The Changing Landscape of Chemotherapy-Induced Nausea and Vomiting Prevention – The Role of the Pharmacist

Learning Objectives:
1. Define chemotherapy-induced nausea and vomiting (CINV) and list the risk factors that contribute to CINV;
2. Describe the differences between agents used for CINV, including dosage recommendations based on concomitant medications;
3. Discuss the recommended prevention and treatment for acute and delayed CINV;
4. Develop a CINV prevention and treatment strategy for a patient receiving highly or moderately emetogenic chemotherapy; and
5. Compare the efficacy of antiemetic monotherapy and in combination for moderate and high risk emetogenic chemotherapy.

Post-test/Rationale

1. Which of the following pharmacologic agents should be administered before chemotherapy (i.e., on day 1) for a high emetic risk regimen:
   A. Dexamethasone
   B. A 5HT₃ receptor antagonist
   C. An NK₁ receptor antagonist
   D. All of the above***

Correct Answer: D
According to the National Comprehensive Cancer Network (NCCN) guidelines, the 3-drug regimen should be given on day 1 of chemotherapy to prevent acute emesis. If prophylaxis is not given, virtually all patients will vomit in the first 24 hours of chemotherapy. With this 3-drug regimen, about 90% will not vomit.

2. Which of the following recommendations regarding a regimen for breakthrough nausea/vomiting is TRUE:
   A. Studies have shown that olanzapine is superior to aprepitant for the treatment of breakthrough nausea/vomiting
   B. Using an agent with a different mechanism of action, other than what was given for prophylaxis is preferable (e.g., NK₁ or 5HT₃)***
   C. Rolapitant is indicated for the treatment of breakthrough nausea/vomiting at a dose of 90 mg by mouth (PO) daily
   D. A prescription for breakthrough nausea/vomiting should only be provided to patients with a high likelihood of vomiting after chemotherapy
Correct Answer: B
The basic principle is that using an agent with a different mechanism of action, different from those used in the prophylaxis of CINV, will attain the best results. 5HT3 receptor antagonists are widely used for the prophylaxis of CINV in low, moderate, and high emetic risk settings and NK1 receptor antagonists are used for high and moderate emetic risk settings. Therefore, inhibiting other receptors, such as dopamine, histamine, and muscarinic, can confer a pharmacologic advantage. Other agents, such as cannabinoids, may also be considered.

3. Which of the following agents can be administered on days 2 and 3, following a moderate emetic risk chemotherapy regimen to prevent chemotherapy-induced nausea and vomiting (CINV):
   A. Dexamethasone***
   B. Netupitant-palonosetron
   C. Palonosetron
   D. Metoclopramide

Correct Answer: A
According to the NCCN guidelines, 1 pharmacologic agent is needed on days 2 and 3 to prevent delayed emesis following moderate emetic risk regimens. This can be a 5HT3 receptor antagonist, a dexamethasone, or an NK1 receptor antagonist if it was given on day 1. Administering palonosetron on day 2 and 3 is not proper dosing; it should be administered on day 1 of chemotherapy.

4. Which of the following receptors is NOT inhibited by olanzapine:
   A. Histamine
   B. Serotonin type 2
   C. Neurokinin-1***
   D. Dopamine

Correct Answer: C
Olanzapine antagonizes multiple receptors involved in the pathophysiology of CINV, as follows: dopamine (D1, D2, D3, D4), serotonin type 2 (5HT2a and 5HT2c), 5HT3, 5HT6, muscarinic, and histamine.
5. **What is an advantage of using olanzapine for the prevention of CINV?**
   A. Complete response rates in the overall period has been shown to be statistically significantly better with an olanzapine prophylaxis regimen compared with an aprepitant regimen
   B. Rates of delayed emesis has been shown to be statistically significantly better with an olanzapine prophylaxis regimen compared with an aprepitant regimen
   C. Since olanzapine inhibits serotonin receptors, 5HT\textsubscript{3} receptor antagonists do not have to be administered when using an olanzapine prophylaxis regimen
   D. An olanzapine prophylaxis regimen may confer better control of nausea compared with an aprepitant regimen and it is dexamethasone-sparing

Correct Answer: D

In the clinical studies comparing an olanzapine regimen with aprepitant, the endpoint of no nausea in the overall phase was statistically significantly better in the olanzapine group versus the aprepitant group. The olanzapine prophylaxis regimen does not utilize dexamethasone in the delayed phase.

