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Chemotherapy-induced Nausea and Vomiting: Recent Advances in Preventative Pharmacotherapy

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CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING: RECENT
ADVANCES IN PREVENTATIVE PHARMACOTHERAPY

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Chemotherapy induced nausea and vomiting (CINV) leads to morbidity and complications in care and occurs in up to 80% of patients. Despite the recent advances in newly available antiemetics, approximately 50% of patients experience CINV which can have a severe effect on the cancer patient's quality of life. In addition to CINV having a substantial negative impact on the patient's quality of life, it can also lead to chemotherapy delays, dose reductions, or discontinuation of therapy. CINV can be a major barrier to therapy if not treated appropriately. With the development of therapy options in a wider range of classes, it is possible for more patients to better control their CINV. Antiemetic guidelines should be utilized when choosing CINV prevention therapy, both pharmacologic and non-pharmacologic. Nausea and vomiting prevention should be a combination of lifestyle and medication therapy to achieve the best possible results.

Learning Objectives

Pharmacist

- 1 Identify chemotherapy induced nausea and vomiting (CINV) risk factors of patients receiving chemotherapy
- 2 List the antiemetic therapy agents available in the treatment of CINV
- 3 Recommend an antiemetic regimen based on a patient's chemotherapy agent(s) and risk factors
- 4 Identify 4 toxicities to consider with antiemetic therapy agents

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Introduction

Chemotherapy is a treatment course that can lead to many different responses and adverse events. While each patient and specific regimen are different, nausea and vomiting are an extremely common adverse reaction and feared by many patients. Chemotherapy induced nausea and vomiting (CINV) leads to morbidity and complications in care and occurs in up to 80% of patients. Despite the recent advances in newly available antiemetics, approximately 50% of patients experience chemotherapy-induced nausea and vomiting (CINV) which can have a severe effect on the cancer patient's quality of life. Nausea is defined as the feeling of sickness with an inclination to vomit. Retching is the labored movement of abdominal and thoracic muscles before vomiting. Vomiting is the physical motion of expelling stomach contents. There are numerous complications associated with CINV including malnutrition, malabsorption, electrolyte imbalances, aspiration pneumonia, depression, weakness, weight loss, and dehydration. In addition to CINV having a substantial negative impact on the patient's quality of life, it can also lead to chemotherapy delays, dose reductions, or discontinuation of therapy.

There are several different classifications of CINV and each type differs in both pathophysiology and recommended treatment. Acute onset occurs within 24 hours of chemotherapy versus delayed onset which occurs after the 24 hour threshold and can last up to 5 days¹. Anticipatory nausea and vomiting occur before a new cycle of chemotherapy in response to a treatment related stimuli (lights, sounds, smells of the infusion location). Breakthrough nausea and vomiting occurs despite appropriate antiemetic medications and requiring rescue therapy.

Pathophysiology

CINV pathophysiology differs according to the timing of the CINV onset. Acute CINV is mediated via serotonin whereas delayed CINV is mediated via substance P. Nausea is a separate function than retching or vomiting which are brain stem activities. Coordination of the vomiting action is likely loosely coordinated in the medulla, but an anatomically distinct vomiting center likely does not exist. The nausea center in the brain has three separate components that integrate within the medulla of the brain, area postrema, nucleus tractus solitaries, and dorsal vagal complex. It is possible that chemotherapy or metabolites act directly on the area postrema, since it lies outside the blood brain barrier. It is also logical to think that chemotherapy may cause serotonin and substance P release from the enterochromaffin cells in the gastric wall. Release of these substances would send signals to the nucleus tractus solitarius via afferent sensory nerves. Abdominal vagal afferents appear to have the greatest relation to CINV in studies; these afferents have receptors for 5-hydroxytryptamine₃ (5-HT₃), neurokinin-1, and cholecystokinin-1 on the terminal end². The neurotransmitters that have shown to have the most clinical significance in CINV are dopamine, 5-HT₃, and substance P, drug development has been directed towards these transmitters. Of note, endocannabinoids appear to be an additionally significant neurotransmitter group working as an antiemetic agonist that is different from the other neurotransmitter functions².

