Guideline Update on Antiemetics

Clinical Practice Guideline
Special Announcements

• Please check [www.asco.org/guidelines/antiemetics](http://www.asco.org/guidelines/antiemetics) for current FDA alert(s) and safety announcement(s) on antiemetics
Introduction

• ASCO antiemetics guideline was originally published in 1999 and previously updated in 2006

• The scope of this update is largely the same as 2006
  – Evaluation of complementary therapy added
Guideline Methodology: Systematic Review

- A systematic review provided preliminary literature for consideration:
  - Agency for Healthcare Research and Quality (AHRQ)-funded Oregon Evidence-Based Practice Center
- An ASCO Update Committee considered pertinent literature through February 2010:
  - MEDLINE
  - Cochrane Collaboration Library
  - ASCO Annual Meetings
  - Multinational Association for Supportive Care in Cancer (MASCC) Meetings
Guideline Update: Categories for Antiemetics in Oncology

Chemotherapy-Induced Nausea and Vomiting (CINV)

- Emetic risk of chemotherapy
- Combination chemotherapy
- Anticipatory nausea and vomiting
- Complementary therapy
- Adjunctive therapy
- Anticipatory CINV
Guideline Update: Categories for Antiemetics in Oncology

Chemotherapy-Induced Nausea and Vomiting (CINV) (cont’d)

- Special populations
  - High Dose Chemotherapy
  - Multi-day chemotherapy
  - Pediatric Populations

Radiation-Induced Nausea and Vomiting (RINV)

- Emetic risk by radiation site
- Combined chemotherapy and radiation therapy
Background

- **Emesis** (vomiting) is measured by the number of vomiting or retching episodes after treatment.
- **Nausea** is the patient’s perception that emesis may occur.
CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)
Emetic Risk of Antineoplastic Agents: Emetic Risk Categories*

- **Four** emetic risk categories:
  - High (>90%)
  - Moderate (30%–90%)
  - Low (10%–30%)
  - Minimal (<10%)

*Antiemetic risk categories were developed from historic studies*
# 2011 Emetic Risk Categories of Single Agents Antineoplastic

## Emetic Risk Antineoplastic Agents Administered Intravenously

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine</td>
<td>Azacitidine</td>
<td>Fluorouracil</td>
<td>Panitumumab</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Alectuzumab</td>
<td>Bortezomib</td>
<td>Pemetrexed</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Carboplatin</td>
<td>Cabazitaxel</td>
<td>Temsirolimus</td>
</tr>
<tr>
<td>Cyclomustine</td>
<td>Clofarabine</td>
<td>Catumaxomab</td>
<td>Topotecan</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Cyclophosphamide</td>
<td>Cytarabine</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Dactinomycin</td>
<td>&lt;1500 mg/m²</td>
<td>≤1000 mg/m²</td>
<td>2-Chlorodeoxyadenosine</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>Daunorubicin*</td>
<td>Docetaxel</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>Doxorubicin*</td>
<td>Doxorubicin HCL</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Epirubicin*</td>
<td>liposome injection</td>
<td>Busulfan</td>
</tr>
<tr>
<td></td>
<td>Idarubicin*</td>
<td>Etoposide</td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>Gemcitabine</td>
<td>Fludarabine</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>Ixabepilone</td>
<td>Pralatrexate</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>Methotrexate</td>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitomycin</td>
<td>Vinblastine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitoxantrone</td>
<td>Vincristine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel</td>
<td>Vinorelbine</td>
</tr>
</tbody>
</table>

*These anthracyclines, when combined with cyclophosphamide, are now designated as high emetic risk*
CINV: Recommendation by Risk Category, High Emetic Risk

**2011 Recommendation:**

- Three drug combination of NK₁ antagonist, 5-HT₃ receptor antagonist, and dexamethasone
- Adriamycin and cyclophosphamide combination regimens re-classified as highly emetogenic

