Preventing and Managing Chemotherapy-induced Nausea and Vomiting (CINV): Adhering to Clinical Guidelines

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Faculty and Planner Disclosures

No relationships pertinent to this activity.
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• Susan R. Dombrowski, M.S., B.S.Pharm.

ASHP staff have no relevant financial relationships to disclose.
Learning Objectives

• Describe a patient’s risk for developing CINV taking into consideration personal risk factors and category of chemotherapy emetogenicity.

• Discuss key updates to national and international guidelines on the prevention and management of CINV.

• Recommend treatment options for a patient at risk for developing acute and delayed CINV.

• Design a plan to improve the adherence to CINV guidelines in clinical practice.
Polling Question

What do you think is the most feared side effect of chemotherapy?

- Alopecia
- Vomiting
- Progressive multifocal leukoencephalopathy
Scope of the Problem

• Most feared side effect rankings:

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 255)</th>
<th>Women (n = 153)</th>
<th>Men (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

• Vomiting as one of the top 4 side effects:
  – Before chemotherapy: 51%
  – After chemotherapy: 24%

Today’s Outline

• Pathophysiology and Pharmacology of CINV
• Drugs and definitions
• CINV risk factors
• Guidelines for CINV
• Adhering to Guidelines
• Conclusion
Pathophysiology Review

**Higher Centers**
- Fear, dread, anticipation
- (5HT3, NK1, D2, GABA)

**Cerebellum**
- Inner ear; motion
- (H1, M)

**Chemoreceptor trigger zone**
- Blood-borne emetics
- (5HT3, D2, M, CB, opioid)

**Solitary Tract Nucleus**
- Vagal, sympathetic, glossopharyngeal afferents
- (5HT3, D2, M, H, NK1, CB)

**Emetic center in the medulla**
- (NK1)

Vomiting

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition.
Main drugs for today’s discussion

• Corticosteroids
  – Dexamethasone

• Serotonin receptor antagonists (5HT3 RA)
  – Dolasetron
  – Ondansetron
  – Granisetron
  – Palonosetron

• Neurokinin-1 (NK1) receptor antagonists
  – Aprepitant
  – Fosaprepitant

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition.
Other Neurotransmitters, Receptors, and Drugs

- **Histamine (H1)**
  - Diphenhydramine (++++)
  - Promethazine (++++)
  - Prochlorperazine (++)

- **Muscarinic acetylcholine receptors (M)**
  - Scopolamine (++++)
  - Diphenhydramine (++)
  - Promethazine (++)

- **Dopamine (D2)**
  - Haloperidol (++++)
  - Metoclopramide (+++)
  - Olanzapine (++++)
  - Prochlorperazine (++++)
  - Promethazine (++)

- **Cannabinoid (CB)**
  - Dronabinol
  - Nabilone

- **GABA**
  - Lorazepam

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition.
Definitions

• Acute – nausea or emesis that occurs in the first 24 hours after chemotherapy
• Delayed – nausea or emesis that occurs after the first 24 hours after chemotherapy
  – May last up to 2-3 days after chemotherapy administration
  – Commonly seen with cisplatin, carboplatin, cyclophosphamide, ifosfamide, doxorubicin
Definitions

• Anticipatory – nausea or emesis that is a learned reflex response and
  – Triggered by sights, sounds, or smells
  – Due to poor control of nausea or emesis in previous chemotherapy cycles

• Breakthrough – nausea or emesis that occurs despite proper prophylaxis
  – Measured by use of “PRN” medications
CINV Risk Factors: Patient-Specific

- Anxiety, expectation of nausea
- Women > men
- Younger age (i.e., <50 y/o)
- History of motion sickness
- Pregnancy-induced nausea/vomiting
- History of alcohol use
- Anti-emetics inconsistent with guidelines
- Prior chemotherapy and degree of anti-emetic control

CINV Risk Factors: Regimen-Specific

• N/V is a dose-related toxicity

• Single-agent chemotherapy risk categories:
  – High (>90% incidence in acute and delayed)
  – Moderate (30-90% in acute and delayed)
  – Low (10-30% in acute)
  – Minimal (<10% in acute)

• For multi-drug regimens, the drug that has the highest level of emetogenicity determines the regimen’s emetic risk level

