Optimizing Prevention & Treatment Strategies in the Management of Chemotherapy Induced Nausea & Vomiting (CINV)

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Objectives

- Safety and efficacy of novel therapies and advanced approaches to prevent CINV
- Evaluate effective treatment strategies for improving outcomes
- Review updates of current guidelines
  - Accepted management strategies
- Updated information on antiemetic agents
Nausea and Vomiting

Prevention and Control of CINV
Mechanisms of CINV

Mechanisms of Chemotherapy-Induced Nausea and Vomiting

Central
Chemotherapy
Peripheral
Mechanisms of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy

Peripheral

Enterochromaffin cell

Serotonin release

Mechanisms of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy

Peripheral

Enterochromaffin cell

Serotonin release

Vagal afferent 5-HT$_3$ receptors
Mechanisms of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy

Peripheral

Central

Dorsal vagal complex
Area postrema

Enterochromaffin cell

Serotonin release

Vagal afferent 5-HT₃ receptors

Brainstem
NK₁ receptors
Substance P

Dorsal vagal complex
Area postrema

Enterochromaffin cell

Serotonin release

Vagal afferent 5-HT₃ receptors
Neurotransmitters Involved in CINV

- Substance P
- Histamine
- Serotonin
- Endorphins
- Acetylcholine
- Dopamine
- GABA*

*Gamma-aminobutyric acid

CINV: Differential Involvement of Neurotransmitters Over Time

<table>
<thead>
<tr>
<th>Acute (Day 1)</th>
<th>Delayed (Days 2–5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly serotonin-independent mechanisms (peripheral)</td>
<td>Predominantly substance P–dependent mechanisms (central)</td>
</tr>
</tbody>
</table>

0 8 12 24 48 72 96 120

Hours After Cisplatin

Risk Factors for CINV

Risk Factors Related to the Patient

- Low alcohol consumption (< 10 drinks/week)
- Younger age (< 50 y.o.)
- Female gender
- History of motion sickness
- Poor control with prior chemotherapy
Classification of Acute Emetogenic Potential of Single Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Emetogenicity</th>
<th>% of Emesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Moderate</td>
<td>30 – 90%</td>
</tr>
<tr>
<td>Low</td>
<td>10 – 30%</td>
</tr>
<tr>
<td>Minimal</td>
<td>&lt; 10%</td>
</tr>
</tbody>
</table>

Single Chemotherapeutic Agents with Highest Potential for Acute Emesis

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;90% Frequency of Emesis)</td>
<td>AC combination</td>
</tr>
<tr>
<td></td>
<td>Carmustine &gt; 250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Cisplatin &gt; 50 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide &gt; 1,500 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin &gt; 60 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Epirubicin &gt; 90 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide &gt; 10 g/m²</td>
</tr>
<tr>
<td></td>
<td>Mechlorethamine</td>
</tr>
<tr>
<td></td>
<td>Streptozocin</td>
</tr>
</tbody>
</table>
# Emetic Potential of Oral Chemotherapy Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to High</td>
<td>Altretamine, Busulfan &gt; 4 gm/day, Cyclophosphamide &gt; 100 mg/m²/day, Estramustine, Etoposide, Lomustine (single day), Procarbazine, Temozolomide &gt; 75 mg/m²/day</td>
</tr>
</tbody>
</table>

## Single Chemotherapeutic Agents with Moderate Potential for Acute Emesis

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (30-90% Frequency of Emesis)</td>
<td>Aldesleukin &gt; 12-15 mill IU/m², Amifostine &gt; 300 mg/m², Arsenic trioxide, Azacitadine, Bendamustine, Busulfan, Carboplatin, Carmustine &lt; 250 mg/m², Cisplatin &lt; 50 mg/m², Clofarabine, Cyclophosphamide &lt; 1,500 mg/m², Cytarabine &gt; 200 mg/m², Daunorubicin, Doxorubicin &lt; 60 mg/m², Epirubicin &lt; 90 mg/m², Idarubicin, Ifosfamide &lt; 10 g/m², Interferon&gt; 10 mill IU/m², Irinotecan, Melphalan, Methotrexate&gt; 250 mg/m², Oxaliplatin, Temozolomide</td>
</tr>
</tbody>
</table>
### Single Chemotherapeutic Agents with Low Potential for Acute Emesis

