ventricular dysfunction, myocarditis/pericarditis and vasospasms.

As with many other complications, the risk is determined not only by particular medications, but also depends on the following patient-related factors: age (> 65 y.o. and children), female gender (especially pediatric and 66-70 y.o. who are being treated with anthracyclines), concurrent ionizing radiation to chest wall, prior exposure to anthracyclines, underlying cardiac disease (history of MI, active CHF, hypertension, diabetes mellitus, metabolic abnormalities).

Agents that cause most cardiotoxicity are anthracyclines, cyclophosphamide, mitomycin, etoposide, trastuzumab, melphalan, vincristine and bleomycin. Some agents cause dose-dependent toxicity, with specific examples being: aldesleukin, anthracyclines (cumulative lifetime doses have been established), cyclophosphamide, ifosfamide, melphalan and platinum agents.

Patients on regimens involving these cardiotoxic agents are generally monitored closely for cardiologic parameters. In order to avoid necessity of dose reductions due to cardiotoxicity, cardioprotective agent dexrazoxane (Zinecard®) IV is sometimes used. It works by chelating free iron and iron bound to anthracycline complexes thus decreasing anthracycline-induced free radical damage.

**Signs of cardiac toxicity that require referral to the clinic:**
- Fatigue, shortness of breath, progressive weight gain and swelling of the ankles.

**Dermatologic Toxicity**

Dermatologic complications include a large array of dermatologic conditions and can vary in severity. The most common dermatologic reactions are briefly discussed below.

**Palmar-plantar erythrodysesthesia (a.k.a. hand-foot syndrome)**

This refers to the condition when palms of the hands and soles of the feet become dry, red, numb, tingling and swelling may be present. It may interfere with normal daily activities and vigorous exercise / manual labour can exacerbate the reaction. Symptoms improve once therapy is stopped.

This reaction can be caused by the following agents: aldesleukin, amifostine, bleomycin, capecitabine (usually appears early), cisplatin, cyclophosphamide, cytarabine, anthracyclines, docetaxel, erlotinib, etoposide, fluorouracil, hydroxyurea, lapatinib, lomustine, melphalan, 6-mercaptopurine, methotrexate, mitomycin, oxaliplatin, paclitaxel, sunitinib, tegafur, thiotepa, vincristine and vinorelbine.

Patients taking these medications should be counseled on the following:

- Avoid tight shoes and repetitive rubbing pressure to hands or feet (strenuous exercise)
- Apply moisturizers liberally and frequently
- Lanolin-containing creams are especially helpful

**When to refer:** If the condition is not improving or worsening despite intensive use of moisturizers the patient should contact their doctor, as dose reductions or pause in the treatment may be required until the condition has improved.
**Acneiform eruption / folliculitis / pustular rash**

This condition appears as an acne-like rash (note: acne-like - not just typical acne), which is most commonly caused by epidermal growth factors (EGFR) inhibitors (most common with cetuximab, erlotinib, panitumumab and gefitinib). It usually appears within 7-10 days after starting the treatment and commonly involves nasolabial folds, forehead, chin and occasionally on the upper chest, back, scalp and pubic skin. Rarely, some patients may develop full-body folliculitis.

Patients at risk of experiencing this condition should be counseled to avoid sun exposure (using sunscreens with SPF 15 or greater if going outside) and moisturizing the dry areas of the body twice daily with a thick alcohol-free emollient.

For those patients who are already suffering from this side effect treatment options depend on the severity of the condition. Mild rash does not require treatment, while moderate and severe rashes can be treated with clindamycin / hydrocortisone cream with or without oral minocycline or doxycycline. Topical steroids are used routinely. Many acne products, such as benzoyl peroxide / salicylate – based products should be avoided, as they may worsen the rash.

**When to refer:** if the rash is moderate or severe, or does not improve / progresses despite moisturizing the patient should contact their doctor, as dose reductions or stopping the therapy may be required.

**Alopecia (hair loss)**

Some (not all) chemotherapy regimens at certain doses lead to hair loss, which grows back within few weeks to a month after the treatment is done. As it grows back it may be slightly different in terms of color and texture, which is important for the patient to be aware of.

