BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults

Protocol Code: SCNAUSEA

Tumour group: SUPPORTIVE CARE

Physician Contact: Dr. Paul Hoskins

ELIGIBILITY

• Adults receiving chemotherapy.

• Drug acquisition: Antiemetics are considered supportive treatment. These agents are not BC Cancer benefit drugs and are not covered by any BC Cancer program. Patients being treated with these agents should have prescriptions filled at a community pharmacy and must arrange their own payment for the drugs.

EXCLUSION CRITERIA

• Pediatric patients.

• Radiation-induced nausea and vomiting.

APPROACH TO TREATMENT

• The goal is NO nausea or vomiting.\textsuperscript{1-3}

• It is far easier to prevent nausea and vomiting than to treat it.\textsuperscript{1,2}

• Anticipatory nausea and vomiting is a conditioned response, and can only happen after a negative past experience.\textsuperscript{1,2}

• Ensure optimal antiemetic therapy for every cycle of chemotherapy.

• Use of guidelines: This is a general reference based upon best available evidence and is not intended to replace the clinical judgment of individual practitioners caring for individual patients.
**PROPHYLACTIC ANTIEMETIC REGIMENS FOR IV AND COMBINED IV / ORAL CHEMOTHERAPY**

- For multiple days of chemotherapy, repeat antiemetics before each treatment (*Exception: netupitant-palonosetron is dosed on day 1 only*).
- See comment below table for ORAL chemotherapy regimens.
- For prophylaxis after prior treatment failures, refer to Figure 1.

<table>
<thead>
<tr>
<th>EMETOGENICITY</th>
<th>PRE-CHEMOTHERAPY</th>
<th>POST-CHEMOTHERAPY</th>
</tr>
</thead>
</table>
| **High (HEC)** | dexamethasone\(^6\) 8 to 12 mg PO\(^1,3\)  
PLUS NK\(^1\) and 5-HT\(^3\) ANTAGONIST  
- netupitant-palonosetron 300 mg-0.5 mg\(^\text{†}\) PO\(^\text{†}\)  
- OR  
- aprepitant\(^\dagger\) 125 mg PO\(^7,9\)  
- PLUS one 5-HT\(^3\) antagonist\(^\text{‖}\):  
  - ondansetron 8 mg PO\(^3\)  
  - granisetron 1 mg PO\(^17,19\)  
  - palonosetron 0.5 mg PO\(^17,19\)  
+/- olanzapine\(^\text{‖}\) 5 to 10 mg PO\(^{15,16,18}\) | dexamethasone\(^5\) 4 mg PO evening of chemo,\(^7\) then BID x 2 to 4 days\(^2,3\)  
- No post-chemotherapy netupitant-palonosetron  
- OR  
- aprepitant\(^\dagger\) 80 mg PO daily on days 2 and 3, IF aprepitant used on day 1\(^2,8,9\)  
+/- ONE ANTIEMETIC “AS-NEEDED” (if not using olanzapine):  
  - prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days\(^3,18\) OR  
  - metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days\(^3,4,18,19\)  
+/- olanzapine 5 to 10 mg PO daily on days 2, 3 and 4 (if olanzapine used on day 1\(^15,18\); do not use with prochlorperazine or metoclopramide) |
| **Moderate (MEC)** | dexamethasone\(^6\) 8 to 12 mg PO\(^3,18\)  
PLUS ONE 5-HT\(^3\) ANTAGONIST:  
- ondansetron 8 mg PO\(^3\)  
- granisetron 1 mg PO\(^17,19\)  
- palonosetron 0.5 mg PO\(^17,19\)  
+/- olanzapine\(^\text{‖}\) 5 to 10 mg PO\(^{15,16,18}\) | dexamethasone\(^5\) 4 mg PO evening of chemo,\(^7\) then PO BID x 2 to 3 days\(^2,3\)  
- PLUS ONE 5-HT\(^3\) antagonist\(^\text{‖}^\text{‡}\):  
  - ondansetron 8 mg PO\(^3\)  
  - granisetron 1 mg PO\(^17,19\)  
  - palonosetron 0.5 mg PO\(^17,19\)  
+/- olanzapine\(^\text{‖}\) 5 to 10 mg PO daily on days 2 and 3\(^3,15,16,18\) (if olanzapine used on day 1\(^15\); do not use with prochlorperazine or metoclopramide) |
| **Low** | dexamethasone\(^5\) 4 to 12 mg PO\(^7,14\)  
- prochlorperazine 10 mg PO\(^{16\,\text{OR}}\)  
- metoclopramide 10 to 20 mg PO\(^{3,18\,\text{OR}}\)  
- ondansetron 8 mg PO\(^{17,19\,\text{OR}}\)  
- granisetron 1 mg PO\(^{17,19\,\text{OR}}\)  
- no prophylaxis\(^19\) | dexamethasone 4 mg BID PRN for up to 2 to 3 days\(^1,3\)\(^2\,\text{OR}^\text{‡}\)  
- prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days\(^3,18\)\(^2\,\text{OR}^\text{‡}\)  
- metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days\(^3,4,18,19\)\(^2\,\text{OR}^\text{‡}\)  
- no prophylaxis\(^3,18,19\) |
| **Minimal (Rare)** | Prophylactic treatment not normally required\(^16,19\) | prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days\(^1,18\)\(^2\,\text{OR}^\text{‡}\)  
- metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days\(^3,4,18,19\)\(^2\,\text{OR}^\text{‡}\)  
- no prophylaxis\(^3,18,19\) |
Pre-chemotherapy is interpreted as 30 to 60 minutes prior to the start of chemotherapy