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
</table>
| Low (10-30% Frequency of Emesis) | Amifostine < 300 mg  
Aldesleukin < 12 mill IU/m²  
Cabazitaxel  
Cytarabine (low dose) 100-200 mg/m²  
Docetaxel  
Doxorubicin (liposomal)  
Eribulin  
Etoposide  
5-Fluorouracil  
Flouxuridine  
Gemcitabine  
Interferon > 5 < 10 mill IU/m²  
Ixabepilone |
|                        | Methotrexate > 50 < 250 mg/m²  
Mitomycin  
Mitoxantrone  
Paclitaxel  
Paclitaxel-albumin  
Pemetrexed  
Pentostatin  
Pralatrexate  
Romidepsin  
Thiotepa  
Topotecan |

### Single Chemotherapeutic Agents with Minimal Potential for Acute Emesis

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
</table>
| Minimal (<10% Frequency of Emesis) | Alemtuzumab  
Asparaginase  
Bevacizumab  
Bleomycin  
Bortezomib  
Cetuximab  
Cladribine  
Cytarabine < 100 mg/m²  
Decitabine  
Denileukin diftitox  
Dexrazoxane  
Fludarabine  
Interferon < 5 mill IU/m²  
Iplimumab |
|                        | Methotrexate < 50 mg/m²  
Nelarabine  
Ofatumumab  
Pamitumumab  
Pagaspargase  
Peginterferon  
Rituximab  
Temsirolimus  
Trastuzumab  
Valrubicin  
Vinblastine  
Vincristine  
Vinorelbine |
## Emetic Potential of Oral Chemotherapy Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal to Low</td>
<td>Bexarotene</td>
</tr>
<tr>
<td></td>
<td>Busulfan &lt; 4 mg/day</td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide &lt;100 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td>Everolimus</td>
</tr>
<tr>
<td></td>
<td>Fludarabine</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
</tr>
<tr>
<td></td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
</tr>
<tr>
<td></td>
<td>Lapatinib</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
</tr>
<tr>
<td></td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td>Temozolomide &lt;75 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
</tr>
<tr>
<td></td>
<td>Thioguanine</td>
</tr>
<tr>
<td></td>
<td>Topotecan</td>
</tr>
<tr>
<td></td>
<td>Tretinoin</td>
</tr>
<tr>
<td></td>
<td>Vandetanib</td>
</tr>
<tr>
<td></td>
<td>Vorinostat</td>
</tr>
</tbody>
</table>

## Emetigenicity of Commonly Used Combination Regimens

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Commonly Used Combinations</th>
<th>Chemotherapy Agents</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>AC</td>
<td>Doxorubicin Cyclophosphamide</td>
<td>High</td>
</tr>
<tr>
<td>Breast</td>
<td>CMF</td>
<td>Cyclophosphamide Methotrexate Fluorouracil</td>
<td>Moderate</td>
</tr>
<tr>
<td>Non-Small-Cell Lung</td>
<td>Carboplatin/ Paclitaxel</td>
<td>Carboplatin Paclitaxel</td>
<td>High</td>
</tr>
<tr>
<td>Colorectal</td>
<td>FOLFOX</td>
<td>5FU Leucovorin Oxaliplatin</td>
<td>Moderate</td>
</tr>
<tr>
<td>Colorectal</td>
<td>FOLFIRI</td>
<td>5FU Leucovorin Irinotecan</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Prevalence and Impact of CINV

- 70-80% of patients receiving chemotherapy
- Delayed CINV: up to 80% of patients 24-72 hours after receiving chemotherapy
- Anticipatory CINV: 14-63% of patients
  - Median of 33%
Side Effects Most Distressing to Patients Undergoing Emetogenic Chemotherapy

Identical Surveys Conducted Before and After the Availability of 5-HT₂ Antagonists Show Little Change in Patient Perceptions

<table>
<thead>
<tr>
<th>Rank</th>
<th>Symptoms</th>
<th>Rank</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
<td>1</td>
<td>Nausea</td>
</tr>
<tr>
<td>2</td>
<td>Nausea</td>
<td>2</td>
<td>Loss of hair</td>
</tr>
<tr>
<td>3</td>
<td>Loss of hair</td>
<td>3</td>
<td>Vomiting</td>
</tr>
</tbody>
</table>