Emetic Risk Categories

  – Proposed five categories of emetic risk
  – Algorithm for multi-drug chemotherapy

  – Consolidated risk categories
  – No longer “calculate” emetogenicity of multi-drug regimens

• NCCN Guidelines list these:
Emetic Risk Categories

- **High**
  - Cyclophosphamide/doxorubicin combination
  - Cisplatin
  - Higher doses of specific chemotherapy agents

- **Moderate**
  - Carboplatin, oxaliplatin
  - Anthracyclines (relatively lower doses)
  - Nitrogen mustards

- **Low**
  - Antimicrotubules (e.g., taxanes) and antimetabolites

- **Minimal**
  - Monoclonal antibodies, vinca alkaloids
Emetic Risk Categories – Oral

• Moderate to high
  – Cytotoxic chemotherapy
  – Crizotinib

• Minimal to low
  – Capecitabine
  – “-nibs”

Overall Emetic Risk

• Overall emetic risk will never be below the regimen’s risk level.
• The presence of patient risk factors may (or may not) increase the overall emetic risk.
Prophylaxis for CINV: General Principles

• Anticipatory
  – Lorazepam if fearful or poor control after previous cycle
• Acute
  – Typically administered IV in the infusion center
• Delayed
  – Some IV drugs will cover delayed
  – May receive prescription to take as scheduled
• Breakthrough
  – Should always receive a prescription that is PRN
  – Use a different MOA than for prophylaxis
# CINV Guidelines

<table>
<thead>
<tr>
<th></th>
<th>ASCO&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ESMO/MASCC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NCCN&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expert panel</strong></td>
<td>Select ASCO members</td>
<td>Multinational (10 countries, 5 continents)</td>
<td>Representatives from NCCN member institutions</td>
</tr>
<tr>
<td><strong>Multidisciplinary?</strong></td>
<td>Some</td>
<td>High</td>
<td>Some</td>
</tr>
<tr>
<td><strong>Methodology</strong></td>
<td>Systematic review</td>
<td>Systematic review</td>
<td>Consensus-based</td>
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<tr>
<td><strong>Last updated</strong></td>
<td>June 2011</td>
<td>Jan 2013</td>
<td>Aug 2013</td>
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<tr>
<td><strong>Comments</strong></td>
<td>Addresses pediatrics and radiation</td>
<td>Multi-organization collaboration</td>
<td>Tied to reimbursement via compendium</td>
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</table>

# Single-day Chemotherapy: Prophylaxis Principles

<table>
<thead>
<tr>
<th>Emetic risk (emesis incidence)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;90%)</td>
<td>✓✓✓✓</td>
<td>✓✓✓</td>
<td>✓✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>Moderate (30-90%)</td>
<td>✓✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>Low (10-30%)</td>
<td>✓✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal (&lt;10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Guideline Recommendations: High Emetogenicity, Acute

- Day 1 of single-day regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>ASCO¹</th>
<th>ESMO/MASCC²</th>
<th>NCCN³</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK1 RA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5HT3 RA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes - palonosetron preferred</td>
</tr>
</tbody>
</table>

Alternate regimen: Olanzapine instead of NK1 RA

Others supportive care:
- Lorazepam
- Diphenhydramine

Consider:
- Lorazepam
- H2 blocker, PPI
Guideline Recommendations: High Emetogenicity, Delayed

- Days 2 through 4 of single-day regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>ASCO¹</th>
<th>ESMO/MASCC²</th>
<th>NCCN³</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK1 RA</td>
<td>Days 2-3</td>
<td>Days 2-3</td>
<td>Days 2-3</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Days 2-3 or Days 2-4</td>
<td>Days 2-4</td>
<td>Days 2-4</td>
</tr>
<tr>
<td>5HT3 RA</td>
<td>No</td>
<td>No</td>
<td>No (palonosetron preferred)</td>
</tr>
<tr>
<td>Alternate regimen</td>
<td></td>
<td></td>
<td>Olanzapine instead of NK1 RA</td>
</tr>
<tr>
<td>Other supportive care</td>
<td>L Lorazepam, Diphenhydramine</td>
<td>Consider: L Lorazepam, H2 blocker, PPI</td>
<td></td>
</tr>
</tbody>
</table>
Case: HEC

• TJ is a 33 year-old woman with a new diagnosis of breast cancer. She is a smoker, drinks socially, and exercises regularly. Her medical history is significant for: hypothyroidism, anxiety, GERD, and nausea during pregnancy.

