



Cancer Care Ontario

2019 Antiemetic Recommendations for Chemotherapy-Induced Nausea and Vomiting: A Clinical Practice Guideline

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the leading and most feared side effects of chemotherapy and can have a significant impact on patients' quality of life during treatment. With the availability of novel agents for CINV and more effective antiemetic regimens, the incidence of CINV has improved over the years. However, optimal CINV prevention relies on the appropriate emetic risk classification of chemotherapy regimens and regimen-specific antiemetic prophylaxis.

There is variation in practice across the province with regard to optimal CINV prevention and management. With new evidence around CINV, there was a need to update the Cancer Care Ontario (CCO) 2013 Antiemetic Report. Adopting these recommendations in practice can have significant benefit to patients, as adherence to antiemetic guidelines has been associated with improved CINV outcomes^{1,2}.

This guideline was developed by a working group of subject matter experts in oncology, which included medical oncologists, pharmacists and nurses. After a literature review was conducted, the Working Group met via teleconference and corresponded through email to review and assess the quality of the evidence, and contribute to the development of the recommendations. The guideline was then circulated for expert review. This document provides updated, evidence-informed recommendations and expert consensus where evidence is insufficient, on prevention and management of CINV to reflect current best practices.

Important updates to the 2013 Antiemetic Report include new recommendations for the use of olanzapine and the novel combination product, NEPA, suggestions for multiple day chemotherapy, discussion around cannabinoids, changes to recommendations for carboplatin, new recommendations for oral chemotherapy and breakthrough CINV, and changes to emetic classification of certain chemotherapy regimens.

The most notable changes for implementation of these recommendations include the addition of olanzapine to the prophylaxis of high emetic risk chemotherapy (HEC), the addition of neurokinin-1 receptor antagonists (NK₁ RA) to the antiemetic regimen for carboplatin with area under the curve (AUC) ≥ 5 , and the change in classification of dactinomycin to moderate emetic risk (MEC) from high emetic risk (HEC). A summary of changes to emetic risk of regimens in the CCO Drug Formulary is provided in [Appendix 1](#).

Summary of Recommendations

Clinical Question 1

What is the optimal prevention strategy for nausea and vomiting with highly emetogenic chemotherapy (HEC) in adult patients who receive single day intravenous chemotherapy?

Recommendation 1.1: Adults who receive HEC should be offered primary prophylaxis with a four-drug regimen consisting of a neurokinin-1 receptor antagonist (NK₁ RA), serotonin receptor antagonist (5-HT₃ RA), dexamethasone, and olanzapine. For patients at increased risk of sedation, clinical judgement should be used to determine the need for olanzapine, especially in patients at lower risk of CINV.

Recommendation 1.2: Olanzapine

Adults who receive HEC should be offered olanzapine at a dose of 5 mg PO prior to chemotherapy, and 5 mg PO daily (or 2.5 mg PO bid) continued on days 2 to 4. For patients at increased risk of sedation, clinical judgement should be used to determine the need for olanzapine, especially in patients at lower risk of CINV.

Recommendation 1.3: Palonosetron

Adults who receive HEC may be offered palonosetron as an alternative to other 5-HT₃ RA. One 5-HT₃ RA is not preferred over another based on the available evidence.

Recommendation 1.4: NEPA

For adults who receive HEC, the combination agent, NEPA (NK₁ RA, netupitant/ 5-HT₃ RA, palonosetron) is a reasonable alternative to an NK₁ RA plus a 5-HT₃ RA.

Recommendation 1.5: Dexamethasone with Anthracycline plus Cyclophosphamide (AC)

Adult patients who receive an anthracycline plus cyclophosphamide for a breast cancer indication should receive a four-drug regimen as part of HEC prophylaxis. If palonosetron is the 5-HT₃ RA used, dexamethasone does not need to continue after day 1. If other 5-HT₃ RAs are used for AC, the need for dexamethasone beyond day 1 is uncertain. Clinicians may choose to limit dexamethasone to day 1, especially when intolerance to steroids, or comorbid conditions exist that make minimizing corticosteroid use desirable.

Clinical Question 2

What is the optimal prevention strategy for nausea and vomiting with moderately emetogenic chemotherapy (MEC) in adult patients who receive single day intravenous chemotherapy?

