Chemotherapy-induced Nausea and Vomiting

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Abstract

Nausea and vomiting are commonly observed and feared side effects of chemotherapy. Understanding of the physiological mechanisms of chemotherapy-induced nausea and vomiting (CINV) has led to the development of several classes of anti-emetic, including substance P antagonists, serotonin antagonists, and dopamine antagonists. The newest of these agents include aprepitant and palonosetron, which are very effective in treating emesis in highly emotegenic chemotherapies. Several organizations, including the Multinational Association of Supportive Care in Cancer (MASCC), the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO), have developed guidelines for classification and treatment of CINV. The aim of this article is to summarize current gold standards of anti-emetics and treatment guidelines, as well as introducing innovations such as approaches to breakthrough and refractory nausea and vomiting, alternative therapies, and transdermal delivery systems.

Keywords

Nausea and vomiting, anti-emetics, chemotherapy

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Traditionally, nausea and vomiting are among the most commonly observed, as well as feared, side effects for patients who are receiving chemotherapy.[1] Despite modern anti-emetic therapy, in patients taking highly emetogenic chemotherapy the incidence of nausea and vomiting has been reported to be up to 60 and 50%, respectively;[2,3] additionally, anticipatory symptoms may occur in up to 40% of patients.[4] It is estimated that in 70–80% of patients, pre-medication and symptomatic treatment can avoid or ameliorate chemotherapy-induced nausea and vomiting (CINV).[5] Prior to routine use of modern anti-emetics, up to 20% of patients were not able to complete or delayed doses of their chemotherapy program.[6] In the 1990s, the introduction of serotonin receptor antagonists (5HT3 antagonists) and corticosteroids further improved control of nausea and emesis.[7] Modern classes of anti-emetic include 5HT3 antagonists, substance P neurokinin 1 receptor antagonists, motility agents, phenothiazine, benzodiazepines, and corticosteroids (see *Table 1*). Control of CINV is important as it allows patients to complete chemotherapy protocols and enhances the quality of life of patients in therapy. Despite modern anti-emetic regimens, a significant number of patients continue to experience symptoms of nausea and vomiting, and healthcare providers have been shown to underestimate the incidence of CINV.[3,8] Seventy-five percent of patients with nausea and 50% of those with vomiting reported a negative impact on the performance of activities of daily living when queried with the Functional Living Index–Emesis (FLIE) questionnaire.[9]

Mechanisms of Chemotherapy-related Nausea and Vomiting

While the precise mechanism of CINV stimulation remains unknown, there are known anatomical zones of the central nervous system, neuronal pathways, and neurochemical mechanisms underlying the process of emesis.[7] Mechanisms by which antineoplastic agents may induce emesis include direct actions on medullary centers, cell damage in the gastrointestinal tract, and learned cortical responses.[10] The chemotherapy trigger zone (CTZ) and vomiting center (VC) are two well-known anatomical centers in the central nervous system attributed to nausea and vomiting.[11] Signals in blood as well as spinal fluid can interact with the CTZ because it is a circumventricular structure in the fourth ventricle, outside of the blood–brain barrier. The VC is located in the lateral reticular formation of the medulla. Signals from the CTZ act on the VC and induce efferent impulses to the salivation center, abdominal muscles, respiratory tract, and cranial nerves, which induce emesis. The vestibular system, pharynx and gastrointestinal tract, and cortical structures may also activate the VC.[7]

Several neurotransmitters have been identified that mediate emesis including dopamine, histamine, acetylcholine, serotonin, protachykinin-1, and γ-aminobutyric acid (GABA). Dopamine receptors have been found mainly in the area postrema that act primarily as emesis-inducing transmitters.[12] High concentrations of histamine and cholinergic receptors

have been identified in neural networks associated with emesis such as the nucleus tractus solitarius.[13] Serotonin receptors, found on the vagal afferent and other neurons of the gastrointestinal tract, have been theorized to modulate emesis outside of central nervous system stimuli.[14] In animal models, cisplatin has been shown to cause release of serotonin from small intestinal mucosa that binds to splanchnic and vagal 5HT3 receptors or 5HT3 receptors in the brainstem to stimulate emesis.[15] Protachykinin-1 is one of the most recently investigated neurotransmitters. It acts on central brain areas involved in control of vomiting including the brainstem, nucleus tractus solitarius, and area postrema.[16] Understanding of the neuronal pathways and neurotransmitter functions has led to the development of several classes of neurotransmitter-receptor-targeted anti-emetic agents.