Hair loss is mostly seen with the following agents: actinomycin, bevacizumab, bleomycin, busulfan, capecitabine, dactinomycin, epirubicin, floxuridine, irinotecan, ixabepilone, mechlorethamine, methotrexate, mitomycin, teniposide, topotecan, amsacrine, cyclophosphamide, daunorubicin, doxorubicin, docetaxel, etoposide, ifosfamide, paclitaxel, vinblastine, vincristine and vindesine

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**Hepatic Toxicity**

Hepatic toxicity mostly consists of idiosyncratic reactions. The risk is higher for the patients with pre-existing hepatic disease, particularly hepatotoxic chemotherapy agents, co-administration of other hepatotoxic medications, and other comorbidities posing hepatic risks. Patients at risk factors have their liver function assessed at baseline and frequently throughout the treatment course.

Hepatotoxic chemotherapy agents include:

- aldesleukin, altretamine, arsenic oxide, asparaginase, bevacizumab, bleomycin, bortezomib, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dasatinib, decitabine, doxorubicin, erlotinib, etoposide, fludarabine, fluorodeoxyuridine, fluorouracil, flutamide, gefitinib, gemcitabine, gemtuzumab ozogamicin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon-alpha, irinotecan, melphalan, 6-mercaptopurine, methotrexate, mitomycin, mitoxantrone, ondansetron, oxaliplatin, pemetrexed, pentostatin, plicamycin, procarbazine, sorafenib, streptozocin, taxanes, temozolomide, thalidomide, topotecan, trastuzumab and vincristine.

Combination therapies present a higher incidence of hepatotoxicity than single agent therapies.
Neurotoxicity

This usually first manifests itself in the hands and feet, and eventually it progresses to involve arms and legs entirely. The sensations may be described as tingling, numbness, shooting, burning pain or sensitivity to temperature and the condition can be quite debilitating. Neurotoxicity is one of the most common reasons that make chemotherapy intolerable to many patients and it is most commonly seen with the following agents: carboplatin, cisplatin, docetaxel, oxaliplatin, paclitaxel, thalidomide and vincristine.

Management

Prevention using vitamin E 300mg/day can be used sometimes as a preventative measure. Oxaliplatin administration is commonly preceded by calcium / magnesium infusion, which has the role of preventing the neurotoxicity and allow the patient to benefit from chemotherapy benefits longer than otherwise would be possible. Gabapentin 200-300mg/day or carbamazepine 200-600mg/day can be also seen occasionally for prevention of neurotoxicity.

Treatment is usually based on one of the following treatment options:

- Gabapentin 500mg/day – 1800mg/day
- Lamotrigine 300mg/day
- Topical amitriptyline, baclofen and ketamine
- Tricyclic Anti-depressants
- Venlafaxine

Ocular Toxicity

A variety of chemotherapy agents may pose risks to eyesight. Although relatively uncommon, such complication are usually severe and irreversible, and may involve optic nerve defects, blurred vision, cataracts, conjunctivitis, corneal ulcers, diplopia, edema, keratitis, ocular pain, retinal damage, and vascular issues. Referral to the treating doctor should be made without hesitance if the patient starts complaining of changes to their vision.

Pulmonary Toxicity

Many chemotherapy agents may cause pulmonary toxicities, therefore, if the patient manifests signs and symptoms related to breathing, do no hesitate to refer the patient to the clinic for further investigation.

Factors that increase the risk of pulmonary toxicity include the following:

- Cumulative dose: bleomycin, busulfan, carmustine, aldesleukin
- Older age
- Elevated CrCl (bleomycin)
- Concurrent radiotherapy or combination therapies with bleomycin, busulfan, mitomycin, cyclophosphamide, doxorubicin, actinomycin
- Preexisting lung disease

Treatment commonly involves discontinuation of the offending agent and corticosteroids therapy.
Renal Toxicity

Many agents may cause renal toxicity, and this involves potential dosing reductions of the medications that are eliminated renally.

The following agents are associated with nephrotoxicity:
- aldesleukin, aminoglutethimide, asparaginase, azacitidine, bevacizumab, carboplatin, carmustine, cetuximab, cisplatin, cyclophosphamide, gemcitabine, gefitinib, ifosfamide, imatinib, interferon-alfa and gamma, lomustine, methotrexate, mitomycin, nitrosureas, oxaliplatin, pentostatin, plicamycin, streptozocin, trimetrexate and vincristine.

Agents eliminated renally include:
- bleomycin, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, etoposide, hydroxyurea, ifosfamide, melphalan, methotrexate, nitrosureas (carmustine, lomustine, semustine, streptozocin), pentostatin and topotecan.

