OVERVIEW OF CHEMOTHERAPY-INDUCED AND RADIOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting can result in serious metabolic derangements, nutritional depletion and anorexia, deterioration of patients' physical and mental status, esophageal tears, fractures, wound dehiscence, withdrawal from potentially useful and curative antineoplastic treatment, and degeneration of self-care and functional ability. Despite advances in pharmacologic and non-pharmacologic management, nausea and vomiting remain 2 of the more distressing and feared side effects to cancer patients and their families, and incidence may be underestimated by physicians and nurses. Nausea and vomiting were identified in the top three adverse events associated with chemotherapy that patients found bothersome. The original survey was performed in the early 1980's, and has subsequently been repeated in the era of the $5\text{-}HT_3$ RA. Nausea and vomiting remain in the top 3 most troublesome adverse events associated with cancer chemotherapy.

DEFINITIONS

NAUSEA is the desire to vomit without the associated expulsion of GI contents. It is also described as the feeling in the throat or epigastric region alerting the patient that vomiting is imminent.

- Involves loss of gastric tone and motility.
- Nausea of often causes more discomfort than vomiting, and is much more difficult to treat. It is typically greater in the delayed phase of treatment. The availability of aprepitant has impacted delayed nausea and vomiting.
- Assessment: typically via the visual analog scale, where a patient is asked to place a "check mark" on the line that most reflects their nausea. The scale is 10 mm in length, with 0 being "no nausea", ranging to 10 = "nausea as bad as it could possibly be".
- Nausea has a variable response to therapy, and despite recent advances, still remains a very troublesome side effect of chemotherapy.

VOMITING: expulsion of the gastric contents, and is characterized by the contraction of the abdominal and diaphragmatic muscles, the sphincter (lower esophageal) contracts and the gastric contents are expelled.

- Assessment of vomiting: in terms of the number of emetic episodes in 24 hours. Typically the responses are as follows:
    - A complete response means that the patient had no emesis within 24 hours and received no rescue medications.
    - A major response is 1 to 2 episodes of vomiting in any 24 period with or without rescue medications.
    - A minor response is 3 to 5 episodes of vomiting in any 24 period with or without rescue medications.
    - Failure is greater than 5 episodes of emesis in any 24 period.
- There may be slight modifications to his definition in published trials. Always ensure criteria are similar when comparing studies.

RETCHING: labored movement of abdominal and thoracic muscles before vomiting.

- Quantified in terms of the number of episodes per 24 hours.
- Like nausea, it does not respond well to medication.

ANTICIPATORY EMESIS: Anticipatory nausea and vomiting occur following a prior experience of emesis that leads to a conditioned or learned response (not associated with stimulation of neuroreceptors).

- Risk factors for anticipatory emesis include: female sex; patients who experienced chemotherapy induced emesis in the past; patients with anxiety/depression. These patients may begin vomiting at the sight of the clinic or nurse or simply when their IV line is flushed. These patients can be very difficult to manage; therefore the goal is prevention of emesis from the beginning so that anticipatory emesis does not develop. Benzodiazepines such as lorazepam have an amnesic effect and so are often used to prevent this problem; alternatively behavior modification techniques can be attempted.

ACUTE EMESIS: Occurs within 24 hours of drug administration. Begins within 1 – 2 hours, peaks within 4 – 10 hours and resolves or subsides within 12 – 24 hours. Associated with a high frequency and degree of severity.

- It is responsive to therapy and can be effectively prevented with adequate prophylaxis.
- Prevention of acute emesis often decreases the occurrence or severity of delayed emesis which may last for up to 5 days after chemotherapy. A study by Roila et al [*J Clin Oncol* 1991] showed that delayed emesis occurred in 14 of 53 patients (26%) with no acute emesis, compared to 17 of 32 patients (53%) with acute emesis.

DELAYED EMESIS: Delayed emesis is vomiting that occurs up to 16 – 24 hours after chemotherapy and lasts up to 96 hours.