*Highly emetogenic chemotherapy (HEC), Moderately emetogenic chemotherapy (MEC)

§Dexamethasone doses may be individualized. When netupitant-palonosetron is used with AC protocols, omission of day 2 to 4 dexamethasone doses is recommended. In general, lower dexamethasone doses and/or shorter durations may be considered for patients on non-CISplatin regimens. Steroids are not recommended as antiemetics for immunotherapies.

‡Netupitant-palonosetron 300 mg-0.5 mg capsules are a fixed dose, combination product given on day 1 only.

†For inpatients unable to swallow:
- Consider replacing pre-chemotherapy aprepitant with fosaprepitant IV 150 mg
- Post-chemotherapy fosaprepitant NOT needed, dose of 5-HT3 antagonist and dexamethasone remain the same (fosaprepitant 150 mg confers comparable serum level to aprepitant 125 mg which seems sufficient to cover days 2 and 3)

‖No additional 5-HT3 antagonist is required if netupitant-palonosetron combination used

¶Consider adding olanzapine if nausea / vomiting not controlled with 5-HT3 antagonist plus dexamethasone plus NK1 antagonist in previous cycle, especially if delayed nausea is a concern. Note: olanzapine adverse drug reactions including sedation and QTc prolongation, drug interactions and black box warning of increased mortality in elderly patients with dementia. Olanzapine should NOT be used with metoclopramide, prochlorperazine, or haloperidol due to increased risk of extrapyramidal symptoms.

#For multiday chemotherapy regimens:
- Limited data exist for netupitant-palonosetron. Efficacy has been shown with standard dosing of 1 capsule on day one of a three-day HEC regimen.
- Limited data support dosing oral aprepitant over extended days.
- Suggested regimens based on 5-day cisplatin regimens:

<table>
<thead>
<tr>
<th>aprepitant</th>
<th>5-HT3 antagonist</th>
<th>dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mg PO day 1, then 80 mg PO days 2 to 7</td>
<td>days 1 to 5</td>
<td>days 1 to 8</td>
</tr>
<tr>
<td>125 mg PO day 3, then 80 mg PO days 4 to 7</td>
<td>days 1 to 5</td>
<td>days 1 and 2</td>
</tr>
</tbody>
</table>

- Suggested regimens based on 3 day MEC and HEC regimens:

<table>
<thead>
<tr>
<th>aprepitant</th>
<th>5-HT3 antagonist</th>
<th>dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mg PO day 1, then 80 mg PO days 2 to 7</td>
<td>On treatment days</td>
<td>days 1 to 8</td>
</tr>
</tbody>
</table>

PROPHYLACTIC ANTIEMETIC REGIMENS FOR ORAL CHEMOTHERAPY:

High or moderate emetogenic risk:
- choose one 5-HT3 antagonist pre-chemotherapy as listed for HEC/MEC in table above
- post chemotherapy breakthrough dosing as listed for HEC/MEC in table above

Low or minimal (rare) emetogenic risk:
- prn recommended
- if nausea/vomiting occurs:
  - metoclopramide 10 to 20 mg PO pre-chemotherapy then q6h prn OR
  - prochlorperazine 10 mg PO pre-chemotherapy then q6h prn (max 40 mg/day) OR
  - choose one 5-HT3 antagonist as listed in table above for low emetogenic risk, given daily prn
- post chemotherapy breakthrough dosing as listed in table above for low/minimal (rare) emetogenic risk
ADDITIONAL TREATMENT NOTES

- If IV administration of a 5-HT\textsubscript{3} antagonist is clinically indicated, use the same IV dose as the oral dose for ondansetron and granisetron.\textsuperscript{3} In contrast, palonosetron 0.5 mg PO is equivalent to palonosetron 0.25 mg IV\textsuperscript{17,19}.
- Single doses of 5-HT\textsubscript{3} antagonists are as effective as multiple doses.\textsuperscript{3,5}
- First generation 5-HT\textsubscript{3} antagonists (ondansetron, granisetron) are equally effective. Choose based on availability and cost.\textsuperscript{1-3,5}
- Palonosetron, a second generation 5-HT\textsubscript{3} antagonist, has a longer duration of action compared to first generation 5-HT\textsubscript{3} antagonists.\textsuperscript{25}
- First generation 5-HT\textsubscript{3} antagonists may increase the risk of arrhythmia and Torsade de Pointes in patients:
  - with congenital long QT syndrome, congestive heart failure, or bradyarrhythmias
  - with pre-existing hypokalemia or hypomagnesemia,
  - using medications that prolong QT interval or cardiotoxic chemotherapy.
  - ECG monitoring is recommended in the above patients.\textsuperscript{13,20}
- Except for highly emetogenic chemotherapy, a corticosteroid \textit{alone} is the cornerstone of therapy for prevention of delayed nausea and vomiting. There is no role for the routine use of 5-HT\textsubscript{3} antagonists more than 24 hours after chemotherapy.\textsuperscript{1-3,6}
- Currently available NK\textsubscript{1} antagonists are equally effective.\textsuperscript{18,19}
- Olanzapine may be included on days 1 to 4 of HEC or on days 1 to 3 of MEC for additional control of delayed nausea.\textsuperscript{15-18} A lower dose of 5 mg should be considered for elderly and over-sedated patients. Other cautions include:
  - Increased risk of death in elderly patients with dementia related psychosis\textsuperscript{2}
  - Concomitant administration of parenteral olanzapine and parenteral benzodiazepine is not recommended (toxicity may occur regardless of route)\textsuperscript{18}
  - QTc prolongation (see above monitoring recommendations for 5-HT\textsubscript{3} antagonists)
  - Sedation, most notable on day 2
  - Fall risk
  - Extrapyramidal symptoms
- Olanzapine and single-agent palonosetron are not covered by PharmaCare.\textsuperscript{27}

DETERMINING EMETOGENICITY OF CHEMOTHERAPY

- Emetogenicity\textsuperscript{18}: percentage of patients who will experience acute emesis if not treated.
  - high = greater than 90%
  - moderate = 30% to 90%
  - low = 10% to less than 30%
  - minimal (rare) = less than 10%
- Combination chemotherapy:
  - Consult chemotherapy protocol.
  - If emetogenicity is not specified, consult Cancer Drug Manual.
  - Treat for the most emetogenic agent\textsuperscript{1} OR use Hesketh Algorithm.