**Dosing:**

- Day 1: NK₁ antagonist (aprepitant 125 mg OR fosaprepitant 150 mg) + 5-HT₃ receptor antagonist (*options on next slide*) + dexamethasone 12 mg
- Day 2: dexamethasone 8 mg + if NK₁ antagonist = aprepitant, then aprepitant 80 mg
- Day 3: if NK₁ antagonist = aprepitant, then aprepitant 80 mg and dexamethasone 8 mg (*dexamethasone may be given for 3 or 4 days*). If NK₁ antagonist = fosaprepitant, then dexamethasone 8 mg twice daily on days 3-4
CINV: Recommendation by Risk Category, High Emetic Risk

<table>
<thead>
<tr>
<th>5-HT&lt;sub&gt;3&lt;/sub&gt; Receptor Antagonist Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-HT&lt;sub&gt;3&lt;/sub&gt; Receptor Antagonist</strong></td>
</tr>
<tr>
<td>Granisetron</td>
</tr>
<tr>
<td>Ondansetron</td>
</tr>
<tr>
<td>Palonosetron</td>
</tr>
<tr>
<td>Dolasetron</td>
</tr>
<tr>
<td>Ramosetron</td>
</tr>
<tr>
<td>Tropisetron</td>
</tr>
</tbody>
</table>
CINV: Recommendation by Risk Category, Moderate Emetic Risk

- **2011 Recommendation:**
  - Two drug combination of palonosetron and dexamethasone
  - If palonosetron is not available, any of the first-generation 5-HT₃ receptor antagonists may be used—preferably ondansetron or granisetron

**Dosing:**
- Palonosetron 0.25 g IV OR 0.50 mg oral, day 1 only
- Dexamethasone 8 mg (IV or oral), days 1-3
CINV: Recommendation by Risk Category, Moderate Emetic Risk

• Aprepitant* not recommended, though clinicians may consider its use
  – If clinicians opt to use aprepitant, dosing:
    • Aprepitant: 125 mg day 1, 80 mg days 2 and 3
    • 5-HT3 receptor antagonist dosing as on slide 11, no preferred agent
    • Dexamethasone: 12 mg on day 1 ONLY

*Note: No data available at the time of the update on fosaprepitant in moderate risk setting
CINV: Recommendation by Risk Category, Low and Minimal Emetic Risk

- **2011 Recommendation:**

  **Low Emetic Risk:**
  - A single 8 mg dose of dexamethasone before chemotherapy is suggested.

  **Minimal Emetic Risk:**
  - No antiemetic should be administered routinely before or after chemotherapy.
CINV: Combination Chemotherapy

2011 Recommendation:
Administer antiemetics appropriate for the component chemotherapeutic agent of greatest emetic risk

Note: Adriamycin and cyclophosphamide combinations are now classified as highly emetogenic
CINV: Adjunctive Drugs

2011 Recommendation:

- Lorazepam and diphenhydramine are useful adjuncts to antiemetic drugs, but are not recommended as single agent antiemetics.
CINV: Complementary therapy

2011 Recommendation:

No published RCT data which met inclusion criteria (for the systematic review) are currently available to support a recommendation about such therapies.
Special Emetic Populations: High-Dose Chemotherapy with SCT or BMT

2011 Recommendation:

- A 5-HT3 receptor antagonist combined with dexamethasone is recommended.
- Aprepitant should be considered, although evidence to support its use is limited.
Special Emetic Populations: Multi-day Chemotherapy

2011 Recommendation:

- Antiemetics appropriate for the emetogenic risk class of the chemotherapy should be administered for each day of the chemotherapy and 2 days afterward, if appropriate.