CINV Risk Factors

When determining a patient's risk of CINV, the patient's specific characteristics are considered in addition to the specific cancer and chemotherapy agents being utilized. Chemotherapy regimens range from minimal to high emetic risk depending on the percentage of patients who experience nausea and vomiting with the regimen. Highly emetogenic chemotherapy (HEC) are regimens that cause nausea or vomiting in more than 90% of patients who receive it, moderately emetogenic chemotherapy (MEC) is 31-90%, low is 10-30% and minimal is less than 10% of patients².

Risk of emesis depends not just on the chemotherapy regimen but on patient specific factors as well. Females, younger patients (under 50), history of motion sickness, previous nausea and vomiting episodes, and concurrent radiation all increase a patient's risk of CINV. Patients who had nausea or vomiting with a previous chemotherapy regimen are more likely to have nausea or vomiting associated with another regimen. Patients with a history of chronic alcoholism (>1.5 oz per day) are less likely to develop CINV.

FDA Approved CINV Prevention and Treatment

Medications with CINV FDA indications include Neurokinin₁ Receptor Antagonists (NK1RA), Serotonin₃ Receptor Antagonists (5-HT₃RA), corticosteroids, dopamine receptor antagonists, cannabinoids, phenothiazines, butyrophenones, metoclopramide, olanzapine, and others. There are other medications used as supportive antiemetic therapy, such as promethazine, though they do not necessarily carry a CINV FDA label. Major clinical trials and pearls of use for each medication class and commonly used medications are outlined below.

Serotonin₃ Receptor Antagonists

At this time there are five 5-HT₃RA approved for CINV management: dolasetron, granisetron, ondansetron, tropisetron, and palonosetron. This class of drugs is the cornerstone of prophylactic treatment in MEC and HEC. These medications as a class have shown better efficacy in acute nausea prevention than delayed. Oral (PO) and intravenous (IV) dosage has been shown to have equivalent efficacy². The first generation 5-HT₃RA (dolasetron, granisetron, ondansetron, tropisetron) have been demonstrated to be clinically equivalent in terms of efficacy and adverse reactions². Studies specific to each 5-HT₃RA are outlined below.

Ondansetron was the first in this class approved as an injectable in 1991 and oral in 1992. The agents approved since then have mainly been approved on a non-inferiority basis. In the pivotal trial, ondansetron was compared to metoclopramide or placebo in patients receiving different chemotherapy regimens (cisplatin, cyclophosphamide, methotrexate, fluorouracil). The efficacy of ondansetron proved to be similar to metoclopramide with an improved adverse effect profile in a meta-analysis of six randomized control trials. Results of this analysis were reported in relative risk (RR) for zero emesis or nausea at 24 hours. RR of zero emesis with ondansetron was 1.72 (95% CI 1.45 to 1.97) and was similar for nausea (RR= 1.78, 95% CI 1.39 to 2.13).

Granisetron was compared to ondansetron in large, 14 study, meta-analysis for use of CINV. The analysis looked at studies with more than 25 patients per arm and utilized granisetron versus ondansetron in the setting of acute and delayed CINV in both MEC and HEC. There was no significant difference between the two therapies in any measure tested.

Dolasetron was compared to granisetron in an open-label pilot study. Patients all received dexamethasone 20 mg IV prior to chemo and then either received 100 mg PO dolasetron or 2 mg PO granisetron. The results show that patients treated with granisetron experienced total control of nausea and vomiting more than patients receiving dolasetron (69.2 vs 23.1%, $p < 0.05$). The results showed that granisetron is significantly more effective in preventing CINV for HEC and MEC.

Tropisetron was compared to granisetron for prophylaxis of acute CINV in a pooled analysis of 12 studies¹¹. There was a significant overall advantage of granisetron over tropisetron ($p=0.042$). Of the pooled studies, 10 out of 12 totals demonstrated granisetron superiority with a 6.4% difference in response rate, the response rate in cisplatin therapy was 5.4% and non-cisplatin therapy was 7.3%. The overall conclusion of this analysis was that granisetron has a marginal but potentially beneficial efficacy in controlling CINV.

