Treatment of chemotherapy- and radiotherapy-induced nausea and vomiting (CINV/RINV)

HOT SPOT

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Pathophysiology

Chemotherapy-induced nausea and vomiting (CINV)

- Neuronal connections from the abdominal portion of the vagal nerve that lead to the brain stem appear to play the largest role in CINV. Numerous receptors (5-hydroxytryptamine [5-HT_3], neurokinin-1 [NK-1], and cholecystokinin-1 [CK-1]) for neurotransmitters are located on the ends of these vagal nerve connections, which also lie in close proximity to endocrine cells of the proximal small intestine (Hesketh, 2008). Through either direct intestinal or blood-borne mechanisms, chemotherapeutic agents stimulate these endocrine cells to release their mediators (5-HT, Substance P, and cholecystokinin), which, when binding to their appropriate receptors, creates a vagal stimulus that arrives in the brain stem, ultimately activating the emetic reflex (Hesketh).

5-Hydroxytryptophan (5-HT—Serotonin)

- Serotonin receptors are grouped into seven main families; of these, the 5-HT_3 group of receptors have been found to occur in the highest frequency in the gut (Herrstedt, 2008). Agents designed to block these receptors have been shown to produce antiemetic effects and now form the backbone of nearly all antiemetic regimens—5-HT_3 Receptor Antagonists (RAs).

Substance P

- Receptors for Substance P (neurokinin-1) are found throughout the central nervous system, as well as in the gastrointestinal tract (Hesketh, 2008). Evidence suggests that unlike 5-HT_3 RAs, the main site of action for NK-1 RAs is likely in the CNS (Hesketh).

Radiotherapy-induced nausea and vomiting (RINV)

- The onset and duration of RINV are felt to be shorter than in patients receiving chemotherapy (Horiot, 2004). Description of an "acute radiation syndrome" includes a sudden episode of nausea and vomiting typically occurring within 90 minutes of treatment and lasting roughly five hours (Horiot).

Risk factors

Chemotherapy

- Age: Younger patients are at greater risk of experiencing CINV than are older patients (<50 years versus >50 years of age) (Hesketh, 2008; Schwartzberg et al., 2009; National Comprehensive Cancer Network [NCCN], 2009).
- Gender: Female patients are at greater risk of experiencing CINV than are male patients (Hesketh, 2008; NCCN, 2009).
- Alcohol use: Previous history of high amounts of alcohol use reduces the chances of experiencing CINV (Hesketh, 2008).
- Previous experience: Patients who have previously experienced CINV are at greater risk than those who have not. Also, patients who have a high expectation that they will experience CINV are more likely to have this occur (Hesketh, 2008).
- Chemotherapy: The dose, schedule, and route of administration of the chemotherapeutic agent(s), as well as the inherent emetogenic potential of each antineoplastic contributes to the risk of developing CINV (NCCN, 2009).

Radiotherapy

- The factors that have been attributed to increasing the risk for RINV secondary to radiation are the portion of the body that is receiving the radiation (e.g., upper abdomen), single and total dose, fractionation, and field size of the radiation itself (NCCN, 2009; Feyer, 2004). Patient-related risk factors include age (< 55 years), gender, concurrent or recent chemotherapy, and psychological state (Feyer).

Phases of CINV

- *Anticipatory:* This represents the time period before chemotherapy is administered, often occurring just prior to receiving the treatment. It is a learned response that has arisen due to previous CINV experience (severity and duration contribute to this) (NCCN, 2009).
- *Acute:* This phase is considered to be the initial 24 hours immediately after chemotherapy has been administered.
- *Delayed:* This is the time period that begins after the initial 24 hours following chemotherapy (i.e., hour 25 onwards).
- *Breakthrough:* Not a phase per se, but represents the instances where vomiting is not controlled despite prophylaxis with anti-emetic medications and/or requires rescue medications (NCCN, 2009).
- *Refractory:* Emesis occurring in treatment cycles where prophylaxis and/or breakthrough medications have failed in previous cycles (NCCN, 2009; MASCC, 2008).

Emetogenic potential

Chemotherapy

- *Highly Emetogenic Chemotherapy (HEC):* A risk of emesis in >90% of patients (e.g., Cisplatin, carmustine, cyclophosphamide (≥1500 mg/m^2), procarbazine) (MASCC, 2008).
- *Moderately Emetogenic Chemotherapy (MEC):* A risk of emesis in 30% to 90% of patients (e.g., Doxorubicin, oxaliplatin, Epirubicin, Irinotecan, cyclophosphamide [<1500 mg/m^2], temozolamide) (MASCC, 2008).
- *Low-Risk Emetogenic Chemotherapy (LEC):* A risk of emesis in 10% to 30% of patients (e.g., Paclitaxel, docetaxel, gemcitabine, trastuzumab, 5-Fluorouracil, capecitabine) (MASCC, 2008).
- *Minimally Emetogenic Chemotherapy:* Denotes a risk of emesis in <10% of patients (e.g., Bleomycin, vinblastine, vincristine, vinorelbine, fludarabine, Methotrexate [oral], chlorambucil, hydroxyurea) (MASCC, 2008).