Treatment of CINV
Highly Emetogenic Chemotherapy: NCCN Guidelines, 2014

The Big Three

- Serotonin Antagonist
- Steroid
- Neurokinin 1 (NK1) Antagonist
  - +/- Lorazepam, or H2 blocker, or proton pump inhibitor
Serotonin Antagonists

Dolasetron 100 mg po  or
Granisetron
- 2 mg po or 1 mg po bid
- .01 mg/kg (max 1 mg) IV
- Transdermal patch 3.1 mg/24 hr patch q 7 days
  - Apply 24 – 48 hrs before chemotherapy  or
Ondansetron
- 16-24 mg po
- 8-16 mg IV  or
Palonosetron 0.25 mg IV (preferred)
### Palonosetron

- 5-HT<sub>3</sub> receptor antagonist synthesized to have a prolonged duration of action
- Beneficial features
  - Long half-life: ~40 hours vs 4–8 hours
  - Greater receptor binding affinity: 100-fold higher

### Palonosetron vs Ondansetron in Highly Emetic Chemotherapy

- Randomized, multicenter, double-blind, stratified, parallel-arm trial
- Active comparator trial
  - Palonosetron 0.25 mg IV
  - Palonosetron 0.75 mg IV
  - Ondansetron 32 mg IV
- Dexamethasone used on day 1 prior to chemotherapy at investigator’s discretion

Subset Analysis of Patients Receiving Dexamethasone (N = 447)

Complete response (%)

Acute (0–24 h) | Delayed (24–120 h) | Overall (0-120 h)
---|---|---
Palonosetron 0.25 mg + dex | 64.7 | 42.0 | 40.7
Palonosetron 0.75 mg + dex | 62.7 | 41.3 | 35.3
Ondansetron 32 mg + dex | 55.8 | 28.6 | 25.2

*97.5% CI for differences between palonosetron 0.25 mg and ondansetron 32 mg indicates palonosetron superiority


Add a Steroid
Steroid

- Dexamethasone
  - Day #1: 12 mg po or IV
  - Day #2-4: 8 mg po qd
    - If given with NK1 antagonist aprepitant pills orally for 3 days (125, 80, 80 mg)
    - If given with fosaprepitant 150 mg IV on Day #1, give 8 mg po bid on days 3-4

The effect of adding dexamethasone to 5-HT₃ antagonists for acute emesis

Jantunen et al, Eur J Cancer 1997; 33: 66

![Graph showing the effect of adding dexamethasone to 5-HT₃ antagonists](image-url)
Delayed Nausea and Vomiting

- Meta-analysis of 32 randomized controlled trials with 5,613 patients (J Clin Oncol, 2000, Ioannidis et al)
  - The data suggested superiority of dexamethasone over a serotonin antagonist for preventing delayed emesis

NK1 Antagonist
Aprepitant: Mechanism of Action

- Selective high affinity antagonist of human substance P/neurokinin 1 (NK1) receptors
- Little or no affinity for serotonin, dopamine, and corticosteroid receptors
- Animal and human PET scan studies show that it crosses the blood brain barrier and occupies brain NK1 receptors

Aprepitant Blocks Brain NK₁ Receptors in Humans

Binding of PET tracer to NK₁ receptors prior to aprepitant dosing

Blockade of NK₁ receptors after aprepitant dosing
**NK1 Antagonist**

- **Aprepitant (oral)**
  - Day #1: 125 mg po
  - Days #2-3: 80 mg po qd
- **Fosaprepitant 150 mg (IV)**
  - Day#1 only

**Aprepitant in Patients Receiving Cisplatin: 2 Randomized Trials**

Randomize

- Ondansetron + Dexamethasone
- Ondansetron + Dexamethasone + Aprepitant

**Versus**

Aprepitant Phase III Trial 052: Complete Response (N = 520)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Aprepitant treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (days 1–5)*</td>
<td>52</td>
<td>73</td>
</tr>
<tr>
<td>Acute (day 1)*</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Delayed (days 2–5)*</td>
<td>56</td>
<td>75</td>
</tr>
</tbody>
</table>