In a large meta-analysis, palonosetron was compared to the first generation 5-HT₃RAs in terms of efficacy and safety in MEC and HEC. This meta-analysis was comprised of 9 studies and a total of 3463 encounters. The analysis showed that patients receiving palonosetron has a significantly lower incidence of emesis on the first day (RR = 1.11, 95% CI: 1.05–1.17), from 2 to 5 days (RR = 1.26, 95% CI: 1.16–1.36) and the overall 5 days (RR = 1.23, 95% CI: 1.13–1.34). There was no significant difference in adverse effects or drug safety.

Depending on the dose of 5-HT₃RA, changes in ECG recordings have been reported may increase risk of QT interval prolongation. These agents should be avoided in patients with congenital long QT syndrome⁶. Monitoring with an ECG in patients with concomitant electrolyte abnormalities, cardiac failure, arrhythmias, or using other QT prolonging drugs is recommended. Headache, dizziness, constipation, diarrhea, fever, malaise, and transient increases in serum transaminases are the most common side effects associated with 5-HT₃RA antagonists².

Generic Name	Brand Name	Dosage Forms
Dolasetron	Anzemet	PO
Granisetron	Kytril, Granisol, Sancuso, Sustol	PO, IV, Patch
Ondansetron	Zofran	PO, orally disintegrating tablets (ODT), IV
Palonosetron	Aloxi	IV

Neurokinin₁ Receptor Antagonists

The NK-1RA are the newest prevention option for CINV. The class contains four medications at this time: aprepitant, fosaprepitant, netupitant, and rolapitant. Aprepitant was the first in class, approved in 2003, for oral use². The next approval in this class was fosaprepitant IV which is a prodrug of aprepitant and converted within 30 minutes of administration.

Aprepitant therapy has been studied in MEC and HEC with success. In the process of FDA approval aprepitant 125 mg PO on day 1 and 80 mg PO on days 2-3 of chemotherapy in combination with ondansetron 32 mg IV and dexamethasone 8 mg days 2-4 was compared to ondansetron 32 mg IV and dexamethasone 12 mg day 1 and 8 mg days 2-4 alone for HEC cisplatin regimens. In the 5 days after chemotherapy the aprepitant group had 62.7% of patients achieve complete response versus 43.3% in the placebo group. It is important to consider that aprepitant and corticosteroids are both metabolized through cytochrome P-450 3A4 pathway leading to an increased dexamethasone serum concentration when combined².

Rolapitant was approved in this class in 2015. Rolapitant has the benefit of not interacting with cytochrome p-450 3A4. In the approval trials, rolapitant was given in combination with a 5-HT₃RA and dexamethasone. The phase III trials utilized to show rolapitant efficacy assessed use in both HEC and MEC regimens. In HEC regimens patients in the group that received rolapitant 180 mg PO in addition

to granisetron 10 µg/kg IV on day 1 and dexamethasone 20 mg on day 1 and 8 mg twice a day on days 2-4 had significantly higher complete responses than in the active placebo group, 73% vs 58%; odds ratio 1.9. 95% CI 1.3-2.7; p=0.006.

The most common adverse effects associated with NK-1RA class are fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, dehydration, and mild elevation of serum transaminase levels¹⁵.

Generic Name	Brand Name	Dosage Forms
Aprepitant	Cinvanti	PO, IV
Fosaprepitant	Emend	IV
Netupitant/palonosetron	Akynzeo	PO, IV
Rolapitant	Varubi	PO, IV

Corticosteroids

The most benefit with corticosteroid uses for CINV has been show in combination with 5-HT₃RA and NK-1RA, although they can also be utilized alone. The corticosteroids that have the most experience in this indication are dexamethasone and methylprednisolone. Methylprednisolone 125 mg IV was shown to be superior to metoclopramide 20 mg IV in women receiving cyclophosphamide, methotrexate, and 5-fluorouracil. Dexamethasone was shown to be superior to placebo or no treatment in a meta-analysis totaling 5613 patients in 32 studies against both acute (OR = 2.22; 95% CI 1.89–2.60) and delayed emesis (OR = 2.04; 95% CI 1.63–2.56). As this was a meta-analysis there was not a standard dose but half of the studies used 20 mg for acute and overall patients got an average of 56 mg between acute and delayed phase. Corticosteroids are often utilized in combination for HEC and MEC but can be used as monotherapy for low emetic risk chemotherapy.

Adverse effects associated with corticosteroids use include insomnia, indigestion, agitation increased appetite, weight gain, and acne, but these are usually not associated with short-term use.

