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Chemotherapy Symptom Management: Helping Each Patient with Their Journey

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LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Describe common symptoms related to chemotherapy.
2. Outline different treatment strategies for the management of chemotherapy related symptoms.
3. List risk factors/causative agents for specified chemotherapy related symptoms.
4. Classify the various routes of adminstration, mechanisms of action and types of cancer therapy a patient can receive and how that can impact chemotherapy related symptoms.
5. Explain the role of a pharmacy technician helping a patient with chemotherapy symptom management.

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Chemotherapy Symptom Management: Helping Each Patient with Their Journey

Introduction

Cancer Definition

Cancer is not a single disease as many different types of cancer exist. Cancer occurs when a single type of cell grows out of control. It can occur in the blood or it can create a solid tumor mass. The full mechanism that leads to the development of cancer is not completely understood. There are genetic, environmental factors as well as age and gender that have a role in the development of cancer, or carcinogenesis.[1]

Types of Chemotherapy (Cancer Treatment)

There are three main groups of medications that fall under today's modern anti-cancer therapy umbrella: traditional chemotherapy, hormonal therapy, and biologic therapy. Traditional chemotherapy, such as doxorubicin and etoposide, will cause apoptosis (cell death) of cancerous and healthy cells. This leads to many of the general toxicities and side effects seen with traditional chemotherapy such as myelosuppression (decrease in cells that provide immunity) and nausea/vomiting. These side effects will be discussed in more depth later. Hormonal therapies manipulate the endocrine system in cancers such as breast and prostate cancer. Biologic therapies have a more focused target and this leads to a different spectrum of toxicities depending on the targets of the therapy.

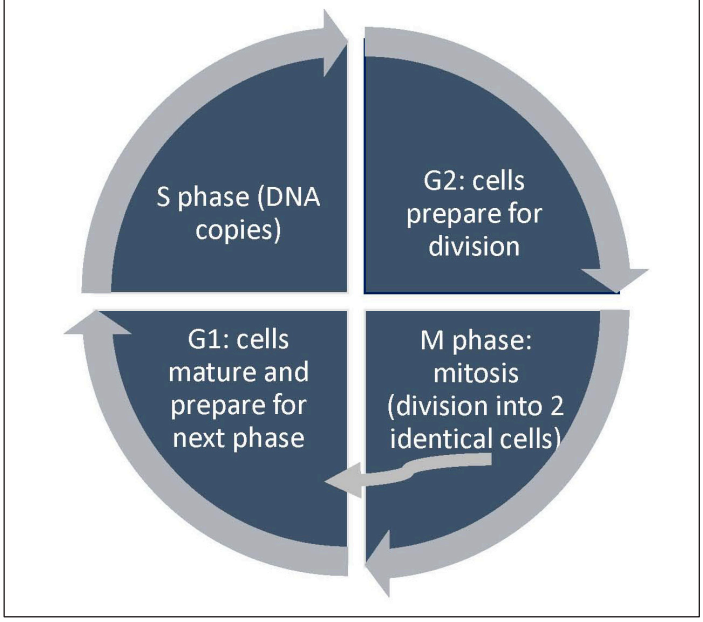
Traditional Therapy

Traditional chemotherapy has been around since 1941 when Louis Goodman and Alfred Gilman first administered nitrogen mustard to patients with lymphoma (a cancer that starts in lymphocyte cells which are part of the immune system).[1] These agents cause cell death by attacking specified points during cell replication and typically have more impact on rapidly dividing cells. However, these rapidly dividing cells are not always just cancer cells. Gastrointestinal cells, hair follicles, and bone marrow are normal cells that have rapid growth and therefore are more affected by traditional chemotherapy. This is why many give traditional chemotherapy a nickname of "poison"—it kills whatever active cells it encounters. Traditional chemotherapy can be cell cycle phase specific or cell cycle phase non-specific. The cell cycle is composed of 4 phases: G1, S, G2 and M. The G1 phase is when the cell prepares DNA for synthesis and synthesis then occurs in the S phase. The G2 phase is where the cell prepares for mitosis (division of the cell nucleus) by producing RNA and proteins and then the M phase is mitosis where the cellular division into two cells occurs. Depending on the mechanism of action of chemotherapy agents, they can affect different points of the cell cycle and some affect all phases **(Figure 1)**.

Hormonal Therapy

Hormonal therapies typically decrease or remove a hormone from the system that is related to the growth of that specific tumor. This class tends to have less major organ damage compared to the other groups of anti-cancer drugs, however, they are not without adverse effects.[1] Corticosteroids (e.g.. prednisone, dexamethasone) can also be used for their killing effects on cancer DNA against a variety of cancers such as lymphoma and multiple myeloma.[1]

Figure 1. Normal Cell Cycle[1]



Biologic Therapy

Biologic therapies consist of targeted therapies, such as monoclonal antibodies and tyrosine kinase inhibitors, as well as immune-mediated therapies, which can use the patient's own immune system to start an attack on the cancerous cells. Biologic therapies tend to have adverse effects related to their common target. For example, bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor (VEGF) while pazopanib is a tyrosine kinase inhibitor that also targets VEGF. These drugs have overlapping toxicities, even though they have a different mechanism of action, since they have the same target. Drugs that target VEGF are associated with hypertension and proteinuria (protein spilling into the urine). Note the suffixes of these drug names give you a clue as to the type of biologic therapy. Drugs ending in "mab" are monoclonal antibodies while drugs ending in "nib" are tyrosine kinase inhibitors.

Monoclonal Therapy

Monoclonal antibodies are specific antibodies to a single antigen, or target, on the cell surface. They are made by cloning a specific cell for a specific target. There are different ways to manipulate monoclonal antibodies (mAbs) to change their mechanism of action. Most mAbs have a direct killing effect when the antibody interacts with the antigen. However, some mAbs do not cause cell death when they bind with their target; so in order to achieve cell kill, they have a toxin attached to the mAb and when the mAb interacts with its target the mAb and the toxin are internalized by the cell which then leads to apoptosis. A mAb with a toxin attached is called a conjugated monoclonal antibody. The third mechanism of action is when the mAb interacts with a target and prevents signaling cascades that would have led to cell growth and proliferation. An example of this is bevacizumab as it targets VEGF and therefore VEGF is not able to bind with its target. This leads to blocking blood vessel growth which prevents tumor growth by cutting off the nutrient supply. Immune mediated therapy/immune checkpoint agents treat cancer by targeting the immune system and enhancing or inducing a response. Many of these agents are mAbs and their targets are still extracellular (outside the cell). One component of the immune system is the T-cell. T-cells normally identify foreign cells in the body and label them for destruction.[1] These drugs can be compared to pressing the gas pedal on a car. The anti-cancer agents currently on the market rev up the immune system (press the gas pedal) enhancing T-cell signaling, thereby increasing the number and duration that T-cells can attack foreign cells such as cancer cells.

Protein Kinase Inhibition

Tyrosine kinases are enzymes involved in the activation of many proteins needed for cell signaling cascades. They differ from mAbs because the tyrosine kinase target is inside the cell. Tyrosine kinase inhibitors (TKIs) prevent this activation of the protein thereby preventing the signal cascade.[1] Since TKIs need to get inside the cell they are smaller molecules compared to mAbs and they are typically oral medications. As mentioned before, the targets of TKIs can be the same as mAbs, but the location of the target is within the cell while the mAb target is on the surface of the cell **(Figure 2)**.

While there are many different types of anti-cancer therapy, most cancers are treated with various combinations of surgery, radiation and medications to work against cancer cells throughout the body. These combinations of therapy come with a vast array of toxicities as well and therefore cancer patients can need substantial supportive care to manage through the toxicities.

Chemotherapy-Induced Adverse Effects or Symptoms

In order to assess symptoms of chemotherapy consistently, the National Cancer Institute compiled a consensus document called the Common Terminology Criteria for Adverse Events (CTCAE).[2] The latest version was released in 2010. It provides criteria to describe the severity of each adverse event (AE) by a grading scale of up to 5 options, 1 through 5, with 1 being the most mild and 5 related to death due to the AE.[2]

Myelosuppression

Myelosuppression (low blood cell counts) is the most common dose-limiting adverse effect of traditional chemotherapy, although it is not seen with all agents.[1] In order to understand myelosuppression, first take a look at how the bone marrow works to make new cells. The normal bone marrow makes a variety of different cells with three main groups of cells: white blood cells (WBC), red blood cells (RBC) and platelets.[3] White blood cells can be

neutrophils (fight infections), eosinophils (increase with allergic reactions), basophils (part of an inflammatory response), monocytes/macrophages (ingest foreign bodies such as bacteria), or lymphocytes (immune cells such as T-cells). With myelosuppression, some or all of these cells are decreased. See **Figure 3**.[4]

When it comes to myelosuppression, typically neutrophils (most common WBC that eat foreign bodies such as bacteria) are the most impacted white blood cell. This is likely due to its short life span of about 6-12 hours and therefore its rapid turnover into new cells.[3] Following chemotherapy, a low point in the neutrophil count is typically seen around 10 to 14 days. This is called a nadir. The neutrophil count typically recovers by 3 to 4 weeks after chemotherapy. Neutrophils are needed in the body to help fight off infections. When the absolute neutrophil count (ANC) falls below 500, the risk for infection increases; this is called neutropenia. The ANC can be calculated by multiplying the neutrophil percentage by the total WBC count. For example, if your lab reports that you have 67% neutrophils and your total WBC is 1,230 cells/mcL, you would use the following equation:

(%/100) * WBC = ANC

So, for our example:

(67%/100) * 1230 = ANC

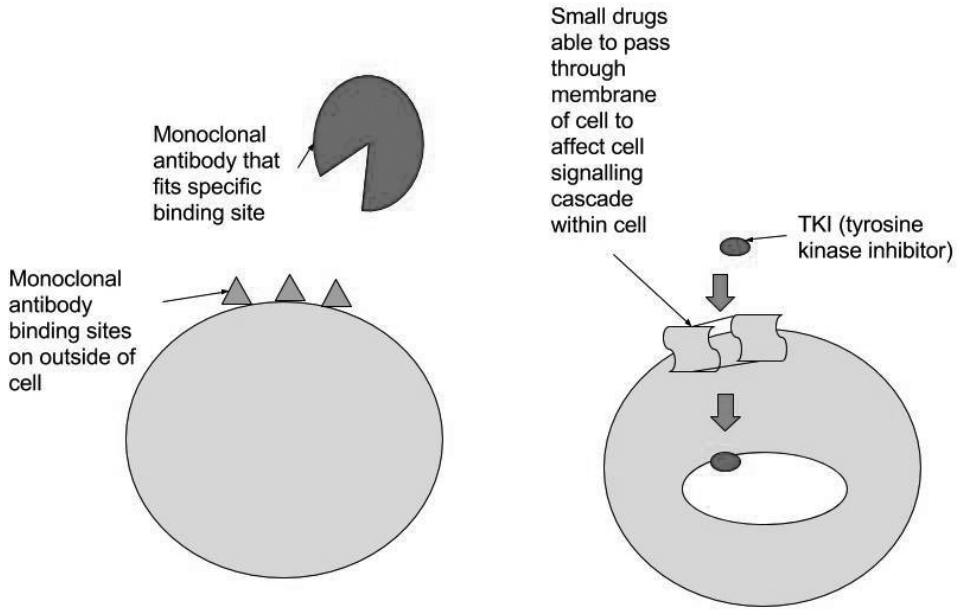
0.67 * 1230 = 824 neutrophil cells/mcL

Now, read on to see what this number means!

