PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #285
CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nishant Tageja MD, Hunter Groninger MD

Background Clinical trials based on pre-clinical studies have better defined the role of pharmacotherapies in controlling both acute and delayed onset chemotherapy-induced nausea and vomiting (CINV) (1-6). This Fast Fact offers a critical appraisal of CINV treatment guidelines specifically considering new antiemetic drugs.

Pathophysiology As a response to chemotherapy, substance P, cholecystokinin, and 5-hydroxytryptamine (5-HT3), are segregated from enterochromaffin cells in the gastrointestinal mucosa (7). 5HT3 and NK-1 receptors in vagal afferent nerves, along with central 5HT-2, NK-1, dopamine, serotonin, histamine, GABA, and cannabinoid receptors in the brain stem chemoreceptor trigger zone and vomiting center process the emetogenic stimuli leading to nausea and/or vomiting (8-10).

Classification Historically CINV has been classified according to time of onset.

- *Acute CINV* occurs within minutes to several hours after chemotherapy administration, reaching maximal intensity after 5–6 hours, and usually resolving within 24 hours (11,12).
- *Delayed CINV* occurs more than 24 hours (peaking at 48-72 hours) after chemotherapy (11,12).
- *Anticipatory emesis* precedes drug administration, and generally occurs after a previous negative vomiting experience with chemotherapy (13).

Drug and guideline development have focused on the degree of emetogenicity of a chemotherapy regimen: highly emetogenic chemotherapy (HEC) drugs (CINV in at least 90% of patients after chemotherapy); moderately emetogenic (MEC) drugs (30–90%), low emetogenic (LEC) drugs (10-30%); and minimal emetogenicity (<10%). Most of the research has focused on preventing *episodes of vomiting*. Less is known about reducing nausea independent of vomiting.

Expert Guidelines: Highly Emetogenic Chemotherapy (HEC) (4-6):

- Glucocorticoid: *dexamethasone* 12 mg PO/IV day 1, then 8 mg PO days 2–4
- 5-HT3-receptor antagonist PO/IV on day 1 (e.g., *palonosetron*, *granisetron*). First-generation 5-HT3 receptor antagonists are no longer recommended for routine use (14).
- NK-1 antagonist: *aprepitant* 125 mg PO day 1, then 80 mg PO days 2–4, or *fosaprepitant* 150 mg IV day 1 only.

Key points:

- A meta-analysis concluded there is strong evidence for glucocorticoids' efficacy for prophylaxis of acute and delayed CINV with both HEC and MEC (2).
- First generation 5-HT3 receptor antagonists (e.g. ondansetron, granisetron, dolasetron, tropisetron) are effective in controlling acute CINV when combined with corticosteroids. None is clearly superior over the other (1).
- Palonosetron (a second generation 5HT3 receptor antagonist) has a longer half-life (about 40 hr), stronger binding affinity for the receptor, and does not cause QT prolongation. Some guidelines prefer palonosetron to first generation 5HT3 antagonists (5,6); however, key comparative studies did not include NK-1 antagonists which are now widely used.
- NK-1 receptor antagonists aprepitant and fosaprepitant have been approved for prevention of acute and delayed CINV from HEC and MEC. Fosaprepitant, a water-soluble pro-drug that is converted to aprepitant has a longer half-life and more convenient dosing but is not otherwise known to be superior to aprepitant (15,16).
- For patients with refractory CINV, consider substituting olanzapine for the NK-1 antagonist. (17)
- Evidence for integrative medicine strategies was not strong enough to be included in current CINV guidelines.

Guidelines: Moderately Emetogenic Chemotherapy (MEC) For MEC drug regimens, expert guidelines recommend a combination of corticosteroid and 5HT-3 receptor antagonist to manage acute CINV. As noted above, certain guidelines recommend palonosetron over first generation 5HT-3

antagonists, although the evidence behind this is modest (level IIB evidence). For refractory CINV following MEC, consider adding a NK-1 antagonist. (18)

Guidelines: Low and Minimally Emetogenic Chemotherapy For patients on low emetogenic chemotherapy (LEC), a single anti-emetic agent such as 5-HT3-receptor antagonist, dexamethasone or a phenothiazine should be used prior to chemotherapy. An antiemetic following chemotherapy should be administered only if indicated. No antiemetic should be routinely administered prior to minimally emetogenic chemotherapy.

Anticipatory nausea Patients should be counseled regarding the risks of CINV prior to initiation of chemotherapy to prevent anticipatory CINV. Prophylactic antiemetic therapy should be begun and the use of anti-anxiety medications should be considered prior to the first cycle of chemotherapy to prevent anticipatory CINV. Although clinical data is limited, mind-body therapies, (e.g. hypnosis, biofeedback, relaxation training, guided imagery) can help prevent or lessen anticipatory CINV. (19)

Breakthrough nausea Breakthrough nausea/vomiting, defined as an event that occurs despite best preventative therapy, probably will not respond to the same class of drugs as used during unsuccessful prophylaxis. When patients develop nausea or vomiting post-chemotherapy on days 1-5 despite adequate prophylaxis, consider a 3-day regimen of oral olanzapine (10 mg PO daily) or oral metoclopramide (10 mg PO tid) (20). A blinded, RCT found olanzapine to be more effective than metoclopramide in this situation (20). Although evidence is limited, acupuncture/acupressure may be a useful adjunct strategy to manage acute chemotherapy-induced vomiting. (21)

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Authors' Affiliations: National Institutes of Health Clinical Center, Bethesda, MD.
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