- Incidence varies from 20 – 93% patients [Reference: Fabi A, et al. *Support Care Cancer* 2003;11:156 – 61]. It occurs via different transmitters than acute emesis. Health-care providers frequently underestimate the incidence of delayed N/V with MEC and HEC [Reference: Grunberg SM, et al. *Cancer* 2004;100:2261 – 9].
- Delayed emesis can occur following the administration of a number of chemotherapy agents with moderate to high emetogenicity.
- Delayed emesis has been less extensively studied than acute emesis.
- Cisplatin is the most widely studied drug known to cause delayed emesis and is the "prototype drug".
- Prognostic factors for the development of delayed nausea and vomiting include the following: presence of acuter nausea and vomiting; cisplatin dose (more likely with increased doses); gender and age.
- The majority of clinical trials evaluating delayed emesis evaluate the emetic episodes and nausea VAS scores from 24 hours to 120 hours following chemotherapy.
- Mechanism of action involves other receptors apart from the serotonin receptors, and is thought to be mediated via the action of Substance P on the neurokinin-1 receptors.

BREAKTHROUH EMESIS: is emesis that occurs despite optimum prophylaxis. This needs to be treated and should be treated with agents from a different class to those used in the prophylaxis setting.

NEUROPHYSIOLOGY OF NAUSEA AND VOMITING (See Figure 1)

Progress has been made in understanding the neurophysiologic mechanisms that control nausea and vomiting. Both are controlled or mediated by the central nervous system but by different mechanisms. Nausea is mediated through the autonomic nervous system. Vomiting results from the stimulation of a complex reflex that is coordinated by a putative true vomiting center, which may be located in the dorsolateral reticular formation near the medullary respiratory centers. The vomiting center presumably receives convergent afferent stimulation from several central neurologic pathways, including the following:

- A chemoreceptor trigger zone (CTZ).
- The cerebral cortex and the limbic system in response to sensory stimulation (particularly smell and taste), psychologic distress, and pain.
- The vestibular-labyrinthine apparatus of the inner ear, in response to body motion.
- Peripheral stimuli from visceral organs and vasculature (via vagal and spinal sympathetic nerves) as a result of exogenous chemicals and endogenous substances that accumulate during inflammation, ischemia, and irritation.

The CTZ is located in the area postrema, one of the circumventricular regions of the brain on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle. Unlike vasculature within the blood-brain diffusion barrier, the area postrema is highly vascularized with fenestrated blood vessels, which lack tight junctions (zonae occludentes) between capillary endothelial cells. The CTZ is anatomically specialized to readily sample elements present in the circulating blood and cerebrospinal fluid (CSF).

Currently, evidence indicates that acute emesis following chemotherapy is initiated by the release of neurotransmitters from cells that are susceptible to the presence of toxic substances in the blood or CSF. Area postrema cells in the CTZ and enterochromaffin cells within the intestinal mucosa are implicated in initiating and propagating afferent stimuli that ultimately converge on central structures corresponding to a vomiting center. The relative contribution from these multiple pathways culminating in nausea and vomiting symptoms is complex and is postulated to account for the variable emetogenicity (intrinsic emetogenicity and mitigating factors, i.e., dosage, administration route, exposure duration) and emetogenic profile (i.e., time to onset, symptom severity, and duration) of agents.