Neutropenic Fever

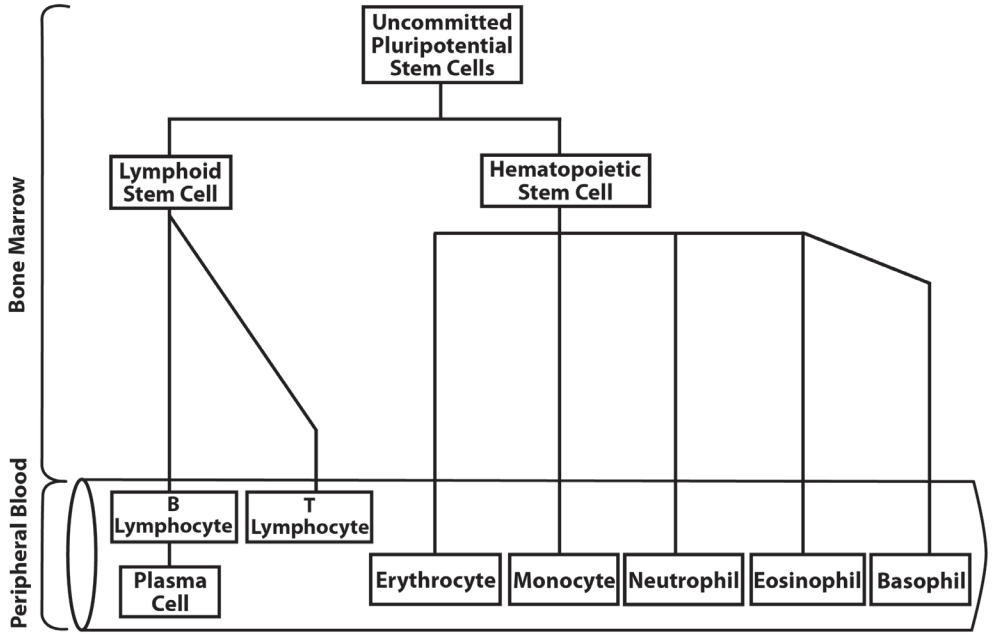
In a person with neutropenia, the signs and symptoms of infection may not be easily seen. This is because one needs neutrophils in order to yield a response such as redness, swelling or development of pus. Without these signs, the remaining symptom is a fever. Neutropenic fever is defined as a single temperature taken orally of 101° F (38.3° C) or an oral temperature of 100.4° F (38° C) sustained for 1 hour.[5,6] These fevers are in a patient with neutropenia, defined as less than 500 neutrophils/mcL or less than 1,000 neutrophils/mcL with the expectation to decline to less than 500 neutrophils/mcL over the next 48 hours.

Figure 2. Monoclonal Antibody and Tyrosine Kinase Inhibitor Target Comparison



Adapted from McManus Balmer C and Wells Valley A. Cancer Treatment and Chemotherapy. In: Talbert RL, DiPiro JT, Matzke GR, et al, Eds. *Pharmacotherapy: A Pathophysiologic Approach*, 8th ed. New York, NY:McGraw-Hill, 2011.

Figure 3. Hematopoeisis[4]



Adapted from Hutson HR, Johnson AM, Hematology; red and white blood cell tests. In: Lee M, *Basic Skills in Interpreting Laboratory Data*, 5th ed. Bethesda, MD: ASHP ©2013.

Management of Neutropenic Fever

When a person has neutropenic fever, it is considered an oncologic emergency. Depending on an initial risk assessment, a patient can then be treated with oral antibiotics as an outpatient or will need to be admitted to the hospital for intravenous (IV) antibiotics. The primary qualities of the antibiotics selected for neutropenic fever are broad coverage of infectious bacteria including a specific organism called pseudomonas **(Table 1)**.

Selection of antibiotics can be based on multiple factors including recent antibiotic exposure, drug allergies, infection history, possible sources of infection/likely pathogens, insurance coverage, side effects, drug-drug interactions and antibiotic sensitivities at the institution.

As a technician, there are many potential ways to improve quality of care to patients receiving antibiotics for neutropenic fever. Whether in a hospital or filling a prescription for discharge, checking allergies and obtaining a complete list of medications for drug-drug interactions is crucial. In the hospital setting, getting the drug to the patient in a time effective manner is also important.[7]

Prevention of Neutropenic Fever

Colony-stimulating factors (CSFs) have been explored to prevent infections in patients. There are two types of CSFs available in the US, granulocyte-CSFs (G-CSF) and granulocyte-macrophage-CSFs (GM-CSF). G-CSFs stimulate production of neutrophils while GM-CSFs promote granulocytes and monocytes/macrophages. Granulocytes is a group of cells that includes the neutrophils, basophils and eosinophils as all of these cells contain

Table 1. Antibiotic Options for Neutropenic Fever[5,6]

Oral options	IV options
amoxicillin-clavulanate (Augmentin) + ciprofloxacin (Cipro)	piperacillin-tazobactam (Zosyn)
	cefepime (Maxipime)
	Carbapenems: meropenem (Merrem), doripenem (Doribax), imipenem-cilastatin (Primaxin)
	ceftazidime (Fortaz, Tazicef) - (depending on geographical susceptibilities)

granules in their nucleus. Of the granulocytes, the neutrophil granulocyte is most common, thus even though G-CSFs and GM-CSFs stimulate production of all granulocytes, it is the neutrophil production that is the main benefit of these agents.

CSFs can be used to reduce the incidence, severity and duration of neutropenia when used as prophylaxis (prevention) for neutropenia after chemotherapy. When used for prophylaxis of chemotherapy-induced neutropenia it is recommended that they not start any sooner than 24 hours after the last dose of chemotherapy.[5,8,9,10] Timing of G-CSF with chemotherapy can be tricky as there is now a product with delayed administration of G-CSF. There are two main groups of G-CSF: filgrastim and pegfilgrastim. Filgrastim and pegfilgrastim are compared and contrasted in **Table 2**.

Side Effects of Neutropenic Fever Management

Common side effects of G-CSF include injection site irritation and bone pain. The bone pain occurs because of the effects of the growth factor on the bone matrix. Increasing production of neutrophils results in crowding in the bone marrow until the neutrophil cells are released from the bone matrix and into the peripheral blood. An over-the-counter agent, loratadine, has been effective for treating bone pain associated with myeloid growth factors.

Tumor Lysis Syndrome (TLS)

Certain types of cancer, such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and highly aggressive Non-Hodgkin lymphoma (NHL), have an increased risk for the development of TLS.[11,12,13] In general, a cancer with a high proliferation rate and high response rate to chemotherapy carries an increased risk of TLS. Other risk factors include renal dysfunction, dehydration, hypotension and acidic urine.

TLS is an oncologic emergency. It occurs when cancer cells are lysed (destroyed) either spontaneously or due to anti-cancer therapy. When lysed, these cells release uric acid from the breakdown of DNA as well as potassium and phosphorus, electrolytes from within the cell (intracellular ions). This leads to hyperuricemia (high blood uric acid), hyperkalemia (high blood potassium) and

Table 2. Comparison of Granulocyte-Colony Stimulating Factors[8,9,10]

	Filgrastim	Pegfilgrastim
Brand names	Neupogen, Granix, Zarxio	Neulasta, Neulasta Onpro kit
Dosing	Adults and pediatrics: 5 mcg/kg subQ or IV daily for up to 14 days	Adults: 6 mg subQ x 1 Pediatric: 100 mcg/kg (up to 6 mg)
Timing for administration	24-72 hours after completion of cytotoxic chemotherapy. Do not administer 24 hours prior to or after chemotherapy.	24-72 hours after completion of cytotoxic chemotherapy. Do not administer in the period between 14 days before and 24 hours after completion of cytotoxic chemotherapy. See onset of action for timing with application of device difference.
Onset of action	1-2 days after day 1 of injections	1-2 days after administration. Delivery kit administers drug 27 hours after application of device, therefore can be applied on same day as chemotherapy pending administration occurs 24 hours after end of administration of cytotoxic chemotherapy.
Preparations available	300 mcg, 480 mcg Vials and pre-filled syringes	6 mg pre-filled syringe 6 mg delivery kit

SubQ: subcutaneous; IV: intravenous

hyperphosphatemia (high blood phosphate) which can cause end-organ damage to the kidneys, heart and central nervous system (CNS). Hyperphosphatemia can lead to hypocalcemia (low blood calcium) due to binding of phosphorus and calcium to form crystals.

Management of TLS

The end effects of TLS can be severe, including acute renal failure, seizure, cardiac arrhythmias and sudden death. Therefore, prophylactic measures, especially in high risk patients, are critically important. These include aggressive hydration with normal saline, diuresis and prevention of uric acid formation using allopurinol. Allopurinol inhibits xanthine oxidase which is an enzyme needed to form uric acid. By inhibiting this enzyme, allopurinol decreases the amount of circulating uric acid. Caution does need to be taken with hydration in patients with low cardiac ejection fractions or congestive heart failure (CHF) as these patients will accumulate fluid throughout their body including the lungs; and excess fluid in the lungs can cause shortness of breath and respiratory distress. Allopurinol is not able to break down the uric acid already formed within the body. If uric acid is elevated, then an enzyme called rasburicase can be used. Rasburicase is a form of urate oxidase. By providing urate oxidase to the body, uric acid is broken down into allantoin which is more soluble in the urine and therefore more easily excreted. Rasburicase has numerous dosing regimens.[11,12,14,15,16,17,18,19,20] These range from the FDA approved dosing of 0.15-0.2 mg/kg/day IV for 5 days to single flat doses of 3-7.5 mg.

