CME

Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and oncology nurses involved in the management of cancer patients receiving chemotherapy.

Statement of Need/Program Overview

Several neurotransmitters are involved in the sensation of nausea and the need to vomit. This primitive defense mechanism developed evolutionarily with multiple mechanisms and redundancies. When left uncontrolled, chemotherapy-induced nausea and vomiting (CINV) has a severe impact on patients. The major risk factor for CINV is the intrinsic emetogenicity of the chemotherapy. The risk of CINV is higher in younger people and in women. Predictive tools are in development. Proper management can ameliorate or avoid CINV. Several classes of agents are approved for prevention and treatment. The 5-HT_3 receptor antagonists were the first group studied, and ondansetron was the first to be successful. The NK_1 receptor antagonists were developed more recently. They had a strong impact on delayed vomiting. Newer approaches to CINV include rolapitant, a long-acting NK_1 receptor antagonist, and NEPA, a fixed-dose capsule that combines the long-acting NK_1 receptor antagonist netupitant with the second-generation 5-HT_3 receptor antagonist palonosetron. The most important aspect to management of CINV is prevention by using the right prophylaxis, whether it is a single drug for chemotherapies with low emetogenicity, 2 or 3 drugs for moderately emetogenic regimens, or 4 drugs for highly emetogenic chemotherapy. Detailed management guidelines, with recommendations based on data from phase 3 clinical trials, provide effective approaches for prevention and treatment. Management is improved when guideline recommendations are followed.

Educational Objectives

After completing this activity, the participant should be better able to:

- Discuss the pathophysiology of CINV
- Identify the incidence and impact of CINV with regard to both highly and moderately emetogenic therapy
- Explain the rationale for the use of antiemetic agents in the prevention of CINV
- Evaluate the efficacy and safety data supporting the use of approved antiemetic agents in the prevention of CINV

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Lee S. Schwartzberg, MD—Consultant: Eisai, Helsinn, Merck, and Tesaro

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CME

CLINICAL UPDATE

Current Developments in Supportive Care

Chemotherapy-Induced Nausea and Vomiting: Strategies for Prevention and Treatment

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A CME Activity
Approved for
1.0 *AMA PRA*
Category 1 Credit(s)™

This activity is supported by an independent educational grant from Eisai Inc. and Helsinn Therapeutics (US) Inc.

Jointly provided by Postgraduate Institute for Medicine and Millennium Medical Publishing

PIM Postgraduate Institute for Medicine

Release Date: December 1, 2017
Expiration Date: December 31, 2018
Estimated time to complete activity: 1.0 hours
Project ID: 12952

H&O What is the pathophysiology of CINV?

LS A great deal is known about the pathophysiology of chemotherapy-induced nausea and vomiting (CINV). Several neurotransmitters are involved in the sensation of nausea and the need to vomit. This primitive defense mechanism developed evolutionarily with multiple mechanisms and redundancies. There are 2 major centers: one in the gastrointestinal (GI) tract and one in the brain stem. In the enterochromaffin cells of the GI tract, toxic substances in the stomach trigger serotonin receptors, specifically 5-hydroxytryptamine 3 (5-HT_3).[1] A signal sent through the vagus nerve to the brain stem initiates the nausea and vomiting reflex. Signals sent efferently down the vagus nerve fire the parasympathetic nerves, causing the coordinated sequence of muscle contractions known as the retching syndrome, which leads to emesis.

In the brainstem, the chemoreceptor trigger zone contains other receptors that can be triggered by noxious substances in the blood. The most important receptor is for neurokinin 1 (NK_1). The NK_1 receptor is triggered by the neuropeptide substance P, causing nausea and vomiting through the mechanism of blood sensing. A strong relationship exists between the brain stem and the proximal intestinal tract. The NK_1 receptor is also active in the stomach and the proximal intestine. The dopamine receptor is another important pathway. There may be other pertinent receptors, such as histamine receptors, corticosteroid receptors, and cannabinoid receptors.

H&O How is CINV characterized?

LS Acute CINV occurs within the first 24 hours after initiation of the drug. Delayed CINV usually occurs 2 to 5 days after the infusion. Nausea and vomiting are somewhat less intense in the delayed phase than in the acute phase. The first phase is mediated primarily by the 5-HT_3 receptor, whereas the delayed phase is mediated primarily by the NK_1 receptor.