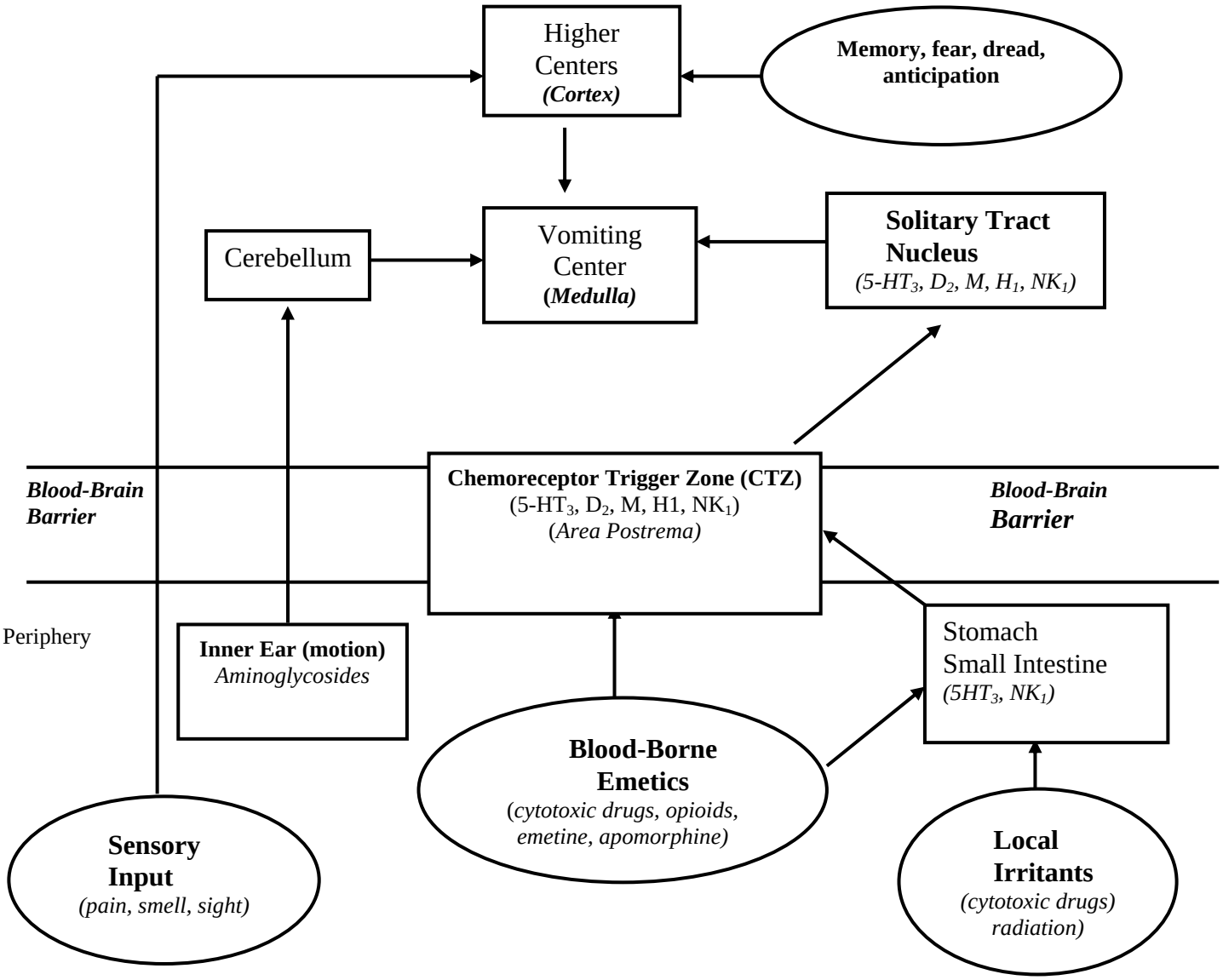


Figure 1: Physiology of Chemotherapy-Induced Nausea and Vomiting (adapted from Theresa Mays, BCOP Review Course)

RISK FACTORS FOR NAUSEA AND VOMITING:

CHEMOTHERAPY-RELATED FACTORS: including emetogenicity of each agent in the chemotherapy regimen; time to onset of emesis and duration of emesis; dose of drug administered; method of administration - may be differences depending on IV bolus vs. intermittent infusion vs. CIVI; effect of combination therapy.

Emetogenicity of a regimen is based on the emetogenicity of each agent within the combination. The most common method for classifying the emetogenicity of antineoplastic agents is the Hesketh classification system.

