Prevention and Treatment of Chemotherapy Induced Nausea and Vomiting

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With thanks to Steven Grunberg and Frankie Holmes
### Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

<table>
<thead>
<tr>
<th>Rank</th>
<th>1983(^1)</th>
<th>1993(^2)</th>
<th>1995(^3)</th>
<th>1999(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td>2.</td>
<td>Nausea</td>
<td>Constantly tired</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
</tr>
<tr>
<td>3.</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Thought of coming for treatment</td>
<td>Effect on family</td>
<td>Constantly tired</td>
<td>Vomiting</td>
</tr>
<tr>
<td>5.</td>
<td>Length of time treatment takes</td>
<td>Vomiting</td>
<td>Having to have an injection</td>
<td>Changes in the way things taste</td>
</tr>
</tbody>
</table>

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Association Between CINV and QOL (FLIE Interference Scores) in the Community Oncology Setting

- Prospective observational study in patients receiving emetogenic chemotherapy; 82% women; mean age 51 years
- FLIE = Functional Living Index – Emesis

Other consequences of CINV: increased cost, delayed or reduced treatment, hospitalization

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# Emetogenicity of Chemotherapy

<table>
<thead>
<tr>
<th>Emetogenic Classification</th>
<th>Incidence of Emesis</th>
<th>Index Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 90%</td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxorubicin: (AC or &gt;60 mg/m²)</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-90%</td>
<td>Cyclophosphamide ≤1500 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Low</td>
<td>10-30%</td>
<td>Eribulin</td>
</tr>
<tr>
<td>Minimal</td>
<td>&lt; 10%</td>
<td>Vinorelbine</td>
</tr>
</tbody>
</table>

Chemotherapy-Induced Emesis: Risk Factors

• Patient-related risk factors:\(^1\):
  – Younger age
  – Female gender
  – No/minimal prior history of alcohol use
  – Prior CINV
  – Anxiety

• Treatment-related risk factors:\(^1,2\):
  – Moderate to high emetogenicity of chemotherapy agents or regimens
  – Moderate to high drug dose

Chemotherapy-Induced Emesis: Classification

• Classification\(^1\):
  – Acute (0-24 hr after chemotherapy)
  – Delayed (24-120 hr after chemotherapy)
    • May last up to 6 days
    • Incidence without treatment 20\%-90\%
  – Anticipatory (prior to chemotherapy)
    • Experienced by up to 25\% of patients by 4th chemotherapy cycle\(^2\)

• Potential to cause:
  – Dehydration and electrolyte imbalance\(^1,3\)
  – Impaired health-related quality of life\(^4,5\)
    • Negative impact on activities of daily living
  – Rehospitalization\(^6\)

Principles and Goals of Therapy

- The goal is to prevent nausea and vomiting
  - Be aware of toxicities/drug interactions
  - Acute is generally easier to control than delayed
  - Control should be maintained for at least 3 days
- IV and oral drugs overall are similar in effectiveness
- Personalize therapy for treatment and patient factors
- Consider non-chemotherapy related causes
- Consider use of an H2 blocker or PPI to prevent dyspepsia, which can mimic nausea
- Lifestyle measures may help
  - Eat small meals, choose healthful foods, eat food at room temperature, etc
Natural History of Delayed Nausea and Vomiting

Percent with Nausea or Vomiting

Kris, J Clin Oncol 3:1379, 1985
Delayed Nausea/Vomiting after Complete Protection from Acute Nausea/Vomiting

Percent of Patients with Delayed Symptoms

IGAR, Support Care Cancer 8:229, 2000
Neurotransmitters / Therapies Associated With Emesis

Emetic Reflex

- Histamine
- GABA
- Dopamine/DA RAs
- Substance P/NK-1 receptor antagonists
- Cannabinoids
- Endorphins
- Acetylcholine
- Serotonin/5-HT₃ receptor antagonists

DA = dopamine; GABA = gamma-aminobutyric acid; NK = neurokinin; RAs = receptor antagonists.
Three Major Classes of Anti-Emetic Drugs

- **Steroids** (dexamethasone)
- **5HT\(_3\) receptor antagonists**
  - 2\(^{nd}\) generation: palonosetron (IV only)
    - T1/2 40 hours
    - Effective for both acute and delayed CINV as a single IV infusion
  - 1\(^{st}\) generation: ondansetron, granisetron (also in transdermal form), dolasetron (PO only)
    - Primarily effective for acute CINV, also for rescue
- **Neurokinin-1 antagonists**
  - Aprepitant (po x 3d), fosaprepitant (IV x 1)
  - Effective for delayed CINV when given with a 5HT\(_3\) RA
## Chemotherapy – Emesis Prevention

<table>
<thead>
<tr>
<th>HIGH EMETIC RISK</th>
<th>MODERATE EMETIC RISK</th>
<th>LOW EMETIC RISK</th>
<th>MINIMAL EMETIC RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (5-HT₃) antagonist: Dolasetron or Granisetron or Ondansetron or Palonosetron (preferred) AND Steroid* AND Neurokinin (NK₁) antagonist ± Lorazepam ± H2 blocker or PPI</td>
<td>Serotonin (5-HT₃) antagonist: Dolasetron or Granisetron or Ondansetron or Palonosetron (preferred) AND Steroid* WITH / WITHOUT Neurokinin (NK₁) antagonist† ± Lorazepam prn ± H2 blocker or PPI</td>
<td>Dexamethasone OR Metoclopramide OR Prochlorperazine ± Lorazepam prn ± H2 blocker or PPI</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

