Current and Emerging Therapeutic Options in the Management of Chemotherapy-Induced Nausea and Vomiting (CINV)

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Objectives

- Mechanisms of CINV
- Patient and treatment-related risk factors
- Strategies to improve patient communication and CINV assessment in order to improve patient outcomes
- Guideline-based best practice recommendations
Nausea and Vomiting

Mechanisms of CINV
Mechanisms of Chemotherapy-Induced Nausea and Vomiting

- Central
- Peripheral

Chemotherapy

- Enterochromaffin cell
- Serotonin release

Mechanisms of Chemotherapy-Induced Nausea and Vomiting
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
- Central
- Dorsal vagal complex
- Area postrema
- Enterochromaffin cell
- Serotonin release
- Vagal afferent 5-HT$_3$ receptors
Mechanisms of Chemotherapy-Induced Nausea and Vomiting

- Brainstem NK\(_1\) receptors
- Substance P
- Dorsal vagal complex
- Area postrema
- Enterochromaffin cell
- Serotonin release
- Vagal afferent 5-HT\(_3\) receptors

**Neurotransmitters Involved in CINV**

- Substance P
- Histamine
- Serotonin
- Endorphins
- Acetylcholine
- GABA\(^*\)
- Dopamine

\(^*\)Gamma-aminobutyric acid.

Acute Vs. Delayed CINV

- **Acute CINV**
  - Nausea and vomiting that occurs within the first 24 hours after administration of chemotherapy

- **Delayed CINV**
  - Nausea and vomiting starting more than 24 hours after administration of chemotherapy, typically lasting 3-4 days

CINV: Differential Involvement of Neurotransmitters Over Time

![Diagram showing the involvement of neurotransmitters over time](image.png)
Types of CINV

- **Anticipatory CINV**
  - Conditioned response, happens after a negative past experience with chemotherapy

- **Breakthrough CINV**
  - Occurs despite appropriate prophylaxis, and requires rescue

- **Refractory CINV**
  - Repeated need for rescue when prior rescue efforts have failed