Electrolyte management is also a part of the treatment for TLS.[11,13,19] Since hyperkalemia can lead to cardiac arrhythmias, quick acting therapies are needed. Sodium polystyrene sulfonate is a cation exchange resin that removes potassium via the gastrointestinal system. This is not a good option for TLS as it can take hours to days for the effect. Faster options include loop diuretics such as furosemide (this also aids in diuresis) or regular insulin which shifts the potassium back into the cells. However, realize that there are disadvantages to using regular insulin for TLS. The first is that if 50 mL of dextrose 50% is not given immediately after the insulin, the patient could be at risk for hypoglycemia. The second concern is that shifting the potassium back into cells may not be fully effective if more cells are continuing to lyse. If cardiac changes are noted on the monitor, then giving 1 gram of calcium gluconate can help stabilize the heart membranes. Hyperphosphatemia can be managed with phosphate binders such as calcium acetate, aluminum hydroxide and sevelamer or reduction of intake via diet modifications. Both hyperkalemia and hyperphosphatemia can be managed with emergent hemodialysis in severe situations. Calcium supplementation with IV calcium gluconate can be considered in severe hypocalcemia (less than 7 mg/dL or 25% change from baseline).

Test Your Knowledge #1

Match the supportive care medication with the symptom (use each once).

1. _____ Rasburicase	A. Treat hyperphosphatemia
2. _____ Pegfilgrastim	B. Treat hyperuricemia
3. _____ Furosemide	C. Treat hyperkalemia
4. _____ Sevelamer	D. Prevent neutropenic fever

Answers on page 28.

Gastrointestinal

Nausea and Vomiting

Therapy options for chemotherapy-induced nausea and vomiting (CINV) have continued to grow. Prevention has become the preference and there are many options to tailor for a specific patient since there are many medications with different mechanisms of action, routes of administration and side effect profiles. Certain patients may be at higher or lower risk for nausea and vomiting. Younger patients and females are at higher risk as well as those who have a pre-treatment expectation of severe nausea as well as those with a history of motion sickness or morning sickness.[21,22,23] Patients with a history of high alcohol consumption have a lower risk of developing nausea and vomiting.

There are risk factors related to the patient's therapy as well. The main two are emetogenicity and chemotherapy dose. Emetogenicity relates to the frequency a particular agent or therapy induces emesis (vomiting).[21] There is not one universally accepted classification system for emetogenicity. The most commonly used system within the US divides the risk into four categories: high, moderate, low and minimal risk of emesis. The categories are grouped

based upon the percentage of patients who have emesis in the absence of antiemetics **(Table 3)**. Antiemetic regimens are selected based upon the drug with the highest emetogenicity category.

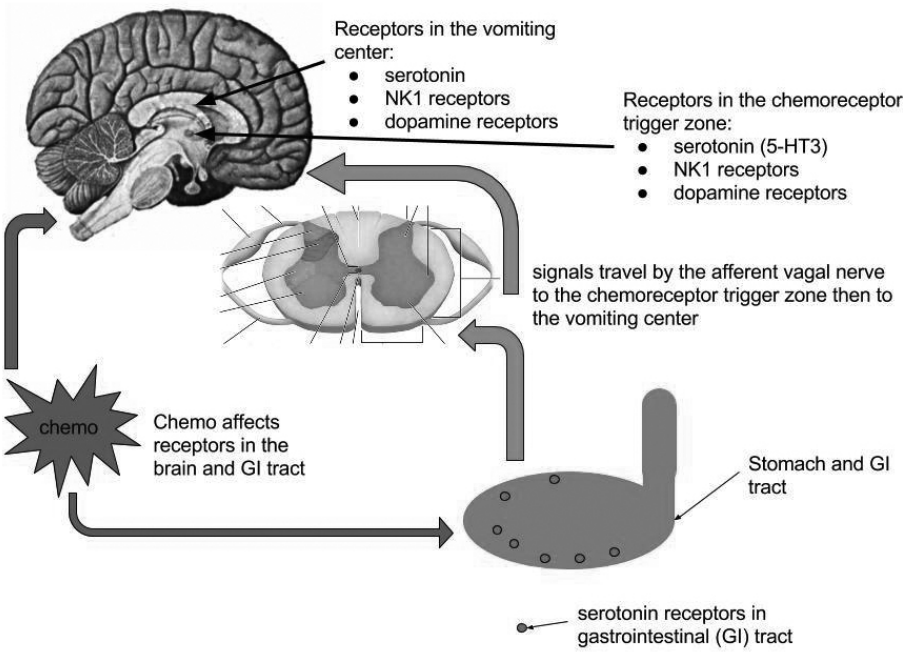
Vomiting is considered a motor-reflex response which may or may not be preceded by nausea.[21] It primarily involves the central nervous system both as the system that receives noxious stimuli and as the system that generates the response pathway which leads to nausea and vomiting. There are three main areas of the brain involved in the vomiting pathway: chemoreceptor trigger zone (CTZ), cortex/limbic region and vomiting center.[21,23] Chemotherapy acts as the noxious stimuli and causes irritation in the gastrointestinal tract. This leads to release of serotonin (5-HT) from enterochromaffin cells in the gastrointestinal (GI) tract which bind to serotonin type 3 receptors (5-HT3) in the GI tract. Nerve impulses then travel along the afferent vagal nerve to the CTZ and vomiting center and substance P is activated. Substance P binds to neurokinin-1 (NK-1) receptors and activates the central vomiting pathway. Similarly, other neurotransmitters are activated in the CTZ and vomiting center such as dopamine, cannabinoids, histamine and acetylcholine activating the pathway via various mechanisms.

Table 3. Emetogenicity Categories for Chemotherapy [21,22,23]

Emetogenicity Category	Frequency of Eemesis
High	> 90%
Moderate	30-90%
Low	10-30%
Minimal	<10%
>: greater than; <: less than	

Of note, there are a few different categories of CINV to consider when deciding on antiemetics: acute, delayed, breakthrough, anticipatory and refractory.[21,22,23] Acute CINV occurs within 24 hours of chemotherapy while delayed occurs after 24 hours. Breakthrough is CINV that occurs despite adequate antiemetics, while refractory is unmanageable with the current regimen. Anticipatory CINV occurs after inadequately controlled CINV—it leads to a conditioned response of nausea and vomiting different from the activation of the previously described neurotransmitters. For example, a patient who became nauseous after eating lunch or taking their pills may become nauseous or even vomit at the mere sight of pills or food because they are recalling their nausea or vomiting and associating it with those triggers, leading to the conditioned response. The different mechanisms of action

Figure 4. Pathway of Nausea and Vomiting[21,23]



Adapted from Hesketh PJ. Chemotherapy-induced nausea and vomiting. *N Engl J Med* 2008;358:2482-94 and Frame D. Best Practice management of CINV in oncology patients: I. Physiology and Treatment of CINV. *J Support Oncol* 2010;8:5-9.

of antiemetics make some more effective than others for different categories of CINV.

Most studies for antiemetics focus on their effects with a single day regimen of chemotherapy. The antiemetic regimen is typically for 3 days with the 1 day of chemotherapy. This leads to many questions of how to adjust an antiemetic regimen with a multi-day chemotherapy regimen. The National Comprehensive Cancer Network (NCCN) has consensus recommendations for antiemetics with multi-day regimens of oral chemotherapy regimens based upon the oral chemotherapy agent being used.[22] With intravenous multi-day regimens, the recommendations are vague and depend upon the agents included in the multi-day regimen. For example, a 5-day regimen that gives cisplatin (highly emetogenic) on each of 5 days would warrant a different antiemetic regimen than a 5-day regimen that gives cisplatin on day 1 only and 5-fluorouracil (low emetogenicity) on all 5 days. One principal that many clinicians use is to have the antiemetic regimen continue for 2 days after the last day of the agent with the higher level of emetogenicity.[24] Therefore, in the examples mentioned above, a high emetogenicity antiemetic regimen would be used for the 5 days of the cisplatin regimen and 2 days after while the second regimen would use a highly emetogenic antiemetic regimen for the 2 days of cisplatin and the 2 days after (total 4 days) followed by a low emetogenicity regimen for the 5th day of the regimen.

Options For Prevention And Breakthrough

Serotonin (5-HT3) Antagonists

There are currently four 5-HT3 antagonists: ondansetron, dolasetron, granisetron and palonosetron. While most have similar mechanisms of action, there are some differences amongst the agents that lend to selecting one over the other **(Table 4, *page 12-13*)**.[21,22,23] One difference seen amongst the 5-HT3 antagonists is with the available formulations. All have an intravenous (IV) formulation although it is currently recommended to avoid use of IV dolasetron due to cardiac events such as QT prolongation and torsades de pointes. Granisetron has a transdermal patch available, however, it is key to counsel patients to apply the patch 24 hours prior to receiving chemotherapy in order to allow time for the patch to take effect. While the IV and PO formulations of ondansetron, dolasetron and granisetron are given daily, the IV formulation of palonosetron has a longer duration of action so only 1 dose is needed for a 3-day antiemetic regimen. This difference is important because 5-HT3 antagonists are primarily used to prevent acute CINV, but with the long half-life of palonosetron, it is also effective for delayed CINV.

Test Your Knowledge #2

Name 4 drugs used for chemotherapy-induced nausea and vomiting.

1. _____
2. _____
3. _____
4. _____

Answers on page 28.