Breakthrough CINV refers to episodes of nausea and vomiting that occur even when the patient is receiving appropriate therapy.[2] It is still an unmet need in a minority of patients. Anticipatory nausea can occur in patients who had poor control of CINV during prior chemotherapy.[3] It becomes a vicious cycle.

H&O How emetogenic are common chemotherapies?

LS Intravenous chemotherapy drugs are sorted into 4 emetogenic categories (Table 1). The list of highly emetogenic agents is fairly small. It includes cisplatin, high-dose cyclophosphamide, and dacarbazine. The classification of carboplatin has recently changed. In guidelines from the National Comprehensive Cancer Network (NCCN),

Table 1. Emetic Risk of Common Chemotherapy Agents

Emetic Risk	Percentage of Patients With Emesis	Chemotherapy
High	>90	Carboplatin (AUC ≥4) Cisplatin Anthracycline/ cyclophosphamide Dacarbazine
Moderate	30 to 90	Carboplatin (AUC <4) Cyclophosphamide Doxorubicin Irinotecan Oxaliplatin
Low	10 to 30	5-Fluorouracil Paclitaxel Docetaxel Pemetrexed
Minimal	<10	Bortezomib Cetuximab Decitabine Rituximab

AUC, area under the curve.

carboplatin is considered highly emetogenic when given at a higher dose that reaches an area under the curve of 4 or greater.[4] With highly emetogenic chemotherapy, the incidence of CINV would be greater than 90% in the absence of any preventive therapy.[4]

With moderately emetogenic chemotherapy, the incidence of CINV would be between 30% and 90% in the absence of therapies. Moderately emetogenic chemotherapy is a much broader group consisting of many different drugs. Some of the most commonly used moderately emetogenic drugs are oxaliplatin, irinotecan, low-dose carboplatin, and doxorubicin or cyclophosphamide used as single agents.

Chemotherapies with low emetogenic potential, such as 5-fluorouracil, paclitaxel, docetaxel, and pemetrexed (Alimta, Lilly), have an incidence of CINV of 10% to 30% without prophylaxis.[4] Those with minimal potential have an incidence of 10% of less.

H&O What is the impact of CINV?

LS Uncontrolled CINV has a profound impact on patients.[5] A common, pervasive impact of CINV is that patients cannot function normally. Significant nausea that persists for days can impact quality of life. Nausea is also associated with other symptoms, such as anxiety. Patients who are anxious can often develop nausea. Chemotherapy can cause anorexia or an unpleasant taste in the mouth, leading to nausea.

In addition to these impacts on quality of life, CINV can delay the administration of life-prolonging or curative therapies. This disruption can have a significant downstream effect on the patient's long-term outcome. Patients with nausea and vomiting may require hydration with intravenous fluids. The most serious impact, which occurs occasionally, is hospitalization for dehydration and uncontrolled vomiting and retching. A rare occurrence is an esophageal tear caused by severe retching.

The goal is to prevent CINV and allow patients to live as normally as possible during treatment with chemotherapy. It is certainly desirable to avoid hospitalization and unscheduled office visits.

H&O Do clinicians underestimate the incidence and impact of CINV?

LS Some complacency has crept into the prevention of CINV because the strategies may seem rote to many clinicians. However, the problem of CINV is not completely solved. In surveys, clinicians consistently underestimate the incidence of CINV,[6,7] particularly in the delayed phase. Almost all patients are now treated with antiemetic agents before emetogenic chemotherapy, so episodes of nausea and vomiting no longer occur in the presence of clinicians. Antiemetic agents work relatively well in the acute phase, so it is rare to see patients with immediate or near-immediate nausea and vomiting.

There is an unmet need in the control of delayed nausea and vomiting.[8] Clinicians may not see patients for up to 3 weeks after chemotherapy is administered. Typically, patients do not like to talk about their adverse events, for fear that treatment might be withheld. Patients may also minimize the events when recalling them from weeks before.

H&O What are the risk factors for CINV, and are there predictive tools?

