Management of Patients With Chemotherapy-Induced Nausea and Vomiting

Sally Yowell Barbour, PharmD, BCOP, CPP
Duke University Hospital
Learning Objectives

1. Describe the various mechanisms of action for agents used to manage chemotherapy-induced nausea and vomiting (CINV), such as NK1 and 5-HT$_3$ receptor antagonists

2. Recall chemotherapy agents that are highly and moderately emetogenic

3. Demonstrate how advanced practitioners should anticipate and prevent delayed CINV in cancer patients

CINV = chemotherapy-induced nausea and vomiting.
Financial Disclosure

• Dr. Barbour has nothing to disclose.
Background/History
### Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Fatigue</td>
</tr>
<tr>
<td>2</td>
<td>Nausea</td>
<td>Constantly tired</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Nausea</td>
</tr>
<tr>
<td>3</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Vomiting</td>
<td>Constantly tired</td>
<td>Sleep disturbances</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>
<td>Weight loss</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>
<td>Loss of hair</td>
</tr>
</tbody>
</table>

CINV Remains a Challenge

• National and international guidelines (NCCN, ASCO, and MASCC) exist to guide clinicians in the use of antiemetics with CINV
  • Antiemetic guidelines result in significant improvement in the control of emesis with better resource utilization
• Many practices have EMRs with chemotherapy regimens prebuilt that include supportive care
• Multiple classes of drugs are available to manage CINV
• Despite progress in effective antiemetic prophylaxis, many patients still experience emesis with chemotherapy, particularly during the delayed phase

ASCO = American Society of Clinical Oncology; EMRs = electronic medical records; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network.
CINV Remains a Challenge (cont)

- Patients are not always prescribed effective guideline-based antiemetic regimens
- Nonadherence to antiemetic regimens, particularly delayed regimens
- Inability to afford medications
- Guidelines don’t address all scenarios
  - Current guidelines based primarily on two factors:
    - Emetogenicity of single-dose chemotherapy
    - Pattern of CINV (e.g., acute, delayed)

- Lack of data on:
  - How to incorporate additional patient-specific emetic risk factors
  - Multiday chemotherapy
  - Stem-cell transplant
  - Oral agents
  - Pediatric patients
Patient Case

- AH is a 44-year-old female teacher with no significant PMH.
- Presents with a 4-month history of weakness and fatigue and an associated 8-kg unintentional weight loss.
- She has never smoked and does not drink alcohol.
- She has three children and experienced significant morning sickness with all of her pregnancies.
- She is found to have a 10-cm cecal mass and multiple liver lesions.
- Biopsy of a liver lesion confirms the diagnosis of adenocarcinoma, and she is coming in to get her first cycle of FOLFOX.
- What is her risk for CINV?

FOLFOX = leucovorin, 5-fluorouracil, and oxaliplatin; PMH = past medical history.
Risk Factors for CINV

- Emetogenicity of chemotherapy
- Younger age (<50 years old)
- Female
- Low alcohol intake history
- History of motion sickness
- History of emesis during pregnancy

## Emetogenic Potential of Single Antineoplastic Agents

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Risk in &gt;90% of patients</td>
</tr>
<tr>
<td>Moderate</td>
<td>Risk in 30%–90% of patients</td>
</tr>
<tr>
<td>Low</td>
<td>Risk in 10%–30% of patients</td>
</tr>
<tr>
<td>Minimal</td>
<td>&lt;10% at risk</td>
</tr>
</tbody>
</table>

# Emetogenic Potential of IV Antineoplastic Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
</table>
| **High** | - AC combination, defined as doxorubicin or epirubicin with cyclophosphamide  
           | - Carmustine >250 mg/m²                                               |
|         | - Cisplatin                                                          |
|         | - Cyclophosphamide >1,500 mg/m²                                      |
|         | - Dacarbazine                                                        |
|         | - Doxorubicin ≥60 mg/m²                                              |
|         | - Epirubicin >90 mg/m²                                               |
|         | - Ifosfamide ≥2 g/m² per dose                                        |
|         | - Mechlorethamine                                                    |
|         | - Streptozocin                                                       |
| **Moderate** | - Aldesleukin >12–15 million IU/m²                                  |
|         | - Amifostine >300 mg/m²                                              |
|         | - Arsenic trioxide                                                   |
|         | - Azacitidine                                                        |
|         | - Bendamustine                                                       |
|         | - Busulfan                                                           |
|         | - Carboplatin                                                        |
|         | - Carmustine ≤250 mg/m²                                              |
|         | - Clofarabine                                                        |
|         | - Cyclophosphamide ≤1,500 mg/m²                                      |
|         | - Cytarabine >200 mg/m²                                              |
|         | - Dactinomycin                                                       |
|         | - Daunorubicin                                                       |
|         | - Dinutuximab                                                        |
|         | - Doxorubicin <60 mg/m²                                              |
|         | - Epirubicin ≤90 mg/m²                                               |
|         | - Idarubicin                                                         |
|         | - Ifosfamide <2 g/m² per dose                                        |
|         | - Interferon alfa ≥10 million IU/m²                                  |
|         | - Irinotecan                                                         |
|         | - Melphalan                                                          |
|         | - Methotrexate ≥250 mg/m²                                            |
|         | - Oxaliplatin                                                        |
|         | - Temozolomide                                                       |
|         | - Trabectedin                                                        |