The following are the general guidelines for dose adjustments based on the creatinine clearance (% of the recommended dose based on the indication):

- **Capecitabine**
  - 30-50ml/min: 75%
  - < 30ml/min: omit the dose

- **Cyclophosphamide**
  - 10-50ml/min: 75%
  - < 10ml/min: 50%

- **Cytarabine**
  - 30-60ml/min: 50%
  - < 30ml/min: omit the dose

- **Fludarabine**
  - 30-60ml/min: 75%
  - 10-30ml/min: 50%
  - < 10ml/min: omit the dose
  - ESRD: 80% followed by daily dialysis

- **Hydroxyurea**
  - 10-60ml/min: 75%
  - < 10ml/min: 50%

- **Lomustine**
  - < 60ml/min: omit the dose

- **Mercaptopurine**
  - Adjust by either decreasing the dose or increasing the interval

- **Methotrexate**
  - 30-60ml/min: 50%
  - < 30ml/min: omit the dose

- **Zoledronic acid**
  - 50-60ml/min: 3.5mg
  - 40-49ml/min: 3.3mg
  - 30-39ml/min: 3mg
  - < 30ml/min: omit the dose
WHEN SHOULD YOU REFER YOUR PATIENTS?

**REFER TO EMERGENCY DEPARTMENT OR IMMEDIATELY CONTACT THE CLINIC:**

- **Fever over 100°F or 38°C by an oral thermometer** with or without signs of infection (chills, cough, pain or burning when urinating)
- **Bleeding problems** (black/tarry stools, blood in urine, extensive bruising, etc.)
- **Allergic reaction soon after treatment**: flushing, rash, itching, dizziness, face swelling, breathing problems
- **Nausea, vomiting or diarrhea that are uncontrolled** with recommended measures
- **Signs of heart problems**: fast/uneven heartbeat, chest pain/pressure, shortness of breath, difficulty breathing, swelling of ankles, fainting when on a regimen including either anthracyclines, aldesleukin, cyclophosphamide, ifosfamide, melphalan, platinum agents or newer biologic agents
- **Hypotension** signs/symptoms
- **Severe headache not controlled with acetaminophen** or if headache occurs together with nausea / vomiting and/or changes in eyesight
- **Seizures** or altered state of consciousness

**REFER TO THE TREATING DOCTOR:**

- **Signs of severe anemia** (lightheadedness, shortness of breath)
- **Signs of liver problems** (jaundice, white/clay-colored stools)
- **Sore throat / mouth that causes difficulty when swallowing**
- **Severe diarrhea (> 7 loose stools/day or lasting longer than 24 hours with loperamide therapy)**
- **Easy bruising/ minor bleeding**
- **Redness / swelling / pain where the needle was placed**
- **Skin rash / acne that persists or progresses despite recommended measures**
- **Changes in eyesight**
- **Signs of a gout flare-up**
- **Hand-food reactions that are moderate or severe or persist / progress despite recommended measures**
- **Signs of kidney problems: lower back pain**
- **Severe skin reaction where you have had radiation**
- **Numbness or tingling in feet or hands.**
- **Muscle or joint pain, which is severe or bothersome**
SAFE HANDLING OF ORAL ANTI-CANCER AGENTS:

Many guidelines on this topic have been developed for hospital and clinic practice, however, such information tailored to community pharmacies is not easily found. Although the staff in community pharmacy is mainly dealing with tablets that are often coated, they are still being exposed to chemicals that have been established to be carcinogenic and teratogenic.

Am I really at risk?

Due to the fact that anti-cancer agents are not the most common medications we are dealing with we often tend to underestimate the exposures we have and the significance of them. Examples of exposures to cytotoxic medications in community pharmacy setting include:

- Counting out uncoated tablets / capsules from a stock bottle
- Preparing unit-dosing systems (blister packs)
- Crushing tablets to formulate liquid dosage forms
- Compounding cytotoxic powders
- Contact with drug from touching the exteriors of the drug containers, counting trays, work surface areas and prescription bottle
- Cleaning drug-preparation areas
- Handling contaminated wastes (empty multidose bottles, vials)

Routes of exposure:

In a community pharmacy setting, cytotoxic chemicals are most prone to enter the body via inhalation and skin contact / absorption. Trends have been found detecting that even small constant exposure may result in increased incidence of genotoxicity, fetal loss, congenital malformations and infertility.