Complete response (%)

*P < 0.001


Recent Addition to NCCN Guidelines for Highly Emetogenic Chemotherapy
**Olanzapine**

- Olanzapine: atypical antipsychotic
  - FDA indications: schizophrenia, bipolar disorder
- Blocks multiple neurotransmitters
  - Dopamine
  - Serotonin
  - Catecholamines
  - Acetylcholine
  - Histamine
- Side effects: sedation, weight gain

**Olanzapine-containing regimen**

- Olanzapine 10 mg p.o. days #1-4 (instead of an NK1 antagonist)
- Palonosetron 0.25 mg IV day #1
- Dexamethasone 20 mg IV day #1
  - +/- Lorazepam, or H2 blocker, or proton pump inhibitor
Olanzapine for Highly Emetogenic Chemotherapy: Complete Response
Navari, J Supp Oncol, 2011

- 251 pts
- Olanzapine p.o.
- Palonosetron
- Dexamethasone
- CR: No emesis, no rescue
- 97% (acute)
- 77% (delayed)
- Aprepitant p.o.
- Palonosetron
- Dexamethasone
- CR: No emesis, no rescue
- 87% (acute)
- 73% (delayed)

Olanzapine for Highly Emetogenic Chemotherapy: No Nausea
Navari, J Supp Oncol, 2011

- 251 pts
- Olanzapine p.o.
- Palonosetron
- Dexamethasone
- No nausea
- 87% (acute)
- 69% (delayed)
- Aprepitant p.o.
- Palonosetron
- Dexamethasone
- No nausea
- 87% (acute)
- 38% (delayed)
Olanzepine Warning

- Olanzepine must be used with caution in elderly patients
- Black box warning: Increased mortality in patients with dementia-related psychosis

Other Guidelines
Highly Emetogenic Chemotherapy

- ASCO (American Society of Clinical Oncology)
  - Last updated 2011
  - Does not include olanzapine
- MASCC (Multinational Association of Supportive Care in Cancer)
  - Last updated January, 2013
  - Does not include olanzapine
Moderately Emetogenic Chemotherapy: NCCN Guidelines, 2014

The Big Three – With Some Differences

- Serotonin Antagonist
- Steroid
- Neurokinin 1 Antagonist (Sometimes)
- Day #2-3 treatment is different
Moderately Emetogenic Chemotherapy: Day #1

- Serotonin Antagonist
  - Same as Highly Emetogenic Chemotherapy
- Steroid
  - Same as Highly Emetogenic Chemotherapy
- NK1 Antagonist
  - For select patients receiving carboplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate

Different on Days #2-3

- Serotonin antagonist monotherapy
  - Continue the serotonin antagonist given on day #1
  - Palonosetron, which is long acting, only needs to be dosed on Day #1
    OR
- Steroid monotherapy
  - Dexamethasone 8 mg po or IV qd
    OR
- NK1 antagonist (if used on Day #1) +/- steroid
New Addition to NCCN Guidelines for Moderate Emetogenicity

- Addition of the Olanzepine/palonosetron/dexamethasone regimen as an alternative treatment

Palonosetron vs Ondansetron in Moderately Emetic Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Palonosetron 0.25 mg</th>
<th>Palonosetron 0.75 mg</th>
<th>Ondansetron 32 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (0–24 h)</td>
<td>81.0</td>
<td>73.5</td>
<td>68.6</td>
</tr>
<tr>
<td>Delayed (24–120 h)</td>
<td>74.1</td>
<td>64.6</td>
<td>55.1</td>
</tr>
<tr>
<td>Overall (0–120 h)</td>
<td>69.3</td>
<td>58.7</td>
<td>50.3</td>
</tr>
</tbody>
</table>

* 97.5% CIs for the difference vs ondansetron indicates superiority ($P < 0.025$)

Aprepitant in Moderately Emetogenic Chemotherapy (N=857)