Recommendation 2.1: MEC regimens excluding carboplatin AUC \geq 5

Adults who receive MEC, excluding carboplatin regimens with an area under the curve (AUC) \geq 5, should be offered primary prophylaxis with a 5-HT₃ RA and dexamethasone, on day 1. Olanzapine or an NK₁ RA may be added, as prophylaxis, to subsequent cycles if the patient experiences suboptimal control of CINV. Clinicians should continue to assess patient response throughout chemotherapy treatment in order to optimize the use of these agents; consider adding olanzapine if the patient experiences suboptimal control of nausea and NK₁ RA if the patient experiences suboptimal control of emesis.

Recommendation 2.2: Carboplatin AUC \geq 5

Adults who receive chemotherapy regimens with carboplatin AUC \geq 5, should be offered primary prophylaxis with an NK₁ RA in addition to a 5-HT₃ RA and dexamethasone. Olanzapine may be added, as prophylaxis, to subsequent cycles if the patient experiences suboptimal control of CINV.

Recommendation 2.3: Palonosetron

Adults who are treated with MEC may receive palonosetron as an alternative to other 5-HT₃ RAs. One 5-HT₃ RA is not preferred over another based on the available evidence

Recommendation 2.4: Dexamethasone duration

For adults treated with oxaliplatin- or carboplatin-based regimens, there is insufficient evidence to recommend dexamethasone beyond day 1 for prevention of CINV.

Clinical Question 3

What is the optimal prevention strategy for nausea and vomiting with low (LEC) and minimally emetogenic chemotherapy in adult patients who receive single day intravenous chemotherapy?

Recommendation 3.1: Adults who receive LEC should be offered a single dose of dexamethasone prior to chemotherapy.

Recommendation 3.2: Adults who receive minimally emetogenic chemotherapy should not be routinely offered antiemetic prophylaxis.

Clinical Question 4

What is the optimal prevention strategy for nausea and vomiting in adult patients who receive high-dose chemotherapy for stem cell transplantation (SCT)?

Recommendation 4: Adults who receive high-dose chemotherapy for SCT should be offered a three-drug antiemetic regimen of an NK₁ RA, a 5-HT₃ RA and dexamethasone.

Clinical Question 5

What is the optimal prevention strategy for nausea and vomiting in adult patients who receive multiple-day intravenous chemotherapy?

Recommendation 5.1: Adults who receive multiple-day chemotherapy regimens should be offered the antiemetic agents appropriate for the chemotherapy agent(s) with the highest emetic risk on the day of chemotherapy, and for up to 2 days after completion of chemotherapy.

Recommendation 5.2: Adults who receive 5-day cisplatin regimens should be offered a four-drug antiemetic regimen consisting of aprepitant, a 5-HT₃ RA, dexamethasone, and olanzapine. Aprepitant, dexamethasone, and olanzapine should be continued for up to 2 days after chemotherapy.

Clinical Question 6

What is the role of cannabinoids in the prevention or treatment of chemotherapy-induced nausea and vomiting?

Recommendation 6: Due to the lack of high quality clinical trials, no recommendation can be made to incorporate synthetic or non-synthetic cannabinoids as part of standard antiemetic therapy. If a cannabinoid is used, it should be after optimal therapy (including combination therapy with a 5-HT₃ RA, NK₁ RA, dexamethasone and olanzapine) has failed to provide adequate control of nausea and vomiting. If used, patients should be guided to access products with consistent concentrations.

Clinical Question 7

What is the optimal treatment for adult patients who experience nausea and vomiting secondary to chemotherapy, despite optimal prophylaxis (breakthrough)?

Recommendation 7.1: Adult patients who experience CINV despite optimal prophylaxis and did not receive olanzapine prophylactically, should be offered olanzapine 5 mg daily or 2.5 mg bid in addition to the standard antiemetic regimen.

Recommendation 7.2:

Adult patients who experience CINV despite optimal prophylaxis and have already received olanzapine, may be offered olanzapine 5 mg bid (for a total of 10 mg/day) or a drug of a different class in addition to continuing the standard antiemetic regimen.

Clinical Question 8

What is the optimal prevention strategy for nausea and vomiting in adult patients who receive single day oral chemotherapy?

Recommendation 8: There is insufficient evidence to recommend routine antiemetic prophylaxis prior to an oral chemotherapy. In the event that a patient develops significant nausea or vomiting, consider initiating a routine prophylactic antiemetic agent. Clinical judgement should be used for individual cases where primary prophylaxis may be warranted.