As the number of oral chemotherapy agents increases and more and more patients fill their chemotherapy in community pharmacies, reliable guidelines and protocols should be established to protect the safety of the staff.

In 2007 Pharmacy Times Journal has published a study by Susan Goodin (“Safe Handling of Oral Chemo Agents in Community Settings”) that provides practical recommendations specifically designed for community pharmacies.

Practical suggestions:

1. Identify hazardous drugs used in your pharmacy and update the list annually
2. Affix appropriate labels indicating safe handling precautions
3. Develop dose verification procedures to reduce medication errors and limit your exposure to the hazardous drugs.
4. Establish and follow recommendations that would ensure cleaning work area in the safest manner
5. Refuse to reconstitute powders if you do not have access to a negative-pressure environment
6. Do not cut / crush the tablets or open the capsules, unless you have been trained specifically in hazardous drugs handling
7. Compounding should be performed by specially trained staff and only if safety technology is available (negative-pressure or NIOSH-approved aspirator, etc.)
8. Personnel preparing oral chemotherapy (counting, packaging) should wear double gloves
9. Hands should be washed before putting gloves on and after taking them off
10. If splashing is potentially expected – use eye protective equipment
11. Use a separate counting tray and clean it after each use while you are still wearing personal protective equipment.
12. Dispose of empty containers and unused cytotoxic agents in chemotherapy-disposal container

The following is a list of oral anti-cancer agents that are hazardous:

- **Hormonal agents:**
  - Anastrazole, bicalutamide, exemestane, letrozole, megestrol, progesterone, tamoxifen

- **Alkylating agents:**
  - Busulfan, chlorambucil, cyclophosphamide, lomustine, melphalan, temozolomide

- **Antimetabolites:**
  - Capecitabine, mercaptopurine, methotrexate, thioguanine

- **Tyrosine kinase inhibitors:**
  - Imatinib, dasatinib, erlotinib, gefitinib, sorafenib, sunitinib

- **Miscellaneous:**
  - Etoposide, hydroxyurea, isotretinoin, tretinoin (Vesanoid), lenalidomide, procarbazine, thalidomide
REFERENCES:

- 2009 Oncology Pharmacy Preparatory Review Course: Symptom Management
- BC Cancer Agency: http://www.bccancer.bc.ca/default.htm - multiple subsections
- Chemotherapy Drugs and Side Effects Information – Chemo Care: http://chemocare.com/
  http://theoncologist.alphamedpress.org/content/12/9/1143.full
- Canadian Association of Pharmacy in Oncology: http://www.capho.org/
- National Cancer Institute: http://www.cancer.gov/
- American Cancer Society: http://www.cancer.org/
- Doctor-approved cancer information from ASCO: http://www.cancer.net/portal/site/patient
- Formulas for Calculating Body Surface Area (BSA): http://www.halls.md/body-surface-area/refs.htm

Mandatory pre-reading material:
- What is cancer? http://cancer.gov/cancertopics/cancerlibrary/what-is-cancer
- Chemotherapy Side Effects Fact Sheet: http://cancer.gov/cancertopics/coping/chemo-side-effects
# APPENDIX 1