**Complete Response (CR): no emesis and no rescue medication.**


<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Aprepitant (n=433)</th>
<th>Standard (n=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: 0-24</td>
<td><strong>76</strong></td>
<td><strong>69</strong></td>
</tr>
<tr>
<td>(Day 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed: 24-120</td>
<td><strong>55</strong></td>
<td><strong>49</strong></td>
</tr>
<tr>
<td>(Days 2-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall: 0-120</td>
<td><strong>51</strong></td>
<td><strong>42</strong></td>
</tr>
<tr>
<td>(Days 1-5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Acute: 0-24 (Day 1)**

**Delayed: 24-120 (Days 2-5)**

**Overall: 0-120 (Days 1-5)**

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Aprepitant in Moderately Emetogenic Chemotherapy: % Patients with No Nausea

**Nausea-Free (% of Patients)**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Aprepitant (n=430)</th>
<th>Standard (n=424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: 0-24</td>
<td><strong>61</strong></td>
<td><strong>59</strong></td>
</tr>
<tr>
<td>(Day 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed: 24-120</td>
<td><strong>37</strong></td>
<td><strong>36</strong></td>
</tr>
<tr>
<td>(Days 2-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall: 0-120</td>
<td><strong>33</strong></td>
<td><strong>33</strong></td>
</tr>
<tr>
<td>(Days 1-5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other Guidelines
Moderately Emetogenic Chemotherapy

- ASCO and MASCC
  - Palonosetron, Day #1
    - May substitute another serotonin antagonist
  - Dexamethasone, Days #1-3

Low Emetic Risk
Chemotherapy:
NCCN Guidelines, 2014
Low Emetic Risk Chemotherapy

Day 1 – Start before chemotherapy
Repeat daily for multiday doses of chemotherapy
- Dexamethasone 12 mg po/IV q.d.  \textit{or}
- Metoclopramide 10-40 mg po/IV, then q 4-6hr prn  \textit{or}
- Prochlorperazine 10 mg po/IV, then q 4-6 hr prn  \textit{or}
- Serotonin antagonist
  - Dolasetron, granisetron, or ondansetron
- +/- Lorazepam 0.5-2 mg po/IV q 4-6 hrs prn
- +/- H2 blocker or proton pump inhibitor

Other Guidelines
Low Emetogenicity Chemotherapy

- ASCO
  - Dexamethasone, single 8 mg dose before chemotherapy
- MASCC
  - No difference
Minimal Emetic Risk Chemotherapy: NCCN Guidelines, 2014

Minimal Emetic Risk Chemotherapy

No routine prophylaxis
Other Guidelines
Minimal Emetogenicity Chemotherapy

- ASCO and MASCC
  - No difference

Oral Chemotherapy: NCCN Guidelines
**Oral Chemotherapy:**
**High to Moderate Emetic Risk**

Start before chemotherapy and continue daily

- Serotonin antagonist
  - Dolasetron 100 mg po qd
  - Granisetron 2 mg po qd or 1 mg po bid
  - Ondansetron 16-24 mg po qd
- +/- Lorazepam 0.5-2 mg po or sub-lingual q 4-6 hrs prn
- +/- H2 blocker or proton pump inhibitor

**Oral Chemotherapy:**
**Low to Minimal Emetic Risk**

Start before chemotherapy and then prn

- Metoclopramide 10-40 mg po and then q 4-6 hrs prn
- Prochlorperazine 10 mg po and then q 4-6 hrs prn
- Haloperidol 1-2 mg po and then q 4-6 hrs prn
- Serotonin antagonist
  - Dolasetron, granisetron, or ondansetron
- +/- Lorazepam 0.5 – 2 mg po q 4-6 hrs prn
- +/- H2 blocker or proton pump inhibitor
Anticipatory Nausea: NCCN Guidelines

Anticipatory Nausea/Vomiting

- Prevention with optimal antiemetics
- Behavioral therapy
  - Relaxation techniques
  - Guided imagery
  - Music therapy
- Acupuncture/acupressure
- Alprazolam 0.5-2 mg po tid beginning on night before treatment or
- Lorazepam 0.5-2 mg po on night before and morning of treatment
Breakthrough Nausea: NCCN Guidelines

*Give an additional agent from another drug class p.r.n

- **Atypical antipsychotic**
  - Olanzapine 10 mg po qd x 3 days
- **Benzodiazepine**
  - Lorazepam 0.5-2 mg po or IV q 4-6 hrs
- **Cannabinoid**
  - Dronabinol 5-10 mg po q 3 or 6 hrs
  - Nabilone 1-2 mg po bid
Breakthrough Therapy