Risk Factors for CINV
Risk Factors

Which of the following is a risk factor for CINV?
- A. Male gender
- B. Heavy alcohol consumption
- C. Age < 50
- D. Smoker
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>
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</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</td>
<td>AC combination</td>
</tr>
<tr>
<td></td>
<td>Carmustine &gt; 250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</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; 2 g/m²</td>
</tr>
<tr>
<td></td>
<td>Mechlorethamine</td>
</tr>
<tr>
<td></td>
<td>Streptozocin</td>
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</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</td>
<td>Aldesleukin &gt; 12-15 mill IU/m²</td>
</tr>
<tr>
<td></td>
<td>Amifostine &gt; 300 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Arsenic trioxide</td>
</tr>
<tr>
<td></td>
<td>Azacitadine</td>
</tr>
<tr>
<td></td>
<td>Bendamustine</td>
</tr>
<tr>
<td></td>
<td>Busulfan</td>
</tr>
<tr>
<td></td>
<td>Carboptatin</td>
</tr>
<tr>
<td></td>
<td>Carmustine &lt; 250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Clofarabine</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide &lt; 1,500 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Cytarabine &gt; 200 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Dactinomycin</td>
</tr>
<tr>
<td></td>
<td>Daunorubicin</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin &lt; 60 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Epirubicin &lt; 90 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Idarubicin</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide &lt; 2 g/m²</td>
</tr>
<tr>
<td></td>
<td>Interferon &gt; 10 mill IU/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
</tr>
<tr>
<td></td>
<td>Melphalan</td>
</tr>
<tr>
<td></td>
<td>Methotrexate &gt; 250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>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)** | Ado-trastuzumab emtansine  
Amifostine < 300 mg  
Aldesleukin < 12 mill IU/m²  
Belinostat  
Blinatumomab  
Brentuximab vedotin  
Cabazitaxel  
Carfilzomib  
Cytarabine (low dose) 100-200 mg/m²  
Docetaxel  
Doxorubicin (liposomal)  
Eribulin  
Etoposide  
5-Fluorouracil  
Floxuridine  
Gemcitabine  
Interferon > 5 < 10 mill IU/m²  
Ixabepilone  
Methotrexate >50 <250 mg/m²  
Mitomycin  
Mitoxantrone  
Omacetaxine  
Paclitaxel  
Paclitaxel-albumin  
Pemetrexed  
Pentostatin  
Pralatrexate  
Romidepsin  
Thiotepa  
Topotecan  
Ziv-aflibercept |
| **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  
Ipilimumab  
Methotrexate < 50 mg/m²  
Nelarabine  
Nivolumab  
Obinutuzumab  
Ofatumumab  
Panitumumab  
Pagaspargase  
Peginterferon  
Pembrolizumab  
Pertuzumab  
Ramucirumab  
Rituximab  
Siltuximab  
Temsirolimus  
Trastuzumab  
Valrubicin  
Vinblastine  
Vincristine  
Vincristine (liposomal)  
Vinorelbine |
## Emetic Potential of Oral Chemotherapy Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate to High</strong></td>
<td>Altretamine</td>
</tr>
<tr>
<td></td>
<td>Busulfan &gt; 4 gm/day</td>
</tr>
<tr>
<td></td>
<td>Ceritinib</td>
</tr>
<tr>
<td></td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide &gt; 100 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Estramustine</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
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<tr>
<td></td>
<td>Lenvatinib</td>
</tr>
<tr>
<td></td>
<td>Lomustine (single day)</td>
</tr>
<tr>
<td></td>
<td>Mitotane</td>
</tr>
<tr>
<td></td>
<td>Olaparib</td>
</tr>
<tr>
<td></td>
<td>Panobinostat</td>
</tr>
<tr>
<td></td>
<td>Procarbazine</td>
</tr>
<tr>
<td></td>
<td>Temozolomide &gt; 75 mg/m²/day</td>
</tr>
<tr>
<td></td>
<td>Vismodegib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
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</thead>
<tbody>
<tr>
<td><strong>Minimal to Low</strong></td>
<td>Afatinib</td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
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<tr>
<td></td>
<td>Bexarotene</td>
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<tr>
<td></td>
<td>Busulfan &lt; 4 mg/day</td>
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<tr>
<td></td>
<td>Cabozantinib</td>
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<tr>
<td></td>
<td>Capecitabine</td>
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<tr>
<td></td>
<td>Chlorambucil</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide &lt;100 mg/m²/day</td>
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<tr>
<td></td>
<td>Dasatinib</td>
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<tr>
<td></td>
<td>Dabrafenib</td>
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<td></td>
<td>Erlotinib</td>
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<td></td>
<td>Everolimus</td>
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<tr>
<td></td>
<td>Fludarabine</td>
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<td></td>
<td>Gefitinib</td>
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<td></td>
<td>Hydroxyurea</td>
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<td></td>
<td>Ibrutinib</td>
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<tr>
<td></td>
<td>Idelalisib</td>
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<tr>
<td></td>
<td>Imatinib</td>
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<tr>
<td></td>
<td>Lapatinib</td>
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<tr>
<td></td>
<td>Lenalidomide</td>
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<td></td>
<td>Melphalan</td>
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<td></td>
<td>Mercaptopurine</td>
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<td></td>
<td>Methotrexate</td>
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<td>Nilotinib</td>
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<td></td>
<td>Palbociclib</td>
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<td></td>
<td>Pazopanib</td>
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<td>Pomalidomide</td>
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<td>Ponatinib</td>
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<tr>
<td></td>
<td>Regorafenib</td>
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<tr>
<td></td>
<td>Ruxolitinib</td>
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<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>Thioguaine</td>
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<tr>
<td></td>
<td>Topotecan</td>
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<td>Trametinib</td>
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<td></td>
<td>Tretinoin</td>
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<tr>
<td></td>
<td>Vandetanib</td>
</tr>
<tr>
<td></td>
<td>Vemurafenib</td>
</tr>
<tr>
<td></td>
<td>Vorinostat</td>
</tr>
</tbody>
</table>
Prevalence and Impact of CINV

Prevalence 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%
Perceptions and Reality: Moderately Emetogenic Chemotherapy

- MD/RN prediction
- Patient experience

Acute Nausea: 31% MD/RN, 47% Patient experience
Acute Vomiting: 17% MD/RN, 28% Patient experience
Delayed Nausea: 24% MD/RN, 57% Patient experience
Delayed Vomiting: 9% MD/RN, 41% Patient experience

MD/RN: Physicians and nurses from 6 oncology practices.
Patients: 75% women; 90% received agents with moderate emetogenic risk.