• She will receive her first cycle of chemotherapy, consisting of:
  – Cyclophosphamide 600 mg/m2 IV on day 1
  – Doxorubicin 60 mg/m2 IV on day 1
  – Every 21 days for 4 cycles
Case: HEC

• What are her risk factors for developing CINV?
• Will the presence of these risk factors change your strategy for prophylaxis?
• What classes of medications will be utilized in this case?
• What is your antiemetic regimen?
# HEC Scenario

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo</strong></td>
<td>Dox 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CTX 600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emetic risk</strong></td>
<td>High</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td><img src="%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93" alt="✓✓✓✓✓" /></td>
<td><img src="%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93" alt="✓✓✓✓✓" /></td>
<td><img src="%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93" alt="✓✓✓✓✓" /></td>
<td><img src="%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93" alt="✓✓✓✓✓" /></td>
<td><img src="%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93%E2%9C%93" alt="✓✓✓✓✓" /></td>
</tr>
<tr>
<td><strong>Drug Classes</strong></td>
<td>NK1 RA</td>
<td>NK1 RA</td>
<td>NK1 RA</td>
<td>Steroid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5HT3 RA</td>
<td>Steroid</td>
<td>Steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Steroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scheduled</strong></td>
<td>Aprep PO</td>
<td>Aprep PO</td>
<td>Aprep PO</td>
<td>Dex PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ondan IV</td>
<td>Dex PO</td>
<td>Dex PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dex IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRN</strong></td>
<td>Benzo H2/PPI</td>
<td>Benzo H2/PPI</td>
<td>Benzo H2/PPI</td>
<td>Benzo H2/PPI</td>
<td>Benzo H2/PPI</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Other</td>
<td>Other</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>
### Guideline Recommendations: Moderate Emetogenicity, Acute

- **Day 1** of single-day regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>ASCO&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ESMO/MASCC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NCCN&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK1 RA</td>
<td>May add</td>
<td>No</td>
<td>May add</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>8 mg</td>
<td>8 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>5HT3 RA</td>
<td>Yes - palonosetron</td>
<td>Yes - palonosetron</td>
<td>Yes (palonosetron preferred)</td>
</tr>
<tr>
<td>Alternate regimen</td>
<td></td>
<td></td>
<td>Olanzapine + 5HT3 RA + Dex</td>
</tr>
<tr>
<td>Other supportive</td>
<td>• Lorazepam</td>
<td></td>
<td>Consider:</td>
</tr>
<tr>
<td>care</td>
<td>• Diphenhydramine</td>
<td></td>
<td>• Lorazepam</td>
</tr>
</tbody>
</table>

**Consider:**
- H2 blocker, PPI
Guideline Recommendations: Moderate Emetogenicity, Delayed

- Days 2 through 3 of single-day regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>ASCO&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ESMO/MASCC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NCCN&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK1 RA</td>
<td>May add</td>
<td>No</td>
<td>Consider one:</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Days 2-3</td>
<td>Days 2-3</td>
<td>• Nothing if palonosetron used in acute</td>
</tr>
<tr>
<td>5HT3 RA</td>
<td>No (palonosetron preferred)</td>
<td>No (palonosetron preferred)</td>
<td>• NK1 RA +/- dex if used in acute</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Dex days 2-3</td>
</tr>
</tbody>
</table>

Alternate regimen

- Olanzapine

Other supportive care

- Lorazepam
- Diphenhydramine

Consider:

- Lorazepam
- H2 blocker, PPI
Case: MEC

• TW is a 65 year-old man with a diagnosis of lung cancer. He is a former smoker and non-drinker. Her medical history is significant for: CAD (s/p MI in 2005), HTN, hypercholesterolemia. Today, he is scheduled for his second cycle of chemo, and he reports poor control of the emesis during the previous cycle.