## Emetogenic Potential of IV Antineoplastic Agents (cont.)

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>- Ado-trastuzumab emtansine</td>
</tr>
<tr>
<td></td>
<td>- Amifostine ≤300 mg</td>
</tr>
<tr>
<td></td>
<td>- Aldesleukin ≤12 million IU/m²</td>
</tr>
<tr>
<td></td>
<td>- Blinatumomab</td>
</tr>
<tr>
<td></td>
<td>- Brentuximab vedotin</td>
</tr>
<tr>
<td></td>
<td>- Cabazitaxel</td>
</tr>
<tr>
<td></td>
<td>- Carfilzomib</td>
</tr>
<tr>
<td></td>
<td>- Cytarabine (low dose)</td>
</tr>
<tr>
<td></td>
<td>- Docetaxel</td>
</tr>
<tr>
<td></td>
<td>- Doxorubicin (liposomal)</td>
</tr>
<tr>
<td></td>
<td>- Eribulin</td>
</tr>
<tr>
<td></td>
<td>- Etoposide</td>
</tr>
<tr>
<td></td>
<td>- 5-fluorouracil</td>
</tr>
<tr>
<td></td>
<td>- Flouxuridine</td>
</tr>
<tr>
<td></td>
<td>- Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>- Interferon alfa &gt;5 - &lt;10 million IU/m²</td>
</tr>
<tr>
<td></td>
<td>- Ixabepilone</td>
</tr>
<tr>
<td></td>
<td>- Methotrexate &gt;50 mg/m² - &lt;250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Mitomycin</td>
</tr>
<tr>
<td></td>
<td>- Mitoxantrone</td>
</tr>
<tr>
<td></td>
<td>- Necitumumab</td>
</tr>
<tr>
<td></td>
<td>- Omacetaxine</td>
</tr>
<tr>
<td></td>
<td>- Paclitaxel-album</td>
</tr>
<tr>
<td></td>
<td>- Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>- Pemetrexed</td>
</tr>
<tr>
<td></td>
<td>- Pentostatin</td>
</tr>
<tr>
<td></td>
<td>- Piralatrexate</td>
</tr>
<tr>
<td></td>
<td>- Romidepsin</td>
</tr>
<tr>
<td></td>
<td>- Talimogene laherparepvec</td>
</tr>
<tr>
<td></td>
<td>- Thiotepa</td>
</tr>
<tr>
<td></td>
<td>- Topotecan</td>
</tr>
<tr>
<td></td>
<td>- Ziv-aflibercept</td>
</tr>
<tr>
<td><strong>Minimal</strong></td>
<td>- Alemtuzumab</td>
</tr>
<tr>
<td></td>
<td>- Asparaginase</td>
</tr>
<tr>
<td></td>
<td>- Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>- Bleomycin</td>
</tr>
<tr>
<td></td>
<td>- Bortezomib</td>
</tr>
<tr>
<td></td>
<td>- Cetuximab</td>
</tr>
<tr>
<td></td>
<td>- Cladribine</td>
</tr>
<tr>
<td></td>
<td>- Cytarabine &lt;100 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Daratumumab</td>
</tr>
<tr>
<td></td>
<td>- Decitabine</td>
</tr>
<tr>
<td></td>
<td>- Denileukin diftitox</td>
</tr>
<tr>
<td></td>
<td>- Dextrazoxane</td>
</tr>
<tr>
<td></td>
<td>- Elotuzumab</td>
</tr>
<tr>
<td></td>
<td>- Fludarabine</td>
</tr>
<tr>
<td></td>
<td>- Interferon alfa ≤5 million IU/m²</td>
</tr>
<tr>
<td></td>
<td>- Ipilimumab</td>
</tr>
<tr>
<td></td>
<td>- Methotrexate ≤50 mg/m²</td>
</tr>
<tr>
<td></td>
<td>- Nelarabine</td>
</tr>
<tr>
<td></td>
<td>- Nivolubab</td>
</tr>
<tr>
<td></td>
<td>- Ofatumumab</td>
</tr>
<tr>
<td></td>
<td>- Panitumumab</td>
</tr>
<tr>
<td></td>
<td>- Pegasparagse</td>
</tr>
<tr>
<td></td>
<td>- Peginterferon</td>
</tr>
<tr>
<td></td>
<td>- Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>- Pertuzumab</td>
</tr>
<tr>
<td></td>
<td>- Rituximab</td>
</tr>
<tr>
<td></td>
<td>- Temsirolimus</td>
</tr>
<tr>
<td></td>
<td>- Trastuzumab</td>
</tr>
<tr>
<td></td>
<td>- Valrubicin</td>
</tr>
<tr>
<td></td>
<td>- Vinblastine</td>
</tr>
<tr>
<td></td>
<td>- Vincristine</td>
</tr>
<tr>
<td></td>
<td>- Vincristine (liposomal)</td>
</tr>
<tr>
<td></td>
<td>- Vinorelbine</td>
</tr>
</tbody>
</table>

Emetogenic Potential of Oral Antineoplastic Agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate-high</strong></td>
<td></td>
</tr>
<tr>
<td>• Altretamine</td>
<td>• Estramustine</td>
</tr>
<tr>
<td>• Busulfan (≥4 mg/day)</td>
<td>• Etoposide</td>
</tr>
<tr>
<td>• Crizotinib</td>
<td>• Lomustine (single day)</td>
</tr>
<tr>
<td>• Cyclophosphamide (≥100 mg/m²/day)</td>
<td>• Mitotane</td>
</tr>
<tr>
<td>• Procarbazine</td>
<td></td>
</tr>
<tr>
<td>• Temozolomide (&gt;75 mg/m²/day)</td>
<td>• Trifluoridine/tipiracil</td>
</tr>
<tr>
<td><strong>Minimal-low</strong></td>
<td></td>
</tr>
<tr>
<td>• Afatinib</td>
<td>• Everolimus</td>
</tr>
<tr>
<td>• Alectinib</td>
<td>• Fludarabine</td>
</tr>
<tr>
<td>• Axitinib</td>
<td>• Gefitinib</td>
</tr>
<tr>
<td>• Bexarotene</td>
<td>• Hydroxyurea</td>
</tr>
<tr>
<td>• Bosutinib</td>
<td>• Imatinib</td>
</tr>
<tr>
<td>• Busulfan (&lt;4 mg/day)</td>
<td>• Lapatinib</td>
</tr>
<tr>
<td>• Cabozantinib</td>
<td>• Lenalidomide</td>
</tr>
<tr>
<td>• Capecitabine</td>
<td>• Melphalan</td>
</tr>
<tr>
<td>• Chlorambucil</td>
<td>• Mercaptopurine</td>
</tr>
<tr>
<td>• Cobimetinib</td>
<td>• Methotrexate</td>
</tr>
<tr>
<td>• Cyclophosphamide (&lt;100 mg/m²/day)</td>
<td>• Nilotinib</td>
</tr>
<tr>
<td>• Dasatinib</td>
<td>• Pazopanib</td>
</tr>
<tr>
<td>• Dabrafenib</td>
<td>• Pomalidomide</td>
</tr>
<tr>
<td>• Erlotinib</td>
<td>• Ponatinib</td>
</tr>
<tr>
<td>• Regorafenib</td>
<td></td>
</tr>
</tbody>
</table>

Based on AH’s risk of CINV, what do current guidelines suggest as the appropriate antiemetic regimen?
## Overview of Guidelines for Acute Nausea and Vomiting: NCCN/ASCO/MASCC

<table>
<thead>
<tr>
<th>Emetic Risk Group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5-HT$_3$ + DEX + NK1&lt;br&gt;Olanzapine-based</td>
</tr>
<tr>
<td>• AC</td>
<td>5-HT$_3$ + DEX + NK1</td>
</tr>
<tr>
<td>• Carboplatin</td>
<td>5-HT$_3$ + DEX + NK1</td>
</tr>
<tr>
<td>Moderate</td>
<td>5-HT$_3$ + DEX&lt;br&gt;Olanzapine-based</td>
</tr>
<tr>
<td>Low</td>
<td>5-HT$_3$ or DEX or DA</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

DA = dopamine antagonist; DEX = dexamethasone.

## Overview of Guidelines for Delayed Nausea and Vomiting: NCCN/ASCO/MASCC

<table>
<thead>
<tr>
<th>Emetic Risk Group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>DEX + NK1*</td>
</tr>
<tr>
<td></td>
<td>Olanzapine-based</td>
</tr>
<tr>
<td>• AC</td>
<td>NK1* +/- DEX or NONE</td>
</tr>
<tr>
<td>• Carboplatin</td>
<td>None if NK1 used</td>
</tr>
<tr>
<td>Moderate</td>
<td>DEX or 5-HT₃</td>
</tr>
<tr>
<td></td>
<td>Olanzapine-based</td>
</tr>
<tr>
<td>Low</td>
<td>No routine prophylaxis</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

*Depends on NK1 used

New Agents in CINV
Netupitant

- Netupitant is available as a fixed-dose combination of oral netupitant and oral palonosetron (also known as NEPA)
- FDA approval: For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC
- Selective substance P NK1 receptor antagonist

- Extensively metabolized primarily by CYP3A4, and to a lesser extent by CYP2C9 and CYP2D6
- Moderate inhibitor of CYP3A4
- After oral administration of a single dose, the drug was measurable in plasma between 15 minutes and 3 hours after dosing
- Cmax are attained in approximately 5 hours

FDA = US Food and Drug Administration; HEC = highly emetogenic chemotherapy.
Phase III Study: Aapro et al.