Neurokinin-1 (NK-1) Antagonists

Only aprepitant and fosaprepitant were available early in 2015, but at the end of 2015 there were two new NK-1 antagonists: rolapitant and netupitant.[25,26] NK-1 antagonists prevent substance P from binding with the NK-1 receptor within the CNS and help prevent delayed CINV.[23] Fosaprepitant is the prodrug (parent formulation) of aprepitant and comes as an IV formulation while aprepitant is the oral version. Aprepitant is given daily in a 3-day antiemetic regimen while fosaprepitant is given on the first day only. Rolapitant was approved in October of 2015 as an oral NK-1 antagonist option that only needs to be given for 1 dose for a 3-day antiemetic regimen. Netupitant is not available as a single agent, but is part of a combination oral drug with a 5-HT3 antagonist, palonosetron (of note, palonosetron is not available in an oral formulation as a single agent). The combination agent netupitant/palonosetron is given on 1 day of a 3-drug regimen.

Corticosteroids

The mechanism by which corticosteroids work for CINV is not fully understood.[21,22] Dexamethasone is the corticosteroid most frequently used as an antiemetic. It is important to note that steroids may also be part of the chemotherapy regimen in certain disease states such as multiple myeloma and lymphoma. If a patient is receiv-

ing a steroid for anti-cancer purposes, the doses are typically higher than those for antiemetics. Corticosteroids do have an array of side effects including hyperglycemia, irritability, insomnia and psychosis in severe cases.

Dopamine antagonists

Most agents with anti-dopaminergic effects also have effects on other receptors **(Table 4, *page 12-13*)**.[21,22,23,24,25,26] The selection amongst dopamine antagonists depends partially on which of the other receptors each agent affects and the severity or frequency of the side effects noted with each agent. Extrapyramidal symptoms (EPS) are one of the side effects associated with dopamine antagonists. EPS are involuntary muscle movements or contractions. Olanzapine is an antipsychotic agent that has recently found a frontline use in CINV.[22] Years prior, olanzapine was used for breakthrough CINV and now it is used up front in place of a NK-1 antagonist. Olanzapine antagonizes dopaminergic, histaminic, alpha-adrenergic and 5HT2 receptors.

Histamine antagonists

Histamine antagonists include some agents commonly found over-the-counter (OTC) such as meclizine, diphenhydramine and scopolamine. These can be more useful for nausea and vomiting associated with motion (similar to motion sickness) or diphenhydramine may be preferred when a drug is needed for both nausea and preventing a hypersensitivity (allergic) reaction.

Cannabinoids

Synthetic cannabinoids, such as dronabinol and nabilone, can be useful for refractory (difficult to treat) nausea and vomiting. They also have a unique added benefit of appetite stimulation.[22,23] However, they do cause side effects that prevent many patients from being able to utilize these agents, specifically altered mental status, dizziness and postural hypotension (drop in blood pressure when standing up). These types of side effects put patients at risk for falls which has the potential to be especially dangerous in patients post chemotherapy with low platelets who are at increased risk for bleeding. It is also important to note that these synthetic cannabinoids are not the same as medical marijuana. Medical marijuana is now legal in an ever growing number of states. The synthetic cannabinoids are lab created versions of a few of the isomers identified in medical marijuana, but do not have all the same properties as medical marijuana. Advantages of the synthetic cannabinoids are that they come in an oral formulation that does not need to be smoked and are without the risk of exposure to pesticides while grown (which could be inhaled in the plant forms). They are also regulated by the US Food and Drug Administration (FDA) for containing the claimed active ingredients.

Benzodiazepines

Benzodiazepines do not target any of the before mentioned antiemetic receptors. In fact, it is not even known if they truly have any antiemetic properties. However, they are very effective at managing anxiety and therefore can be very effective for anticipatory nausea.

Diarrhea and Constipation

Both diarrhea and constipation are common side effects seen with chemotherapy and supportive care for chemotherapy.[28] Constipation is typically defined as less than three bowel movements per week while diarrhea is defined as an increase of at least four stools per day from the patient's baseline bowel habits.[2,29] Constipation is most commonly described with the symptoms of gastrointestinal pain, distention (bloating), nausea and vomiting. Many of the medications that cause constipation **(Table 5, *page 14*)** do so by slowing down or inhibiting gastrointestinal motility (movement).[29,30,31] If left untreated, the constipation can become severe and lead to an ileus, which is an obstruction of the gastrointestinal tract. The best therapy is prevention of constipation and this is accomplished with the use of scheduled stimulant laxatives such as senna or bisacodyl.[29,31] It is usually effective to give these stimulant laxatives in combination with a stool softener, such as docusate to prevent straining with bowel movements, especially with patients with low platelets as the straining could lead to bleeding. There is one agent that can treat a specific type of constipation. Methylnaltrexone is an opioid receptor antagonist that acts only on the opioid receptors in the gastrointestinal tract to treat opioid-induced (e.g. morphine, hydrocodone) constipation and typically produces a bowel movement within four hours after the subcutaneous injection is administered.

Diarrhea occurs due to damage of the epithelial (outer cell layer) lining of the gastrointestinal tract by chemotherapy.[27,29] Damage leads to inflammation and irritation of the bowel lining and decreases the ability to absorb

Table 4. Summary of Antiemetic Agents, Available Dosage Forms and Type of CINV Treated[21,22,23,24,25,26]

Class	Agent	Dosage forms	Unique attributes	Type of CINV
5-HT3 Antagonists	Ondansetron (Zofran)	IV, PO	4 oral forms: tablet, solution, oral film and oral dispersable tablet	Acute
	Dolasetron (Anzemet)	IV, PO	IV formulation has been associated with QT prolongation and other cardiac effects and is no longer recommended for CINV prevention	Acute
	Granisetron (Kytril)	IV, PO, transdermal patch		Acute
	Palonosetron (Aloxi)	IV	Longer half-life (40 hours)	Acute, delayed
NK-1 Antagonists	Aprepitant (Emend)	PO	Give daily	Delayed
	Fosaprepitant (Emend)	IV	1 dose for 3 days	Delayed
	Rolapitant (Varubi)	PO	1 dose for 3 days	Delayed
	Netupitant	PO	Only in combination product with palonosetron oral. 1 dose for 3 days (Akynzeo)	Delayed
Corticosteroids	Dexamethasone (Decadron)	IV, PO		Acute, delayed
Dopamine antagonists	Metoclopramide (Reglan)	IV, PO		Acute
	Prochlorperazine (Compazine)	IV, PO	Also acts as alpha-adrenergic antagonist and anticholinergic	Acute
	Promethazine (Phenergan)	IM, IV, PO, suppository	Also acts as alpha-adrenergic antagonist and anticholinergic IM route is preferred over IV due to risk of tissue damage	Acute
	Trimethobenzamide (Tigan)	IM, PO		Acute

Class	Agent	Dosage forms	Unique attributes	Type of CINV
Dopamine antagonists (continued)	Haloperidol (Haldol)	IV, IM, PO	Also acts as alpha-adrenergic antagonist, peripheral vascular dilator, and reduces effect of epinephrine Black Box Warning for QT prolongation and other cardiac arrhythmias Haloperidol IM injections are typically long-acting salt formulations and are used for psychiatric indications (e.g. lactate, decanoate).	Acute
	Droperidol (Inapsine)	IV	Also acts as alpha-adrenergic antagonist, peripheral vascular dilator, and reduces effect of epinephrine Black Box Warning for QT prolongation and other cardiac arrhythmias	Acute
	Olanzapine (Zyprexa)	IM, PO	Also acts on 5-HT2, histamine, alpha-adrenergic	Acute, delayed
Histamine antagonist	Hydroxyzine (Atarax)	PO		Acute
	Scopolamine (Transderm Scop)	Transdermal patch	Also anticholinergic activity. Apply behind ear once every three days.	
	Diphenhydramine (Benadryl)	IV, PO	Also anticholinergic activity	Acute
	Meclizine (Antivert)	PO	Chewable form	Acute
Cannabinoid antagonist	Dronabinol (Marinol)	PO		Acute
	Nabilone (Cesamet)	PO		Acute
Benzodiazepines	Lorazepam (Ativan)	IV, PO	Anxiolytic	Anticipatory

CINV: chemotherapy-induced nausea and vomiting; 5-HT3: serotonin type 3 receptors; NK-1: neurokinin-1; IV: intravenous; PO: oral; IM: intramuscular; 5-HT2: serotonin type 2 receptors

Table 5. Agents that Cause Constipation and Diarrhea[28,29,30,31,32]

Constipation	Diarrhea
Vincristine	Irinotecan
5HT3 antagonists (ondansetron, etc.)	Capecitabine
Anticholinergics (diphenhydramine)	Continuous 5-fluorouracil
Thalidomide	Metoclopramide
Arsenic trioxide	Immune checkpoint agents (i.e. ipilimumab, nivolumab)
Opioids (pain medication)	Tyrosine kinase inhibitors
5HT3: serotonin type 3 receptor	

fluids and nutrients. Severe diarrhea can lead to dehydration, electrolyte abnormalities and even hospitalization.[27,31-33] Management can include non-pharmacologic (non-medication) options such as avoiding alcohol and lactose-containing products, eating small frequent meals, and maintaining adequate hydration (8-10 glasses of clear fluids) as well as keeping a symptom diary. Loperamide is the mainstay for treatment of drug-induced diarrhea. Loperamide inhibits gastrointestinal motility via the opioid receptor on the intestinal muscles. Usual dosing is 4 mg x 1 dose, followed by 2 mg every 4 hours or after every bowel movement with a maximum of 16 mg per day.

Irinotecan-related diarrhea is different from the other agents that cause diarrhea.[27,31-33] It occurs in two phases, acute and delayed diarrhea. Acute irinotecan-induced diarrhea occurs within the first 24 hours after receiving irinotecan and is due to irinotecan acting as an acetylcholinesterase inhibitor, thus increasing acetylcholine and causing a cholinergic response. A cholinergic response is opposite to the desired effects of the anti-cholinergic drugs discussed previously for nausea and vomiting. With a cholinergic response, patients can present with symptoms that correlate with the "SLUDGE" acronym. SLUDGE stands for Salivation (excess saliva), Lacrimation (excess tear production), Urination, Diaphoresis (sweating), Gastrointentinal upset (diarrhea), Emesis (vomiting). To treat acute irinotecan-induced diarrhea the anticholinergic agent, atropine, can be administered subcutaneously or intravenously. Delayed irinotecan-induced diarrhea occurs after 24 hours beyond irinotecan administration. The active agent in irinotecan leads to increased production of large watery stools. This type of diarrhea can also be treated with loperamide, however, the daily maximum of 16 mg/day listed on the OTC package does not apply. With irinotecan-induced diarrhea patients should take 4 mg x 1 dose and then 2 mg every 2 hours until diarrhea-free for 12 hours. It is important that patients understand this difference in dosing with irinotecan-related diarrhea as loperamide is available OTC and patients could easily read the package instructions not realizing the dosing is different for irinotecan-induced diarrhea.