HESKETH CLASSIFICATION:

One of the most common classification systems for the emetogenicity of a particular chemotherapeutic agent is referred to as the "Hesketh" classification [Reference: Hesketh PJ, et al. *J Clin Oncol* 1997;15:103 - 9]. This is based upon research performed and published by Paul Hesketh and colleagues in the mid-90's. These researchers assigned individual antineoplastic agents to a particular emetogenic level. Classification was based on the likelihood of a particular agent causing emesis in an adult patient who had not received prior antiemetic agents.

Antineoplastic agents were categorized into 5 levels:

Level 1: agents within this class are not really considered to be emetogenic. There is a less than 10% risk of patients experience acute [≤ 24 hours after chemotherapy] emesis without antiemetic prophylaxis. Examples can be seen in the accompanying table (Table 1);
Level 2: agents within this class cause acute emesis in between 10% and 30% of patients;
Level 3: agents within this class cause acute emesis in between 30% and 60% of patients;
Level 4: agents within this class cause acute emesis in between 60% and 90% of patients; and
Level 5: agents that are extremely emetogenic, where nearly all patients (> 90%) will experience an emetic episode if routine antiemetic therapy is not provided.

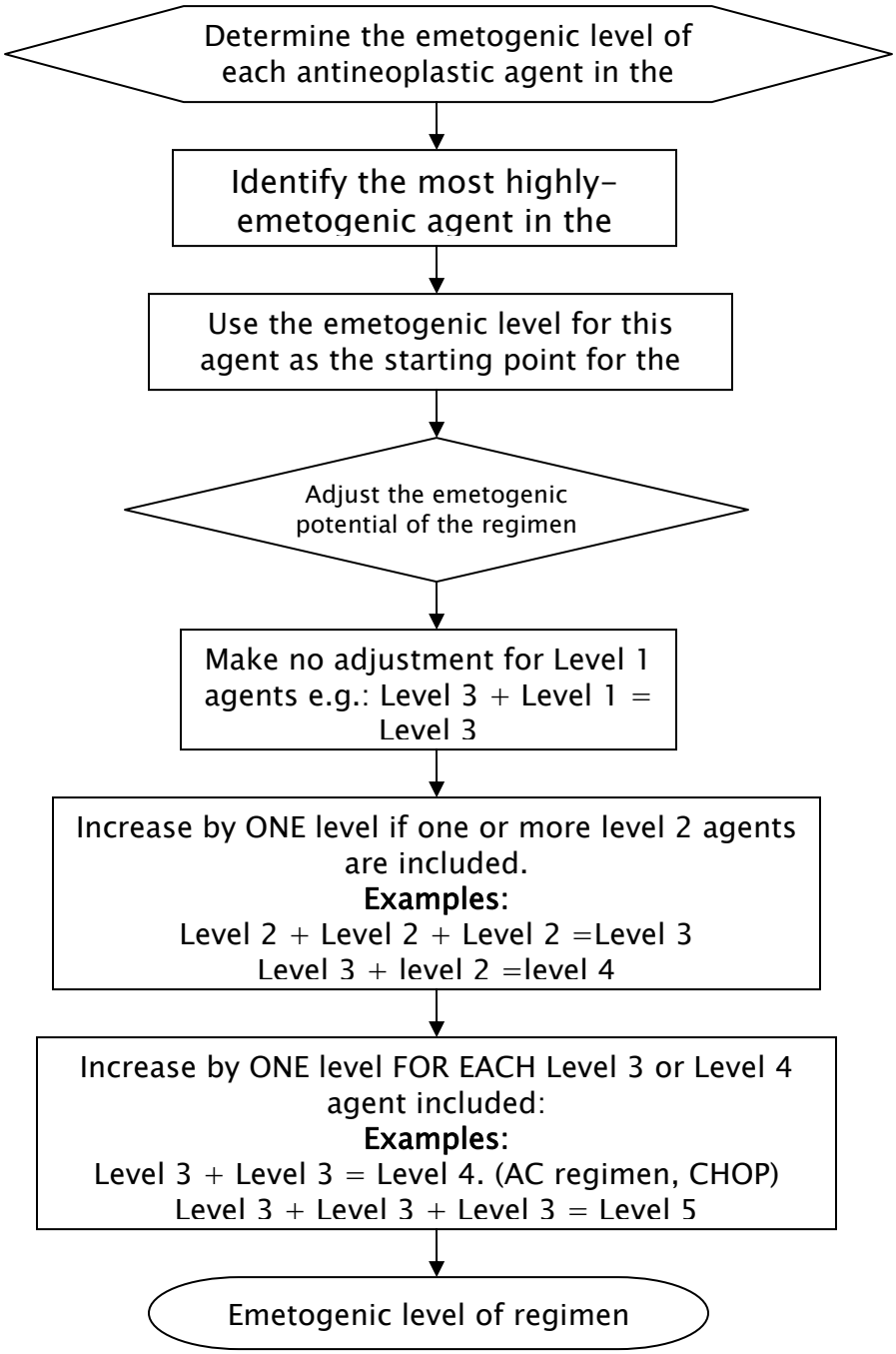
This classification system not only evaluated the risk of emesis with single agents, but also formulated an "algorithm" to assist in classifying the emetogenicity of combination chemotherapy. The algorithm for defining the emetogenicity of combination chemotherapy is outlined in Figure 2, and can be described as follows:

1. Identify the most emetogenic agent in the combination.
2. Assess the relative contribution of the other agents to the overall emetogenicity of the combination. When considering other agents, the following "rules" apply:
   (a) Level 1 agents do not contribute to the emetogenicity of a given regimen.
   (b) Adding one or more level 2 agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination.
   (c) Adding level 3 or 4 agents increases the emetogenicity of the combination by one level per agent.

EMETOGENICITY OF CHEMOTHERAPEUTIC AGENTS

EMETOGENIC LEVEL	AGENT	
5 (High)	Carmustine > 250 mg/m^2 Cisplatin ≥ 50 mg/m^2 Cyclophosphamide ≥ 1500 mg/m^2 Dacarbazine ≥ 1000 mg/m^2 /dose Etoposide 60 mg/kg (high dose for BMT)	Lomustine > 60 mg/m^2 Mechlorethamine Pentostatin (doses of 10 mg/m^2) Streptozocin
4 (Moderate)	Amifostine 910 mg/m^2 Carboplatin ≥ 300 mg/m^2 or AUC ≥ 3 Carmustine ≤ 250 mg/m^2 Cisplatin 20-50 mg/m^2 Cyclophosphamide > 750 to ≤ 1500 mg/m^2 Cytarabine > 1000 mg/m^2 Dactinomycin	Daunorubicin > 50 mg/m^2 Doxorubicin > 60 mg/m^2 Epirubicin > 90 mg/m^2 Lomustine ≤ 60 mg/m^2 Melphalan (intravenous) ≥ 50 mg/m^2 Methotrexate > 1000 mg/m^2 Procarbazine (oral)
3 (Moderate)	Aldesleukin Amifostine > 300 - ≤ 500 mg/m^2 Arsenic trioxide Carboplatin < 300 mg/m^2 or ≤ AUC 2 Cyclophosphamide ≤ 750 mg/m^2 Cyclophosphamide (oral) Dacarbazine 150 to 200 mg/m^2 Daunorubicin ≤ 50 mg/ m^2 Doxorubicin 20 to 60 mg/m^2	Epirubicin ≤ 90 mg/m^{2}Gemtuzumab ozogamicin Hexamethylmelamine (oral) Idarubicin Ifosfamide Irinotecan Lomustine < 60 mg/m^2 Methotrexate 250 to 1000 mg/m^2 Oxaliplatin
2 (Low)	Amifostine < 300mg/m^2 Capecitabine Cytarabine 100 – 200 mg/m^2 Docetaxel Doxorubicin < 20 mg/m^2 or CIVI Etoposide 5-Fluorouracil < 1000 mg/m^2 Gemcitabine Liposomal doxorubicin	Liposomal daunorubicin Methotrexate > 50 to < 250 mg/m^2 Mitomycin Mitoxantrone Paclitaxel Pemetrexed Temozolomide Teniposide Thiotepa Topotecan
1 (Minimal)	Alemtuzumab Androgens Asparaginase Bevacizumab Bexarotene (oral) Bleomycin Bortezomib Busulfan (oral, 4 mg/kg/day) Cetuximab Chlorambucil Cladribine Cytarabine 100 mg/m^2 CIVI Denileukin diftitox Estramustine Fludarabine Gefitinib Hydroxyurea Ibritumomab tiuxetan	Imatinib Interferon α 2a Letrozole Melphalan (oral) Mercaptopurine Methotrexate ≤ 50 mg/m^2 Pegasapragase Pentostatin 2 - 5 mg/m^2 [6] Rituximab Tamoxifen Thalidomide Thioguanine (oral) Tositumomab Trastuzumab Tretinoin Vinblastine Vincristine Vinorelbine