A randomized phase III study evaluating the efficacy and safety of a fixed-dose combination of netupitant and palonosetron, for prevention of CINV following MEC.

- **N = 1,455**
  - Chemo-naive
  - AC chemo

**Randomized 1:1**

**Oral netupitant 300 mg/palonosetron 0.50 mg**
+ **oral dexamethasone 12 mg**

**Oral palonosetron 0.50 mg**
+ **oral dexamethasone 20 mg**

MEC = moderately emetogenic chemotherapy.
Phase III Study: Aapro et al. (cont)

- **Primary endpoint:** CR (no emesis, no rescue medication) during the delayed (25–120 h) phase in cycle 1
  - The use of rescue medication for treatment of nausea/vomiting was considered treatment failure
  - Metoclopramide tablets were provided
  - Alternative rescue (excluding 5-HT₃ or NK1 receptor antagonist) allowed at investigator discretion

- **Secondary endpoints:**
  - CR during the acute (0–24 hr) and overall (0–120 hr) phases
  - No scheduled antiemetics in delayed setting
  - After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1

CR = complete response.
Results: Primary Endpoint CR Delayed

- CR: No emesis, no rescue medication
- Based on full analysis set of 1,449 patients

Results: Secondary Endpoints CR Acute/Overall

- CR: No emesis, no rescue medication
- Based on full analysis set of 1,449 patients

Aapro et al. Study: Conclusions

• The overall incidence, type, frequency, and intensity of treatment-emergent adverse events were comparable between the two treatment groups
  • Among the patients reporting adverse events, the majority (85%) reported adverse events of mild/moderate intensity

• The most common treatment-related adverse events were headache and constipation

• Netupitant/palonosetron plus dexamethasone was superior to palonosetron plus dexamethasone in preventing CINV following MEC* in acute, delayed and overall phases of observation

• Combination offers guideline-based prophylaxis with a convenient, single-day treatment

*Anthracycline/cyclophosphamide
Rolapitant

- Oral, NK1 selective, competitive antagonist
- FDA approval: In combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC
- The metabolic route is an important differentiating factor
  - Moderate inhibitor of 2D6, BCRP, and Pgp
  - Does NOT inhibit or induce CYP3A4
  - Less potential for significant drug interactions
    - No adjustment to dexamethasone
- Available as 90-mg oral tablets

**Phase III Study: Schwartzberg et al.**

Global, randomized, double-blind, placebo controlled phase III study evaluating the efficacy and safety of rolapitant in MEC

- **Rolapitant 180 mg + granisetron 2 mg po + dexamethasone 20 mg po (n = 684)**
- **Placebo + granisetron 2 mg po + dexamethasone 20 mg po (n = 685)**

N = 1,369
- MEC or HEC naive
- MEC*

* Cyclophosphamide (<1,500 mg/m²), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine (>1 g/m²).

Phase III Study: Schwartzberg et al. (cont)

- **Primary endpoint:** Proportion of patients achieving a CR (no emesis or use of rescue medication) in the delayed phase (>24–120 h after initiation of chemotherapy) in cycle 1

- **Secondary endpoints:**
  - Proportions of patients with CR in the acute (0–24 h after chemotherapy) and overall (0–120 h) phases
  - No emesis in acute, delayed, and overall phases
  - No clinically significant nausea (maximum nausea on a visual analogue scale <25 mm) in the overall phase
  - Time to first emesis or use of rescue medication
  - QOL

- **All patients received granisetron 2 mg po days 2–3**

QoL = quality of life.
Results: Primary Endpoint CR Delayed Phase

Chemotherapy: cyclophosphamide (<1,500 mg/m²), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine (>1 g/m²)

Complete Response Rate (%)

- Control (n=666)
- Rolapitant 200 mg (n=666)

Delayed Phase (>24–120 hr): 61.6% vs 71.3% (P <0.001)

Acute Phase (0–24 hr): 80.3% vs 83.5% (P =0.143)

Overall Phase (0–120 hr): 57.8% vs 68.6% (P <0.001)

mITT = modified intention to treat.
Results: Secondary Endpoints CR Acute/Overall

mITT Population

- Chemotherapy: cyclophosphamide (<1,500 mg/m²), doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine (>1 g/m²)
- More than 50% of patients received AC chemotherapy

Schwartzberg et al. Study: Conclusions

• Rolapitant was well tolerated
  • Frequencies of treatment-emergent adverse events similar to those reported in the active control group
  • The most common treatment-related treatment-emergent adverse events were constipation, fatigue, dizziness, and headache

Potential Advantages/Challenges With Oral NK1 Antagonists

Potential Advantages
• Administration as an all-oral combination agent
  - No injection site reactions
• A single-dose regimen given on the day of chemotherapy only (Aapro study)
• A dexamethasone sparing regimen
  - No steroids given on days 2–4 in some trials

Challenges
• Patients unable to tolerate orally administration
• Cost, procurement, and reimbursement
• Administration challenges
  - Drug availability
  - Timing of dosing
  - Anticipatory nausea and vomiting
Olanzapine

- Olanzapine is an oral antipsychotic agent
- It affects a variety of neurotransmitter receptors
  - Binds to alpha1, dopamine, histamine H1, muscarinic, and serotonin type 2 (5-HT₂) receptors
- Most common side effect is sedation
- Multiple phase II and phase III trials have indicated antiemetic activity
  - Studies have often had small sample sizes, were not always double-blind, and were of low power
- What is its role?
  - Initial therapy as a replacement for an NK1 receptor antagonist
  - As the fourth drug in a combination or in a regimen for patients who have not done well on the first cycle
  - Breakthrough CINV

Phase III Trial of Olanzapine Combined With NK1, $5HT_3$, and Dexamethasone (ALLIANCE 221301)

A randomized, double-blind, phase III trial was performed in chemotherapy-naive patients receiving cisplatin (> 70 mg/m$^2$) or cyclophosphamide-anthracycline-based chemotherapy.

Olanzapine 10 mg po + aprepitant* 125 mg po + $5HT_3$ po + dexamethasone 12 mg po (n = 192)

Placebo + aprepitant* 125 mg po + $5HT_3$ po + dexamethasone 12 mg po (n = 188)


* Fosaprepitant allowed
Phase III Trial of Olanzapine Combined With NK1, 5HT$_3$, and Dexamethasone (ALLIANCE 221301) (cont)

- Primary endpoint: No nausea
  - Nausea was measured on a 0–10 visual analog scale, with 0 being “no nausea at all” and 10 being “nausea as bad as it can be”

- Secondary endpoint
  - CR (no emesis and no use of rescue medications)

- All patients received
  - Aprepitant 80 mg days 2–3 (if oral used)
  - Dexamethasone 8 mg days 2–4
  - Olanzapine/placebo 10 mg days 2–4

### Phase III Trial of Olanzapine Combined With NK1, 5HT\textsubscript{3}, and Dexamethasone (ALLIANCE 221301) (cont)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3 drugs + olanzapine (n = 192)</th>
<th>3 drugs + placebo (n = 188)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No nausea: Acute</td>
<td>74%</td>
<td>45%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No nausea: Delayed</td>
<td>42%</td>
<td>25%</td>
<td>.001</td>
</tr>
<tr>
<td>No nausea: Overall</td>
<td>37%</td>
<td>22%</td>
<td>.002</td>
</tr>
<tr>
<td>CR: Acute</td>
<td>86%</td>
<td>65%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CR: Delayed</td>
<td>67%</td>
<td>52%</td>
<td>.007</td>
</tr>
<tr>
<td>CR: Overall</td>
<td>64%</td>
<td>41%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sedation scores &gt;5 on day 2</td>
<td>20%</td>
<td>7%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Olanzapine Summary

- Improvement in nausea control
- Provides four-drug option for CINV
- Option for a regimen without NK1 antagonist
- Major side effect is sedation
AH received ondansetron, aprepitant, and dexamethasone and experienced 2 episodes of acute emesis in the first 24 hours with severe nausea.