• He is receiving chemotherapy consisting of:
  – Carboplatin AUC = 6 IV on day 1
  – Pemetrexed 500 mg/m2 IV on day 1
  – Bevacizumab 15 mg/kg IV on day 1
  – Every 21 days for 4-6 cycles
Case: MEC

- What are his risk factors for developing CINV?
- What additional information would you like to have?
- Which chemotherapy agent in this regimen causes the highest level of emetogenicity?
- What classes of medications will be utilized in this case?
- What is your antiemetic regimen?
# MEC Scenario 1

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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</thead>
<tbody>
<tr>
<td><strong>Chemo</strong></td>
<td>Carbo 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pem 500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bev 15</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Emetic risk</strong></td>
<td>Moderate</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
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<tr>
<td><strong>Prophylaxis</strong></td>
<td>✓ ✓ ✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td><strong>Drug Classes</strong></td>
<td>5HT3 RA</td>
<td>Steroid</td>
<td>Steroid</td>
<td></td>
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<td></td>
<td>Steroid</td>
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<tr>
<td><strong>Scheduled</strong></td>
<td>Palon IV</td>
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<td>Dex PO</td>
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<tr>
<td></td>
<td>Dex IV</td>
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<td><strong>PRN</strong></td>
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<td>Benzo</td>
<td>Benzo</td>
<td>Benzo</td>
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<td>Other</td>
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</table>
MEC Scenario 2: If treated by Scenario 1 already

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<th>Day 1</th>
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<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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</thead>
<tbody>
<tr>
<td><strong>Chemo</strong></td>
<td>Carbo 6</td>
<td>Pem 500</td>
<td>Bev 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emetic risk</strong></td>
<td>Moderate</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>🟢🟢🟢</td>
<td>🟢🟢</td>
<td>🟢🟢</td>
<td>🟢</td>
<td></td>
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<tr>
<td><strong>Drug Classes</strong></td>
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<td>5HT3 RA</td>
<td>NK1 RA Steroid</td>
<td>Steroid</td>
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<td>Palon IV</td>
<td>Aprep PO</td>
<td>Dex PO</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palon IV</td>
<td>Dex IV</td>
<td>Aprep PO</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dex IV</td>
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<td>Aprep PO</td>
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<td></td>
<td></td>
<td></td>
<td>Dex PO</td>
<td></td>
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<tr>
<td><strong>PRN</strong></td>
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<td>Benzo Other</td>
<td>Benzo Other</td>
<td>Benzo Other</td>
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CINV: Low and Minimal

• Low

<table>
<thead>
<tr>
<th></th>
<th>ASCO(^1)</th>
<th>ESMO/MASCC(^2)</th>
<th>NCCN(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer one dose before chemo:</td>
<td>Dexamethasone 8 mg</td>
<td>Dexamethasone -OR- 5HT3 RA -OR- Dopamine RA (metoclopramide)</td>
<td>Dexamethasone -OR- 5HT3 RA -OR- Dopamine RA (metoclopramide, prochlorperazine)</td>
</tr>
</tbody>
</table>

• Minimal
  – No routine prophylaxis
Polling Question

Is it appropriate to use palonosetron for the prevention of CINV in low emetic regimens?

- Yes
- No
- Don’t know
Something for PRN (Breakthrough)

- Attack a different receptor
  - Prochlorperazine 10 mg IV/PO Q6 hr PRN 😊
  - Metoclopramide 10-40 mg IV/PO Q4-6 hr PRN 😊
  - Promethazine 12.5-25 mg IV/PO Q4 hr PRN
  - 5HT3 dosing varies (just make sure it’s not above the max recommended dose per day)
  - Haloperidol 0.5-2 mg PO Q4-6 hr PRN
  - Dronabinol 5-10 mg PO Q3-6 hr PRN
  - Nabilone 1-2 mg PO BID PRN
  - Dexamethasone 12 mg PO/IV daily if not already given
  - Olanzapine 10 mg PO daily for 3 days
  - Droperidol 2.5-5 mg IV Q4-6 hr PRN 😞
Big 3 Dosing Pearls

• NK1 receptor antagonists
  – **PO**: Aprepitant 125 mg 1 hour before chemotherapy on day 1, then 80 mg on days 2 and 3
  – **IV/PO**: Fosaprepitant 115 mg IV 30 minutes before chemotherapy on day 1, then aprepitant 80 mg PO on days 2 and 3
  – **IV**: Fosaprepitant 150 mg IV 30 minutes before chemotherapy on day 1 (this is like giving 3 days of aprepitant)