Generic Name	Brand Name	Dosage Forms
Dexamethasone	Decadron	PO, IV
Methylprednisone	Medrol	PO

Other Agents

Olanzapine is a dopamine and 5-HT₃RA typically classified as an anti-psychotic. There have been a couple phase II trials showing efficacy in both acute and delayed CINV. A meta-analysis of trials that looked at prophylactic and breakthrough use of olanzapine supported use of olanzapine in prophylactic regimens and monotherapy for breakthrough treatment. For HEC the improved rates of complete response with olanzapine were not statically significant compared to aprepitant but secondary endpoints did see statistically significant improvements: no delayed nausea (69 vs 38 %; p<0.01) and no nausea in overall period (69 vs 38 %; p<0.01). Olanzapine adverse effects include somnolence, fatigue, hypotension, constipation, dizziness, dyspepsia, and restlessness.

Dopamine antagonists are used as supportive preventative therapy for CINV. These agents consist of metoclopramide, promethazine, and prochlorperazine. The adverse effect profile of these medications is also not necessarily appealing to patients with metoclopramide causing extrapyramidal symptoms. This class was the mainstay of CINV prevention prior to the 5-HT₃RA but has been moved to a supportive, breakthrough role due to not statistically better efficacy and higher rates of more severe adverse effects.

Cannabinoids are an ever-emerging drug product but have been on the market through the FDA for CINV since 1985. Dronabinol and nabilone are the two synthetic cannabinoids on the market. In a systematic review, cannabinoids were shown to be more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, or haloperidol: RR 1.38 (95% confidence interval 1.18 to 1.62) with a number needed to treat of 6 for controlling nausea. The downfall with cannabinoids, especially nabilone, is the adverse effects such as drowsiness (52-66%), dizziness (59%), euphoria (11-38%), and xerostomia (22-36%). An advantage to dronabinol is a better adverse effect profile, euphoria (24%) is the only adverse effect over 10%.

Benzodiazepines do have some utility in CINV, the largest indication is anticipatory and breakthrough nausea and vomiting. The antianxiety effects are generally more beneficial than the anti-nausea. A study published in 1985 compared lorazepam 2-5 mg/m² IV to metoclopramide 2mg/kg IV. The study showed no statistical difference in efficacy between the groups but showed benefit with lorazepam in terms of patient preference.

Generic Name	Brand Name	Dosage Forms
Olanzapine	Zyprexa	PO, ODT
Prochlorperazine	Compazine	PO, IV, IM, PR
Chlorpromazine	Thorazine	PO, IV, PR
Promethazine	Phenergan	PO, IV, PR

Haloperidol	Haldol	PO, IV
Lorazepam	Ativan	PO, IV
Dronabinol	Marinol, Syndros	PO
Nabilone	Cesamet	PO
Metoclopramide	Reglan	PO, IV

Complementary Therapies

The National Cancer Institute outlines several non-pharmacologic treatment options for CINV. Some of the highlighted topics include dietary alterations, hypnosis, acupuncture, acupressure, relaxing techniques, and behavioral therapy. These treatment options are best utilized in attempt to prevent anticipatory nausea.

Acupuncture is a technique that includes inserting and controlling thin needles into acupuncture points. Nine studies have suggested acupuncture can reduced CINV severity through a biologic effect of acupuncture-point stimulation. The proportion of patients experiencing acute vomiting in the acupuncture group was 22% compared to 31% in the control group. Acupuncture is considered safe for patients.

Massage therapy was evaluated in a pediatric randomized controlled trial with 70 patients. Massages were provided in 20-minute intervals 24 hours and 30 minutes prior to chemotherapy start time and 24 hours after chemotherapy. The severity and timing of vomiting in the massage group was 0.24 and 0.31 times lower than that control group, respectively ($p < 0.05$). However, there was no difference in vomiting incidence between the two groups ($p = 0.192$).

Prophylaxis Based on Regimen

The overall approach to CINV management is prophylaxis. Patients need to be protected during their full emetic risk period based on the chemotherapy they are receiving. When patients are receiving more than one chemotherapy in combination antiemetic should be chosen based on highest risk. Encourage patients to utilize non-pharmacologic approaches of preventing nausea in addition to their prophylactic regimen.