What would you give for breakthrough CINV?
Breakthrough CINV

- Give additional agent from a different class
- Consider around-the-clock rather than as prn administration
- If the patient is vomiting, IV or rectal administration may be required
- Before next cycle of chemotherapy, reassess response to antiemetics in both acute and delayed setting
  - Consider an alternative regimen if needed
  - Add NK1 RA if not previously included
  - Olanzapine

prn = as needed.
Impact of CINV on QoL

• HOPA patient survey
  • 400 patients receiving chemotherapy

• Results
  • Nearly three of four patients who had experienced CINV said it made them want to avoid future chemo, and the majority said it had caused them to alter their lives
    • 56% cancelled personal plans
    • 46% changed eating habits
    • 43% avoided exercise or physical activity
    • 38% called in sick to work
    • 30% had more negative outlook on prognosis

HOPA = Hematology/Oncology Pharmacy Association.
ANCHOR Study: CINV Decreases QoL

- Nausea has a greater negative impact on QoL than vomiting, $P = .0097$
- HEC has a greater negative impact on than MEC, $P = .0049$

**Functional Living Index - Emesis**

- Nausea: HEC patients
- Nausea: all patients
- Nausea: MEC patients
- Vomiting: HEC patients
- Vomiting: all patients
- Vomiting: MEC patients

**Patients with Nausea or Vomiting (%):**

- Day 1: 60%
- Day 2: 50%
- Day 3: 40%
- Day 4: 30%
- Day 5: 20%

**Days After Chemotherapy:**

- Day 1
- Day 2
- Day 3
- Day 4
- Day 5

ANCHOR = Anti-nausea Chemotherapy Registry.

The Advanced Practice Provider’s Role in Managing CINV

- Participate in development or implementation of institution-specific guidelines
  - Tailor guidelines to patient population
- Ensure adherence to guidelines
  - Build into EMR order sets
  - Part of chemotherapy order verification process
- Participate in planning patient therapy
  - Assess for additional CINV risk factors
- Educate oncology team, including physicians, nurses, physician assistants, and pharmacists
- Provide patient education
  - Address insurance obstacles
  - Improve adherence with greater involvement in patient education
- Assess initial and ongoing patient risk factors
- Create medication management protocols
Creating Local Guidelines Based on National/International Guidelines

- Developing local guidelines using a consensus of national/international guidelines will:
  - Optimize patient care
    - Standardize the ordering, preparation, and administration of antiemetic therapies
  - Serve as an educational tool for new staff
  - Provide a systematic method of assessment and adjustment of treatment in challenging patients
  - Aid in containing the cost of medications
  - Avoid unnecessary healthcare resource utilization
Pharmacist-Driven Management to Improve Adherence to Institutional Protocol/Guidelines

- Single-center chart review study at major academic medical center
- 106 patients receiving inpatient chemotherapy
  - 55 managed according to pharmacist-driven protocol; 51 by physician-driven protocol
- In physician-managed group, 20% of patients received excessive CINV prophylaxis vs. 2% in pharmacist-managed group
- Number of breakthrough doses (primary endpoint) did not differ between groups
  - Excessive prophylaxis could have contributed to excess cost without improved results

<table>
<thead>
<tr>
<th>Adherence to guidelines</th>
<th>Pharmacist-managed group (n = 55)</th>
<th>Physician-managed group (n = 51)</th>
<th>All patients (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, number (%)</td>
<td>47 (85)$^a$</td>
<td>17 (33)</td>
<td>64 (60)</td>
</tr>
<tr>
<td>No, number (%)</td>
<td>8 (15)</td>
<td>34 (67)</td>
<td>42 (40)</td>
</tr>
</tbody>
</table>

Consequences of Overtreatment and Undertreatment

- Financial costs
  - Copays
- Side effects
  - Constipation, headaches
  - Blood sugars, insomnia
- Excess pill burden
- Patient confusion
- Nonadherence
- Uncontrolled CINV
- Anticipatory CINV
- Poorly controlled CINV may result in
  - Increased utilization of healthcare resources
    - Clinic visits for fluids and/or additional antiemetics
    - Hospitalization
  - Dehydration and electrolyte imbalance
  - Impaired health-related QoL
    - Negative impact on activities of daily living
  - Hesitancy to continue with potentially curative treatment
Key Takeaways

- CINV is still a significant problem for many patients, especially delayed CINV
- New agents have been incorporated into national guidelines
  - NK1 receptor antagonists products offer similar clinical efficacy
    - Potential advantages/challenges
    - Olanzapine offers alternative regimen and appears to offer improved efficacy in nausea
- A therapeutic approach of combining antiemetics with different mechanisms gives best results in preventing CINV
- Advanced practice providers, nurses, and pharmacists should play key roles in helping to assess and manage CINV
CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

CHRISTOPHER CAMPEN, PharmD, BCOP

We're delighted to have our next speaker join us. Please welcome Dr. Sally Barbour of the Duke University Hospital as she discusses management of patients with chemotherapy-induced nausea and vomiting.

DR. BARBOUR

Okay, thanks everybody. Today we’re going to be talking about some of the recent advancements in the management of patients with chemotherapy-induced nausea and vomiting. The learning objectives are here, but, basically, [we’ll] talk about the different agents that are available, talk about some of the risk factors and looking at the emetogenicity of our chemotherapy agents as some of those have been somewhat reclassified. And then really talk about how we as advanced practitioners can play a role in anticipating and preventing nausea and vomiting in our cancer patients.

I have nothing to disclose. I always like to start out with just a little bit of background, which I know we all are well aware that nausea and vomiting is one of the side effects that patients really fear the most. And they talk to their friends, and they know that they’re going to throw up, and they come and they talk to you and it’s one of the things they’re most concerned about. And this is a good table to show where we’ve come from and to reiterate that we still have some work to do.

Back in the ’80s, nausea and vomiting and specifically vomiting was one of the things that patients feared the most. As we’ve had advancements in our...
pharmacologic management of this side effect with the introduction of the serotonin receptor antagonists, you can see that vomiting really fell, while not off, it fell down in the rankings, and nausea was still an issue. And as we’ve introduced newer agents, such as the NK1 antagonists, and learned better how to categorize the risk factors, we see vomiting again has continued to stay while in the top five, down towards the bottom. But you can see that nausea continues to be a problem and that continues to be one of the main problems that we face today in management of these patients. We know that it remains a challenge.

There are numerous international and national guidelines that are available that I’m sure you’re all well familiar with. They’re all updated on a regular basis. MASCC we recently updated this year, NCCN and ASCO, of which I’m lucky enough to be on those guidelines, are in the process of updating their guidelines. Those guidelines are great, and they’re accessible to everyone and they offer a really great framework to make sure that patients and practitioners use the most appropriate antiemetics for their patients. A lot of practices whether you like it or not have electronic medical records, and one of the benefits of this is that we can pre-build templates and we can build these templates with appropriate antiemetics so that patients are getting appropriate prophylactic regimens.