*Use of steroids is contraindicated with drugs such as interleukin-2 (IL-2, aldesleukin) and interferon
†As per high emetic risk prevention, an NK1 antagonist should be added (to dexamethasone and a 5-HT3 antagonist regimen) for selected patients receiving other chemotherapies of moderate emetic risk (e.g. carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate)

Recent data suggests that gabapentin may help prevent CINV (Cruz et al, 2012)
PPI = proton pump inhibitor

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Palonosetron vs. Ondansetron or Dolasetron (Breast Cancer Subset) – Complete Response

- 100% female; mean age 52 years; 63% chemotherapy-naïve
- Majority of women receiving cyclophosphamide and/or doxorubicin combination
- Concomitant dexamethasone pretreatment received by 2.6% of patients

**Experimental Design**
- Palonosetron 0.25 mg IV (n=242)
- Ondansetron 32 mg/Dolasetron 100 mg IV (n=234)

**Complete Response (No Emesis, No Rescue)** (% of Patients)

- **Acute: 0-24 (Day 1)**
  - Palonosetron: 54.7%
  - Ondansetron/Dolasetron: 63.2%
  - *p<0.025 (Fisher’s exact test)

- **Delayed: 24-120 (Days 2-5)**
  - Palonosetron: 39.7%
  - Ondansetron/Dolasetron: 58.7%
  - *p<0.001

- **Overall: 0-120 (Days 1-5)**
  - Palonosetron: 49.6%
  - Ondansetron/Dolasetron: 34.2%
  - *p<0.001

**Notes**

- Complete Response includes patients who did not experience emesis and did not require rescue medication.

**References**

Time Course of Emesis following Cisplatin with a 5-HT₃ Antagonist or Aprepitant

Hesketh, Support Care Cancer 10:365, 2002
SPECIAL TOPICS:

• Toxicity
• Patient perception
• Anticipatory emesis
• Breakthrough treatment
• Polymorphisms
Toxicity of Primary Agents

• 5HT3 receptor antagonists
  – Headache
  – Constipation
  – Prolonged QT

• NK1 receptor antagonist
  – Drug-drug interactions
    • Substrate, moderate inducer and moderate inhibitor of CYP3A4, and inducer of CYP2C9
    • More with oral form than IV due to 1\textsuperscript{st} pass metabolism
    • Most important: coumadin
Perception vs Reality
Highly Emetogenic Chemotherapy

Percent of patients

Acute Nausea
Acute Vomiting
Delayed Nausea
Delayed Vomiting

MD/RN Prediction
Patient Experience

Grunberg, Cancer 100:2261, 2004
Anticipatory Emesis

- Prevention is critical
  - Use optimal antiemetic therapy during every cycle of treatment
- Behavioral therapy
  - Relaxation/desentization
  - Hypnosis/guided imagery
  - Music therapy
- Acupuncture/acupressure
- Alprazolam or lorazepam the night before and morning of treatment
## Breakthrough Treatment

**General principle: add one agent from a different drug class sequentially**

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine</td>
<td>Lorazepam 0.5-2 mg PO or IV q 4-6h</td>
</tr>
<tr>
<td>Cannabinoid</td>
<td>Dronabinol 5-10 mg PO q 3-6h</td>
</tr>
<tr>
<td></td>
<td>Nabilone 1-2 mg PO BID</td>
</tr>
<tr>
<td>Other</td>
<td>Haloperidol 0.5-2 mg</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide 10-40 mg PO/IV q 4-6h</td>
</tr>
<tr>
<td></td>
<td>Olanzapine 10 mg PO qd x 3</td>
</tr>
<tr>
<td></td>
<td>Scopolamine patch q 72h</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>Prochlorperazine 25 mg supp PR q 12h or 10 mg PO/IV q 6h</td>
</tr>
<tr>
<td></td>
<td>Promethazine 12.5-25 mg PO/IV q 4h</td>
</tr>
<tr>
<td>Serotonin 5-HT3 RA</td>
<td>Dolasetron 100 mg PO qd</td>
</tr>
<tr>
<td></td>
<td>Granisetron 1-2 mg PO qd /1 mg PO BID/ 0.01 mg/kg (max 1 mg) IV</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 16 mg PO/IV qd</td>
</tr>
<tr>
<td>Steroid</td>
<td>Dexamethasone 12 mg PO/IV daily</td>
</tr>
<tr>
<td>Neurokinin-1 RA</td>
<td>Add aprepitant/fosaprepitant to subsequent cycles</td>
</tr>
</tbody>
</table>
Cyp3A4 Polymorphisms and Emesis: Population Effects with Granisetron Based Therapy

Conclusions

• Antiemetic control has been a highly successful area of cancer supportive care
• Better understanding of mechanisms of action will allow identification of improved antiemetics and more effective therapy
• Nausea remains a significant problem
• The ultimate goal remains Total Control of chemotherapy-induced nausea and vomiting
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