Definitions of Chemotherapy-related Nausea and Vomiting

When recommending anti-emetic regimens, most guidelines take into account the emetogenicity of the antineoplastic agent being used, as well as the type of nausea and vomiting being treated. Three commonly referenced guidelines have been published by the Multinational Association of Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN).[17–19] Antineoplastic agents are classified into four emetogenic risk groups: high, moderate, low, and minimal (see *Table 2*). Each risk group has been defined by the percentage of patients having emetic episodes when given an antineoplastic agent without anti-emetic prophylaxis. Correspondingly, high, moderate, low, and minimally emetic agents produce emesis in 90, 30–90, 10–30, and fewer than 10% of patients, respectively. As emesis potential has been stringently tested in only a few agents, difficulty arises in assigning data-supported risk categorization to all antineoplastic agents; therefore, categorization of some agents has been by experience rather than by data.[20–22]

Patterns of CINV have also been defined based on symptom onset and duration, and include acute, delayed, breakthrough, refractory, and anticipatory CINV. Acute CINV begins within the first 24 hours after chemotherapy has started. Acute CINV can be further subdivided into nausea and vomiting occurring within the first 12 hours, and delayed acute nausea and vomiting occurring from 12 to 24 hours.[23] Peak acuity usually occurs within six to seven hours of initiation of chemotherapy. Delayed nausea and vomiting develops more than 24 hours after chemotherapy initiation and may last for six to seven days.[24] Carboplatin, cisplatin, cyclophosphamide, and doxorubicin are often associated with delayed nausea and vomiting.[25] The most important risk factor for delayed nausea and vomiting is the presence of acute nausea and vomiting; however, the incidence of delayed nausea and vomiting in the absence of acute nausea and vomiting has been reported to be 18–36% after receiving highly emetogenic chemotherapy.[2,8] Due to the delay in symptoms from the time of chemotherapy infusion, delayed nausea and vomiting may be under-recognized. In a study of perceptions among physicians and nurses, 75% of providers underestimated the incidence of delayed nausea and vomiting.[2] Breakthrough nausea and vomiting occurs despite anti-emetic prophylaxis and requires rescue medication. Refractory nausea and vomiting refers to symptoms that occur during subsequent treatment cycles after incomplete control in earlier cycles.[23] Patients experiencing breakthrough nausea and vomiting are at risk for refractory nausea and vomiting and anticipatory nausea and vomiting.[20,26] Anticipatory nausea and vomiting begins before chemotherapy, and is often associated with a history of poorly controlled acute and delayed CINV. Symptoms of anticipatory nausea and vomiting can be precipitated by taste, odor, sight, and anxiety, and this type of nausea may be difficult to treat. Up to 20% of patients may develop anticipatory nausea and vomiting by the fourth cycle of chemotherapy.[27] It may respond to prophylactic use of anti-anxiety agents, such as alprazolam and lorazepam; however, there are limited data from prospective trials.[28] Current recommendations for treatment also include behavioral interventions (i.e. medications, relaxation), systematic desensitization, and aggressive control of acute and delayed nausea and vomiting.[18]

Table 1: Common Anti-emetic Agents

Anti-emetic	Trade Name	Adverse Effect	Adverse Effect Management
Substance P Antagonist			
Aprepitant	Emend	Fatigue	
Serotonin Antagonists			
Dolasetron	Anzemet	Constipation	Prophylactic laxatives
Granisetron	Kytril	Constipation	Prophylactic laxatives
Ondansetron	Zofan	Constipation	Prophylactic laxatives
Palonosetron	Aloxi	Constipation	Prophylactic laxatives
Dopamine Antagonists			
Metoclopramide	Reglan	EPS Akathesia	Diphenhydramine, lorazepam, benztropine
Prochlorperazine	Compazine	EPS	Diphenhydramine, lorazepam, benztropine
Haloperidol	Haldol	EPS	Diphenhydramine, lorazepam, benztropine
Antihistamine			
Promethazine Diphenhydramine	Phenergan Benadryl		
Cannabinoids			
Dronabinol	Marinol	Confusion, ataxia	Re-evaluate dose/usage Try single qhs dose
Nabilone	Cesamet	Confusion, ataxia	Re-evaluate dose/usage Try single qhs dose
Corticosteroids			
Dexamethasone	Decadron	Delirium, anxiety, insomnia	Re-evaluate dose/usage
Methylprednisolone	Solumedrol	Delirium, anxiety, insomnia	Re-evaluate dose/usage
Anxiolytics			
Lorazepam	Ativan	Confusion, sedation	Re-evaluate dose/usage
Atypical Antipsychotics			
Olanzapine	Zyprexa Zydis	Sedation	Re-evaluate dose/usage

EPS = extrapyramidal symptoms; qhs = every bedtime.