As I mentioned, we’ve introduced a lot of new drugs over the past 30 years, and those have really made some advancements in how we’ve been able to manage this problem. But, despite all of this, as I alluded to, we still have a lot of patients that are fearful, a lot of patients that have problems with nausea and
vomiting, and more in the delayed setting, and at least in my practice and at least what the literature shows, it’s nausea that continues to be a significant problem.

Why does it remain a problem if we have all these great guidelines and we have all these great drugs? One is that they don’t get prescribed appropriately. There’s a lot of data out there that shows that people, people meaning us, providers underestimate how well or not well patients are doing. We don’t necessarily follow the appropriate guidelines -- either it’s because of lack of awareness or people don’t think that this patient really needs that or whatever the guidelines -- and there’s data out there that shows that they’re not necessarily followed. We have patients that can’t afford their antiemetics, so there’s issues with nonadherence.

The guidelines don’t address all scenarios, so obviously there are a lot of regimens that are multiday. We have patients in stem cell transplant and those aren’t addressed in the guidelines, so you’re focused on more single-day chemotherapy.

We’re not doing patient case, but I am introducing one that will guide the discussion as we go through. This is probably someone who’s familiar to a lot of folks in this room, AH. She’s a 44-year-old female, she really has no significant past medical history, she presents with a 4-month history of weakness and fatigue. She has never smoked, she doesn’t drink, she’s got three young children, she’s busy, she had morning sickness with all of her pregnancies, and she ends up being diagnosed with a 10-cm cecal mass and liver lesion. She is going to be starting FOLFOX chemotherapy, so what is her risk factor for nausea
and vomiting? Again, you all know FOLFOX, it’s leucovorin, 5-FU, and oxaliplatin.

When we’re working with patients, the first thing to look at is what their risk factors are. Obviously the first is to look at what chemotherapy they’re getting and how likely is that chemotherapy or that combination of chemotherapy agent - - what is the emetogenicity of that regimen? And we’ll talk a little bit more about that in the next couple of slides.

Other risk factors that we know contribute to risk, although we don’t necessarily know the best way to incorporate all of them, are things such as younger age. We know that the younger patients are -- it’s harder; they’re more at risk for having issues with nausea and vomiting. Females are more at risk, patients that don’t have a significant alcohol intake history, patients that do have a history of nausea with motion sickness or with pregnancy. When we look at this patient, she pretty much has all sorts of risk factors that are going to contribute and increase her risk of having nausea and vomiting.

Looking more specifically at the regimens themselves, all of the guidelines categorize the agents in one of four different factors. Our high-risk factor drugs are drugs that in greater than 90% of patients we know that if we did nothing are going to cause patients to have nausea and vomiting. The moderate-risk category, which is arguably very wide ranging and sometimes where we run into issues, is our regimen or drugs that cause emetogenicity in 30 to 90% of patients. Again, there’s a significant difference between if you’re in the 85%
versus 35%. And then we have our low and minimal, which for the most part don’t require a whole lot of antiemetic prophylaxis.

Looking more specifically -- and these are based on the current version of the NCCN guidelines -- what are the regimens or the drugs that are considered high risk? I would say that the two that stand out the most and that are probably the most widely used are cisplatin, and any dose of cisplatin is classified as highly emetogenic. And then AC combination, which used to be moderately emetogenic, and that is one of the things that when we look at some of the studies that are in moderately emetogenic chemotherapy, a significant amount of those patients were receiving AC, which now all the guidelines, whether they have reclassified them as high or put them in their own separate class but treat them as high for the purpose of this, they’re all high. All those patients should be receiving all our recommendations for highly emetogenic chemotherapy.

Some of our more common drugs in the moderate setting or moderate category are drugs like carboplatin, which, again, is one of the drugs that’s been discussed a lot in the guidelines this year, lower doses of some of our anthracyclines, irinotecan, and oxaliplatin. When we look at our patient, she’s getting oxaliplatin, which is moderate, and her other chemotherapy drug is low. She’s getting a moderate emetogenic chemotherapy regimen, but, again, she pretty much has all of those risk factors; she’s young, she’s a female, she didn’t drink, she didn’t smoke, and she had nausea when she was pregnant. While she’s moderate in terms of her chemotherapy, one could argue that you would treat her as a high-risk patient based on all of her other risk factors.
Again, the lower emetogenic regimens are regimens like docetaxel, paclitaxel, pemetrexed; these are regimens that only cause nausea or vomiting in about 10 to 30% of patients, and then the minimal agents are there.

One of the challenges that the guidelines historically have not addressed, but at least the NCCN guidelines have attempted in the past several years, is to incorporate the oral chemotherapy agents -- there’s a ton of them out there -- and trying to add them to the guidelines to provide some guidance with how to best manage these. And for the most part, these drugs have fallen into a minimal to low category, but there are a few, such as oral cycle ifosfamide, procarbazine, that really have the potential to cause nausea and vomiting. NCCN has attempted to provide some guidance, and in patients receiving those drugs, they do recommend giving scheduled antiemetics, at least for some part of the treatment.

Again, AH, she’s receiving a moderate emetogenic regimen, potentially you could increase her to a high risk. What is the best thing to give her, and what do the guidelines actually recommend? As I mentioned, there are really three large groups out there that have put out guidelines; MASCC updated theirs in the spring, NCCN and ASCO are in the midst of updating theirs. I don’t know when they’ll be out, but they are in the works. But for the most part, the guidelines are pretty much in agreement with how they recommend patients be treated.

For patients receiving highly emetogenic chemotherapy regimens, really all of these patients should be receiving a three-drug regimen consisting of a serotonin antagonist, NK1 antagonist, and dexamethasone. As I mentioned, AC
is -- whether it’s re-categorized as high or has been given its own separate category -- is also recommended to be treated with a three-drug regimen. And new to the MASCC guidelines is carboplatin. Carboplatin has been pulled out of the moderate set, moderate category, and has been recommended to be treated with a three-drug regimen similar to the high-risk drugs.

The NCCN guidelines have always listed carboplatin as one of those drugs that you could consider using an NK1 antagonist and adding it to the two-drug regimen if your patient was at high risk. But, at least to date, ASCO and NCCN have left carboplatin in the moderate category.

For those drugs that are in the moderate category, again, the recommendation is a serotonin antagonist plus dexamethasone, and then for low, any one of either dexamethasone, a dopamine antagonist, or a serotonin antagonist are recommended. And then, again, for minimal emetogenic drugs, no prophylaxis is recommended.

Olanzapine you see listed there. Olanzapine is another drug that we’ll talk a little bit about more later, which has been listed in the NCCN guidelines as an option. And the regimen listed in the NCCN guidelines actually substitutes olanzapine for an NK1 antagonist. There is a lot of data out there with olanzapine, and we’ll get to that a little bit more about that later.

For the delayed setting, again, it really depends on what you’ve given in the acute setting. For highly emetogenic regimens, patients should be receiving scheduled antiemetics in the delayed setting. One thing you will notice is there is no serotonin antagonist recommended to be scheduled. It is a knee-jerk reaction;
I find that everybody prescribes every serotonin antagonists, but in the highly emetogenic setting; it is not recommended in the delayed setting. Depending on what NK1 antagonist is given, it will or won’t be continued in the delayed setting, so if you’re using fosaprepitant, it’s just a one-time dose.