MASCC (Multinational Association of Supportive Care in Cancer) Antiemesis Tool (MAT)

- Purpose is to make sure that the patient communicates his/her complete experience with CINV to the health practitioner

- Page 1: Instructions
  - Definition of nausea and vomiting
  - Parking Lot question
    - How much difficulty did you have parking your car today?
MAT: Pt fills out Page 2 the day after chemo

- In the first 24 hours since chemo, did you have any vomiting? Yes/No
- If you vomited in the 24 hrs since chemo, how many times? ________
- In the 24 hours since chemo, did you have any nausea? Yes/No
- If you had any nausea, please circle or enter the number that most closely resembles your experience.
  __________________

MAT: Pt fills out Page 3, four days after chemo

- Did you vomit 24 hours or more after chemo? Yes/No
- If you vomited during this period, how many times? ________
- Did you have any nausea 24 hours or more after chemo? Yes/No
- If you had any nausea, please circle or enter the number that most closely resembles your experience.
  __________________
Treatment of CINV

Highly Emetogenic Chemotherapy

- Serotonin Antagonist
- NK-1 Receptor Antagonist or Olanzapine
- Steroid
Serotonin Antagonists

Serotonin Antagonist
Given on Day #1

- **Dolasetron** 100 mg po  
- **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  
- **Ondansetron**
  - 16-24 mg po
  - 8-24 mg (max 32 mg/day) IV  
- **Palonosetron** 0.25 mg IV
Palonosetron (Aloxi™)

- 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)

**Acute (0–24 h)**
- Palonosetron 0.25 mg + dex: 64.7%
- Palonosetron 0.75 mg + dex: 62.7%
- Ondansetron 32 mg + dex: 55.8%

**Delayed (24–120 h)**
- Palonosetron 0.25 mg + dex: 42.0%
- Palonosetron 0.75 mg + dex: 41.3%
- Ondansetron 32 mg + dex: 28.6%

**Overall (0–120 h)**
- Palonosetron 0.25 mg + dex: 40.7%
- Palonosetron 0.75 mg + dex: 35.3%
- Ondansetron 32 mg + dex: 25.2%

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


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**NK1 Antagonists**
NK1 Receptor Antagonists

- Aprepitant
  - Fosaprepitant is the IV prodrug formulation
- Rolapitant
- Netupitant
  - Part of a fixed combination with palonosetron in a capsule

Mechanism of Action

- Selective high affinity antagonist of human substance P/neurokinin 1 (NK1) 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

Tracer Binding
Low High

Aprepitant in Patients Receiving Cisplatin: 2 Randomized Trials

Randomize

Ondansetron + Dexamethasone

Versus

Ondansetron + Dexamethasone + Aprepitant

Aprepitant Phase III Trial 054: Complete Response (N = 523)

![Graph showing the comparison of complete response rates between control and Aprepitant treatment group.](image)

*P < 0.001


---

**Rolapitant**

- FDA approval granted on September 2, 2015
  - Indicated in combination with other antiemetic agents for prevention of delayed nausea and vomiting associated with initial and repeat courses of chemotherapy including, but not limited to, highly emetogenic chemotherapy
  - No induction of CYP3A4
  - 180-hour half-life
  - >90% receptor occupancy rate for 5 days

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*Note: The image contains the graph showing the complete response rates, which are not transcribed here.*
Rolapitant: 2 Randomized Trials in HEC Chemotherapy