6. **Which of the following statements best describes the efficacy profile of NEPA:**
   A. NEPA has been shown to be statistically better than a regimen consisting of aprepitant plus a 5HT\textsubscript{3} receptor antagonist at controlling emesis caused by high emetic risk regimens in the overall period
   B. The efficacy of NEPA is consistent with the a regimen involving aprepitant plus a 5HT\textsubscript{3} receptor antagonist for the prevention of CINV caused by high emetic risk regimens
   C. NEPA has been shown to be statistically inferior compared with a regimen consisting of aprepitant plus a 5HT\textsubscript{3} receptor antagonist for controlling emesis caused by high emetic risk regimens in the delayed period
   D. The efficacy of NEPA is unknown because no clinical trials have compared NEPA with a regimen containing aprepitant

Correct Answer: B

While some studies using NEPA included a comparator arm containing aprepitant, the studies were not designed to demonstrate superiority. The results with NEPA were consistent with those seen with aprepitant.
7. Which of the following statements can be concluded from the studies of rolapitant for the treatment of CINV:

A. Rolapitant is effective for the prevention of delayed emesis in patients receiving highly or moderately emetogenic chemotherapy**
B. Rolapitant is effective for the prevention of delayed emesis in patients receiving highly emetogenic chemotherapy, but not moderately emetogenic chemotherapy
C. Rolapitant is more effective than aprepitant for the prevention of delayed emesis in patients receiving highly emetogenic chemotherapy
D. Rolapitant is less effective than aprepitant for the prevention of delayed emesis in patients receiving highly emetogenic chemotherapy

Correct Answer: A
Rolaipitant was compared with placebo for the treatment of patients receiving high and moderate emetic risk regimens and demonstrated efficacy in these indications. It has not been compared directly with other NK₁ receptor antagonists.

8. Which of the following statements best describes the safety and/or drug interaction profiles with NEPA and rolapitant:

A. The safety and drug interaction profile is identical to other established agents within their respective classes
B. Side effects are similar to other established agents within their respective classes, but rolapitant has a different drug interaction profile**
C. Due to differences in pharmacodynamics, both NEPA and rolapitant have a higher rate of adverse events compared with other established agents within their respective classes
D. Due to differences in pharmacokinetics, both NEPA and rolapitant have a lower rate of adverse events compared with other established agents within their respective classes

Correct Answer: B
In all the clinical studies, the rates and profiles of adverse events with NEPA and rolapitant were similar to other pharmacologic agents within their class. Rolapitant inhibits, and is a substrate of, a different CYP isoenzyme and the drug interaction profile is different.
9. Pharmacists can help providers increase their adherence to guideline recommendations for the prophylaxis and treatment of CINV by implementing which of the following in the pharmacy setting:

   A. Counseling patients regarding the adverse effects of their antiemetic therapy
   B. Finding the lowest-cost therapy for patients
   C. Integrating the guideline recommendations into clinical decision support systems***
   D. Identifying drug interactions between CINV regimens and the patient’s ongoing medications

Correct Answer: C
While all of these are important functions that a pharmacist should perform, the question asks about how to improve adherence to guidelines from a systems-based standpoint. Integrating guidelines into support tools will help achieve this.

10. Based on the approval of new products for preventing CINV, which of the following is an important consideration when deciding on a CINV regimen:

   A. There are many prophylaxis regimens available for preventing the CINV caused by high emetic risk regimens
   B. Using a rescue medication with a different mechanism of action than those used for prophylaxis will tend to improve breakthrough nausea and vomiting control
   C. Patients now have both oral and intravenous options that are administered or taken before chemotherapy and no longer require repeat dosing on subsequent days
   D. All of the above are important considerations***

Correct Answer: D
Guidelines have incorporated other NK₁ receptor antagonists into their recommendations and olanzapine is an option for high-risk regimens. Changing mechanism of action to address breakthrough nausea and vomiting is an important concept. The new oral agents also exhibit therapeutic concentrations for the duration of the 120-hour, post-chemotherapy time period and, thus, repeat dosing is no longer necessary.