But if you’re using aprepitant, it’s 3 days, if you’re using one of the newer agents, it’s also just 1 day, so that really depends. And then in the moderate setting, it’s also recommended that patients should be receiving some scheduled antiemetic, and the guidelines are pretty consistent in recommending either a corticosteroid, such as dexamethasone, or a serotonin antagonist. And then for patients receiving low or minimal emetogenic regimens, no routine prophylaxis is recommended, although, obviously, we all know it, but it’s always good to remind folks that everybody should go home with something to have available as needed.

I’ll just shift into some of the newer agents that are available. There are two new NK1 antagonists that have become available in the last year or so. The first is netupitant, which is a fixed dose combination of netupitant, plus palonosetron. It’s often referred to as NEPA. It’s FDA approved for the prevention of acute and delayed nausea and vomiting in patients receiving either initial or repeat courses of chemotherapy. This is selective NK1 receptor antagonist. In terms of some of the potentials for drug interactions, it is metabolized by 3A4 and it is an inhibitor 3A4. Similar to aprepitant and fosaprepitant, there is the potential for drug interactions with this NK1 antagonist. As I mentioned, it’s given as a single dose, and, again, there is a potential for the drug interaction. You’ll see
that, similar to when you’re using aprepitant or fosaprepitant, the dexamethasone
dose is adjusted.

There are a lot of studies out there; for the sake of time, I’m just going to
share one with you. This is a phase III study looking at the netupitant
palonosetron combination in patients receiving moderately emetogenic
chemotherapy. Again, as I alluded to at the beginning, these patients are
receiving AC-based chemotherapy, which at the time of this study was
moderately emetogenic, but as we know now is really high emetogenic. So it’s
important to keep those things in mind when you’re evaluating these studies.

They looked at about 1,400 patients. They were randomized to receive the
NK1 serotonin antagonist combination with dex or just palo index, both given
orally and both just given on the day of chemotherapy. No patients received any
scheduled antiemetics, so they just got their antiemetics on day one and then
had PRN metoclopramide given to them. The primary endpoint was complete
response, so no emesis and no use of rescue. And it was during the delayed
phase, so they’re looking at the efficacy in that roughly 25- to 120-hour period
following cycle one. Their secondary endpoints were similar CR, but in the acute
and in the overall phase.

If you look here at their primary endpoint, again, which was efficacy in the
delayed phase, they met their endpoint -- no surprise. It was a statistically
significant difference in the patients that received the combination that included
the NK1 antagonist.
And then looking at their secondary endpoints, you can see that, again, in the acute, as well as the overall phase, they also showed a statistically significant improvement in the patients that received the NK1 antagonist compared to those who did not.

Their conclusions were, obviously, that this was an effective combination; it offered the potential for a convenient, single-day prophylactic CINV regimen, again, because these patients didn’t receive any scheduled antiemetics in the delayed in the setting. As we would expect, the most common side effects were headache and constipation, and they didn’t see a whole lot of other side effects or side effects that you would expect.

The other agent that’s become recently available is rolapitant, so this is also an oral agent; an IV agent is coming soon. But, currently, all that’s available on the market is the oral agent, which is, again, an NK1 selective receptor antagonist. Again, it’s FDA approved to be used with other agents in the prevention of delayed nausea and vomiting. And one of the differences with this drug with some of the other NK1 antagonists is the potential lack of drug interactions. This does not inhibit 3A4, and we always talk about 3A4. And, yes, there are a lot of other enzymes, but 3A4 is the big one and it doesn’t inhibit that. There is not the potential or the similar risk of potential as you see with other NK1 antagonists.

What’s important to remind folks is that if they’re using this, you don’t have to adjust the dexamethasone dose. And I think there’s some people that are young enough in their practice that the only thing that they know is the 12 mg...
dexamethasone dose. So if you’re using this, I think it’s important to remind folks that they do need to increase that dexamethasone dose back up to 20 mg. It is available, as I mentioned, right now as oral tablets only, but, again, an IV formulation is in the works.

Again, numerous studies, but I’m just sharing one in the moderately emetogenic setting. This is a phase III study by Lee Schwartzberg and colleagues looking, in a phase III study, looking at patients receiving moderately emetogenic chemotherapy. These are patients getting cycle ifosfamide and doxorubicin. It’s moderately emetogenic, but in reality some of the regimens are actually more highly emetogenic.

These patients received an all oral regimen and they received rolapitant, granisetron, and dexamethasone, or placebo with dexamethasone and granisetron. A little bit different than the previous study is that these patients did receive scheduled antiemetics in the delayed setting, so for 2 days they received scheduled granisetron. The endpoints are similar with the primary endpoint being complete response in the delayed phase and secondary endpoints, there were numerous ones, but in terms of efficacy, again, looking at the efficacy in the acute and then the overall phase. In terms of their primary endpoint of complete response in the delayed phase, they found a significant difference in the patients [taking] rolapitant as opposed to patients who did not receive an NK1 antagonist.

In looking at their secondary endpoints, the middle section there is efficacy in the acute phase, and they actually didn’t see a significant difference, but they
did see a significant difference in the overall phase; hence, their approval is in the delayed setting.

The conclusion is similar to the previous study, the NK1 antagonist rolapitant was well tolerated, it offered benefit. And we see our most common side effects as headaches and constipation, which are typically associated with our serotonin antagonists that they’re all getting.

What are some of the potential advantages with these oral NK antagonists, and what are some of the potential disadvantages? I’m just curious, I know there’s no audience response, but how many of you are using these newer oral NK1 antagonists in your practice? They do offer some advantages; they are all oral combination, offer you the potential to use an all oral combination if you’re using oral dex and oral serotonin antagonists. I think any of us that have used fosaprepitant are aware that there’s potential injection site reactions. People react sometimes to the fosaprepitant, so it does offer an alternative there; again, the convenience of that single, 1-day regimen. And at least in the APRON study where they didn’t receive anything in the delayed setting, it offers that option, so if you have patients where you are concerned with adherence, you know, that offers a benefit.

And a lot of folks continue to have concerns about dexamethasone and the use of dexamethasone. So we use dexamethasone in our patients, but if you have concerns, just the fact that they’re not giving steroids in the delayed setting and, again, going back to that everything being given on day one, so it does offer that opportunity.
With everything there’s advantages and challenges or disadvantages, so at least some of the challenges that in talking to folks around the country and at least at our own institution we’ve run into is not everybody can take something oral, so there’s that option. And it’s come down to cost and the ability to obtain the drugs and get them on formulary and all that. I think that’s really been more of our challenge.

And then at least at our institution, the patients aren’t allowed to get drugs and then bring them to the treatment room, so that offers challenges as well. But the drugs themselves work and are very effective.

Just the last new drug, which I’ll use quotations for, is olanzapine. Olanzapine, as we all know, has been around for a really, really long time, so it’s not new at all. It’s an antipsychotic, which is something that when I use it in patients I always have to make sure that I tell them, so when they go to the pharmacy they’re not shocked. There have been a lot of studies with olanzapine, phase II studies, small studies. Rudy Navari is really the champion of this drug in using it in the CINV setting. What is its role? There have been studies looking at it as, as I mentioned, part of a three-drug combination taking the place of the NK1 receptor antagonist. There’s studies -- and we’ll look at one of them where it’s been used in combination -- so as a fourth drug, and then in the breakthrough setting. The most common side effect is sedation, which is not minimal.