HESKETH ALGORITHM\textsuperscript{7}

- Identify the most highly emetogenic agent in the combination, then add the contribution of other agents using the following rules:
  - high/moderate: increase emetogenicity of the combination by one level per agent.
  - low: increase emetogenicity of the combination by one level, regardless of how many such agents are added.
  - rare: do not contribute.
TREATMENT FAILURES
If a patient experiences nausea or vomiting despite optimal prophylactic therapy, complete steps 1, 2, and 3 as follows:

1. Rule out or treat other causes of nausea and vomiting:
   - intestinal obstruction, gastroparesis, gastritis
   - medications (pain meds, bronchodilators)
   - brain metastases
   - vestibular dysfunction
   - electrolyte imbalance, uremia
   - infection

2. Control this episode of nausea and vomiting.
   - Approach to treatment of vomiting:
     - give additional antiemetic agent from a different class if vomiting/retching occurs while on antiemetics
     - give 5-HT₃ antagonist +/- dexamethasone if vomiting/retching occurs after antiemetics are finished
     - use rectal, parenteral or sublingual route of administration
     - use around-the-clock dosing rather than prn until vomiting stops
     - monitor and correct hydration and electrolytes as required
     - consider admission to hospital

Possible additional ongoing antiemetics to use if patient is:

<table>
<thead>
<tr>
<th>vomiting</th>
<th>nauseated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>haloperidol 0.5 to 2 mg PO/IV every 4 to 6 hours¹⁸</td>
<td>olanzapine 5 to 10 mg PO daily (if not previously given and if not using metoclopramide, prochlorperazine or haloperidol)¹⁷,¹⁸</td>
</tr>
<tr>
<td>scopolamine 1.5 mg transdermal patch q72 hours¹⁸</td>
<td>dimenhydrinate 100 mg PO every 12 hours alternating with prochlorperazine 10 mg PO every 12 hours (for a q6h regimen)³</td>
</tr>
<tr>
<td>nabilone 1 to 2 mg PO bid¹⁸</td>
<td>prochlorperazine 25 mg PR every 12 hours or 10 mg PO/IV every 6 hours¹⁸</td>
</tr>
<tr>
<td></td>
<td>metoclopramide 10 to 20 mg PO every 4 to 6 hours¹⁸</td>
</tr>
<tr>
<td></td>
<td>nabilone 1 to 2 mg PO bid¹⁸</td>
</tr>
</tbody>
</table>

*5-HT₃ antagonist plus dexamethasone if above choices are ineffective³

3. Plan prophylactic regimen for next cycle using Figure 1.
Figure 1. SUBSEQUENT ANTIEMETIC REGIMENS AFTER TREATMENT FAILURE

Did patient have ANY nausea or vomiting last cycle? no

Anxiety or signs of anticipatory nausea and vomiting? yes

Vomited within 24 h of start of chemo? yes

Vomited > 24 h after chemo? no

Acute nausea and vomiting:
Is patient on highest pre-chemo antiemetic regimen?

Controlled

Increase to a higher risk regimen pre-chemo

Continued current management

Acute nausea and vomiting:
May increase or change 5-HT₃ antagonist (anecdotal evidence)

Delayed nausea and vomiting:
treat for duration of emesis + 1 day

Is patient on highest post-chemo antiemetic regimen?

Controlled

Increase to a higher risk regimen post-chemo

Continued current management

Delayed nausea and vomiting:
May add one or more of:
- olanzapine 5 to 10 mg PO daily
- metoclopramide 10 to 20 mg PO q4 to 6h
- LORazepam 0.5 to 2 mg PO/SL bid to qid
- haloperidol 0.5 to 2 mg PO q4 to 6h
- prochlorperazine 25 mg PR q12h or 10 mg PO q6h
- dimenhydrinate 100 mg PO q12h, alternate with prochlorperazine 10 mg PO q12h (i.e., q6h regimen)
- H2 blocker or proton pump inhibitor (if patient has dyspepsia)
- scoPOlamine 1.5 mg transdermal patch q72h

Consider one or more of:
- nabolone 1 to 2 mg PO q12h
- behavioural modification
- inpatient chemo (monitoring, hydration and electrolyte replacement prn)

May change chemo regimen
REFERENCES (see appendix for separate document “Antiemetic Guidelines”)

20. BC PharmaCare Limited Coverage Drugs. Accessed 16 Dec 2019 at: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-olanzapine
27. BC PharmaCare Limited Coverage Drugs. Accessed 16 Dec 2019 at: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program/limited-coverage-drugs-olanzapine