• 5HT3 receptor antagonists
  – Palonosetron has a long half-life (30-40 hours); like giving multi-day doses of short half-life 5HT3 RAs
  – Doses of other 5HT3 RAs have been going down

• Dexamethasone
  – Dose is generally 8-16 mg/day
  – Upwards of 20 mg used without aprepitant/fosaprepitant
Dosing Scenarios

- **High Emetogenicity Chemotherapy (HEC)**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK1 RA</td>
<td>Fosaprep 150 mg IV</td>
<td>No further dosing needed</td>
<td></td>
</tr>
<tr>
<td>Dex</td>
<td>12 mg IV</td>
<td>8 mg PO</td>
<td>8 mg PO</td>
</tr>
<tr>
<td>5HT3 RA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- **Moderate Emetogenicity Chemotherapy (HEC)**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK1 RA</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dex</td>
<td>8 mg IV/PO</td>
<td>8 mg PO</td>
<td>8 mg PO</td>
</tr>
<tr>
<td>5HT3 RA</td>
<td>Palonosetron 0.25 mg IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- PRN for breakthrough required through all days
- Consider lorazepam and acid suppression
Common Adverse Effects by Drug Class

• NK1 Receptor Antagonists
  – Somnolence/fatigue
  – Hiccups
  – Diarrhea

• 5HT3 Receptor Antagonists
  – Headache
  – Constipation
  – QT interval prolongation (dose-related)
Common Adverse Effects by Drug Class

• Steroids (i.e., dexamethasone)
  – Insomnia/hyperactivity
    • Steroid psychosis: agitation, anxiety, irritability, restlessness, mania, delirium, hallucination, etc.
  – Increase in blood sugar
  – Gastrointestinal
Common Adverse Effects by Receptor Modulation

• Dopamine Antagonists
  – Extrapyramidal side effects (e.g., dystonia)
  – Drowsiness/dizziness
• Histamine Antagonists
  – Drowsiness/dizziness
• Muscarinic Antagonists
  – Drowsiness/dizziness
  – Dry mouth, blurred vision, etc.
• Cannabinoid receptors
  – Hallucinations
  – Other CNS side effects
Adverse Effect Clinical Pearls

• Use steroids with caution in diabetics
• Premedication with prochlorperazine can mitigate side effects from cannabinoids
• Prochlorperazine vs. Promethazine
  – Prochlorperazine: D > H
    • EPS > drowsiness
  – Promethazine: H > D
    • Drowsiness > EPS
• Metoclopramide inhibits 5HT3 at high doses, but causes bad EPS (do not use it like this!)
Multiday Chemotherapy Regimens

• E.g., Cisplatin 25 mg/m$^2$ and etoposide 100 mg/m$^2$ on days 1, 2, & 3; every 3 week cycle

• Basic principles:
  – No good evidence; not systematically addressed in GLs
  – Consider the risk of acute emesis every day that chemotherapy is given
  – Consider drugs that may cause delayed emesis and note timing
  – Patients may be at risk for both acute AND delayed on specific days of the cycle

# Multiday Chemo Scenario

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin</strong></td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Etoposide</strong></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Final</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiemetic regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Cisplatin**: High dose on Days 1, 2, and 3; Delayed on Days 4, 5, and 6.
- **Etoposide**: Low dose on Days 1, 2, and 3.
- **Final Antiemetic regimen**: Dexamethasone (Dex) IV on Days 1 and 2; Dexamethasone (Dex) PO and Aprepitant (Aprep) PO on Days 4 and 5; Dexamethasone (Dex) PO on Day 6.

Antiemetic Dosing Concerns: Multi-day Chemo

• 5HT3 RAs:
  – Palonosetron every other day dosing (e.g., days 1, 3, and 5)
  – Consider long-acting formulations

• NK1 RAs:
  – Optimal duration not yet defined
  – Daily for 5 days?
  – Starting on Day 3 of a 5-day regimen?