Mucositis

Mucositis is the inflammation, breakdown and ulceration of the mucosal barrier in the mouth and gastrointestinal (GI) tract.[28,34] It is a common side effect of chemotherapy and typically occurs 5-7 days after a standard dose of chemotherapy. This timing correlates with the drop in white blood cell counts and tends to improve with the recovery of neutrophils. Breakdown of the mucosal barrier can increase the risk of infection because bacteria can pass from the mouth and GI tract into the circulation system (blood). Along with the risk of infection, mucositis negatively impacts a patient's quality of life as it can cause significant pain and impair the ability and desire to eat, thus making it difficult to maintain adequate hydration and nutrition.

Risk factors for mucositis include the dose and type of chemotherapy agent received with alkylating agents and topoisomerase II inhibitors having higher rates of mucositis **(Table 6)**.[34,35] Mouth hygiene risk factors include patients with poor dental hygiene, ill-fitting dentures, or pre-existing oral lesions. Other risk factors include being Caucasian or receiving chemotherapy with radiation.

The full mechanism of mucositis is not fully understood, however, a pathway of five stages for the development of mucositis has been described: 1) initiation, 2) up-regulation of messengers, 3) signaling and amplification, 4)

Table 6. Anti-Cancer Agents Associated with Mucositis[34,35]

Drug class	Specific agents
Alkylating agents	Actinomycin, busulfan, chlorambucil, cisplatin, cyclophosphamide, melphalan, mechlorethamine, mitomycin, oxaliplatin, procarbazine, thiotepa
Toposiomerase II inhibitors	Daunorubicin, doxorubicin, epirubicin, etoposide, idarubicin, irinotecan, mitoxantrone, topotecan
Anti-metabolites	Capecitabine, cytarabine, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, thioguanine
Microtubule inhibitors	Docetaxel, ixabepilone, paclitaxel, vinblastine, vincristine, vinorelbine
Monoclonal antibodies	Alemtuzumab, Bevacizumab, cetuximab, panitumumab, trastuzumab
Tyrosine kinase inhibitors	Erlotinib, imatinib, lapatinib, sunitinib
Miscellaneous	Bortezomib, interferon, everolimus

ulceration, and 5) healing.[34] Initiation is due to chemotherapy or radiation causing damage and death of the GI cells and tissues. During the second phase, pro-inflammatory cytokines (proteins that help communication between cells) are up-regulated (increased in number) and released and these lead to more tissue damage and apoptosis (cell death). The amplification phase includes activation of positive feedback loops which cycle to further increase the number of pro-inflammatory cytokines. The fourth phase, ulceration, is the phase most commonly seen as the outward symptom in patients as cell death and deterioration of the mucosal lining have physical changes that can be visualized such as sores. This phase is associated with further inflammation and pain as well as the development of infections. Gastrointestinal cells turnover within 7 to 14 days typically, therefore the healing phase involves the new growth of GI epithelial cells.

Current therapy options for prevention and treatment of oral mucositis are somewhat limited. The main way to prevent and treat mucositis is through proper mouth hygiene as supported by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines; however, no specific oral hygiene regimen is recommended.[36] Typically oral hygiene includes daily teeth cleaning with topical fluoride, flossing and frequent use of mouth rinses. There are a few key points with basic oral care with cancer patients as these patients can be at risk for gum bleeding if they have low platelet counts. Therefore, it is typically recommended to use a soft bristle toothbrush and to monitor for any bleeding of the gums when brushing teeth or flossing. There are many mouthwashes available as well as normal saline, sodium bicarbonate and calcium phosphate and none are recommended over the others based on clinical trials. However, one mouthwash is recommended against by the MASCC/ISOO guidelines: chlorhexidine. This should be avoided since it contains alcohol which acts as a drying agent and can increase the risk of drying out the lining of the mouth, thus leading to cracking.

Many agents have been evaluated for prevention and treatment of oral and gastrointestinal mucositis, however, the data is difficult to interpret for numerous reasons including a lack of standardization of evaluation scoring for mucositis.[35,36] The MASCC/ISOO guidelines provide a comprehensive review of the available literature and recommendations for and against specific agents based on published literature. The options and recommendations/suggestions are summarized in **Table 7,** ***page 17***.

Pain

Cancer pain is a common concern for patients as it occurs in about 65% to 85% of patients with advanced cancer and is found in about 30% of patients at diagnosis.[37,38] Pain for most cancer patients can be relieved by treating the underlying cause of the pain; altering the central perception of pain with medications; and non-pharmacologic techniques and by altering the transmission of pain to the central nervous system with medications. The International Association for the Study of Pain defines pain

as an unpleasant sensory (physical) and emotional experience associated with actual or potential tissue damage, or described in relation to such damage.[38,39] Quality of life is significantly impacted by pain management and there is increasing evidence that survival is linked to symptom management in cancer patients. Control of pain in a cancer patient needs a multi-layered approach and continual reassessment. Historically, the World Health Organization had a 3-tiered algorithm for the treatment of cancer pain.[37,39] The first step would be to utilize non-steroidal anti-inflammatory drugs (NSAIDs) and if that was not sufficient then treatment would be escalated to a "weak" opioid, followed by a "strong" opioid. This algorithm offers an over-simplified approach as cancer pain is considerably more complex and in need of a more in depth assessment of the pain of a cancer patient as well as more non-traditional options for therapy.

Types of Pain

In order to understand the various options for cancer pain therapy, one should first understand the different types of pain a patient may describe. There are two general types of pain: nociceptive (nerve pain that goes away after injury heals) and neuropathic (nerve pain that is chronic).[37,39] Nociceptive pain can further be divided into visceral and somatic pain as nociceptive pain is the result of injury to these structures which results in activation of nociceptors. Somatic nociceptive pain is typically described as sharp, localized and throbbing and it tends to affect parts of the body controlled by voluntary skeletal muscle and spine. Bone pain from metastases tends to be somatic nociceptive pain. Visceral nociceptive pain tends to affect the organs, especially those in the chest and abdomen. It is described as diffuse (wide spread), aching and cramping. Neuropathic pain occurs when there is damage to the central or peripheral nervous systems. Burning, sharp or shooting pain is typically used to describe neuropathic pain.

Pain Management

Cancer pain is managed via a broad array of pharmacologic and non-pharmacologic modalities. Non-pharmacologic options include physical, cognitive (mind) and spiritual considerations.[37] Physical options include heat or cold, massage or acupuncture. Cognitive methods can include breathing relaxation techniques, imagery and psychosocial support. Spiritual needs assessment should be part of the comprehensive plan to focus on the patient's cultural beliefs. Pharmacologic options include non-opioid analgesics, opioid analgesics, adjuvant analgesics and miscellaneous analgesics.

Scoring of pain helps with the management of cancer pain. A numerical scale with 0 meaning no pain and 10 meaning the worst pain imaginable can be divided into 3 levels of pain.[37,39] Mild pain is associated with pain scores of 1-3 while moderate pain is 4-6 and severe pain is 7-10. Pain management can be performed in either an outpatient or inpatient setting with the inpatient setting typically reserved for those with acute, severe pain or a pain crisis. In general, gathering of a patient's medication history, along with frequency of use of rescue pain medications and overall assessment of pain and side effects can help to optimize the overall pain regimen. Technicians in roles where they conduct a medication history review can gather pertinent information to help triage when the patient needs to see the pharmacist or have the pharmacist contact a physician to intervene. Next is a review of the classes of pharmacologic options available for pain management.

Non-Opioid Analgesics

Non-opioid analgesics include NSAIDs (e.g. ibuprofen, naproxen) and acetaminophen (APAP). These agents are useful for mild pain and may also be used in combination with opioids to augment the effect of each individual agent.[37,39,40] Both medications can be purchased

Test Your Knowledge #3

List 3 symptoms of visceral pain and neuropathic pain.

Visceral

1. _____
2. _____
3. _____

Neuropathic

1. _____
2. _____
3. _____

Answers on page 28.

Table 7. Summary of MASCC/ISOO Recommendations for Mucositis[36]	
Gastrointestinal mucositis (not including the oral cavity)	
Recommended for use:	• Amifostine ≥ 340 mg/m^2 to prevent radiation proctitis in patients receiving standard-dose radiation for rectal cancer. • Octreotide ≥ 100 mcg subQ BID to treat diarrhea unresponsive to loperamide.
Suggested for use:	• Amifostine to reduce incidence of esophagitis in patients with non-small cell lung cancer receiving chemoradiation. • Sucralfate enemas to treat chronic radiation-induced proctitis in patients who have rectal bleeding. • Sulfasalazine 500 mg orally BID to prevent radiation-induced enteropathy in patients receiving external beam radiation for pelvic malignancy. • *Lactobacillus*-containing probiotics to prevent chemotherapy and/or radiation-induced diarrhea in patients with pelvic malignancies. • Hyperbaric oxygen to treat radiation-induced proctitis in patients receiving radiation therapy for a solid tumor.
Recommended AGAINST use:	• Systemic sucralfate, administered orally, should not be used to treat GI mucositis in patients receiving radiation for solid tumor. • Aspirin, mesalamine and olsalazine, administered orally, should not be used to prevent radiation-induced diarrhea in patients receiving radiation for pelvic malignancy.
Oral mucositis	
Recommended for use:	• Oral cryotherapy (ice chips) for 30 minutes to prevent oral mucositis in patients receiving bolus fluorouracil. • Palifermin 60 mcg/kg/day x 3 days prior to conditioning treatment and for 3 days post-transplant to prevent oral mucositis in patients with hematological malignancies receiving high-dose chemotherapy and TBI + autologous HSCT. • Low-level laser therapy be used to prevent oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy with or without TBI. • Patient-controlled analgesia with morphine be used to treat oral mucositis pain in patients undergoing HSCT. • Benzydamine mouthwash to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation without concomitant chemotherapy.
Suggested for use:	• Oral care protocols to prevent oral mucositis in all age groups across all cancer treatment modalities. • Oral cryotherapy to prevent oral mucositis in patients undergoing HSCT receiving high-dose melphalan with or without TBI. • Low-level laser therapy to prevent oral mucositis in patients receiving radiation without chemotherapy for head and neck cancer Transdermal fentanyl to treat oral mucositis in patients receiving standard or high-dose chemotherapy with or without TBI. • Morphine mouthwash to treat oral mucositis in patients receiving moradiation for head and neck cancer. • Doxepin mouthwash to treat oral mucositis. • Oral zinc supplements to prevent oral mucositis in patients with oral cancer receiving chemotherapy or radiation.
Recommended AGAINST use:	• Polymixin/tobramycin/amphotericin B and bacitracin/clotrimazole/gentamicin for prevention of oral mucositis in patients with head and neck cancer receiving radiation. • Sucralfate mouthwash to prevent oral mucositis in patients receiving chemotherapy or radiation. • Sucralfate mouthwash to treat oral mucositis in patients receiving chemotherapy or radiation.
SubQ: subcutaneous; BID: twice daily; GI: gastrointestinal; TBI: total body irradiation; HSCT: hematopoeitic stem cell transplant; ≤: less than or equal to; ≥: greater than or equal to	