Classes of Anti-emetic

5-HT3 Antagonists

Introduced in the 1990s, 5-HT3 antagonists are considered to be highly effective in prophylaxis of acute CINV. Almost all anti-emetic regimens of at least moderately emetogenic chemotherapies include 5-HT3 antagonists.[29] These agents are well-established in the management of acute emesis; however, their role is less clear in the management of

Table 2: Common Emetogenic Regimens

Highly Emetogenic Agents
Altretamine, carmustine, cisplatin, cyclophosphamide >1,500mg/m^2, dacarbazine (DTIC), dactinomycin, ifosfamide (Ifex) >1.5g/mg/m^2, lomustine (CCNU), mechlorethamine (nitrogen mustard), methotrexate >1,000mg/m^2, pentostatin, procarbazine, streptozocin
Combinations: ABVD, AC, AIM, BEP, CAF, CAV-IE, ChIVPP, CHOP/R-CHOP, DHAP, ECF, gemcitabine/cisplatin, hyper-CVAD/MTX/cytarabine, ICE/R-ICE, TPF
Moderately Emetogenic Agents
Aldesleukin >12–15 million units/m^2, amifostine >300mg/m^2, azacitidine, busulfan >4mg/g, carboplatin, carmustine <250mg/m^2, cyclophosphamide <1,500mg/m^2, cytarabine (Ara C) >1,000mg/m^2, dactinomycin, daunorubicin, doxorubicin, epirubicin, etoposide (oral), idarubicin, ifosfamide <1.5g/m^2, imatinib (oral), irinotecan (CPT-11), ixabepilone, lomustine, melphalan, methotrexate 250–1,000mg/m^2, oxaliplatin, temozolamide, vinorelbine (oral)
Combinations: Carboplatin/5-FU/LCV, CMF, CVP, docetaxol/carboplatin, EC, gemcitabine/carboplatin, gemcitabine/oxaliplatin, oxaliplatin/5-FU/LCV, irinotecan/5-FU/LCV, paclitaxel/carboplatin
Low to Minimally Emetogenic Agents
Alemtuzumab, amifostine <300mg/m^2, asparaginase, bevacizumab, bexarotene, bleomycin, bortezomib, busulfan, capcitabine, cetuximab, chlorambucil, cladribine (2-CDA), cytarabine <100mg/m^2, dasatinib, decitabine, dexrazoxane, docetaxol, doxorubicin liposomal, etoposide (VP-16), erlotinib, floxuridine, fludarabine, 5-fluorouracil, gefitinib, gemcitabine, gemtuzumab, hydroxyurea, lapatinib, lenalidomide, mercaptopurine, methotrexate <250mg/m^2, mitomycin C, mitoxantrone, nelarabine, paclitaxel, paclitaxel-albumin, panitumumab, pemetrexed, pentostatin, rituximab, sorafenib, sunitinib, temsirolimus, thalidomide, thioguanine, topotecan, trastuzumab, vinblastine/vincristine, vinorelbine, vorinostat

delayed emesis.[30] 5-HT3 antagonists have been identified to prevent 50–70% of acute CINV.[31] This class includes dolasetron, granisetron, ondansetron, palonosetron, and tropisetron. None of the 5-HT3 antagonists is identified as preferentially recommended by MASCC, NCCN, or ASCO guidelines.

Palonosetron, the newest 5-HT3 antagonist, was introduced in 1993. It has a higher binding activity, estimated to be 100-fold stronger than other 5-HT3 antagonists, and a longer half-life of approximately 40 hours.[32] Palonosetron is available in intravenous preparations only. It is approved by the US Food and Drug Agency (FDA) for preventing acute CINV associated with moderately and highly emetogenic chemotherapy and for the prevention of delayed CINV associated with moderately emetogenic chemotherapy. A randomized double-blind trial of palonosetron versus ondansetron showed higher efficacy rates for palonosetron in controlling both acute (81 versus 69%) and delayed (48 versus 31%) emesis.[33] In a trial against dolansetron, palonosetron was equivalent in preventing acute CINV and superior in preventing delayed CINV after moderately emetogenic chemotherapy.[32] Trials comparing traditional 5-HT3 antagonists with palonosetron have been criticized for not routinely including corticosteroids with traditional 5-HT3s for prevention of delayed CINV.[34] Common side effects of 5-HT3 antagonists include dizziness, headache, and diarrhea or constipation. They are not associated with sedation or extrapyramidal symptoms (EPS). 5-HT3 may also cause asymptomatic electrocardiogram changes including prolonged PT and QTc intervals.