Highly Emetogenic Chemotherapy

Granisetron 10 ug/kg + Dexamethasone 20 mg + Rolapitant 180 mg PO

Granisetron 10 ug/kg + Dexamethasone 20 mg + Placebo PO

**HEC1 (Modified Intention-to-Treat Population, n = 532)**

<table>
<thead>
<tr>
<th></th>
<th>Rolapitant (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed phase (&gt;24-120 hours)</td>
<td>73</td>
<td>56</td>
<td>.0006</td>
</tr>
<tr>
<td>Acute phase (0-24 hours)</td>
<td>84</td>
<td>74</td>
<td>.005</td>
</tr>
<tr>
<td>Overall phase (0-120 hours)</td>
<td>70</td>
<td>56</td>
<td>.001</td>
</tr>
</tbody>
</table>

**HEC2 (Modified Intention-to-Treat Population, n = 555)**

<table>
<thead>
<tr>
<th></th>
<th>Rolapitant (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed phase (&gt;24-120 hours)</td>
<td>70</td>
<td>62</td>
<td>.043</td>
</tr>
<tr>
<td>Acute (0-24 hours)</td>
<td>83</td>
<td>79</td>
<td>.233</td>
</tr>
<tr>
<td>Overall (0-120 hours)</td>
<td>68</td>
<td>60</td>
<td>.084</td>
</tr>
</tbody>
</table>

Rapoport BL, Lancet Oncology, Volume 16, September, 2015
Rolapitant: Randomized Trial in MEC Chemotherapy

<table>
<thead>
<tr>
<th>MEC1 (Modified Intention-to-Treat Population, n = 1369) CR Rate (No emesis, no rescue meds)</th>
<th>Rolapitant (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed phase (&gt;24-120 hours)</td>
<td>71</td>
<td>62</td>
<td>.0002</td>
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<tr>
<td>Acute phase (0-24 hours)</td>
<td>83</td>
<td>80</td>
<td>.143</td>
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<tr>
<td>Overall phase (0-120 hours)</td>
<td>69</td>
<td>58</td>
<td>.0001</td>
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</tbody>
</table>

NEPA

- Oral, fixed-dose combination of 2 drugs in 1 capsule
  - Netupitant 300 mg (NK1 RA)
  - Palonosetron 0.5 mg (Serotonin antagonist)
**NEPA**

- FDA approved on October 10, 2014
- Indicated for prevention of acute and delayed N/V associated with initial and repeat courses of chemotherapy, including, but not limited to, HEC
- Taken 1 hour before start of chemotherapy

1455 pts
AC chemo (MEC*)

- NEPA + dexamethasone 12 mg
- Oral Palonosetron + dexamethasone 20 mg
Overall Complete Response

**NEPA: Efficacy Results From 2 Randomized Phase 3 Clinical Trials: Cycle 1 Overall (0-120 hours) CR**

<table>
<thead>
<tr>
<th>AC MEC Study</th>
<th>NEPA + dexamethasone (n=724)</th>
<th>Oral palonosetron + dexamethasone (n=725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>74%</td>
<td>67%</td>
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<tr>
<td><strong>p = .001</strong></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple-Cycle Non-AC MEC + HEC Study</th>
<th>NEPA + dexamethasone (n=309)</th>
<th>Aprepitant + palonosetron + dexamethasone (no formal efficacy comparisons; included as exploratory) (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>81%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Olanzapine: Instead of an NK1-R Inhibitor?

Olanzapine vs. Aprepitant

HEC
251 pts

Palansetron +Dexamethasone + Aprepitant
(125/80/80 PO D# 1-3)

Palansetron +Dexamethasone + Olanzapine
(10 mg PO D# 1-4)

**Olanzapine vs. Aprepitant**

<table>
<thead>
<tr>
<th></th>
<th>CR acute</th>
<th>CR delayed</th>
<th>CR overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>87%</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>97%</td>
<td>77%</td>
<td>77%</td>
</tr>
</tbody>
</table>

**No Nausea**

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Delayed</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>87%</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>87%</td>
<td>69%</td>
<td>69%</td>
</tr>
</tbody>
</table>

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**Olanzapine vs Fosaprepitant for Chemoradiation**

- 100 pts with H&N or esophageal CA
- Radiation + Cisplatin + 5FU
- Palonosetron .25 IV + Dexamethasone
  - **Olanzapine** 10 mg PO D# 1-4
  - OR
  - **Fosaprepitant** 150 mg IV