The drug classes and total number of drugs recommended for prevention and treatment of CINV differs based on the chemotherapy regimen being used. Differing combinations of drug classes in association with the chemotherapy regimen should be considered. In addition, when determining which drug class of antiemetics to utilize, the toxicity of that specific antiemetic should be considered.

In general, addition of breakthrough medications should be a medication class that the patient is not already receiving. This typical includes atypical antipsychotics, benzodiazepines, cannabinoid,

prochlorperazine, 5-HT₃RA, steroid, or other medications with anti-nausea activity that are not already being utilized.

HEC IV Therapy

According to the American Society of Clinical Oncology (ASCO) antiemetic guidelines, patients receiving a HEC regimen should be offered a four-drug acute prophylactic regimen be used with these chemotherapy regimens. The guidelines recommend the combination of an NK-1RA, 5-HT₃RA, dexamethasone, and olanzapine to be started prior to chemotherapy. Delayed prophylaxis should be a continuation of aprepitant, dexamethasone and olanzapine dosed once daily for days 2-4 depending on the acute prophylaxis utilized. For anthracycline combined with cyclophosphamide regimens, dexamethasone does not need to be continued days 2-4, only olanzapine. If patients experience CINV despite optimal prophylaxis and previously received olanzapine as prophylaxis, then a drug with a different class should be added to prophylactic regimen. For example, lorazepam, dronabinol, or nabilone.

MEC IV Therapy

MEC regimens are generally treated with a two-drug or three-drug prophylactic regimen according to the ASCO guidelines³². Patients receiving MEC IV therapy should be initiated on prophylactic therapy prior to receiving chemotherapy. Acute emesis prevention should be a combination of a 5-HT₃RA and dexamethasone. Delayed prevention should be a continuation of dexamethasone, aprepitant, or 5-HT₃RA for days 2-3 depending on the acute prophylaxis utilized. If patients experience CINV despite the optimal prophylaxis and did not receive olanzapine prophylactically, patient should be offered olanzapine in addition to continuing the standard regimen.

Low/Minimal Emetic Risk IV Therapy

Low emetic risk chemotherapy requires less prophylactic medication coverage than either HEC or MEC. Patients receiving treatments with low emetic risk typically receive a single medication prophylaxis regimen³². Acute, oral prophylaxis of dexamethasone or a 5-HT₃RA should be initiated prior to chemotherapy regimen with a single dose. Minimal emetic risk regimens do not require scheduled antiemetic therapy prior to or after chemotherapy. For both low and minimal risk, the patient can be sent home with breakthrough treatment to be used as needed. Breakthrough therapy generally should be the addition of a different drug class than already being utilized.

Oral Chemotherapy Regimens

Emesis prevention in oral chemotherapy regimens is largely oral based. Patients receiving a moderate to high emetic oral therapy prophylaxis with a 5-HT₃RA should be initiated prior to therapy and continued once daily³². For minimal to low emetic risk regimens, as needed therapy is recommended with a scheduled dose prior to first dose and as needed to follow for any breakthrough nausea.

Case Studies

To illustrate the clinical practicality of a solid understanding of CINV, consider the following cases:

Case #1:

A 40-year old woman with newly diagnosed stage 3 breast cancer is scheduled to receive her first cycle of doxorubicin plus cyclophosphamide administered every 14 days. Her PMH is nonsignificant. She is married with two children younger than age 10. She notes getting seasick on a cruise ship last year. You provide chemotherapy counseling, and realize she is extremely nervous regarding her first cycle of chemotherapy and had poor sleep last night.

In this example, the clinician must fully appreciate the factors contributing to the patient's increased risk of CINV. Certainly, the presence of a history of motion sickness coupled with the patient's age and gender are contributing factors for risk. Patient factors that increase risk of CINV include female gender, younger age, low alcohol intake, motion sickness history, prior chemotherapy, and various other patient factors. Once the risk is identified, the clinician faces choices for premedication regimens. In the case of this patient, let us assume that the following regimens are being considered:

- Ondansetron 16 mg PO, dexamethasone 10 mg IV, and lorazepam 1 mg IV
- Palonosetron 0.25 mg IV, dexamethasone 12 mg IV on day 1, aprepitant 125 mg PO on day 1 and 80 mg PO on days 2 and 3, and olanzapine 10 mg PO daily on days 1-4
- Ondansetron 16 mg IV, dexamethasone 10 mg IV, and lorazepam 1 mg PO, and scopolamine 1.5 mg patch applied for 3 days
- Palonosetron 0.25 mg IV, lorazepam 1 mg IV, and prochlorperazine 10 mg IV

According to the ASCO guidelines, what type of regimen should be utilized?