Corticosteroids

Methylprednisone (MP) and dexamethasone are recommended for prevention of acute CINV for low and moderately emetogenic chemotherapy.[35] The mechanism underlying corticosteroid efficacy is unknown; however, it is hypothesized that MP decreases cisplatin-induced 5-HT release from peripheral blood mononuclear cells.[36] In early studies, dexamethasone was shown to be superior to metoclopramide in patients receiving non-platinum-based regimens.[37] Previously, 5HT3 antagonists—metoclopramide and dexamethasone combinations—were considered standard of care. Multiple studies with 5-HT3 antagonists have demonstrated improved control with the addition of corticosteroids. Study of the addition of aprepitant to standard ondansetron and dexamethasone in highly emetogenic cisplatin therapy showed superior control to the standard therapy, with complete protection of 82.8 versus 68.4%.[38] If given in combination with aprepitant, the dose of the steroid should be decreased as dexamethasone is a sensitive substrate for the cytochrome P450 (CYP P450) 3A4 enzyme. Corticosteroids may cause hyperglycemia in patients with diabetes and may cause changes in mental status.

Substance P Inhibitors

Aprepitant is an oral regimen for the prevention of acute and delayed nausea and vomiting that works by binding to the protachykinin-1 receptor. Protachykinin-1, a mediator of pain, inflammation, nausea, and vomiting, cannot bind to aprepitant-occupied receptors.[39] Other protachykinin-1 receptor antagonists include L-758,298, vofopitant, CP-122,721, and CJ-11,974; however, aprepitant is the only clinically available drug. Aprepitant is an oral regimen that is recommended for a three-day course, and has been shown to control cisplatin CINV in the acute and delayed phase in two randomized, placebo-controlled phase III studies.[40,41] These trials studied 1,099 patients who received 70mg/m^2 cisplatin and who were randomized to receive ondansetron and oral dexamethasone followed by oral dexamethasone twice daily on days two to four after chemotherapy versus aprepitant before chemotherapy followed by aprepitant and dexamethasone daily on days two and three followed by dexamethasone on day four. The aprepitant groups performed better in controlling overall emetic response: 63 and 73% versus 43 and 52% for the control groups.

Data exist that support the notion that aprepitant is effective in controlling nausea and vomiting from moderately emetogenic chemotherapy.[42] MASCC and NCCN guidelines recommend aprepitant as an additional component to corticosteroids and 5HT3 antagonists for prophylaxis against CINV of highly emetogenic chemotherapies.[18]

Recently, fosaprepitant, an intravenous neurokinin-1 receptor antagonist, has been submitted to the FDA as a parenteral alternative to aprepitant.[43] Dizziness, constipation or diarrhea, headache, and weakness are side effects of aprepitant. There exists potential for

drug–drug interactions as aprepitant may effect the metabolism of medications cleared by the CYP3A4 and CYP2c9 enzymatic pathways.[44] Commonly used medications that may be rendered less effective include oral contraceptives and coumadin. The areas under the curve of oral dexamethasone and intravenous methylprednisolone have been shown to be increased with use of aprepitant, and steroid doses should be reduced.[45]

Substituted Benzamides

Metoclopramide was developed for the treatment of diabetic gastroperesis and it acts as a prokinetic agent. High-dose regimens have been shown to reduce and prevent cisplatin-related emesis.[46] Side effects of EPS, anxiety, and depression limit the use of high-dose metoclopramide. Although metoclopramide has been shown to be as effective as 5HT3 antagonists in combination with steroids for prevention of delayed CINV, it is recommended to be used only in special circumstances of steroid or 5-HT3 antagonist intolerance.[47,48]

Cannabanoids

Cannabanoids are controversial, and guidelines recommend their use only in patients intolerant of 5HT3 antagonists or steroids and aprepitant. Cannabinoids should be used with caution because of side effects of sedation, dysphoria, depression, hallucinations, and euphoria. Several small trials and reviews have attempted to discern the effectiveness of cannabinoids; however, their effectiveness in controlling CINV remains questionable.[49–51]

Benzodiazepines

Benzodiazepines can be useful to reduce anxiety and risk of anticipatory CINV. The anti-emetic potential of lorazepam and alprazolam is low; however, they are recommended by MASCC guidelines as they may decrease anticipatory nausea and vomiting. Benzodiazipines have been shown to decrease anticipatory nausea and vomiting from 18 to 0% in a double-blind, placebo-controlled study of women with breast cancer.[28]

Antihistamines

Antihistamines such as diphenhydramine or hydroxyzine have been used to treat emesis related to motion sickness. High levels of H1 and muscarinic receptors in neuronal pathways associated with CINV suggest that antihistamines may be effective; however, their role is poorly defined in treating CINV.[7]

Phenothiazines

Prochlorperazine and thiopropanate were the first drugs found to be superior to placebo in reducing CINV.[52] The effectiveness of phenothiazines is dose-related, and this class of anti-emetic is limited by antidopaminergic side effects of hypotension, restlessness, EPS, and sedation. Concurrent use of phenothiazine, substituted benzamide, and butyrophenone is advised against because of increased risk for movement disorders, including akathisia and EPS.