over-the-counter, so it is imperative to inquire as to what medications a patient is taking when they are looking to add these drugs for cancer pain as they may already be on a combination product containing one of the two non-opioid analgesics. Medications such as Norco and Vicoprofen each contain 325 mg of APAP and 200 mg ibuprofen, respectively, in addition to hydrocodone. There are potential adverse effects even with medications available over-the-counter if they are not taken correctly or if too much is taken. Excessive use of APAP can result in liver toxicity and, in severe cases where patients have prolonged excessive use, they may even need a liver transplant. Taking ibuprofen or other NSAIDs without food or milk can lead to irritation of the stomach tissue lining which can result in a gastrointestinal bleed in some cases. NSAIDs can also be problematic in patients with renal dysfunction as they can increase the risk of acute kidney injury. One additional adverse effect with cancer patients is that they can be at increased risk of bleeding in general with NSAIDs if they have thrombocytopenia (low platelets) as there will be a delay in the body's ability to clot with less platelets present. This can be seen more with cancers that affect the bone marrow such as leukemia and myelodysplastic syndrome or in-between cycles of intense chemotherapy when the bone marrow is suppressed and therefore there are less platelets and other blood cells circulating. However, NSAIDs do work well for bone pain, so there is a role for them with cancer patients, although they do need to be used cautiously.

Opioid Analgesics

The most common opioid analgesic side effects include bowel dysfunction, sedation and nausea/vomiting.[37,39,40] Less common, but more severe adverse effects include hallucinations, respiratory depression, and seizures. These adverse effects can be due to the opioid itself, but can be due to the combination of the opioid and another drug, referred to as a drug-drug interaction (DDI).[41] Drug-drug interactions between opioids and other agents can be due to decreased renal elimination of an opioid, inhibition of opioid metabolism (increased opioid levels), induction of opioid metabolism (decreasing opioid levels); potentiation (increase in signal transmission between nerves) of analgesic efficacy and toxicity; and/or modification of serotoninergic, dopaminergic, adrenergic and cholingeric activity in the CNS.

There are various opioid analgesics available and selection amongst them should include the drug characteristics as well as the patient characteristics (**Table 8**).[37,39,40] Opioids can vary in potency, however, most are described in relation to morphine which is considered the gold standard opioid. Morphine tends to have a wide variety of dosage forms available as well as being cost effective. However, it does have the potential for some concerns with its side effect profile and metabolism as it will have longer effects due to delayed clearance in patients with renal dysfunction. Hydromorphone is a very potent opioid, therefore great caution should be used when dosing it, and should be avoided in opioid-naïve (never previously received opioids) patients. Fentanyl is the most potent of the currently marketed opioids and is available in unique dosage forms such as a transdermal patch and buccal lozenges so they are very helpful with patients who are unable to swallow or who have such high pain needs that they would need to consume a significant number of oral tablets to control their pain. Methadone is a unique opioid in that it also affects the neuropathic pain receptors--this makes it a good option for patients with both visceral (organ) and neuropathic (nerve) pain. However, it does have very unpredictable pharmacokinetics and tends to have great variation in dosing and effect between patients, therefore, it should only be prescribed by those familiar with its properties and able to closely monitor and make dosing adjustments. One thing to note is that this agent is also used by rehabilitation centers for detoxification of persons with addictions to substances such as heroin. One of the main differences in how methadone is used for detoxification versus cancer pain is the dosing. For detoxification, the dosing is typically a large dose once daily (usual maintenance dose is 80-120 mg/day). However, with cancer pain, the dosing is typically every 8 or every 12 hours with a much smaller dose (2.5-10 mg).[37,39]

Miscellaneous Analgesics

Tramadol and tapentadol are atypical opioids which not only work at the opioid receptor, but they also have other targets.[37,40] Tramadol also inhibits the reuptake of the neurotransmitters norepinephrine and serotonin while tapentadol inhibits norepinephrine. There are drug interactions to be aware of due to the inhibition of the neurotransmitter reuptake. Tramadol can cause seizures, especially in patients with renal or liver dysfunction on high doses. Tapentadol may have less potential for causing gastrointestinal side effects such as constipation compared to oxycodone.

Many different classes of drugs can be used in conjunction with opioid analgesics discussed previously. Some of

Table 8. Summary of Opioid Analgesics, Comparable Potency, and Dosage Forms[37,39,40]

Drug	Potency (morphine equivalents)	Dosage forms	Miscellaneous
Morphine	10 mg IV= 30 mg oral	IV, SubQ, oral tablets/capsules (short acting and long acting), oral solution (2 different concentrations), rectal suppository	Can cause histamine release mimicking allergic reaction.
Hydromorphone (Dilaudid)	1.5 mg IV= 7.5 mg oral	Oral tablets (short acting and long acting), oral solution, IV, rectal suppository	
Oxycodone	30 mg oral	Oral tablets and capsules (short acting and long acting), oral solutions	Combination products with APAP.
Hydrocodone	30 mg oral	Oral tablets (short acting and new long acting options)	Combination products with APAP or ibuprofen. Also combinations with anticholinergics, antihistamines, cough expectorants and decongestants.
Methadone (Methadose, Dolophine)	Variable	Oral tablets, oral suspension, IV	
Fentanyl (Duragesic)	12 mcg patch	Transdermal patch, IV, buccal film, sublingual spray, oral lozenge, intranasal spray, sublingual tablet	
Codeine	200 mg oral	Oral tablets (short acting), oral solution	Can cause histamine release mimicking allergic reaction. Variable metabolism amongst people with CYP2D6 abnormality.

IV: intravenous, subQ: subcutaneous; APAP: acetaminophen

these adjuvant analgesics include anticonvulsants, antidepressants, corticosteroids and local anesthetics/topical agents.[37,39,40,42] Antidepressants are commonly used as adjuvant analgesics for cancer pain. These are of additional utility because they can serve a dual purpose of helping with pain as well as mood stabilization or improvement knowing that a cancer diagnosis can trigger depression. The main classes of antidepressants used for cancer pain are tricyclic antidepressants (e.g. amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs; e.g. paroxetine, sertraline, escitalopram), and serotonin/norepinephrine reuptake inhibitors (SNRIs; e.g. venlafaxine, duloxetine). Therefore, if a patient tells you they are taking nortriptyline for pain and not for depression, they likely are taking it primarily for pain.

Anticonvulsants (e.g. carbamazepine, gabapentin, oxcarbazepine, valproic acid, phenytoin, levetiracetam) are typically used for seizures, but they also can be used for pain, especially neuropathic pain.[37,39,40,42] Neuropathic pain can be caused by many different triggers such as diabetes, herpes zoster and specific anti-cancer medications such as taxanes (e.g. paclitaxel and docetaxel), platinums (e.g. cisplatin, carbopatin, oxaliplatin), bortezomib

and vinca alkaloids (e.g. vincristine primarily).[43] Chemotherapy-induced peripheral neuropathy (CIPN) can be very debilitating to activities of daily living and can lead to dose reductions or early discontinuation of the drug. The presentation of CIPN is typically symmetrical (occurs in both sides), starts at the toes or fingertips and is described as a "glove and stocking" progression from the tips of the fingers/toes towards the wrist/ankles. This neuropathy can be irreversible, so it is important to ask patients if they are experiencing this specific type of neuropathy and have them seek further medical attention. Masking the CIPN with agents such as gabapentin or tricyclic antidepressants can be useful once the insulting agent has been stopped, but starting it while continuing therapy can be dangerous as it could lead to unnoticed progression that may not reverse after stopping the chemotherapy agent.

Local anesthetics and topical agents containing lidocaine can be used for localized pain.[42] For example, a patient with an implanted port-a-cath (IV access surgically placed below the skin) would use a topical lidocaine/prilocaine product such as EMLA cream and apply it to the skin above the port-a-cath approximately 30-60 minutes prior to when a needle would be placed into the port-a-cath to administer medications intravenously. This topical agent would numb the skin so the patient would not feel pain when the needle is placed. Another option for local pain would be a lidocaine patch. This can be used when a patient has a specific location for pain, such as after a biopsy or with knee pain.

Ketamine may be an option for cancer-related pain, although there is not much literature to support its routine use at this time.[37,42] It works on a receptor other than the opioid receptor; it works at the N-methyl D-aspartate (NMDA) receptor which is part of the neuropathic pain receptors.

Part of the selection process for opioid analgesics focuses on the dosage forms available with each agent.[37,39,40] While the oral route is the preferred route for control of chronic pain, some patients are not able to swallow so they need pain medications in forms that do not need to be swallowed. In addition to the route that each drug is administered, it is also important to note the time release technology used for each formulation. Time release technology is used for medications with short durations of action to slow the release of the drug into the bloodstream and decrease the frequency a medication needs to be taken within a specified time period. There are many abbreviations related to time release technology that have similar meanings. The most common ones are listed in **Table 9**. It is important to note these types of formulations as it impacts how the drug can be manipulated for administration. Most drugs that have a long acting time release technology cannot be crushed, chewed or split without disrupting the time release, therefore they cannot be taken via a feeding tube.