Recall that, according to the American Society of Clinical Oncology (ASCO) antiemetic guidelines, patients receiving a HEC regimen should be offered a four-drug acute prophylactic regimen to be used with these chemotherapy regimens. The guidelines recommend the combination of an NK-1RA, 5-HT₃RA, dexamethasone, and olanzapine to be started prior to chemotherapy. Delayed prophylaxis should be a continuation of aprepitant, dexamethasone and olanzapine dosed once daily for days 2-4 depending on the acute prophylaxis utilized. So, of the choices presented in this example, the most appropriate premedication regimen is:

- Palonosetron 0.25 mg IV, dexamethasone 12 mg IV on day 1, aprepitant 125 mg PO on day 1 and 80 mg PO on days 2 and 3, and olanzapine 10 mg PO daily on days 1-4

Four days after chemotherapy, the patient presents to the walk-in clinic at an ambulatory infusion clinic with significant CINV. She claims to have kept down two liquid nutritional supplements and 1200 mL of fluid daily for the past 2 days and states that she is "feeling much better now than in prior days." Her laboratory values are remarkable for sodium 134 mEq/L and chloride 93 mEq/L.

The obvious question, then, is what regimen is best for the next cycle of chemotherapy? Upon consultation with colleagues, the following actions are being considered:

- Reeducate patient and administer the same antiemetic regimen
- Schedule ondansetron around the clock for 2 days and change or increase palonosetron to 0.75 mg IV on day 1 of next cycle
- Administer the same antiemetic regimen as before, except add PO dronabinol on day 1
- Administer the same antiemetic regimen as in the previous cycle, except change 5-HT₃ antagonist to granisetron topical patch applied 48 hours before cycle

Which one of the following interventions is best for the next cycle of chemotherapy?

In this case, the clinician should recognize that, of these options, 'administering the same antiemetic regimen as before, except adding PO dronabinol on day 1' is the best course of action for this

patient. Patients who experience breakthrough CINV despite optimal prophylaxis, and who have already received olanzapine should be offered a drug of a different class in addition to continuing the standard antiemetic regimen.

The patient calls the oncologist 4 days before cycle 2 of chemotherapy and she is getting nausea just thinking about receiving more chemotherapy.

Is there anything you could recommend to the oncologists to help her feel better?

This is a case where a clinician may be wise to think outside the traditional parameters. Benzodiazepines have some utility in CINV, with the largest indication being anticipatory and breakthrough nausea and vomiting. The anti-anxiety effects are generally more beneficial in such cases than other anti-nausea agents. In this case, a dosage of lorazepam 1mg PO the night before chemotherapy and the morning of chemotherapy may prove beneficial.

Case 2:

A 71-year old male presents with persistent cough, weight loss, and diarrhea with rectal bleeding. CT chest/abdominal/pelvis reveals a large colon mass with lung metastases. A biopsy of the lung mass shows metastatic adenocarcinoma from the colon. Patient is going to start FOLFOX (oxaliplatin/leucovorin/fluorouracil).

For the purposes of this discussion, let us assume that the following regimens are being considered for this patient:

- Ondansetron 16 mg PO, dexamethasone 10 mg IV, and lorazepam 1 mg IV
- Palonosetron 0.25 mg IV, dexamethasone 12 mg IV on day 1, aprepitant 125 mg PO on day 1 and 80 mg PO on days 2 and 3, and olanzapine 10 mg PO daily on days 1-4
- Palonosetron 0.25 mg IV, dexamethasone 10 mg IV on day 1 and 8 mg PO on days 2 and 3
- Palonosetron 0.25 mg IV, lorazepam 1 mg IV, and prochlorperazine 10 mg IV

Which type of premedication regimens is best for this patient according to the ASCO guidelines?