Butyrophenones

Haloperidol, droperidol, and domperidone have anti-emetic activity by blocking dopamine receptors. The butyrophenones are considered relatively ineffective in treating CINV.[53,54]

Atypical Antipsychotics

Olanzapine, an atypical antipsychotic, has activity at many receptor sites related to CINV including dopamine, serotonin, histaminergic, adrenergic, and muscarinic receptors.[55] Oral as well as sublingual preparations are available. Olanzapine combined with a 5HT3 antagonist and steroids was shown be effective in prevention of acute and delayed CINV in a phase II study.[56] MASCC guidelines suggest olanzapine for refractory and breakthrough emesis.[18] Adverse effects include somnolence, postural hypotension, constipation, dizziness, restlessness, weight gain, hyperglycemia, EPS, and tardive dyskinesia.

Guidelines for the Adminstration and Classification of Anti-emetics

Prophylactic and treatment recommendations have been developed and recently updated by the MASCC, ASCO, and NCCN.[17,18,19] Several general principles apply to anti-emetic use. As dose, route, frequency, and combinations of antineoplastics may affect the degree of symptoms, anti-emetic regimens should be tailored to each chemotherapeutic regimen. Most chemotherapeutic agents produce less nausea and vomiting when given by continuous infusion. Combination anti-emetic regimens may provide greater protection against nausea then single agents.

In general, two agents of the same class should not be used in combination as this can increase side effects and not increase efficacy. Oral anti-emetics are safe, convenient, and cost-efficient compared with other regimens; however, some patients may not be able to swallow or absorb medications through the gastrointestinal tract.[17]

However, patient risk factors that have been identified are currently not incorporated into decision-making guidelines. Patients who are under 50 years of age and have a history of anxiety or of motion sickness are at increased risk for CINV.[57,58] Incidence of CINV has been found to be lower in patients with a history of alcohol use.[21] Female gender is associated with a higher rate of CINV in patients taking cisplatin and 5-fluorouracil.[59] Females with a history of hyperemesis gravidarum or emesis during previous chemotherapy also carry a higher risk for CINV.[21,22]

Highly Emetogenic Chemotherapy

ASCO, NCCN, and MASCC guidelines all recommend 5HT3-antagonist, dexamethasone, and aprepitant within the first 24 hours for prevention of acute CINV caused by highly emetogenic chemotherapy.[17–19] Recommendation for treatment of delayed CINV caused by highly emetogenic chemotherapy includes dexamethasone and aprepitant. In a meta-analysis, which did not include palonosetron, 5HT3 antagonists were not cost-effective in preventing delayed CINV from highly emetogenic chemotherapy.[60]

Moderately Emetogenic Chemotherapy

5-HT3-antagonists with dexamethasone are recommended for acute CINV with moderately emetogenic chemotherapy.[17–19] A double-blind study of addition of aprepitant to regimens containing cyclophosphamide with doxorubicin or epirubicin has shown benefit for the addition of aprepitant to prevention of acute emesis caused by moderate emetic risk agents.[61]

Therefore, ASCO and MASCC suggest the addition of aprepitant to regimens containing anthracycline and cyclophosphamide, while NCCN guidelines suggest aprepitant even more broadly. According to ASCO and MASCC guidelines, for patients with significant probability of suffering delayed emesis with moderately emetogenic chemotherapy, oral dexamethasone, a 5HT3 antagonist, or both should be used.[18] ASCO and MASCC recommend aprepitant for a three-day course if it was used on day one.

Mildly Emetogenic Chemotherapy

Single-agent anti-emetics may be used for prophylaxis of mildly emetogenic chemotherapies. MASCC and ASCO guidelines advise single-agent dexamethasone, while NCCN also recommends prochloperazine or metoclopramide as alternatives.

Treatment of Breakthrough and Refractory Nausea and Vomiting

Strategies to treat breakthrough and refractory nausea and vomiting include an assessment of the previous anti-emetic regimen, chemotherapy regimen, and tumor status. Anti-emetic agents should be reviewed for appropriate dose and schedule. Attention should be focused on whether the appropriate anti-emetic regimen was used for the antineoplastic emetogenic potential. ASCO recommendations do not recommend substituting a different serotonin agonist if another has failed. However, there are randomized double-blind studies supporting change from one 5HT3 antagonist to another.[62] Addition of benzodiazepines (lorazepam or alprazolam), substituting high-dose intravenous metoclopramide for the 5HT3 antagonist, or adding dopamine-receptor antagonists or neuroleptics have been suggested.[18] MASCC and NCCN guidelines suggest the atypical neuroleptic olanzapine.[5] Consideration of tumor response and goals of care have been advocated by ASCO, with emphasis on quality of life while continuing chemotherapies that have the greatest efficacy.[17] If CINV symptoms present in atypical patterns, investigation of other causes should be made, including brain metastases, intestinal obstruction, and other medications (i.e. opioids, bronchodilators).