## Common oral anti-cancer agents: indications and corresponding dosing regimens:

***This is just a general dosing guideline – specific protocol and patient parameters will determine the regimen***

<table>
<thead>
<tr>
<th>Agent (brand name)</th>
<th>Most common uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults dosing regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Anastrozole (Arimidex®)</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>1 mg PO once daily with or without food.</td>
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<tr>
<td>Bicalutamide</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>50 mg PO once daily with or without food.</td>
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</tr>
<tr>
<td>Busulfan (Myleran®)</td>
<td>Conditioning prior to bone marrow transplant, leukemia</td>
</tr>
<tr>
<td>Initial: 0.06 mg/kg or 1.8mg/m² once daily; 4-8 mg (range 1-12 mg) PO once daily (12-20 weeks) Maintenance: 1-3 mg PO once daily (range 2 mg once weekly to 4 mg once daily)</td>
<td></td>
</tr>
<tr>
<td>Note: Treat for at least 3 weeks. Continuous dosing should be considered when remission lasts for less than 3 months Bone marrow transplant: 0.8-1 mg/kg PO every 6 hours for 4 days for a total of 16 doses; may be used in combination with other drugs</td>
<td></td>
</tr>
<tr>
<td>Capecitabine (Xeloda®)</td>
<td>Breast, colorectal, pancreatic cancers</td>
</tr>
<tr>
<td>1250 mg/m² (range 313-1250 mg/m²) PO twice a day for 14 consecutive days starting on day 1 (total dose per cycle 35 000 mg/m² [range 8764 - 35000 mg/m²]) Cycle length: 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Chlorambucil (Leukeran®)</td>
<td>Leukemia, various lymphomas, ovarian cancer</td>
</tr>
<tr>
<td>0.1 mg/kg (range 0.03-0.2 mg/kg) PO once daily</td>
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</tr>
<tr>
<td>Administer on an empty stomach. For further details on dosing regimens, consult the drug monograph at <a href="http://www.bccancer.bc.ca/default.htm">http://www.bccancer.bc.ca/default.htm</a></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan®)</td>
<td>Breast, ovarian cancers, leukemia, various lymphomas, multiple myeloma, neuroblastoma, retinoblastoma</td>
</tr>
<tr>
<td>4 week cycle: 100 mg/m² (range 75-100 mg/m²) once daily for 14 consecutive days (total dose per cycle 1400 mg/m²) 3 weeks cycle: 300 mg/m² (range 200-450 mg/m²) once daily for 5 consecutive days. (total dose per cycle 1500 mg/m² [range 1000-2250 mg/m²])</td>
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<tr>
<td>Dasatinib (Sprycel®)</td>
<td>Leukemia</td>
</tr>
<tr>
<td>100-140 mg PO once daily or 70 mg (range 50-100) PO BID; may be taken without regard to food; separate administration of antacids by 2 hours</td>
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<tr>
<td>Erlotinib (Tarceva®)</td>
<td>Lung cancer</td>
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<tr>
<td>150 mg PO once daily (separate by 1-2 hours from ingestion of food)</td>
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</tr>
<tr>
<td>Etoposide (Vepesid®)</td>
<td>Bladder, cervical, head/neck, lung, ovarian, prostate and testicular cancers, brain tumors, gram cell tumor, lymphoma</td>
</tr>
<tr>
<td>2-3 week cycle: 50 mg – 100 mg PO once daily for 3-10 days (total dose per cycle 150 mg-1000 mg/m²)</td>
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<tr>
<td>Exemestane (Aromasin®)</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>25 mg PO once daily with or without food</td>
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<tr>
<td>Gefitinib (Iressa®)</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>250 mg PO once daily (with or without food)</td>
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</tr>
<tr>
<td>Hydroxyurea</td>
<td>Ovarian, head / neck cancers, leukemia, melanoma</td>
</tr>
<tr>
<td>20-30 mg/kg PO once daily or 80 mg/kg PO every third day. Up to 12 g/day has been used for blast crisis.</td>
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</tr>
<tr>
<td>Imatinib (Gleevec®)</td>
<td>Leukemia, sarcoma</td>
</tr>
<tr>
<td>400-600 mg (range 400-800mg) PO once daily. Administer with food. 2 x 800 mg dose should be administered in two divided doses.</td>
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<tr>
<td><strong>Lenalidomide (Revlimid®)</strong></td>
<td>Multiple myeloma, myelodysplastic syndromes</td>
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<tr>
<td>10mg or 25 mg PO once daily for 21 consecutive days starting on day 1. Administer with food or on an empty stomach.</td>
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<table>
<thead>
<tr>
<th><strong>Letrozole (Femara®)</strong></th>
<th>Breast cancer</th>
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<tbody>
<tr>
<td>2.5 mg PO once daily with or without food.</td>
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<table>
<thead>
<tr>
<th><strong>Lomustine (CeeNU®)</strong></th>
<th>Brain tumors, breast, lung, Hodgkin’s lymphoma, melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-8 week cycle: 75-130 mg/m² PO for one dose on day 1 (total dose per cycle 75-130 mg/m²)</td>
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</tr>
<tr>
<td>Administering on an empty stomach (one hour before or two hours after eating) may help reduce nausea.</td>