LS The major risk factor for CINV is the intrinsic emetogenicity of the chemotherapy, whether administered orally or intravenously. There are also patient risk factors, which have been difficult to characterize. It is known that the risk of CINV is much higher in younger people and in women.[9,10] The highest risk is therefore seen in young women treated with highly emetogenic chemotherapy. Patients who developed morning sickness during pregnancy or who experience motion sickness have a higher risk of CINV. Low intake of alcohol is another risk factor.[11]

Predictive tools are in development. In June 2017, an article in *Annals of Oncology* described a predictive tool

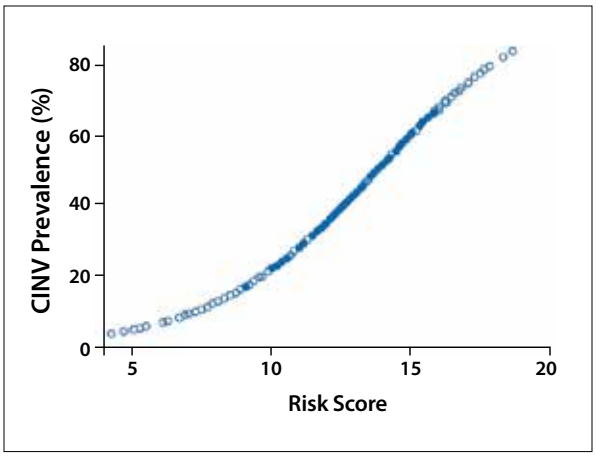

Figure 1. A predictive tool for CINV appeared to have good predictive accuracy and is in the process of being validated. Adapted from Dranitsaris G et al. *Ann Oncol.* 2017;28(6):1260-1267.[12]

drawn from a large series of patients in CINV prospective studies.[12] The tool includes 8 risk factors: patient age younger than 60, the first 2 cycles of chemotherapy, anticipatory nausea and vomiting, history of morning sickness, hours of sleep the night before chemotherapy, CINV in the prior cycle, patient self-medication with nonprescribed treatments, and the use of platinum or anthracycline-based regimens. This tool appeared to have good predictive accuracy (Figure 1), and it is in the process of being validated. Online tools such as this one consider several different characteristics to calculate a patient-related risk factor that can be coupled with the chemotherapy-related risk factors to personalize the prophylaxis approach.

H&O What are patient expectations about CINV?

LS Nausea is one of the most-feared aspects of chemotherapy.[13] Patients tend to overestimate the degree of CINV, particularly vomiting, based on what they have seen in the media or heard from other patients. Horror stories are unusual, but those are the ones that tend to get passed around. Clinicians must explain to patients that there are effective therapies that can minimize or even eliminate CINV. Patient expectations are beginning to change.

H&O What do you tell patients about CINV before treatment?

LS We talk about the likelihood of nausea and vomiting, which varies according to the chemotherapies administered. I explain that we are able to match the antiemetic treatment with the risk of CINV because there are different categories of drugs that can be used together as needed. To avoid giving extra, unneeded drugs, CINV guidelines categorize the degree of prophylaxis needed for the 4 different emetogenic categories. Patients are given preventive therapies before chemotherapy. In addition, we often give patients other medications to take home in case nausea or vomiting occur even with preventive therapy.

I do not instruct patients to change their diet, although eating lightly the day of chemotherapy is probably a good idea. Patients can try to minimize their anxiety, which is tough, particularly for someone who has never received chemotherapy. Patients with a tendency toward anxiety may benefit from antianxiety medications.

H&O What types of therapies are approved for CINV?

LS Several classes of agents are approved for CINV. The 5-HT_3 receptor antagonists were the first group studied, and ondansetron was the first to be successful. Ondansetron changed the entire experience of delivering moderately or highly emetogenic chemotherapy. It markedly reduces vomiting, particularly during the acute phase. The 5-HT_3 receptor antagonists are the cornerstone of antiemetic therapy. They are an option for use even with low-emetogenic chemotherapies.

> Tools are currently in development that incorporate mobile applications or telephone response systems to allow patients to report symptoms in real time.

Corticosteroids are also effective.[14] Their mechanism of action is not completely understood, but they have a generalized impact on neurotransmitters, as well as inhibitory effects. The addition of a corticosteroid to a 5-HT_3 receptor antagonist reduces CINV, and a corticosteroid in combination with another agent is always used with moderately or highly emetogenic chemotherapy. Corticosteroids alone are an alternative option for

emetogenic chemotherapy regimens that usually require a single agent.

The NK_1 receptor antagonists were developed approximately 10 years after the 5-HT_3 receptor antagonists. They had a strong impact on delayed vomiting and a mild impact on delayed nausea. For highly emetogenic chemotherapy, the guidelines recommend use of the combination of a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and dexamethasone.