Radiotherapy

- *High Risk:* Total Body Irradiation (TBI) (MASCC, 2008).
- *Moderate Risk:* Upper abdomen. (MASCC, 2008)
- *Low Risk:* Lower thorax region, pelvis, cranium (radiosurgery), craniospinal. (MASCC, 2008)
- *Minimal:* Head and neck, extremities, cranium, breast. (MASCC, 2008)

Recommendations

(MASCC 2008) (*Revisions expected for 2009)*

Chemotherapy

- Patients receiving HEC are recommended to receive the following medications to prevent CINV:

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Acute: a 5-HT_3 RA, dexamethasone, and aprepitant (or fosaprepitant)
Delayed: aprepitant and dexamethasone (for those patients receiving cisplatin and the above acute antinauseant regimen).

- In those patients who are to receive MEC, the recommended antinauseants are:
  Acute: a 5-HT_3 antagonist, dexamethasone, and aprepitant or fosaprepitant (patients receiving an anthracycline plus cyclophosphamide)//a 5-HT_3 antagonist and dexamethasone (in patients NOT receiving an anthracycline plus cyclophosphamide).
  ** The recommended dose of dexamethasone in the acute setting with MEC is 8 mg IV × 1 dose.*
  Delayed: Dexamethasone or aprepitant (patients receiving an anthracycline plus cyclophosphamide and who were prophylaxed with the above antinauseant three-drug regimen in the acute period)// Dexamethasone alone (in patients who did not receive aprepitant in the acute period).
- The treatment recommended for patients being treated with LEC is:
  Acute: Dexamethasone (low dose)
- In patients being treated with minimally emetogenic chemotherapy regimens, no antiemetic should be routinely given before chemotherapy in patients without a history of nausea and emesis.

Special cases

- Multiple-day cisplatin: a 5-HT_3 antagonist plus dexamethasone for the *acute* phase and dexamethasone for the *delayed* phase.
- Anticipatory nausea and emesis—psychological techniques should be employed to deal with this case.

Radiotherapy

- Those patients who are at high risk for RINV should receive a 5-HT_3 antagonist plus dexamethasone.
- Patients receiving moderately emetogenic radiotherapy should receive a 5-HT_3 antagonist.
- Any patients receiving radiation therapy with low emetogenic potential should receive a 5-HT_3 antagonist for rescue.
- Those patients who are being treated with radiotherapy of minimal risk should receive either a dopamine antagonist or a 5-HT_3 antagonist for rescue purposes.

Medications

(MASCC, 2008)

Corticosteroids

Dexamethasone (Decadron®—Merck Frosst)

- HEC **Acute:** 20 mg × 1 dose, **Delayed:** 8 mg twice daily; MEC **Acute:** 8 mg × 1 dose, **Delayed:** 8 mg once daily or 4 mg twice daily; LEC **Acute:** 4–8 mg × 1 dose

5-HT_3 Receptor Antagonists

Ondansetron (Zofran®—GlaxoSmithKline)

- IV: 8 mg or 0.15 mg/kg; Oral: 16 mg/day

Granisetron (Kytril®—Roche)

- IV: 1 mg or 0.01 mg/kg; Oral: 1–2 mg/day

Dolasetron (Anzemet®—Sanofi-Aventis)

- IV: 100 mg or 1.8 mg/kg; Oral: 100 mg/day

NK-1 Receptor Antagonists

Aprepitant (Emend®—Merck Frosst)

- **Acute:** 125 mg orally once; **Delayed:** 80 mg orally once daily

Fosaprepitant (Emend® IV—Merck Frosst)

- **Acute:** 115 mg IV once

Anti-nauseants—Breakthrough/Refractory CINV
(Hesketh, 2008)

- *Prochlorperazine; Metoclopramide; Domperidone; Dronabinol; Olanzapine; Nabilone*

Helpful hints/facts

- It is the goal to prevent nausea and vomiting in all patients receiving cancer chemo- and/or radiotherapy (NCCN, 2009).
- It is always easier to PREVENT than to treat CINV.
- Choice of the antiemetic agent(s) used should be based on the emetic risk of the therapy, the patient's prior experience with antiemetics, and patient specific factors (NCCN, 2009).
- The lowest effective dose of medication should be used to treat CINV/RINV.
- Combination chemotherapy and radiotherapy increases the risk for nausea and vomiting (Feyer et al., 2005).
- The dexamethasone dose should be reduced by 40% if used concurrently with aprepitant or fosaprepitant (20 mg dose of dexamethasone should be reduced to 12 mg) (MASCC, 2008).
- All 5-HT_3 antagonists are equal in efficacy and adverse effect profile.
- Intravenous and oral formulations of antiemetzcs are equally efficacious and safe (5-HT_3 antagonists) (NCCN, 2009).
- 5-HT_3 RAs are most effective for the ACUTE phase of CINV. Corticosteroids and aprepitant (fosaprepitant) are effective in both the ACUTE and DELAYED phases (Baker et al., 2005).

** Revisions expected for 2009*

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