- Other
  - Haloperidol 0.5 – 2 mg po or IV q 4-6 hrs
  - Metoclopramide 10-40 mg po or IV q 4-6 hrs
  - Scopolamine 1 patch q 72 hours

- Phenothiazine
  - Prochlorperazine 25 mg supp pr q 12 hrs or 10 mg po/IV q 6 hrs
  - Promethazine 12.5 – 25 mg po or IV (central line only) q 4 hrs

Breakthrough Therapy

- Serotonin Antagonists
  - Dolasetron 100 mg po qd
  - Granisetron 1-2 mg po qd, or 1 mg po bid, or 0.01 mg/kg (max 1 mg) IV
  - Ondansetron 16 mg po or IV qd

- Steroid
  - Dexamethasone 12 mg po or IV qd
Future Improvements?

Rolapitant
NK-1 Receptor Antagonist

- Extended plasma half-life (180 hours)
  - Phase II testing: Single dose provides 5-day coverage
- Currently in Phase III testing of oral drug
- 3 randomized, double-blind, placebo controlled trials
  - 2 in HEC (1,060 pts)
  - 1 in MEC (1,350 pts)
Rolapitant
(ASCO poster #94928, 2012)

- Randomized trial in Argentina
- 454 patients receiving highly emetogenic chemotherapy
- Ondansetron + dexamethasone plus:
  - Placebo
  - Rolapitant 10mg
  - Rolapitant 25 mg
  - Rolapitant 100 mg
  - Rolapitant 200 mg

Rolapitant Results
(ASCO poster #94928, 2012)

<table>
<thead>
<tr>
<th></th>
<th>Complete Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>Rolapitant 200 mg</td>
</tr>
<tr>
<td>Overall</td>
<td>47%</td>
</tr>
<tr>
<td>Acute</td>
<td>67%</td>
</tr>
<tr>
<td>Delayed</td>
<td>49%</td>
</tr>
</tbody>
</table>

No Significant Nausea

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>42%</td>
</tr>
<tr>
<td>Acute</td>
<td>73%</td>
</tr>
<tr>
<td>Delayed</td>
<td>48%</td>
</tr>
</tbody>
</table>
Netupitant

- Netupitant: highly selective NK-1 antagonist
- NEPA: oral combination product
  - Netupitant 300 mg + palonosetron 0.50 mg

NEPA Clinical Trial

- Clinical trial
  - 694 pts, Cisplatin chemotherapy
- Palonosetron .5 mg p.o.
- NEPA 100
- NEPA 200
- NEPA 300
- Ondansetron + aprepitant
- All patients received dexamethasone
**NEPA trial: Results**

Complete Response (No emesis or rescue)

<table>
<thead>
<tr>
<th></th>
<th>Complete Response</th>
<th>No Significant Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palonosetron:</td>
<td>76.5%</td>
<td>79.4%</td>
</tr>
<tr>
<td>NEPA 100:</td>
<td>87.4%</td>
<td>80%</td>
</tr>
<tr>
<td>NEPA 200:</td>
<td>87.6%</td>
<td>86.1%</td>
</tr>
<tr>
<td><strong>NEPA 300:</strong></td>
<td><strong>89.6%</strong></td>
<td><strong>89.6%</strong></td>
</tr>
<tr>
<td>Ondans + Aprep:</td>
<td>86.6%</td>
<td>85.8%</td>
</tr>
</tbody>
</table>

**NEPA Randomized Trial**

Annals of Oncology Advance Access, March 5, 2014

- 1455 patients receiving AC chemotherapy
- NEPA + dexamethasone
- Palonosetron + dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>Complete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NEPA</td>
</tr>
<tr>
<td>Overall</td>
<td>74%</td>
</tr>
<tr>
<td>Acute</td>
<td>88%</td>
</tr>
<tr>
<td>Delayed</td>
<td>77%</td>
</tr>
</tbody>
</table>
Randomized placebo controlled trial
- HEC and MEC, 80 pts
- Ondansetron 8 mg + dexamethasone 10 mg + ranitidine 50 mg
  - Gabapentin 300 mg
    - Days -5 and -4: 300 mg qd
    - Days -3 and -2: 300 mg bid
    - Days -1 and 0: 300 mg tid