For moderately emetogenic chemotherapy, the base regimen is a doublet of a 5-HT_3 receptor and dexamethasone. An NK_1 receptor antagonist might be added for high-risk patients. For instance, some patients may be susceptible to CINV with oxaliplatin regimens, and will benefit from a 3-drug regimen including an NK_1 receptor antagonist.

The fourth class of agents targets multiple receptors, including dopamine receptors. An example is olanzapine, an older drug that is an atypical antipsychotic. In well-conducted, randomized phase 3 trials, olanzapine significantly reduced the incidence of delayed nausea,[15] which was an unmet need for patients treated with doxorubicin plus cyclophosphamide or cisplatin.

There are several available 5-HT_3 receptor antagonists and NK_1 receptor antagonists. The first-generation 5-HT_3 receptor antagonists—ondansetron, granisetron, and duloxetine—are equally effective and can be administered orally or intravenously. The second-generation 5-HT_3 receptor antagonist palonosetron has a prolonged half-life and higher receptor binding affinity. This translates into clinical benefit when compared head-to-head with the first-generation 5-HT_3 receptor antagonists.[16] Palonosetron is given only once before initiation of chemotherapy.

The first NK_1 receptor antagonist, aprepitant (Emend, Merck Sharp & Dohme Corp.), is an oral agent with a short half-life. It must be administered for 3 days. An intravenous formulation, fosaprepitant, was developed approximately 5 years ago.[17] It is given in combination with a 5-HT_3 receptor antagonist and dexamethasone before chemotherapy.

H&O What are some newer approaches to CINV?

LS Two oral agents recently became available. Netupitant is a long-acting NK_1 receptor antagonist. Netupitant is combined with the second-generation 5-HT_3 receptor antagonist palonosetron in a fixed-dose capsule known as NEPA (Akynzeo, Helsinn Therapeutics [US]).[18-20] The single capsule provides both classes of agents and is a convenient way for patients to receive antiemetic therapy. In a randomized phase 3 trial comparing NEPA vs palonosetron for the prevention of CINV among patients receiving moderately emetogenic chemotherapy containing cyclophosphamide plus doxorubicin or epirubicin, the rate of complete response was significantly improved in patients who received NEPA during the delayed CINV phase, the overall phase, and the acute phase (Figure 2).[18] When an all-oral regimen is preferred, NEPA can be given with dexamethasone before chemotherapy.

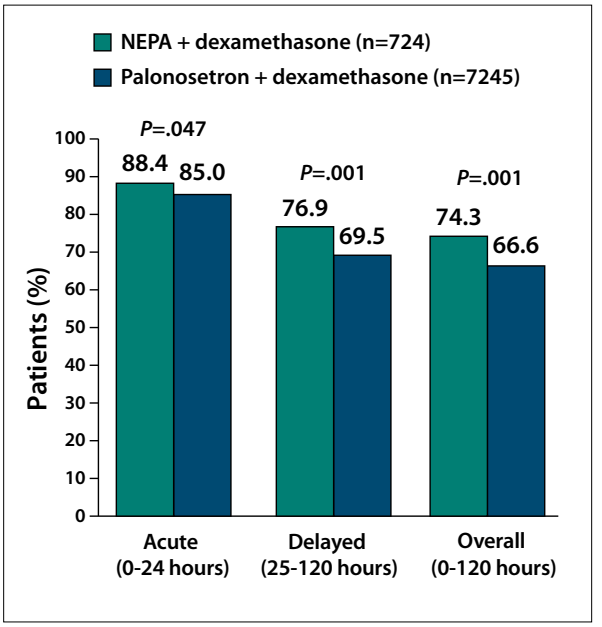

Figure 2. In a randomized phase 3 trial comparing NEPA vs palonosetron in preventing CINV among patients treated with moderately emetogenic chemotherapy, the rate of complete response was significantly improved in patients who received NEPA. CINV, chemotherapy-induced nausea and vomiting. Adapted from Aapro M et al. *Ann Oncol*. 2014;25(7):1328-1333.[18]

Rolapitant (Varubi, Tesaro), a newer long-acting NK_1 receptor antagonist, is currently available in an oral formulation, and an intravenous formulation will be available shortly. It is an effective therapy for highly emetogenic and moderately emetogenic chemotherapy. Two phase 3 trials evaluated the addition of rolapitant to granisetron and dexamethasone in patients treated with highly emetogenic, cisplatin-based chemotherapy.[21] In both studies, complete response rates in the delayed phase were significantly improved for patients in the rolapitant arm compared with patients in the control arm. Another phase 3 trial evaluated the addition of rolapitant to granisetron and dexamethasone in patients receiving moderately emetogenic chemotherapy or the doxorubicin/cyclophosphamide combination.[22] Results demonstrated an improvement in complete response with the addition of rolapitant.