Innovations in Treatment Delivery

Barriers to prevention of CINV, including the impracticality of oral medication for a patient who is already nauseated, difficulty swallowing, and polypharmacy have led to the development of depot transdermal delivery of the 5-HT3 antagonist granisetron. NCCN guidelines advocate the utilization of this transdermal patch 24–48 hours before initiation of moderate- to high-emetic-risk chemotherapy. Subcutaneous administration of granisetron resulted in 27% higher area under the curve levels for 0–12 hours, with similar values at 0–24 hours to intravenous granisetron in a study of 31 patients receiving platinum based chemotherapy. Further trials are necessary to confirm biological equivalence; however, preliminary results suggest equivalent bioavailability.

Alternative Therapies

Randomized trials have attempted to explore non-pharmacological interventions for CINV. Yoga, hypnosis, acupressure, acupuncture-point stimulation, and massage therapy have been shown to have some benefit.[63–67] Although pre-chemotherapy patient education can reduce nausea expectancy, it has no effect on the occurrence of nausea.[68]

Anti-emetics in Children

There are limited data regarding utilization, timing, and dosages appropriate for prophylaxis of CINV in children. 5HT3 antagonists have been shown to be more effective than metoclopramide, phenothiazone, and cannabinoids.[69] The few studies that examine anti-emetics in children receiving chemotherapy have small numbers and suboptimal design.

Future Research Directions

Many research questions remain. Future directions of anti-emetic research should focus on improved understanding of the mechanisms of nausea and vomiting, optimal dosing regimens, and newer, more efficacious, and hopefully less expensive alternatives. ■

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1. Coates A, Abraham, S, Kaye, S, Sowerbutts, et al., On the receiving end—patient perception of the side-effects of cancer chemotherapy, *Eur J Cancer Clin Oncol*, 1983;19:203–8.
2. Grunberg, S, Deuson, R, Mavros, P, et al., Incidence of chemotherapy-induced nausea and emesis after modern antiemetics, *Cancer*, 2004;100(10):2261–8.
3. Herrstedt J, Nausea and emesis: Still an unsolved problem in cancer patients?, *Support Care Cancer*, 2002;10:85–7.
4. Aapro M, Molassiotis A, Olver I, Anticipatory nausea and vomiting, *Support Care Cancer*, 2006;13:117–21.
5. Jordan, K, Sippel, C, Schmoli, H et al., Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: Past, present and future recommendations, *Oncologist*, 2007;12:1143–50.
6. Gralla R, Itri L, Pisko S, et al., Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting, *N Engl J Med*, 1981;305:905–9.
7. Grunberg S, Hesketh P, Control of chemotherapy-induced emesis, *N Engl J Med*, 1993;329(24):1790–96.
8. Hickock J, Roscoe J, Morrow G, et al., Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-hydroxytryptamine-3 antiemetics, *Cancer*, 2003;97:2880–86.
9. Glaus A, Knipping C, Morant R, et al., Chemotherapy-induced nausea and vomiting in routine practice: a European perspective, *Support Care Cancer*, 2004;12:708–15.
10. Hesketh P, Gandara D, Serotonin antagonists: a new class of antiemetic agents, *J Natl Cancer Inst*, 1991;83:613–20.
11. Borison H, Wang S, Physiology and pharmacology of