Rash

There are many medications in general that can cause rashes and anti-cancer medications also have the potential to cause rashes, however, some are via a unique mechanism of action. One specific mechanism seen with anti-cancer medications is with epidermal growth factor receptor inhibitors (EGFRIs).[44,45] Many cancers are asso-

Table 9. Time release technology abbreviations for medications[37,39,40]

Short acting	Long acting
IR: Immediate release	CD: controlled delivery
	CR: controlled release
	DR: delayed release
	ER: extended release
	LA: long-acting
	XL: extended release
	XR: extended release

Test Your Knowledge #4

JS is a 67 year old male with head and neck cancer. He had a G-tube placed (feeding tube that goes directly into his stomach to provide nutrition and medication) to deliver his food and medications to his body while avoiding the need to swallow since he will have significant mucositis from his cancer therapy. Which dosage formulation would be <u>least</u> suited for JS?

A. Transdermal patch
B. Solution
C. Extended release tablets
D. Intranasal spray

Answer on page 28.

Test Your Knowledge #5

JS states that he is taking a lot of medications to help his pain due to his head and neck cancer. Which of the following medications is likely being used for pain? (select all potential pain medications)

A. Duloxetine
B. Gabapentin
C. Morphine
D. Diphenhydramine

Answers on page 28.

ciated with overexpression of EGFR, therefore EGFRIs can be monoclonal antibodies or tyrosine kinase inhibitors used to target this overexpression. For example, erlotinib is used as monotherapy or as part of a treatment regimen for lung and pancreatic cancer, cetuximab and panitumumab are used for colorectal cancer, cetuximab is also used for head and neck cancer and lapatinib can be used for breast cancer. EGFR is also involved with normal skin growth, specifically with the epidermis, therefore one of the main side effects of EGFRIs is with the top layer of skin as the normal pathway for cell growth and turnover is disrupted.[46]

The rash seen with the EGFRIs looks like acne, thus it is called acneiform rash and can occur in up to 80% of patients receiving these agents.[44,46] It occurs because the inhibition of EGFR leads to arrested growth of keratinocytes within the skin and cell death. This results in a thinning of the epidermis and the skin barrier is more prone to tissue damage which then recruits leukocytes and neutrophils and leads to an inflammatory reaction of the skin which presents as a papulopustular rash, or acneiform rash. Think of severe acne—this is what it would look like. However, it means the drug is working and affecting the target it was designed to seek! This can be very problematic for patients as the acneiform rash can be very noticeable as it primarily appears on the face, scalp, upper chest and back. In severe cases it can also lead to scarring and infections.

There are some risk factors for developing a rash.[44] For erlotinib, patients with fair skin, nonsmokers and those older than 70 years of age have more rashes while with cetuximab males and patients less than 70 years of age have more rashes. Monoclonal antibodies tend to cause more severe rashes more frequently than tyrosine kinase inhibitors (10-17% versus 5-9%). The severity of the rash can be assessed using the CTCAE scale discussed previously and is noted for these types of rashes in **Table 10**.

Preventive and treatment options are useful therapies to consider since the therapy causing it is being used to treat cancer. Most patients present with the rash within the first 2-4 weeks of therapy and the inflammatory skin

Table 10. NCI CTCAE Grading Scale on Skin and Subcutaneous Tissue Disorders[2,44,45,46]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acneiform rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus (itching) or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care and ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection and IV antibiotics indicated; life-threatening consequences	Death

BSA: Body surface area; ADL: activities of daily living; IV: intravenous; <: less than; >: greater than

changes tend to decrease in severity after the first 6-8 weeks, therefore preventive therapy should be utilized during the first 6-8 weeks of starting an EGFRI.[44,45,46] Hydrocortisone 1% cream, moisturizer and sunscreen should be applied to the high risk areas twice daily and doxycycline or minocycline antibiotics have been shown to reduce the number of lesions seen during the first 8 weeks. If treatment is needed despite these preventive efforts, stronger topical corticosteroids such as alclometasone 0.05% cream or fluocinonide 0.05% cream can be used, as well as a topical antibiotic such as clindamycin 1%. Isotretinoin can also be used at low doses (20-30 mg/day) to improve quality of life while continuing to benefit from the clinical response to the EGFRI.

Selected Neurotoxicities

Oxaliplatin-Induced Neurotoxicity

In addition to CIPN discussed previously, some of the neurotoxic anti-cancer agents such as oxaliplatin can cause an acute neuropathy syndrome.[43] Oxaliplatin neurotoxicity can start within hours to days after the infusion and manifests as sensitivities to touching cold items, muscle cramps and throat discomfort. It is recommended that patients receiving oxaliplatin avoid cold foods and beverages, use plastic utensils instead of metal ones that can be cold when placed in the mouth, and wear scarves when moderately cool or windy to try to prevent the throat discomfort triggered by cooler weather.

Cancer-Related Fatigue

Fatigue is a common symptom in cancer patients as the disease itself, anti-cancer therapies, and supportive care therapies can all be causes of fatigue. The NCCN defines cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[47] One common cause is anemia, or a hemoglobin less than 10g/dL. This can be due to the cancer itself or due to myelosuppression by the anti-cancer therapy. Anti-cancer agents, especially the immune mediated/immune checkpoint therapies, can cause hypothyroidism which can present as fatigue. Agents most commonly associated with hypothyroidism include aldesleukin, alemtuzumab, axitinib, cisplatin, dasatinib, imatinib, interferon, ipilimumab, lenalidomide, nilotinib, nivolumab, pazopanib, pembrolizumab, sorafenib, sunitinib, thalidomide, vandetanib.[47]

It is important that patients noting fatigue be referred for further evaluation as the fatigue could be caused by pain medications, anti-nausea medications, infection, anemia, hypothyroidism, depression, hormonal deficiencies and many other potential causes. In some cases psychostimulants such as methylphenidate may be considered to help with fatigue after other causes are ruled out. However, non-pharmacologic interventions such as physical activity and psychosocial counseling have some of the best evidence for treating fatigue in cancer patients.[47]

Insomnia

Insomnia is a distressing symptom reported in up to 90% of cancer patients either during or after treatment.[48] It is defined as difficulty falling asleep and/or maintaining sleep at least 3 times per week for at least 4 weeks.[49] Insomnia has the potential to worsen quality of life and therefore is a symptom that can affect morbidity (disease) in cancer patients. Insomnia can be a sign of depression and therefore patients experiencing insomnia should be referred to a health care provider for complete evaluation. There are medications that can also cause insomnia or sleep disturbances such as corticosteroids, stimulants (e.g. caffeine, pseudoephedrine, methylphenidate), antidepressants and antihistamines. Sleep hygiene can be of great help for anyone experiencing insomnia **(Table 11)**. Optimizing sleep can also help improve cancer-related fatigue. While exercise is routinely recommended to help with insomnia, specifics regarding the type and frequency of exercise are not as common. There is new literature to consider incorporation of yoga as a means of physical activity to help with insomnia.[48] Mirtazapine, benzodiazepines (e.g. lorazepam, alprazolam), and hypnotics such as zolpidem all have clinical trials to support their use for insomnia related to cancer.[49] Melatonin is an OTC agent used to help individuals fall asleep, however, it does not have an FDA-labeled indication for insomnia.[49]

Cognitive Dysfunction

There has been an increasing amount of support demonstrating cognitive (knowledge) dysfunction after treatment for cancer.[49] This has been reported by many patients as "chemo brain" and is thought to have long-standing effects on cognitive function, however, in some cases it can also

Table 11. Sleep Hygiene Recommendations[49]

- Regular exercise in the morning and/or afternoon
- Increase exposure to bright light during the day
- Reduce exposure to bright light a few hours before bedtime (including computer and phone screens)
- Avoid heavy meals or eating within three hours of bed
- Avoid alcohol, nicotine or caffeine too close to bedtime
- Enhance sleep environment (dark, quiet room, comfortable temperature)
- Set aside "worry time" before bedtime
- Avoid looking at the clock when awake at night
- Maintain a regular bedtime and waketime every day
- Limit to 1 short nap per day (maximum 30 minutes)
- Turn off electronics and light emitting sources at bedtime

be due to the cancer itself. First line interventions include neuropsychological evaluation to rule out any other causes of neurologic dysfunction and occupational therapy. Additionally, optimal treatment of distress, depression, sleep disturbances, fatigue, medical comorbidities, and contributing symptoms such as pain. If non-pharmacologic interventions are not effective, then pharmacologic interventions can be considered, however they are fairly lacking in data to support their efficacy. Options include methylphenidate and modafinil with modafinil having more consistent results in clinical trials.[49]