Navari, ASCO abstract, 2015
Olanzapine vs Fosaprepitant for Chemoradiation

<table>
<thead>
<tr>
<th>Complete Response (No emesis, no rescue meds) (%)</th>
<th>Olanzapine</th>
<th>Fosaprepitant</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed</td>
<td>76</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>Acute</td>
<td>88</td>
<td>84</td>
<td>NS</td>
</tr>
<tr>
<td>Overall</td>
<td>76</td>
<td>73</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Nausea (%)</th>
<th>Olanzapine</th>
<th>Fosaprepitant</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed</td>
<td>71</td>
<td>41</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Acute</td>
<td>86</td>
<td>77</td>
<td>NS</td>
</tr>
<tr>
<td>Overall</td>
<td>71</td>
<td>41</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

Disclosure

- Olanzapine is approved by the FDA as an anti-psychotic
- It does not have an FDA indication as an antiemetic
Add a Steroid

Steroid: Dexamethasone

- **Day #1**
  - Aprepitant/Fosaprepitant: 12 mg
  - Rolapitant: 20 mg
  - Netupitant (NEPA): 12 mg
  - Olanzapine: 20 mg

- **Day #2-4**
  - Aprepitant, 8 mg q.d. D# 2-4
  - Fosaprepitant, 8 mg qd on D#2, then b.id. D#3-4
  - Rolapitant, 8 mg po bid on D# 2-4
  - Netupitant (NEPA): 8 mg qd on D# 2-4
  - Olanzapine: None
The effect of adding dexamethasone to 5-HT$_3$ antagonists for acute emesis

- Meta-analysis of randomized controlled trials
- Adding a serotonin antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis

Delayed Nausea and Vomiting
Highly Emetogenic Chemotherapy: NCCN Guidelines, 2015

3 Options

NCCN Guidelines for Acute/Delayed CINV
Highly Emetogenic Chemotherapy (HEC)

**Acute**

**Aprepitant- or rolapitant containing regimen**
- NK₁ antagonist
  - Aprepitant 125 mg PO, or
  - Fosaprepitant 150 mg IV once, or
  - Rolapitant 180 mg PO once

AND
- Serotonin (5-HT₃) antagonist
  - Dolasetron 100 mg PO once
  - Granisetron 2 mg PO once, or 1 mg PO twice per day, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24 h transdermal patch applied 24-48 h before chemotherapy
  - Ondansetron 16-24 mg PO once or 8-16 mg IV once
  - Palonosetron 0.25 mg IV once

**Steroid**
- If aprepitant/fosaprepitant: dexamethasone 12 mg PO/IV once
- If rolapitant: dex 20 mg PO/IV once

**Delayed**
- If aprepitant PO given on day 1, aprepitant 80 mg PO daily on days 2 and 3
- If fosaprepitant IV given on day 1, no further aprepitant needed on days 2 and 3

AND
- If aprepitant PO given on day 1, dexamethasone 8 mg PO/IV daily on days 2, 3, and 4
- If fosaprepitant IV given on day 1, dexamethasone 8 mg PO/IV once on day 2, then 8 mg PO/IV BID days 3 and 4
- If rolapitant is given on day 1, dexamethasone 8 mg PO/IV twice daily days 2, 3, 4
NCCN Guidelines for Acute/Delayed CINV
Highly Emetogenic Chemotherapy (HEC)

### Netupitant-containing regimen

<table>
<thead>
<tr>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netupitant 300 mg/palonosetron 0.5 mg PO once</td>
<td>Dexamethasone 8 mg PO/IV on days 2, 3, and 4</td>
</tr>
<tr>
<td>Dexamethasone 12 mg PO/IV once</td>
<td></td>
</tr>
</tbody>
</table>

### Olanzapine-containing regimen

<table>
<thead>
<tr>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine 10 mg PO once</td>
<td>Olanzapine 10 mg PO on days 2, 3, and 4</td>
</tr>
<tr>
<td>Palonosetron 0.25 mg IV once</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone 20 mg IV once</td>
<td></td>
</tr>
</tbody>
</table>
Moderately Emetogenic Chemotherapy: NCCN Guidelines, 2015