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</tr>
<tr>
<td>For further details on dosing regimens, consult the drug monograph at <a href="http://www.bccancer.bc.ca/default.htm">http://www.bccancer.bc.ca/default.htm</a></td>
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<table>
<thead>
<tr>
<th><strong>Megestrol (Megace®)</strong></th>
<th>Breast, endometrial cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>160 or 125 mg/m² (range 160-1600 mg) OR 40-320 mg (range 40-800 mg) or 62.5 -250 mg/m² PO once daily; dose may be divided into four doses a day.</td>
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</tr>
<tr>
<td>400-800 (range 160-800 mg) PO once daily for the treatment of cancer cachexia.</td>
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<thead>
<tr>
<th><strong>Melphan (Alkeran®)</strong></th>
<th>Multiple myeloma, ovarian cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 week cycle: 9 mg/m² PO once daily for four consecutive days starting on day 1 (total dose per cycle 36 mg/m²)</td>
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</tr>
<tr>
<td>Doses can be divided (e.g., BID-QID).</td>
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</tr>
<tr>
<td>Preferable to administer on an empty stomach.</td>
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<tr>
<td>Several variations exist of the combination melphalan and prednisone regimen.</td>
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<table>
<thead>
<tr>
<th><strong>Mercaptopurine (Purinethol®)</strong></th>
<th>Leukemia, non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction: 2.5-5 mg/kg/day PO once daily; maintenance: 1.5-2.5 mg/kg/day PO once daily.</td>
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</tr>
<tr>
<td>Avoid taking tablets with milk or milk based products. Preferably take on an empty stomach, but may be taken with food if needed.</td>
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<table>
<thead>
<tr>
<th><strong>Methotrexate</strong></th>
<th>Bladder, breast, esophageal, gastric, lung, head/neck and testicular cancers, leukemia, non-Hodgkin’s lymphoma, sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-25 mg/m² PO for one dose on day 1 and then day 3 or 4 (total dose per cycle 30-50 mg/m²)</td>
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<tr>
<td>Cycle length: 1 week</td>
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<table>
<thead>
<tr>
<th><strong>Procarbazine (Matulane®)</strong></th>
<th>Brain tumor, Hodkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-6 week cycle: 100 mg/m² (range 60-100 mg/m²) PO once daily or in 2-3 divided doses for 14 consecutive days (range 7-14 days) starting on day 1 or 2 (total dose per cycle 1400 mg/m² [range 700-1400 mg/m²])</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sorafenib (Nexavar®)</strong></th>
<th>Liver, renal cell cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg PO BID (separate by 1-2 hours from ingestion of food)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sunitinib (Sutent®)</strong></th>
<th>GI stromal tumor, pancreatic, renal cell cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 week cycle: 50 mg PO once daily on a schedule of 4 weeks on treatment followed by 2 weeks off may be taken with or without food; daily doses should not exceed 50 mg nor be decreased below 25 mg, except in the case of interactions. Dose modification by 12.5 mg increments is recommended based on individual safety and tolerability.</td>
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<tr>
<td>Continuous: 37.5 mg PO once daily</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Temozolomide (Temodal®)</strong></th>
<th>Brain tumors: astrocytoma, glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg/m² (range 100-200 mg/m²) PO once daily for 5 consecutive days starting on day 1 or for 5 consecutive days starting on day 10 (total dose per cycle = 750 mg/m² [range 500-1000 mg/m²]). Administer with food or on an empty stomach, as long as timing in relation to meals is consistent. Administration on an empty stomach or at bedtime may help reduce nausea and vomiting.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Thalidomide (Thalomid®)</strong></th>
<th>Multiple myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start at 200 mg PO once daily, then increase to the maximum tolerated dose (usual dose range 50-800 mg/day), preferably one hour after meals</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Thioguanine (Lanvis®)</strong></th>
<th>Leukemia, brain tumors, breast cancer, non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3 mg/kg/day or 75-200 mg/m²/day PO once daily in 1-2 divided doses for 5-7 days or until remission is attained. Preferably take on an empty stomach; may be administered with food if needed.</td>
<td></td>
</tr>
<tr>
<td>For suspension recipe consult the drug monograph at <a href="http://www.bccancer.bc.ca/default.htm">http://www.bccancer.bc.ca/default.htm</a></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Tretinoin (Vesanoid®)</strong></th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg/m²/day PO in 2 divided doses. Administer with food.</td>
<td></td>
</tr>
</tbody>
</table>

All dosing regimens are extracted from: [http://www.bccancer.bc.ca/default.htm](http://www.bccancer.bc.ca/default.htm)

Date completed: December 14, 2011