According to the ASCO guidelines, adult patients who are treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT₃ receptor antagonist (day 1) and dexamethasone (day 1). Adult patients who are treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate emetic-risk antineoplastic agents that are known to cause delayed nausea and vomiting may be offered dexamethasone on days 2 to 3. In this case, then, the most appropriate option is:

- Palonosetron 0.25 mg IV, dexamethasone 10 mg IV on day 1 and 8 mg PO on days 2 and 3

The patient returns for his 2nd cycle and reports that he had nausea requiring use of prochlorperazine daily starting from day 3 through 6 after cycle 1 of chemotherapy. Assume that the following interventions are being considered for the 2nd cycle of chemotherapy:

- Adding olanzapine 10 mg PO on day 1 prior to chemotherapy then continuing 10 mg PO days 2-4
- Reeducating patient and administering the same antiemetic regimen
- Adding more 'as needed' antiemetic options for the patient to take at home
- Increasing the dose of palonosetron from 0.25 mg to 1 mg

What intervention is best for the 2nd cycle of chemotherapy, given his nausea despite the recommended preventative regimen?

In this case, *'adding olanzapine 10 mg PO on day 1 prior to chemotherapy then continuing 10 mg PO days 2-4'* may prove most useful. Adult patients who experience nausea or vomiting despite optimal prophylaxis, and who did not receive olanzapine prophylactically, should be offered olanzapine in addition to continuing the standard antiemetic regimen.

Conclusion

CINV can be a major barrier to therapy if not treated appropriately. With the development of therapy options in a wider range of classes, it is possible for more patients to better control their CINV. Going forward it is important to continue testing different combinations of antiemetic agents and classes to best optimize CINV prevention. Antiemetic guidelines should be utilized when choosing CINV prevention therapy, both pharmacologic and non-pharmacologic. Nausea and vomiting prevention should be a combination of lifestyle and medication therapy to achieve the best possible results.

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Chemotherapy-induced Nausea and Vomiting: Recent Advances in Preventative Pharmacotherapy • August 2019

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. PHARMACISTS ONLY: Does this lesson meet the learning objectives? (Circle choice).

Identify chemotherapy induced nausea and vomiting (CINV) risk factors of patients receiving chemotherapy	YES	NO
List the antiemetic therapy agents available in the treatment of CINV	YES	NO
Recommend an antiemetic regimen based on a patient's chemotherapy agent(s) and risk factors	YES	NO
Identify 4 toxicities to consider with antiemetic therapy agents	YES	NO

2. Was the program independent & non-commercial? YES NO

3. Relevance of topic

Low Relevance	Very Relevant
1 2 3 4 5	6 7

4. What did you like MOST about this lesson? _____

5. What did you like LEAST about this lesson? _____

6. How would you improve this lesson? _____

PLEASE MARK THE CORRECT ANSWER(S)

1. A 45 year-old female recently diagnosed with cervical cancer. She is a social drinker and has no history of smoking. Her PMH is positive for hypertension. Her oncologist decides to start her on treatment with cisplatin 50 mg/m² IV on day 1 and gemcitabine 1000 mg/m² on days 1 and 8 every 21 days after undergoing surgery. The oncologist looks to you (the clinical pharmacist) and needs a recommendation for what is the most appropriate antiemetic regimen for day 1 for the prevention of acute and delayed nausea and vomiting.
 - A. Palonosetron 0.25 mg IV day 1, dexamethasone 8 mg IV day 1, aprepitant 150 mg PO day 1
 - B. Fosaprepitant 150 mg IV day 1, palonosetron 0.25 mg IV day 1, dexamethasone 12 mg IV day 1 and 8 mg PO once daily day 2 and 8 mg PO twice daily on days 3 and 4, and olanzapine 10 mg PO days 1-4
 - C. Dolasetron 2 mg PO BID day 1, dexamethasone 12 mg IV day 1, fosaprepitant 150 mg IV day 1
 - D. Dexamethasone 12 mg IV day, fosaprepitant 150 mg IV day 1
2. A 55 year-old male recently diagnosed with EGFR mutation positive non-small cell lung cancer. PMH of 20 years of smoking and drinking > 2 drinks per day. The oncologists prescribed him erlotinib 150 mg orally once daily days 1-28. What antiemetic prophylactic treatment regimen do you recommend to the oncologist?
 - A. Ondansetron 16 mg PO daily and then metoclopramide 20 mg every 4-6 hours as needed
 - B. Haloperidol 1 mg PO every 4 hours after the day of etoposide
 - C. Lorazepam 0.5 mg PO every 4 hours as needed
 - D. Ondansetron 8 mg PO daily starting the day before etoposide
3. A 49 year old female with a history of breast cancer, who has recently presented to clinic with metastases to the lungs. She is now diagnosed with metastatic stage 4 breast cancer. Her oncologist prescribes capecitabine 2000 mg/m²/day PO divided BID days 1-14 and lapatinib 1250 mg PO daily every 21 days. She has been receiving prochlorperazine 10 mg PO every 6 hours as needed. She is complaining of breakthrough nausea and vomiting 10 days into treatment. What antiemetic treatment should she receive for breakthrough nausea and vomiting?
 - A. No changes to antiemetic regimen
 - B. Increase to prochlorperazine 10 mg PO every 2 hours
 - C. Schedule prochlorperazine 10 mg PO every 6 hours
 - D. Change to promethazine 12.5 mg PO every 6 hours as needed