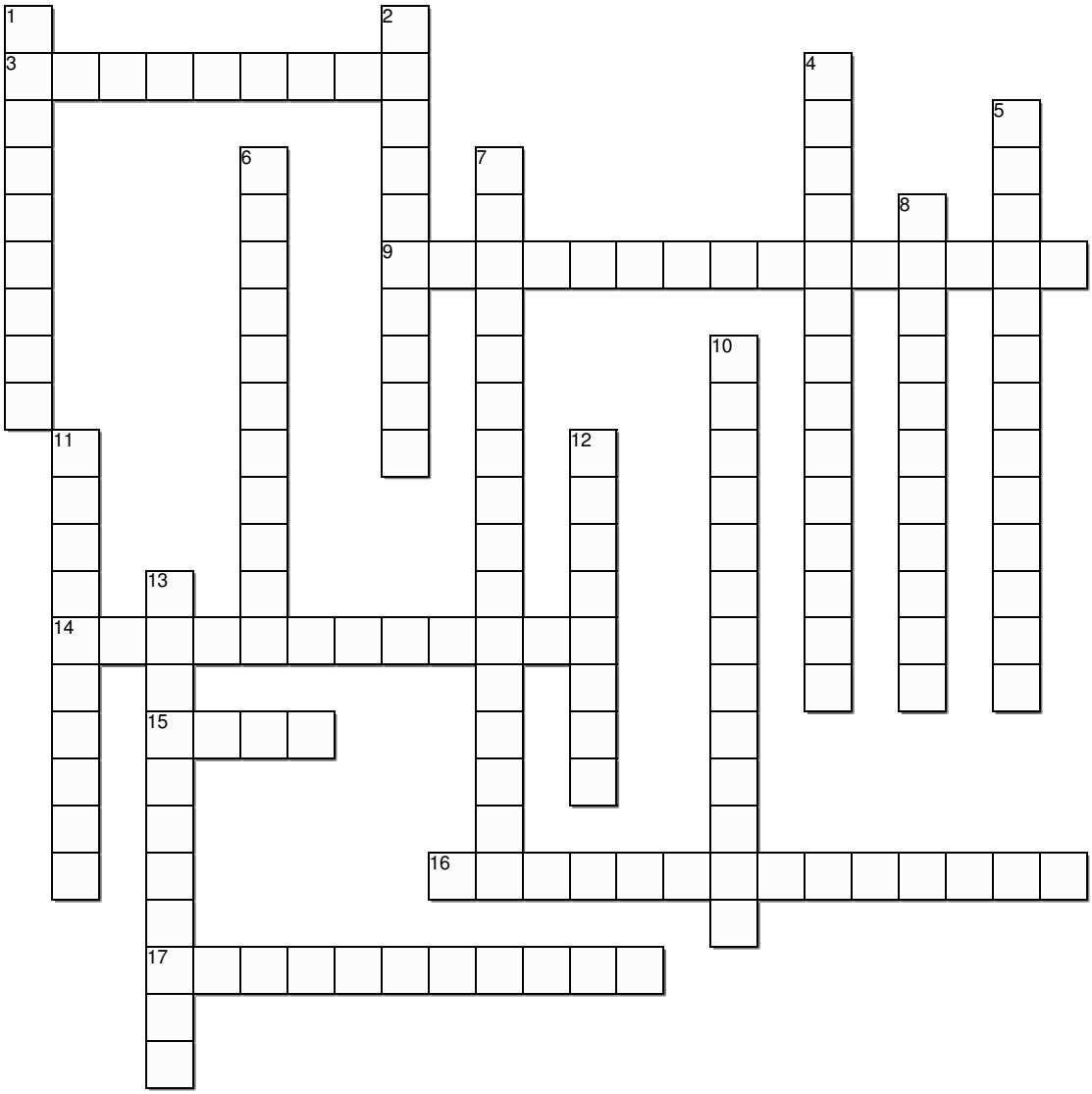
Conclusions

Pharmacy technicians have the opportunity to improve supportive care of cancer patients in various ways. By understanding many of the adverse effects that may affect a cancer patient, they have already started to help with their care. Technicians who assist with taking medication histories (in a hospital or retail setting) are able to directly interact with the patient and obtain a thorough medication list, allergy information and may even be told some concerns the patient is having. The technician can act as a liaison here to make sure the patient's concerns are relayed to the appropriate person (pharmacist, physician, nurse practitioner, physician assistant) so they can be addressed in a timely fashion. Also, by understanding what types of medications a cancer patient may be taking and for what specific indications, they are able to be more complete in obtaining a medication history. For example, a patient filling a prescription for daily use of doxycycline may note that it says on the drug information pamphlet that this medication is used to treat an infection and they note they do not have an infection. However, you see that they are also being prescribed erlotinib so you are able to know that the doxycyline is being used to prevent an infection from a side effect of the erlotinib and know to offer further pharmacist services for counseling on these medications because of the high risk of developing an acneiform rash.

Pharmacy technicians can also help improve the quality of care patients receive within the hospital by knowing that there are certain scenarios such as oncologic emergencies when medications need to get to the patient more efficiently. A pharmacy technician may be delivering an antibiotic to the oncology unit and note that it is a "first dose" so instead of putting it in the medication room, they should bring it directly to the nurse because of the importance of starting this medication for a potential infection. The key take home is that pharmacy technicians have a strong role in the supportive care of all patients and this module has hopefully helped with supportive care for cancer patients.

Test your knowledge 6

Complete the crossword below



Created on TheTeachersCorner.net Crossword Maker

Across

3. 'E' of EGFR
9. drug class used for seizures and neuropathic pain
14. 5HT-3 antagonist combined with netupitant as single oral pill
15. preferred route for control of chronic pain
16. class of drug used for anticipatory nausea and vomiting
17. type of white blood cell that fights off infections

Down

1. generic name of drug used for detoxification and cancer pain
2. 4th stage of the mucositis pathway
4. another name for acneiform rash
5. generic name of drug that uses abbreviation APAP
6. drug that causes cold-induced neuropathy
7. Generic name for drug used to treat opioid-induced constipation
8. generic name of drug used to treat TLS
10. granulocyte-colony stimulating factor given once
11. NK-1 antagonist given daily
12. XL and XR stand for what type of release
13. generic name of drug used to prevent TLS

Answers on page 28.

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ANSWER KEY: TEST YOUR KNOWLEDGE EXERCISES

Exercise #1:
1. B
2. D
3. C
4. A

Exercise #2:
1. Ondansetron, granisetron, dolasetron, palonosetron,
2. Aprepitant, fosaprepitant, rolapitant, netupitant
3. Metoclopramide, prochlorperazine, promethazine, trimethobenzamide, droperidol, olanzapine
4. hydroxyzine
5. Diphenhydramine, scopalomine
6. Dronabinol, nabilone
7. lorazepam
8. dexamethasone

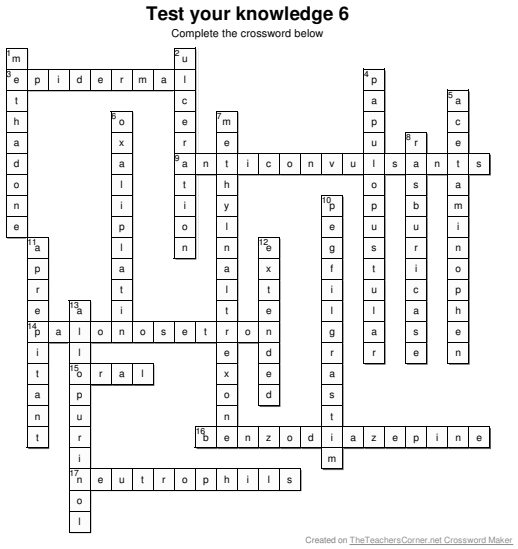
Exercise #3:
Visceral
1. aching
2. diffuse
3. cramping

Neuropathic
1. sharp
2. burning
3. Shooting

Exercise #4:
C. Extended release tablets

Exercise #5:
A. Duloxetine (Cymbalta)
B. Gabapentin (Neurontin)
C. Morphine

Exercise #6:



SELF ASSESSMENT QUESTIONS

1. **In general, traditional chemotherapy works by**:
   A. Targeting rapidly dividing cells
   B. Targeting antigens on cancer cells
   C. Removing hormones related to growth of a tumor
   D. Stimulating the immune system

2. **Which is NOT one of the 3 mechanisms of action of monoclonal antibodies?**
   A. Preventing signaling cascades leading to cell growth and proliferation
   B. Direct killing of the cell by stimulating a cascade for cellular cytotoxicity
   C. Conjugation to a toxin that is internalized by the cell and causes apoptosis
   D. Destroying all rapidly dividing cells

3. **What is the most common dose-limiting adverse effect of traditional chemotherapy?**
   A. Diarrhea
   B. Mucositis
   C. Myelosuppression
   D. Constipation

4. **A patient is neutropenic when their absolute neutrophil count falls below how many neutrophils/mcL:**
   A. 1
   B. 50
   C. 500
   D. 2000

5. **How can a technician improve care for a patient with neutropenic fever?**
   A. Getting the first doses of antibiotics to the patient in a time effective manner
   B. Dose the antibiotic
   C. I have no role as a technician
   D. Start filgrastim

6. **When should filgrastim or pegfilgrastim be administered after completion of chemotherapy?**
   A. During the first 24 hours
   B. Anytime between 24 hours and 30 days
   C. Immediately after completion
   D. Between 24 and 72 hours

7. **What over the counter medication can be used for bone pain with filgrastim or pegfilgrastim?**
   A. Morphine
   B. Diphenhydramine
   C. Loratadine
   D. Loperamide

8. **Ondansetron, palonosetron and granisetron all target which neurotransmitter to prevent or treat nausea and vomiting?**
   A. Neurokinin
   B. Dopamine
   C. Serotonin
   D. Histamine

9. **Which antiemetic can be used for anticipatory chemotherapy-induced nausea and vomiting?**
   A. Lorazepam
   B. Olanzapine
   C. Diphenhydramine
   D. Ondansetron

10. **Which anti-cancer agent causes diarrhea?**
    A. Vincristine
    B. Capecitabine
    C. Thalidomide
    D. Ondansetron

11. **What agent can cause severe diarrhea that needs higher than normal doses of loperamide?**
    A. Vincristine
    B. Irinotecan
    C. Bortezomib
    D. Diphenhydramine

12. **Which of the following anti-cancer agents is NOT associated with mucositis?**
    A. Melphalan
    B. Doxorubicin
    C. Capecitabine
    D. Sorafenib

13. What are the 5 stages in order for the development of mucositis?
A. Healing, up-regulation of messengers, signaling and amplification, ulceration, initiation
B. Initiation, up-regulation of messengers, signaling and amplification, ulceration, healing
C. Signaling and amplification, ulceration, healing, initiation, up-regulation of messengers
D. Initiation, up-regulation of messengers, ulceration, healing, signaling and amplification

14. What is the cornerstone for the prevention and treatment of mucositis?
A. Avoiding chemotherapy
B. Ice chips
C. Mouth hygiene
D. Sucralfate

15. Name the two general types of pain.
A. Visceral and neuropathic
B. Nociceptive and neuropathic
C. Somatic and neuropathic
D. Bone and neuropathic

16. Which analgesic should you avoid in patients with thrombocytopenia?
A. Acetaminophen
B. Morphine
C. Ibuprofen
D. Gabapentin

17. Which opioid analgesic is available as a transdermal patch?
A. Methadone
B. Fentanyl
C. Codeine
D. Hydromorphone

18. Which agent does NOT cause acneiform rash?
A. Cetuximab
B. Erlotinib
C. Lapatinib
D. Bevacizumab

19. Which of the following would be a good non-pharmacologic or sleep hygiene intervention for a cancer patient noting insomnia?
A. Have a glass of wine before bed
B. Watch the clock until you fall asleep
C. Turn off electronics at bedtime
D. Eat a large meal before bed

20. Technicians providing medication history services in hospitals can help enhance the supportive care provided to patients by:
A. Testing for drug allergies
B. Obtaining a more complete medication history
C. Recommending drugs to prescribe
D. Providing immunizations