H&O Do recommendations from guidelines differ?

LS There are 3 major guidelines, from the American Society of Clinical Oncology (ASCO), the NCCN, and the European Society for Medical Oncology/Multinational Association of Supportive Care in Cancer (ESMO/MASCC).[4,23,24] These guidelines are very similar. For highly emetogenic chemotherapy, they recommend a triple combination; the NCCN guidelines offer the addition of olanzapine. For moderately emetogenic regimens, they recommend a 2-drug combination of a 5-HT_3 receptor antagonist plus dexamethasone or a 3-drug combination of a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and dexamethasone. A single therapy is recommended for low-emetogenic chemotherapy.

Management is improved when guideline recommendations are followed. A substantial number of patients are not receiving guideline-specific prophylaxis for CINV,[25-27] which is troublesome. As many as a third of patients treated with highly emetogenic chemotherapy are not receiving an NK_1 receptor antagonist.

H&O What are the options for breakthrough CINV?

LS The most important aspect to management of CINV is prevention by using the right prophylaxis, whether it is a single drug for chemotherapies with low emetogenicity, 2 or 3 drugs for moderately emetogenic regimens, or 4 drugs for highly emetogenic chemotherapy. That being said, several options are available for breakthrough CINV. Olanzapine works well as a rescue medication when it is not used as part of the prophylaxis regimen. Other options include phenothiazines, such as prochlorperazine, which work moderately well. The 5-HT_3 receptor antagonists do not work well as breakthrough medications.

H&O Do CINV therapies have any side effects?

LS Prophylactic therapies for CINV have modest side effects. Constipation and headache are seen in less than 10% of patients treated with 5-HT_3 receptor antagonists or an NK_1 receptor antagonist used alone. A low percentage of patients may develop diarrhea. NEPA has shown little additive toxicity with the combination of an NK_1 receptor antagonist and a 5-HT_3 receptor antagonist.[20] It has proven to be simple to add these agents together.

Olanzapine can be associated with sedation. The sedation is usually mild, particularly when olanzapine is given in combination with dexamethasone. It tends to be significant only on the first day of treatment, even though the regimen is usually given for 3 or 4 days as part of prophylaxis. Dexamethasone, which is used in many other areas besides CINV, has more toxicities than the drugs used specifically for CINV. Frequent use of dexamethasone can cause glucose intolerance, and patients can become hyperactive, leading to an increased appetite.

H&O How should clinicians question patients about their experience with CINV?

LS Before chemotherapy is initiated, clinicians should ask about any risk factors, such as morning sickness during pregnancy, motion sickness, or low use of alcohol. After chemotherapy is started, clinicians should question patients about CINV within the first 5 to 7 days, the peak period. If the next office visit is several weeks later, it can be difficult for patients to recall their experience. Tools are currently in development that incorporate mobile applications or telephone response systems to allow patients to report symptoms in real time. We will likely see more of these types of tools in the future.

H&O Is it helpful to consider nausea and vomiting separately?

LS Nausea and vomiting are clearly related, but they are increasingly being considered separately. Many patients will develop nausea that becomes so severe they vomit. Occasionally, vomiting occurs without a prodrome of nausea. Nausea is subjective, and it seems to have many different triggers. The sensation may utilize other pathways beyond the ones currently targeted to prevent vomiting. Many experts believe that the main issue today is how to manage residual delayed nausea. Management may depend on identifying and blocking other pertinent neurotransmitters.

In the clinical trial setting, nausea and vomiting are measured differently. Vomiting and retching occur in discrete episodes that are easily measured objectively. Nausea can persist for varying amounts of time, and the severity is subjective. Visual analogue scales allow patients to rank the severity of their nausea. There could be better tools to measure the amount of nausea that occurs over a period of time. A useful, validated tool is the Functional Living Index–Emesis, which measures the separate impacts of nausea and vomiting on quality of life and functioning.[28,29]

H&O What are the barriers to effective management of CINV?