4. A 62 year old female recently diagnosed with breast cancer. The oncologist is going to start her on doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV every 21 days for 4 cycles. Prior to her starting cycle 1 of chemotherapy, what would you recommend to the oncologist for acute and delayed nausea and vomiting?
 - A. Dolasetron 100 mg PO day 1, dexamethasone 12 mg IV day 1, fosaprepitant 150 mg IV day 1
 - B. Dolasetron 100 mg PO day 1, dexamethasone 12 mg IV day 1, fosaprepitant 150 mg IV day 1, dexamethasone 8 mg PO days 2, aprepitant 125 mg PO days 2 and 3, dexamethasone 8 mg PO BID days 3 and 4
 - C. Granisetron 2 mg PO day 1, dexamethasone 12 mg IV day 1, fosaprepitant 150 mg IV day 1, granisetron 2 mg PO BID days 2 and 3, dexamethasone 8 mg PO days 2, dexamethasone 8 mg PO BID days 3 and 4
 - D. Ondansetron 16 mg PO day 1, dexamethasone 12 mg PO day 1, aprepitant 125 mg PO day 1, Ondansetron 8 mg PO BID days 2 and 3
5. A patient receiving doxorubicin 60 mg/m² IV and cyclophosphamide 600 mg/m² IV every 21 days complains of nausea and vomiting on day 3. This is described as?
 - A. Acute chemotherapy induced nausea and vomiting
 - B. Delayed chemotherapy induced nausea and vomiting
 - C. Anticipatory chemotherapy induced nausea and vomiting
 - D. Refractory chemotherapy induced nausea and vomiting
6. A patient calls the oncologist 4 days before starting cycle 2 of chemotherapy and is getting nauseous just thinking about receiving more chemotherapy. Is there anything you could recommend to the oncologists to help the patient feel better?
 - A. Phenergan 12.5 mg IV the night before chemotherapy
 - B. Reglan 5 mg PO 5 hours prior to chemotherapy
 - C. There are no options available to help the patient
 - D. Ativan 1 mg PO the night before chemotherapy and the morning of chemotherapy
7. Which of the following increases a patient's risk of CINV?
 - A. Male gender
 - B. Elderly
 - C. Motion sickness history
 - D. No previous chemotherapy
8. Choose the false statement regarding treatment regimen factors impacting CINV risk.
 - A. Rate of administration can influence CINV risk.
 - B. Combination of agents can increase CINV risk.
 - C. All agents pose the same risk of CINV.
 - D. Route of administration has influence on CINV risk.

9. Which of the following medications is not considered first-line treatment for CINV prophylaxis or treatment?
- a. Ondansetron
 - b. Promethazine
 - c. Dronabinol
 - d. Aprepitant
10. Select the regimen with the appropriate dosage for CINV
- a. Aprepitant 80 mg PO daily for 6 days post chemotherapy.
 - b. Ondansetron 8 mg 1 tablet every 12 hours for days 2-3 post chemotherapy.
 - c. Dronabinol 10 mg once daily post chemotherapy.
 - d. Metoclopramide 0.5mg/kg every 6 hours for 2 weeks post chemotherapy.