- Based on limited data, patients receiving 5-day cisplatin regimens should receive aprepitant + 5-HT₃ receptor antagonist + dexamethasone.
Special Emetic Populations: Vomiting and Nausea Despite Recommended Prophylaxis

- **2011 Recommendation**
  - Re-evaluate emetic risk, disease status, concurrent illness, and medications;
  - Ascertain that the best regimen is being given for the emetic risk;
  - Consider adding lorazepam or alprazolam to the regimen; and,
  - Add olanzapine or substitute high-dose intravenous metoclopramide instead of 5-HT₃ receptor antagonist or add dopamine antagonist.
Special Emetic Populations: Anticipatory Emesis

**Anticipatory Emesis:**

- Begins before treatment
- May occur in patients with poor control of vomiting during prior chemotherapy

**2011 Recommendation:**

- Clinicians should always use the antiemetic regimen recommended for the initial chemotherapy based on emetic risk
- Use the most active antiemetic regimens appropriate for chemotherapy
- Behavioral therapy with systematic desensitization
Special Emetic Populations: Pediatric Oncology Patients

- Few research trials evaluate antiemetic therapy in children receiving cancer therapy

2011 Recommendations:

- A $5HT_3$ receptor antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high or moderate emetic risk.

- Due to variation of pharmacokinetic parameters in children, higher weight-based doses of $5HT_3$ receptor antagonists than those used in adults may be required.
RADIATION-INDUCED INDUCED NAUSEA AND VOMITING (RINV)
## RINV: Emetic Risk Categories of Radiation

<table>
<thead>
<tr>
<th>Emetic Risk</th>
<th>Irradiated area</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Total Body (TBI)</td>
</tr>
<tr>
<td></td>
<td>Total Nodal Irradiation</td>
</tr>
<tr>
<td>Moderate</td>
<td>Upper Abdomen</td>
</tr>
<tr>
<td></td>
<td>Upper Body Irradiation</td>
</tr>
<tr>
<td></td>
<td>Half Body Irradiation</td>
</tr>
<tr>
<td>Low</td>
<td>Lower Thorax and Pelvis</td>
</tr>
<tr>
<td></td>
<td>Cranium, Craniospinal, and Head &amp; Neck</td>
</tr>
<tr>
<td>Minimal</td>
<td>Extremities</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
</tr>
</tbody>
</table>
### RINV: 5-HT₃ Receptor Antagonist Dosing

<table>
<thead>
<tr>
<th>5-HT₃ Antagonist</th>
<th>Intravenous</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granisetron¹</td>
<td>1 mg or 0.01 mg/Kg</td>
<td>2 mg</td>
</tr>
<tr>
<td>(preferred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron¹</td>
<td>8 mg or 0.15 mg/Kg</td>
<td>8 mg twice daily</td>
</tr>
<tr>
<td>(preferred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palonosetron²</td>
<td>0.25 mg</td>
<td>0.50 mg</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>100 mg</td>
<td>IV formulation NOT recommended</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

¹ Preferred agents, ² No data on dosing frequency available, every 2nd or 3rd day suggested
RINV: Recommendation by Risk Category, High Emetic Risk

2011 Recommendation

⇒ 5-HT₃ receptor antagonist, before each fraction and at least 24 hours after end of XRT, and a 5-day course of dexamethasone during fractions 1-5.

Dosing:
- 5-HT₃ receptor antagonist: see slide 26
- Dexamethasone: 4mg oral or IV, fractions 1-5
RINV: Recommendation by Risk Category, Moderate Emetic Risk

2011 Recommendation

- 5-HT₃ receptor antagonist before each fraction, throughout course of radiotherapy.
- Patients may be offered a short course of dexamethasone during fractions 1-5.

Dosing:

- 5-HT₃ receptor antagonist: see slide 26
- Consider- Dexamethasone: 4mg oral or IV, fractions 1-5
RINV: Recommendation by Risk Category, Low Emetic Risk

- 2011 Recommendation
  - 5-HT$_3$ receptor antagonist* as rescue or prophylaxis
  - For patients who experience RINV while receiving rescue therapy only, prophylactic treatment should continue until radiotherapy is complete.

Dosing:
- 5-HT$_3$ receptor antagonist: see slide 26
RINV: Recommendation by Risk Category, Minimal Emetic Risk

2011 Recommendation

- 5-HT₃ receptor antagonist* as rescue or prophylaxis
- Prophylactic antiemetics should continue throughout radiation treatment if a patient experiences RINV while receiving rescue therapy.