The one study that I’m just going to share with you is a phase III study that was recently published this July. It’s a phase III study looking at olanzapine combined with an NK1, a serotonin antagonist, and dexamethasone. This is a
phase III trial in highly emetogenic chemotherapy patients; they were receiving either cisplatin or an AC-based chemotherapy regimen. The drugs I mentioned, they could receive either oral aprepitant or they could receive IV fosaprepitant; so it was up to the investigator to choose. They either got olanzapine plus the three drugs, or they got placebo plus the current recommended three-drug regimen.

The primary endpoint, which is different from all the studies that we’ve talked about, was nausea. Nausea continues to be the main problem or one of the most significant problems, and that was the primary endpoint in this study. The secondary endpoint was our complete response of no emesis and no use of rescue. If they got aprepitant, they got the whole 3-day regimen. These patients did receive dexamethasone and olanzapine or placebo for 3 days, as is currently recommended in the guidelines, to receive scheduled antiemetics after highly emetogenic chemotherapy.

In terms of efficacy, again, primary endpoint was nausea. It was statistically significant, pretty significantly, in terms of meeting its primary endpoint of no nausea. In the acute phase, you can see there was a difference of almost 30%. In the delayed and overall phase, it was also statistically significantly better. Their secondary endpoint of complete response was also achieved in the acute and overall setting. As I mentioned, sedation has been the big side effect, and they really find that to be significant on day two, and then it tends to fall back to sort of more normal on days three and four.

In summary, olanzapine has been shown to be effective in a four-drug option, as evidenced by that study. It is an option to use if patients for whatever
reasons can’t tolerate an NK1 antagonist. It has been shown to offer significant improvement in nausea, which has really been the bane of existence for a long time. But you have to recognize that it does have this side effect of sedation, and the current dose that is used in these studies is 10 mg, and I know that there’s a lot of people that when they do use it don’t even think about starting at 10 mg, they use 5. I’ve heard people use 2.5, it’s hard to know. The data is with 10 mg, but this is where you have to look at the guidelines and you look at your patient and try to make the best decision.

Briefly, our patient AH, we decided she was at high risk, so she received a highly emetogenic-based regimen, but she had breakthrough nausea. I just wanted to point out on the tail of olanzapine, to remind folks about breakthrough nausea and vomiting, obviously, when folks are having this you need to use a different agent from a different class. I can’t tell you how many times I see people just give more when people are already on scheduled Zofran, or they’ve gotten palo and they give them more Zofran. Or they’re on a patch and they give them more Zofran. You’ve got to use something from a different class, whatever it is. Obviously, if they’re vomiting, you need to bring them in for something IV.

And then the other thing is, obviously, make sure that you’re constantly reassessing and making changes. If you’ve used a three-drug regimen and they did terrible, add olanzapine, try something different, try something from a different class. And I will say, olanzapine has been compared to metoclopramide in the breakthrough setting and is superior to metoclopramide. Olanzapine has been shown to be an effective agent to use in the breakthrough setting as well.
Just to shift gears a little bit – and this is kind of like preaching to the choir -- but we all know that nausea and vomiting negatively impacts patients’ quality of life. I’m obviously a pharmacist, so I’m using a survey that our hematology/oncology pharmacy association did just to support my point. They did a survey of 400 patients receiving chemotherapy, and as you would expect, three of the four patients who had nausea and vomiting said it negatively impacted their existence. It made them not want to take any more chemo; it had messed with their personal plans; it had caused them to change how they eat; they’ve had to call in sick for work. I think we can’t underestimate that this, even though we think we’re doing a really good job, continues to happen and that it does have a negative impact on their quality of life.

Another study that really just sort of reinforces this -- and if you just look at the top three bars there -- those are all nausea. What this showed is that while we know globally that nausea and vomiting negatively impact a patient’s quality of life, it is really more nausea. Speaking from my own experience, I would rather just throw up and have it be over with, but being continuously nauseous is just miserable. That’s what this showed, that the nausea has a greater negative impact on patients’ quality of life and that it’s more likely associated with highly emetogenic chemotherapy regimens.

What is our role as advanced practice providers? I think we probably know what it is and there’s a lot of potential opportunities for us. Opportunities in, obviously, direct patient care, but also in making sure that people in your institution or your practice are following the guidelines. Whether it be participating
in the development of these guidelines, being that champion, I think it’s important to have someone at your institution -- and the reality is it’s typically not going to be a physician -- really take this up as a cause in making sure that there are guidelines available for people to follow.

If you have an EMR, making sure that those are incorporated into your order sets or somehow a part of -- as pharmacists we make sure that it’s part of their verification process, that when they’re looking at those orders and they see that they’re getting whatever chemotherapy, that it’s part of that to make sure that if they’re getting cisplatin, that there’s also orders for all the appropriate supportive care, including nausea and vomiting.

We’re all involved in taking care of patients and making sure of the planning of their therapy, but making sure that patients are appropriately assessed. It’s one thing to have it all built in the guideline, but FOLFOX is built as moderate. But if you have our patient here who’s got five other risk factors, it’s important to make sure that you’re amending those and remembering that guidelines are just guidelines, and it’s important that we’re all taking part in assessing the patient and making changes if we need to.

One of the biggest things that we all can do is educating our coworkers. It’s amazing, there’s a lot of folks out there that have no idea really what the guidelines -- they haven’t looked at them in so long, they still remember the guidelines from 10 years ago. Every opportunity you have, whether it be with students, with other physicians, with fellows, with coworkers, with new NPs or
new PAs that are coming along, making sure to help educate them on how to best manage these patients is extremely important.

And then one of the other things is patient education. I think patients can’t hear it enough, so whether they’re hearing it from somebody in clinic and then they’re hearing it from somebody in the treatment room, making sure that they’re aware of what the risks are, but making sure they also are very clear in how to take their antiemetic medications if they do have medicines to take in the delayed setting, making sure that -- we always try to do it in advance so that if there are obstacles with them obtaining these medications because they’re expensive or because they don’t have insurance -- I always think, well, gee, Compazine’s cheap, but there are patients that even Compazine at 20 bucks they can’t swing. And olanzapine, that’s cheap, but it’s still not totally cheap. I think I just called the pharmacy the other day and it was like 250 bucks for a month. It’s inexpensive, but it’s not as inexpensive as dexamethasone or something.

But talking to patients and making sure they’re educated and making sure that -- maybe it’s not you that are dealing with those insurance obstacles, but making sure that you’re aware of them so that they can be referred to the appropriate folks. And then constantly an initial and ongoing risk assessment, but also to see how they’re doing. MASCC has a tool; we call back our patients that are high risk the day or two after chemotherapy to see how they’re doing so that we can make changes if we need to, whether it’s a nurse from your treatment area, whether it’s you, whether it’s somebody, those types of things are very helpful and continually reassessing to see how patients are doing.
In terms of the guidelines, we based ours off of NCCN. They’re also very similar. Any of them are great, they offer a great framework to start from and then working with the pharmacist or whoever’s at your institution to help make sure that you work with your formulary or whatever to make sure that you’re making those choices. They have been shown to improve care, they optimize the ordering and how patients -- how well they do. They’re good educational tools, so we use them with our students, we give them to all the fellows, we have pocket cards, and they help contain the cost of medications as well, which is always important to the pharmacy and those folks.

This is an example that I have from the pharmacy literature, but I’m well aware that there’s lots of data like this out there. And it’s a small study; it was only looking at 106 patients, but it drives home the point of how we as more advanced practice providers compared to physicians have a different viewpoint in management. These 106 patients, roughly half of them were managed according to, in this case, a pharmacist protocol, and half of them were managed by the physicians.