vomiting, *Pharmacol Rev*, 1953;5:193–230.
12. Stafanini, E, Clement-Cormier, Y, Detection of dopamine receptors in the area postrema, *Eur J Pharmacol*, 1981; 74:257–60.
13. Wamsley J, Lewis M, Young W, et al., The distribution of histamine H1-recptors in the rat brain: an autoradiographic study, *Neurosci*, 1981;1:176–91.
14. Fozard J, Neuronal 5-HT receptors in the periphery, *Neuropharmacology*, 1984;23:1473–86.
15. Endo T, Minami M, Monma Y, et al., Emesis-related biochemical and histopathological changes induced by cisplatin in the ferret, *J Toxicol Sci*, 1990;15:235–24.
16. Bleiberg H, A new class of antiemetics: the NK-1 receptor antagonists, *Curr Opin Oncol*, 2000;12:284–8.
17. Kris M, Hesketh P, Somerfield M, American Society of Clinical Oncology guidelines for antiemetics in oncology: Update 2006, *J Clin Oncol.*, 2006;24:2932–47.
18. Roila F, Hesketh P, Herrsted J, Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy and radiotherapy-induced emesis: Results of the 2004 Perugia International Antiemetic Consensus Conference, *Ann Oncol*, 2006;17:20–28.
19. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncoogy: Antiemesis, V.3.2008. Available at: www.nccn.org/professionals/physicians_gls/PDF/antiemesis.pdf
20. Lindley C, Bernard S, Fields S, Incidence and duration of chemotherapy-induced nausea and vomiting in the outpatient oncology population, *J Clin Oncol*, 1989;7:1142–9.
21. Hesketh P, Kris M, Grungberg L, et al., A proposal for classifying the acute emetogenicity of cancer chemotherapy, *J Clin Oncol*, 1997;15:103–9.
22. Antiemetic Subcommittee: Antiemetic Sub-committee of the Multinational Association, Prevention of chemotherapy-radiotherapy-induced emesis – Results of the Perugia Consensus Conference, *Ann Oncol*, 1998;9:811–19.
23. Schnell F, Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control, *Oncologist*, 2003;8: 187–98.
24. Kris M, Gralla R, Clark R, et al., Incidence, course and severity of delayed nausea and vomiting following the administration of high-dose cisplatin, *J Clin Oncol*, 1995;3: 1379–84.
25. Gralla R, Osoba D, Kris M, et al., Recommendations for the use of anti-emetics evidence-based, clinical practice guidelines. American Society of Clinical Oncology, *J Clin Oncol*, 1999;17:2971–94.
26. Grunberg S, Osoba D, Hesketh P, Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity–an update, *Support Care Cancer*, 2005;28:80–84.
27. Morrow, G, Roscoe, J, *Anticipatory nausea and vomiting: Models, mechanisms and management. Medical Management of Cancer Treatment Induced Emesis*, London: Martin Dunitz Ltd, 1997; 149–66.
28. Razavi D, Delvaux N, Farvacques C, Prevention of adjustment disorders and anticipatory nausea secondary to adjuvant chemotherapy: A double-blind, placebo-controlled study assessing the usefulness of alprazolam, *J Clin Oncol*, 1993; 11:1384–90.
29. Viale P, Update on the management of chemotherapy induced nausea and vomiting, *J Intraven Nurs*, 2006;29: 283–91.
30. Geling O, Eichler H, Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications, *J Clin Oncol*, 2005;23:1289–94.
31. Jordan K, Hinke A, Grothey A, et al., A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis, *Support Care Cancer*, 2007;5:1023–33.
32. Eisenberg P, Figueroa-Vadillo J, Zamora R., Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist, *Cancer*, 2003;98:2473–82.
33. Gralla R, Lichinitser M, Van der Vegt S, et al., Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron, *Ann Oncol*, 2003;14:1570–77.
34. Aapro M, Optimising antiemetic therapy: what are the problems and how can they be overcome?, *Curr Med Res Opin*, 2005;21:895–7.
35. Aapro M, Present role of corticosteroids as antiemetics, *Recent Results Cancer Res*, 1991;121:91–100.
36. Mantovani G, Maccio A, Esu S, et al., Evidence that cisplatin induces serotonin relaease from human peripheral blood mononuclear cells and that methyprednisolone inhibits this effect, *Eur J Cancer*, 1996;32:1983–5.
37. Ibrahim E, Al-Idrissi H, Ibrahim A, et al., Antiemetic efficacy of high-dose dexamethasone: Randomized, double-blind, crossover study with high-dose metoclopramide in patients receiving cancer chemotherapy, *Eur J Cancer Clin Oncol*, 1986; 22:283–8.
38. Poli-Bigelli S, Rodrigues-Pereira J, Carides A, Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results for a randomized, double-blind, placebo-controlled trial in Latin America, *Cancer*, 2003;97:3090–98.
39. Hesketh P, Grunberg S, Gralla R, The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting, A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin- the Aprepitant Protocol 052 Study Group, *J Clin Oncol*, 2003;97:3090–98.