Identical to Highly Emetogenic (HEC) Guidelines

- Netupitant-containing regimen
- Olanzapine-containing regimen
- Rolapitant-containing regimen (small difference in dosing of dexamethasone on Days 2-3)
Similar to Highly Emetogenic Guidelines for Regimens containing Aprepitant/Fosaprepitant

Day #1

- Serotonin Antagonist
  - Same
- Steroid
  - Same
- NK1 Antagonist
  - Added only for select patients with additional risk factors or who have failed previous therapy with serotonin antagonist and steroid alone

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
- Aprepitant (if used on Day #1) +/- steroid
Low Emetic Risk Chemotherapy: NCCN Guidelines, 2015

Day 1 – Start before chemotherapy
Repeat daily for multiday doses of chemotherapy

- Dexamethasone 12 mg po/IV q.d.  
or
- Metoclopramide 10-40 mg po/IV, then q 4-6 hr prn  
or
- Prochlorperazine 10 mg po/IV, then q 4-6 hr prn  
or
- Serotonin antagonist
  - Dolasetron 100 mg po qd
  - Granisetron 1-2 mg po qd
  - Ondansetron 8-16 mg po qd
Minimal Emetic Risk Chemotherapy: NCCN Guidelines, 2015

No routine prophylaxis
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 1-2 mg po qd
  - Ondansetron 16-24 mg po qd
Oral Chemotherapy: Low to Minimal Emetic Risk

- PRN dosing recommended
- If nausea/vomiting occurs: give ONE of the following (start before chemo and then prn)
  - Metoclopramide 10-40 mg po and then q 4-6 hrs prn or
  - Prochlorperazine 10 mg po and then q 4-6 hrs prn or
  - Haloperidol 1-2 mg po and then q 4-6 hrs prn or
  - Serotonin antagonist
    - Dolasetron 100 mg po qd
    - Granisetron 1-2 mg po qd
    - Ondansetron 16-24 mg po qd

Anticipatory Nausea: NCCN Guidelines
Anticipatory Nausea/Vomiting

- Prevention with optimal antiemetics
- Behavioral therapy
  - Relaxation techniques
  - Guided imagery
  - Music therapy
- Acupuncture/acupressure
- Anxiolytic therapy (begin night before chemo)
  - Alprazolam 0.5-1 mg po or
  - Lorazepam 0.5-2 mg po

Breakthrough Nausea: NCCN Guidelines
Breakthrough Therapy

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

- Atypical antipsychotic
  - Olanzapine 10 mg po 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

- 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 or IV q 6 hrs
  - Promethazine 25 mg supp pr q 6 hrs or 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

Consequences of Untreated CINV
Uncontrolled CINV

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

- **Quality of life costs**
  - One of the most distressing side effects – nausea
  - Dread of future chemotherapy
  - Chemo may have to be stopped or delayed
  - Loss of days at work
Principles of Emesis Control

- Prevention is the goal
- Guidelines should be followed
- Risk of CINV lasts for 3-4 days for highly or moderately emetogenic chemotherapy
- Oral = IV
- Use lowest recommended dose
- Costs of uncontrolled CINV (financial and human) are substantial

Non-Pharmacologic Approaches?
Ginger?

744 pts (576 evaluable)
All got serotonin antagonist + dexamethasone

Placebo vs. ginger dosed b.i.d. (3 days before and 3 days after chemo)

Placebo
0.5 gm
1.0 gm
1.5 gm

Ginger

- Pts ranked nausea on scale of 1-7 four times a day
- Day #1 (acute nausea)
  - All doses of ginger were more effective than placebo
  - 0.5 gm and 1.0 gm were most effective
  - P = 0.013 and 0.003 in each cycle
- Days #2-4 (delayed nausea)
  - Effectiveness weakened
Acupressure?

Acupressure and CINV

  - Review of 9 controlled acupressure studies
    - 7 wristband trials: 4 positive, 3 negative
    - 2 finger acupressure trials: both positive
  - “This review concludes that the effect of acupressure is strongly suggestive but is still not conclusive”
    - Different emetic potentials of the chemo agents
    - Different acupressure modalities
  - Could be recommended as a non-pharmacologic intervention
Thank You