**Gabapentin**
Cruz, Support Care Cancer, 2012

**CR acute**
- Gabapentin: 62%
- Placebo: 40%

Of those patients who had CR acute

**CR delayed**
- Gabapentin: 89%
- Placebo: 60%
Gabapentin, Randomized Trial
(ASCO abstract, 2013, Barton et al)

- 430 patients with HEC
- Day #1: Serotonin antagonist + dexamethasone
- Days #2-4
  - Gabapentin 300 mg b.i.d. + dex vs.
  - Placebo + dex
- Complete response
  - Gabapentin 47%
  - Placebo 41% (p=.23)

Consequences of Untreated CINV
Impact of CINV on Health-Related Quality of Life: Functional Living Index–Emesis (FLIE)

Uncontrolled CINV

- Financial costs
  - Nursing time
  - Physician time
  - Phone assessments
  - Antiemetic rescue medication
  - Additional office visits
  - Visits to the Emergency Room
  - I.V. hydration
  - Hospital admission
Uncontrolled CINV

- Quality of life costs
  - One of the most distressing side effects – nausea
  - Dread of future chemotherapy can lead to anticipatory nausea – increased amount of time dealing with this symptom
  - Chemo may have to be stopped or delayed
  - Loss of days at work

Resource Utilization and Costs
Burke et al, Support Care Cancer, 2011

- Retrospective cohort study
- 2003-2007
- Premier Perspective Database
- Hospital visits with CINV related diagnosis
  - From chemo administration through 30 days, or until 1 day prior to next chemo cycle
- 19,139 pts from 257 hospital outpatient facilities
  - HEC – 16%
  - MEC – 84%
Resource Utilization and Costs
Burke et al, Support Care Cancer, 2011

- 13.8% of pts had CINV-associated visit
  - HEC 18%, MEC 13%
- 0.2% acute CINV, 13.6% delayed CINV

<table>
<thead>
<tr>
<th>Site of Visit</th>
<th>% of Pts</th>
<th>Mean Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>64%</td>
<td>$7,448</td>
</tr>
<tr>
<td>Outpatient</td>
<td>26%</td>
<td>$1,494</td>
</tr>
<tr>
<td>Emergency Room</td>
<td>10%</td>
<td>$ 918</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>$5,299</td>
</tr>
</tbody>
</table>

Medical Claims/Work Loss
Shih et al, Cancer, 2007

- Employees or spouses with cancer
- HEC or MEC
- Data set linking medical claims to work loss
- 25% of pts required medical care for uncontrolled CINV
- 2% had Emergency Room visits
Medical Claims/Work Loss
Shih et al, Cancer, 2007

<table>
<thead>
<tr>
<th></th>
<th>Controlled (1563)</th>
<th>Uncontrolled, Office visit, No ER (471)</th>
<th>Uncontrolled, Office Visit, ER (37)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct Costs (Mean)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$8,132</td>
<td>$10,376</td>
<td>$12,810</td>
</tr>
<tr>
<td>Inpatient</td>
<td>$1,761</td>
<td>$2,500</td>
<td>$4,350</td>
</tr>
<tr>
<td>Outpatient</td>
<td>$5,958</td>
<td>$7,212</td>
<td>$7,718</td>
</tr>
<tr>
<td>Outpatient Prescription Drugs</td>
<td>$412</td>
<td>$663</td>
<td>$743</td>
</tr>
<tr>
<td><strong>Indirect Costs (Productivity Loss)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of employees</td>
<td>829</td>
<td>255</td>
<td>24</td>
</tr>
<tr>
<td>Work loss days</td>
<td>6.1 days</td>
<td>7.2 days</td>
<td>8.9 days</td>
</tr>
</tbody>
</table>

**Principles of Emesis Control**

- Prevention is the goal
- Guidelines should be followed
- Risk of CINV lasts for at least 4 days for highly or moderately emetogenic chemotherapy
- Oral = IV
- Use lowest recommended dose
- Costs of uncontrolled CINV (financial and human) are substantial
Thank You