ALGORITHM FOR CALCULATING THE EMETOGENIC POTENTIAL OF COMBINATION CHEMOTHERAPY REGIMENS



This Hesketh classification system has been modified a number of times, and new antineoplastic agents have been FDA approved and need to be incorporated into the algorithm. The Multinational Association for the Supportive Care in Cancer (MASCC) group has more recently published a **new proposed classification system, which compresses the 5 levels of emetogenicity into four** [Reference: Grunberg SM, et al. *Support Care Cancer* 2005;13:80 – 4].

The proposed system includes categorizing antineoplastics into:

High (> 90%)
Moderate (30 – 90%)
Low (10 – 30%)
Minimal (< 10%) emetogenicity

This compressed classification system has now been endorsed by the American Society of Clinical Oncology, and will serve as the basis for selection of antiemetics [Reference: Kris MG, et al. *J Clin Oncol* 2006;24:2932 – 47; Erratum in *J Clin Oncol* 2006;24:5341 – 2.].

Not only should the emetogenicity of the regimen be considered, but there are a number of other factors that can contribute to the emetogenicity of a particular regimen including the route of administration, the speed with which the medications are infused, as well as several patient-specific factors – see below.

PATIENT-RELATED FACTORS (e.g., prior chemotherapy, degree of antiemetic control on prior cycles/regimens; psychosocial issues (depression); sex (women experience N/V more than males); age (children experience more N/V than adult counterparts); patients with a history of motion sickness or pregnancy-induced N/V). In addition to the planned treatment regimen there are a number of patient characteristics that must be taken into consideration when determining which agents and doses to use as antiemetic prophylaxis:

- It is well known that women do not respond as well as men to the same antiemetic therapy and often have worse experiences with their chemotherapy.
- Patients with a history of heavy alcohol use appear to tolerate chemotherapy much better with less nausea and vomiting.
- Elderly patients (i.e., > 60 years) tolerate chemotherapy better than the younger population. They have less nausea and vomiting, however they may be more sensitive to the sedative effects of dopamine antagonists or lorazepam. Children and very young adults also have difficulty with dopamine antagonists due to the high risk of extrapyramidal side effects.
- It is always important to know the patients history of prior chemotherapy, prior antiemetic therapy, and the outcome of that experience. If a patient has documented evidence of nausea and vomiting to a particular regimen and is scheduled to receive it again, appropriate changes to the antiemetic schedule should be made (i.e., ensure adequate dose of corticosteroid used e.g. 20mg dexamethasone; add an agent with a different mechanism of action to the current antiemetic schedule). Patients who have had a bad experience with nausea and vomiting are usually much more difficult to manage with new treatment.
- Patients with a history of motion sickness and females with pregnancy-induced nausea and vomiting will have an increased risk of CINV.
- Concurrent narcotic analgesic use often increases the nausea and vomiting experienced by patients and can cause additive sedation with lorazepam or dopamine antagonists.
- Poor control of nausea and vomiting during previous cycles of chemotherapy increases the risk of nausea and vomiting in a subsequent cycle.