ADHERING TO CINV GUIDELINES
Adherence to Guidelines: Bending the Curve

Emesis Survival Curve – High Emetogenicity

Increased adherence to guidelines

Current situation at institution

Percentage of patients without emesis

Hours after chemotherapy
Polling Question

At my institution, our adherence to CINV guidelines is:

- High
- Acceptable
- Low
- Don’t know
What are CINV adherence rates?

• Study 1:
  – Adherence to ESMO/MASCC guidelines
  – Chart review of 299 patients between Nov 2008-April 2009

• Study 2:
  – 4,566 patients with lung cancer

CINV Adherence Rates: Study 1

• Overall adherence rate to ESMO/MASCC recommendations:
  – Acute: 61% (181/299)
  – Delayed: 11% (17/148)

• High emetogenicity
  – Day 1 adherence: 71% (69/97) – mostly incorrect use of aprepitant
  – Day 2 and 3 adherence: 20% and 35% - overuse of 5HT3 RA
  – Corticosteroid use was mostly appropriate (did not lower dose for aprepitant)

CINV Adherence Rates: Study 1

• Moderate emetogenicity
  – Day 1 adherence: 66% (66/100) – incorrect use of NK1 antagonist
  – Day 2 and 3 adherence: 33% and 52% - overuse of 5HT3 RA

• Low emetogenicity
  – 11% adherence (6/54) – too many drugs

CINV Adherence Rates: Study 1

• Predictors of non-adherence
  – Low and moderate emetogenicity
  – Better adherence:
    • Higher age
    • Solid tumors
    • Inpatient

• Summary
  – Adherence not optimal
  – 5HT3 antagonists an issue!
  – Some issues with NK1 antagonists

CINV Adherence Rates: Study 2

- Overall adherence rate to NCCN recommendations:
  - Cisplatin-based (High)
    - 5HT3: 78% adherence
    - Dexamethasone: 65% adherence
    - Aprepitant: too low to count (n < 11)
  - Carboplatin-based (Moderate)
    - 5HT3: 83% adherence
    - Dexamethasone: 66% adherence
    - Aprepitant: too low to count (n < 11)

CINV Adherence Rates: Study 2

- Adherence to 5HT3 RA and Dexamethasone trended upward with time
- Predictors of adherence/non-adherence
  - Race
  - Income (higher = more adherence)
  - Education (higher = more adherence)
  - Comorbidity

Data with Adherence

• Prospective, observational, multicenter study in patients with solid tumors receiving HEC or MEC

• Two cohorts:
  – Guideline-consistent (GC), n = 287
  – Guideline-inconsistent (GI), n = 704

• GC had higher rates of:
  – Complete response: 60% vs. 51%; p = 0.008
  – No emesis: 63% vs. 59% (NS)
  – No nausea: 48% vs. 41% NS)
  – No CINV: 43% vs. 34%; p = 0.016

Barriers to Guideline Implementation & Adherence

- Lack of knowledge of guideline recommendations
- Differences in guideline recommendations – confusion
- Cost/financial
- Education of healthcare providers
- Institutional enforcement
- Measuring quality of care & outcomes

Systematic Review: What works to implement guidelines?

• Effective
  – Decision support systems
  – Interactive educational meetings (e.g., tumor boards)
  – Educational outreach (detailing)
  – Procedural justification
  – Reminder system
  – Multi-faceted interventions

Systematic Review: What works to implement guidelines?

• Inconsistent effectiveness
  – Audits, feedback, or peer review
  – Education (CME)
  – Financial incentives
  – Local opinion leaders

• Ineffective
  – Dissemination-only information
  – Traditional education (e.g., grand rounds)

Any evidence with CINV?  
Institution #1

• Steps:
  – Developed local guidelines (included RPh)
  – Education
  – Prospectively monitored adherence
  – Provided adherence/outcome data to prescribers

• Results
  – Baseline adherence was poor
  – Improved with guideline dissemination (not sustained)
  – Sustained improvement with outcome data sharing

Any evidence with CINV? Institution #2

• Steps:
  – Formed multidisciplinary group (including RPh) to develop institutional guidelines
  – Guideline dissemination and education
  – Guideline enforcement: called prescriber
  – Pharmacist-managed option: “Antiemetics per Guidelines”
  – Preprinted order forms

• Results:
  – Good patient-reported satisfaction rates
  – Good adherence after pharmacist-driven ordering (>98%)