The physicians, 20% of those patients received excessive antiemetic prophylaxis, but they didn’t seem to do any different. And you can see in the bottom that the majority of the patients in the pharmacy group followed national guidelines compared to the physicians. You could substitute pharmacist, NP -- and when I say pharmacist, I work in the clinic. I was telling somebody, “I haven’t mixed a chemotherapy drug in 18 years.” In North Carolina we’re licensed by the Board of Medicine as well, so there’s a lot of pharmacists that are working in
clinics. When I say pharmacists, that’s a pharmacist, a PA, and I would say if you substituted that out it would be the same. We probably do a better job following some of these things than our physician colleagues do.

And what are the consequences of this over-treatment or under-treatment? What are the consequences of not following these guidelines? Well, they’re kind of obvious, but there is financial cost. As I go back to everybody giving everybody so much Zofran, it’s generic, but it’s still not cheap. Let me just tell you, it’s still not cheap. Our nurses seem to spend so much time doing prior authorizations and overrides and whatever, so there’s time constraints, there’s financial costs, there’s side effects. The 5-HT₃ antagonists do cause constipation, headaches, increases in your blood sugars with dexamethasone, excess pill burden. So that’s where that 1-day regimen can come in handy.

We have patients get completely just confused, especially with the dex. You take it once, then you take it twice today, and then it can get very confusing, especially when you’ve got patients that might have brain metastasis or other things going on. Somebody I saw in clinic recently who had never had to take a medicine in his life and now all of a sudden he had all these medicines and it’s just overwhelming. And then there’s the obvious downside of uncontrolled nausea and vomiting. If you under-treat patients and they have issues, then you introduce the potential for anticipatory nausea and vomiting.

And then as that survey showed, you have patients that are like, “I’m done, I’m not going to do this anymore.” There’s always that risk of patients no
longer wanting to continue with their care, needing to come to the hospital and increase healthcare resources for fluids, getting admitted to the hospital.

In conclusion, chemotherapy-induced nausea and vomiting, despite all the advances that have been made, and we have made some significant advances over the years, continues to be a problem, especially in the delayed setting and especially nausea. The new agents that have -- the not so new, but finding new use, NK1 receptor antagonist and olanzapine -- they have been shown to be effective and in the case of olanzapine maybe offer better efficacy with nausea. They've all been incorporated in some way into the guidelines.

It'll be interesting to see when the other two new sets of guidelines come out, which I don't honestly know when that's going to be, see how sort of things change. Are they going to follow MASCC and increase carbo to a high? Are they going to incorporate olanzapine in there in a different way? It'll be interesting to see. Again, just to remind everyone to follow the guidelines, to use agents that have different mechanisms of action, to constantly reassess your patients, and to say what we already know, that as advanced practice providers, nurses, and pharmacists, we all play a huge role in managing these patients and continually assessing them.

And with that, I think I have 2 minutes to take questions. Anybody have any questions?

FEMALE The 5H23 is not being indicated in delayed nausea for highly emetic, but in line three they are indicated in moderately. Am I reading that slide incorrectly?
DR. BARBOUR  No. The question was I made a comment about the serotonin antagonists in the delayed setting for highly emetogenic chemotherapy. None of the guidelines recommends scheduled 5H23 antagonists beyond day one in highly emetogenic regimens. None of them. It is listed as an option in the moderate emetogenic regimens in the delayed setting, but it’s not in the highly emetogenic setting.

FEMALE  Does that make sense?

DR. BARBOUR  The data doesn’t support that they really offer a whole lot of benefit in the highly emetogenic setting. There was a meta-analysis I can’t remember how many years ago, but it’s been several years, that the serotonin antagonists have not been listed in the guidelines for scheduled use after highly emetogenic chemotherapy. That doesn’t mean people don’t do it all the time, but it’s not recommended by the guidelines.

FEMALE  And you didn’t mention anything about benzodiazepine.

DR. BARBOUR  The question was about benzodiazepine. Benzodiazepines don’t have a whole lot of benefit in terms of prophylaxis and CINV; their big role is in anticipatory nausea and vomiting. They do have a role in the anticipatory setting, so they can be used as needed or they can be used in patients who do have a significant anticipatory component, but they’re not part of the standard prophylactic regimens for all those levels of chemotherapy.

FEMALE  And then just one more question. Docetaxel. I’m always surprised to see that has a low emetogenic potential, and I just wonder if that’s your experience as well.
DR. BARBOUR  The question was she’s surprised that docetaxel is listed as a low, and is that my experience? We have not had patients have a lot of issues with docetaxel, so at our institution our prophylactic recommendations for our low emetogenic chemotherapies, they get a steroid. That’s what our patients get. But if you have a patient who they’re getting docetaxel, but they’re 35, they’re a female, maybe they need to get bumped up; that’s just looking at the drug, that’s not taking anything else into consideration. Any others?

FEMALE  With these new agents that you mentioned today, are there advantages to these new NK1s over previous ones? Because, obviously, they’re going to be more expensive.

DR. BARBOUR  Right. The question was, is there any advantage to the newer NK1 antagonists over what’s currently available? They haven’t been compared to one another, so you can’t say that efficacy-wise one is better than the other because they’ve all been compared to a 5H23 plus dex, so they’ve all been shown to be efficacious. At least in my opinion, clinically, based on the data that we have -- because we’ve reviewed all of these, our resident actually did it last year as a class review -- clinically, they’re all equally effective; you can at least say that. There is no data that shows that one is better than the other.

But, then you look at, are there other things that might make you choose one more than the other? The rolapitant has the potential for less drug interactions. Depending on your patient and depending maybe on what other medications they’re on or whatever, that’s an advantage that makes you want to use that over another one.
The oral ones, obviously, if you have patients that have issues or have had issues with the IV fosaprepitant, they don’t have, obviously, because they’re oral, the risks for the reaction or the injection site reaction. Up until now your only other option has been to use the 3-day aprepitant, and then you run into adherence and they have to take it for 3 days, so it might offer an advantage in that setting, although I do know that some people just give all the aprepitant on day one or give it on day one.

At least right now we don’t have comparison data, so it’s these sort of other things, other intangible things, that might make you choose one over the other. Your pharmacy doesn’t have to make rolapitant or NK1 antagonists or netupitant, it can be in your Omnicell or whatever. Obviously, we all look at efficacy first, but if all that is equal, then you start looking at some of these other things. And whether all those things are outweighed by the cost, that’s up to each individual place or institution.

MALE If a lot of my patients are going home with prochlorperazine, is there a buildup of side effects with olanzapine and prochlorperazine together?

DR. BARBOUR It’s interesting that you said that. When you talk to Rudy Navari and ask him what did he use for his breakthrough on his study, he’s like, “I don’t know.” But when you talk to some of the other folks, they have given prochlorperazine, Compazine, to their patients that are on olanzapine. I would say that even with all the excitement or the data with olanzapine, people are still very hesitant to switch to that, at least in my experience. I see people add it after
the fact, which contradicts all that we’re told about using everything you’ve got up front, but it still seems to be what people are doing.

We have used the four-drug regimen in patients that are getting cisplatin that are young, that are female, that seem to have everything, and we give them Compazine as their breakthrough. There’s not really anything out there that says once if they’re already on olanzapine what’s the best breakthrough. I think it’s dealer’s choice. And then you run into all the potential drug interactions and Q2C prolongation, but so far that hasn’t really borne out to be anything.

[END]