LS The biggest barrier is that clinicians do not take CINV seriously enough to order the right prophylaxis. That is incongruent because most institutions use electronic health records and computer ordering systems, and it would be easy to add CINV management to the

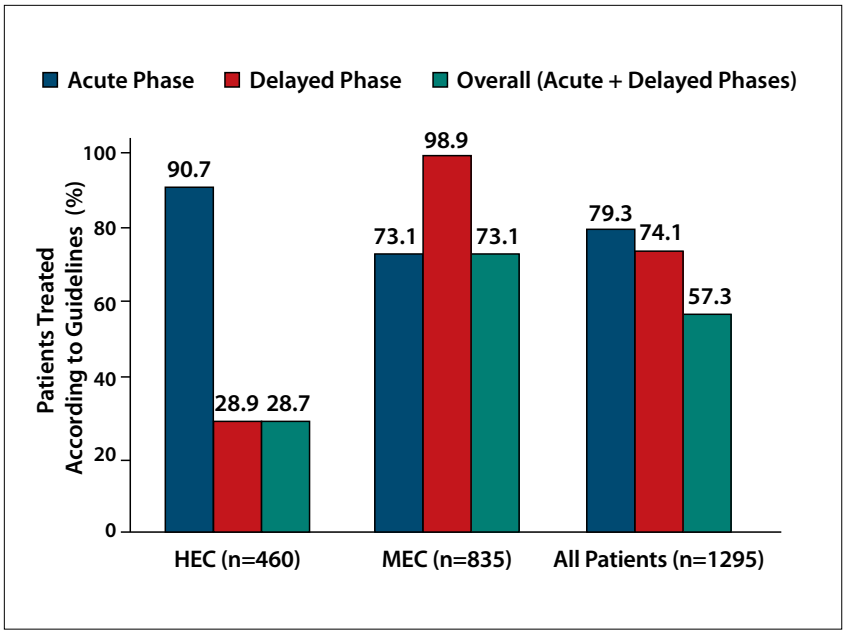

Figure 3. A review of medical records from oncology centers showed that a substantial percentage of patients did not receive guideline-specific therapy for CINV prophylaxis. CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy. Adapted from Gilmore JW et al. *J Oncol Pract.* 2014;10(1):68-74.[30]

protocol. The prophylaxis can be amended after the first cycle of chemotherapy if the patient experiences CINV.

Surveys of claims data suggest that a substantial minority of patients do not receive guideline-specific therapy (Figure 3).[30,31] Sometimes insurance companies or third-party payers require a step-wise approach to treatment, meaning that certain therapies must be tried before moving onto the optimal program. I disagree with this approach.

H&O What are the roles of nurses, pharmacists, and other clinicians?

LS Nurses are very important in terms of education. Before chemotherapy begins, nurses can speak to patients to address their concerns and explain the benefits of CINV prophylaxis, which works very well. At many centers, nurses and/or physician assistants call the patient a few days after administration of chemotherapy to identify any problems with CINV and intervene rapidly, instead of waiting for the next cycle.

In many centers, pharmacists play a critical role in selecting combinations of drugs based on their value and efficacy. Many times, pharmacists are tasked with creating guidelines for the specific order set at an institution. In addition, pharmacists play an important role in educating the patient.

H&O Are there any promising areas of investigation?

LS There are new formulations of older agents. A subcutaneous, delayed-release form of granisetron was recently approved. It has shown superiority to the standard intravenous first-generation 5-HT_3 receptor antagonists, probably because of the delivery.[32,33]

There is interest in the cannabinoids, now that more states are approving medical marijuana and derivatives of marijuana. Although there is anecdotal experience suggesting that cannabinoids might help nausea, it is not yet known from a scientific perspective how cannabinoids work and how they could be added to a standard CINV regimen. This is an area of investigation.

Another area of research is residual nausea. Researchers are using preclinical models to identify other pathways that can be targeted to prevent nausea completely.

H&O Do you have any other recommendations for the prevention and/or management of CINV?

LS My strongest recommendation is for clinicians to pay attention to the antiemetic regimen and to the emetogenicity of the chemotherapy. Clinicians should inform patients that CINV is a common problem that is mostly avoidable if proper steps are taken. In an era in which there are so many exciting new therapies for cancer, we should not forget that supportive care is the bedrock that allows effective delivery of these treatments. One of the most important aspects of supportive care is control of CINV.

Disclosure

Dr Schwartzberg is a consultant for Eisai, Helsinn, Merck, and Tesaro.

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