## Pre-Printed Order Sets

<table>
<thead>
<tr>
<th>DRUG REGIMEN</th>
<th>DOSE, ROUTE, FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIEMETIC</strong></td>
<td></td>
</tr>
<tr>
<td>□ Ondansetron (Zofran) _____ mg _____ (IV/PO) 30 minutes before chemotherapy on day(s)_____</td>
<td></td>
</tr>
<tr>
<td>□ Aprepitant (Emend) 125 mg PO 1 hour before chemotherapy on day 1, then 80 mg PO daily on days 2-3 (Inpatient only! If outpatient, the patient should use own supply)</td>
<td></td>
</tr>
<tr>
<td>□ Prochlorperazine 10 mg PO every 4-6 hours PRN nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>□ Other:</td>
<td></td>
</tr>
<tr>
<td><strong>CORTICOSTEROID</strong></td>
<td></td>
</tr>
<tr>
<td>□ Dexamethasone _____ mg _____ (IV/PO) 30 minutes before chemotherapy on day 1</td>
<td></td>
</tr>
<tr>
<td>□ Dexamethasone _____ mg PO _____ (daily/BID) on days 2-4</td>
<td></td>
</tr>
<tr>
<td><strong>ANTIHISTAMINE</strong></td>
<td></td>
</tr>
<tr>
<td>□ Diphenhydramine (Benadryl) _____ mg _____ (IV/PO) 30 minutes before chemotherapy on day: ________</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>□ Ranitidine (Zantac) 50 mg IV 30 minutes before chemotherapy on day: ________</td>
<td></td>
</tr>
</tbody>
</table>

**Physician Signature:**

**Date:**

**Time:**
Other Resources

• NCCN Chemotherapy Order Templates
  – Preview:  

• MASCC Antiemesis Tool© (MAT)
  – http://www.mascc.org/mat
Implementing Guidelines: Summary

• Local guideline development
• Education of providers
• Decision support is probably the most powerful tool
  – Pre-printed order templates (paper)
  – CPOE
• Challenges
  – Software for ordering systems
  – Updating of order sets
  – Lack of centralized authority
Polling Question

How do you feel about using pre-defined order sets to maximize adherence to CINV GLs?

Love it!

Hate it!

Love-hate relationship!
Conclusion

• CINV is an important side effect to manage
• Guidelines are available from many institutions and authoritative groups
• Institutions should create their own guideline and implementation process
• Use of decision-support tools is key
Self-Assessment Questions

• Which of the following is NOT a patient-specific risk factor for chemotherapy-induced nausea and vomiting?

A. Age  
B. History of previous surgery  
C. Gender  
D. History of alcohol use
Self-Assessment Questions

• The ASCO, ESMO/MASCC, and NCCN guidelines all prefer ______________ as the 5HT3 receptor antagonist of choice to be given on day 1 of moderately emetogenic chemotherapy.

A. Dolasetron
B. Granisetron
C. Ondansetron
D. Palonosetron
Self-Assessment Questions

Which of the following regimens best describes the **Day 1 antiemetic regimen** that should be prescribed for a patient receiving **highly emetogenic chemotherapy**?

A. Dexamethasone alone
B. Dexamethasone + 5HT3 receptor antagonist
C. Dexamethasone + 5HT3 receptor antagonist + NK1 receptor antagonist
D. No routine antiemetics are necessary
Self-Assessment Questions

• Based on a systematic review of the evidence, which of the following strategies have been shown to be effective in incorporating treatment guidelines into practice?

A. Decision support systems
B. Multifaceted interventions
C. Traditional educational session (e.g., grand rounds)
D. A and B
Self-Assessment Questions

• Based on published reports of institutional experience with implementing CINV guidelines, the strategies that seemed to work best was:

A. Allowing pharmacists to order antiemetics with an “Antiemetics per Guidelines” checkbox
B. Providing lectures about CINV at grand rounds
C. Offering financial incentives to prescribers for adherence
D. Bringing in local opinion leaders to educate prescribers
Thank you for joining us.

• Join me again on March 6, 2014 for a live “Ask the Experts” Webinar where I will explore issues raised by participant questions from ASHP Midyear.

• See: http://www.cemornings.com/