Dosing:

- 5-HT₃ receptor antagonist: see slide 26
- Dopamine receptor antagonist: metoclopramide 20 mg oral or prochlorperazine 10 mg oral or IV
Nausea and vomiting during concurrent radiation therapy and chemotherapy

→ Determine antiemetic therapy according to the emetic risk of the chemotherapy, unless emetic risk with planned radiotherapy is higher.
New Antiemetics: FDA approvals since 2006 update

- **Fosaprepitant**
  - NK₁ antagonist, intravenous aprepitant pro-drug
  - Acceptable where NK₁ antagonist indicated

- **Granisetron transdermal system**
  - Patch delivers granisetron continuously over five days
  - Option for multi-day chemotherapy and high or moderate risk radiation therapy

- **Ondansetron ODT**
  - Orally disintegrating tablet
  - Acceptable where 5-HT₃ receptor antagonist indicated
2011 Update Recommendation Changes

CINV

• Highly emetogenic agents:
  – A/C combinations re-classified as highly emetic
• Moderately emetogenic agents:
  – Palonosetron preferred 5-HT\textsubscript{3} receptor antagonist
• Low emetogenic agents
  – No change
• Minimally emetogenic agents
  – No change
• Combination chemotherapy
  – No change
• Adjunctive drugs
  – No change
• Complementary Therapy
  – New question for 2011
2011 Update Recommendation Changes, cont’d

CINV, cont’d

• Pediatric Patients
  – No change

• High-dose chemotherapy with SCT or BMT
  – Consider the addition of aprepitant to antiemetic regimen

• Multi-day chemotherapy
  – Recommended antiemetic regimen for patients receiving 5-day cisplatin:
    aprepitant + 5-HT₃ receptor antagonist + dexamethasone

• Emesis or Nausea despite optimal prophylaxis
  – Option of adding olanzapine to antiemetic regimen

• Anticipatory nausea and vomiting
  – No change
2011 Update Recommendation Changes, cont’d

**RINV**

- **High Risk RINV**
  - Addition of 5-day course of dexamethasone during fractions 1-5
- **Moderate Risk**
  - Consider offering 5-day course of dexamethasone during fractions 1-5
- **Low risk**
  - 5-HT₃ receptor antagonist as either prophylaxis or rescue
  - Patients requiring rescue should receive subsequent prophylactic antiemetic therapy
- **Minimal risk**
  - Patients requiring rescue should receive subsequent prophylactic antiemetic therapy
- **Combined chemotherapy and radiation therapy**
  - No change
# Guideline Methodology:
## Update Committee Members

<table>
<thead>
<tr>
<th>Update Committee Members</th>
<th>Affiliation/Institution</th>
</tr>
</thead>
<tbody>
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<td>Memorial-Sloan Kettering Cancer Center</td>
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<tr>
<td>Gary H. Lyman, MD <em>Co-Chair</em></td>
<td>Duke University</td>
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<td>Paul J. Hesketh, MD Steering Committee</td>
<td>Lahey Clinic Medical Center</td>
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<td>Mark G. Kris, MD Steering Committee</td>
<td>Memorial-Sloan Kettering Cancer Center</td>
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<td>Maurice Chesney</td>
<td>Patient Representative</td>
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<td>Lawrence Memorial Hospital Oncology Center</td>
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<td>Vivantes Clinic of Radiooncology and Nuclear Medicine</td>
</tr>
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<td>The Johns Hopkins Hospital</td>
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</tbody>
</table>
Additional ASCO Resources

- The full guideline, dose/schedule table, guideline summary and patient guide are available at http://www.asco.org/guidelines/antiemetics

- The patient guide is also available at http://www.cancer.net
ASCO Guidelines

This resource is a practice tool for physicians based on an ASCO® practice guideline. The practice guideline and this presentation are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This presentation does not recommend any particular product or course of medical treatment. Use of the practice guideline and this resource is voluntary. The full practice guideline and additional information are available at http://www.asco.org/guidelines/antiemetics. Copyright © 2011 by American Society of Clinical Oncology®. All rights reserved.