40. Poli-Bigelli S, Rodrigues-Pereira J, Carides A, Additon of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin–the Aprepitant Protocol 052 Study Group, *J Clin Oncol*, 2003;21:4112–19.
41. Schmoll H, Aapro M, Pli-Bigelli S, Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment, *Ann Oncology*, 2006;17: 1000–1006.
42. Gralla R, Warr D, Carides A, et al., Effect of aprepitant on antiemetic protection in patients receiving moderately emetogenic chemotherapy plus high-dose cisplatin: analysis of combined data from 2 phase III randomized clinical trial, *Proc Am Soc Clin Oncol*, 2004;22:763 (abstract).
43. Navari R, Fosaprepitant (MK-0517): a neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting, *Expert Opinion Investigational Drugs*, 2007; 16(12):1977–85.
44. Shadle C, Lee Y, Majumdar A, et al., Evaluation of potential inductive effects of aprepitant on cytochrome P450 3A4 and 2C9 activity, *J Clin Pharmacol*, 2004;44:215–33.
45. Massaro M, Lenz K, Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting, *Ann Pharmacother*, 2005;39:77–85.
46. Gralla R, Metoclopramide: a review of antiemetic trials, *Drugs*, 1983;25(Suppl. 1):63–73.
47. Moreno I, Rosell R, Abad A, Comparison of three protracted anti-emetic regimens for the control of delayed emesis in cisplatin-treated patients, *Eur J Cancer*, 1992;28A:1344–7.
48. Kris M, Grall R, Tyson L, Controlling delayed vomiting: Double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin, *J Clin Oncol*, 1989;7:108–14.
49. Tramer M, Carroll D, Campbell F, et al., Cannabanoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review, *BMJ*, 2001;323:1–8.
50. Meiri E, Hereash J, Vredenburgh J, et al., Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting, *Curr Med Res Opin*, 2007; 23(3):4533–43.
51. Cunningham D, Bradley C, Forest G, A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues, *Eur J Cancer Clin Oncol*, 1988;24:685–9.
52. Moertel C, Reitmemeir R, Gage R, A controlled clinical evaluation of antiemetic drugs, *JAMA*, 1963;186:116–18.
53. Saller R, Hellenberecth D, High doses of metoclopramide or droperidol in the prevention of cislatin-induced emesis, *Eur J Cancer Clin Oncol*, 1986;22:1199–1203.
54. Jackson M, Bozzino J, Prasad V, et al., Ineffectiveness of droperidol as antiemetic, *Drug Intell Clin Pharm*, 1985;19:841–2.
55. Bymaster F, Calligaro D, Falcone J, et al., Radioreceptor binding profile of the atypical antipsychotic olanzapine, *Neuropsycopharmacology*, 1996;14:87–96.
56. Navari R, Einhorn L, Passik S, et al., A phase III trial of olanzapine, for prevention of chemotherapy-induced nausea and vomiting. A Hoosier Group Study, *Support Care Cancer*, 2005;13(7):529–34.
57. Aapro M, Optimising antiemetic therapy: what are the problems and how can they be overcome?, *Curr Med Res Opin*, 2005;21:885–97.
58. Doherty K, Closing the gap in prophylactic antiemetic therapy: Patient factors in calculating the emetogenic potential of chemotherapy, *Clin J Oncol Nurs*, 1999;3:113–19.
59. Liaw C, Chang H, Liau C, et al., Reduced maintenance of complete protection from emesis for women during chemotherapy cycles, *Am J Clin Oncol*, 2003;26(1):12–15.
60. Geling O, Eichler H, Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications, *J Clin Oncol*, 2005;23:1289–94.
61. Warr D, Hesketh P, Gralla R, et al., Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy, *J Clin Oncol*, 2005; 23:2833–30.
62. De Wit R, de Boer A, van de Linden G, et al., Effective cross-over to granisetron after failure to ondansetron. A randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy, *Br J Cancer*, 2001;85:1099–1101.
63. Raghavendra R, Nagarathna R, Nagendra H, et al., Effects of an integrated yoga program on chemotherapy-induce nausea and emesis in breast cancer patients, *Eur J Cancer Care*, 2007;16:462–74.
64. Richardson J, McCall G, Richardson A, et al., Hypnosis for nausea and vomiting in cancer chemotherapy: a systematic review of the research evidence, *Eur J Cancer Care*, 2007; 16(5):402–12.
65. Dibble S, Luce J, Cooper B, et al., Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial, *Oncol Nurs Forum*, 2007;34(4):813–20.
66. Ezzo J, Richardson M, Vickers M, et al., Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting, *Cochrane Database Syst Rev*, 2006;2:CD002285.
67. Billhylt A, Bergborn I, Stener-Victorin E, Massage relieves nausea in women with breast cancer who are undergoing chemotherapy, *J Alternative Compl Med*, 2007;13(1):53–7.
68. Shelke A, Roscoe J, Morro J, et al., Effect of nausea expectancy manipulation on chemotherapy induced nausea: a University of Rochester Cancer Center community clinical oncology program study, *J Pain and Sympt Manag*, 2008; 35(4):381–7.
69. Roila F, Feyer P, Maranzano E, et al., Antiemetics in children receiving chemotherapy, *Support Car Cancer*, 2005;13:129–31.