Summary Antiemetic Tables

1. Single Day IV Chemotherapy:

1.1 Highly Emetogenic Chemotherapy (HEC)[†]:

Dosing on day of chemotherapy [‡]	Dosing on subsequent days
Choose one NK₁ receptor antagonist: Aprepitant 125 mg PO OR Fosaprepitant 150 mg IV OR NEPA (netupitant 300 mg + palonosetron 0.5 mg) PO	Aprepitant 80 mg PO daily (days 2 – 3) ^a if started on Day 1
Choose one 5-HT₃ receptor antagonist: Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV OR Palonosetron 0.25 mg IV or 0.5 mg PO ^b	No 5-HT ₃ RA recommended after day of chemotherapy
Dexamethasone ^c 12 mg PO or 10 mg IV	Dexamethasone ^c 8 mg PO or 10 mg IV (days 2 – 3 or 4)
Olanzapine 5 mg PO	Olanzapine 5 mg PO daily (or 2.5 mg BID) days 2 – 4

[†] In breast cancer population receiving a combination of anthracycline and cyclophosphamide (AC), may consider limiting dexamethasone to day 1, when minimizing corticosteroid is desirable. Dexamethasone does not need to be continued after day 1 with the use of palonosetron.

[‡] Antiemetics should be given as a one-time dose (unless otherwise specified) an hour prior to chemotherapy administration, on the day of chemotherapy.

^a Aprepitant is given on subsequent days only if used on day of chemotherapy. Do not give aprepitant on subsequent days if fosaprepitant or netupitant is given on day of chemotherapy.

^b Palonosetron 0.5 mg PO is not approved for HEC by Health Canada.

^c Dexamethasone dose listed is if used with NK₁ receptor antagonist. If NK₁ receptor antagonist is not used, dexamethasone dose is 20 mg on day of chemotherapy and 16 mg on days 2 – 3 (or 4).

1.2 Moderately Emetogenic Chemotherapy (MEC) †:

Dosing on day of chemotherapy*	Dosing on subsequent days
Choose one 5-HT₃ receptor antagonist: Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV OR Palonosetron 0.25 mg IV or 0.5 mg PO	No 5-HT ₃ RA recommended after day of chemotherapy
Dexamethasone 8 mg PO or 10 mg IV	No dexamethasone recommended after day of chemotherapy
OPTIONAL ON SUBSEQUENT CYCLES if inadequate control of CINV in previous cycle[‡]:	
Choose one NK₁ receptor antagonist: Aprepitant 125 mg PO OR Fosaprepitant 150 mg IV OR NEPA (netupitant 300 mg + palonosetron 0.5 mg) PO	Aprepitant 80 mg PO daily (days 2 – 3) ^a if started on Day 1
OR	
Olanzapine 5 mg PO	Olanzapine 5 mg PO daily (or 2.5 mg BID) days 2 – 4

† Patients receiving carboplatin AUC ≥ 5 should receive an NK₁ receptor antagonist up front with a 5-HT₃ receptor antagonist and dexamethasone.

* Antiemetics should be given as a one-time dose (unless otherwise specified) an hour prior to chemotherapy administration, on the day of chemotherapy.

‡ Consider olanzapine if patient experiences suboptimal control of nausea and NK₁ RA if patient experiences suboptimal control of emesis, after the first cycle.

^a Aprepitant is given on subsequent days only if used on day of chemotherapy. Do not give aprepitant on subsequent days if fosaprepitant or netupitant is given on day of chemotherapy.

1.3 Low Emetic Risk Chemotherapy (LEC):

Dosing on day of chemotherapy*	Dosing on subsequent days
Dexamethasone 8 mg PO or 10 mg IV	No dexamethasone recommended after day of chemotherapy

* Antiemetics should be given as a one-time dose (unless otherwise specified) an hour prior to chemotherapy administration, on the day of chemotherapy

1.4 Minimal Emetic Risk Chemotherapy:

Dosing on day of chemotherapy	Dosing on subsequent days
No antiemetics recommended	No antiemetics recommended

2. Multiple Day IV Chemotherapy:

2.1 Highly Emetogenic Chemotherapy (HEC):

Dosing on days of chemotherapy [‡]	Dosing on subsequent days
Aprepitant 125 mg PO on Day 1 then 80 mg PO on remaining days of chemotherapy	Aprepitant 80 mg PO daily (up to 2 days after last dose of chemotherapy)
Choose one 5-HT₃ receptor antagonist: Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV	No 5-HT ₃ RA recommended after day of chemotherapy
Dexamethasone ^a 12 mg PO or 10 mg IV	Dexamethasone ^a 8 mg PO or 10 mg IV (up to 2 days after last dose of chemotherapy)
Olanzapine 5 mg PO	Olanzapine 5 mg PO daily or 2.5mg PO BID (up to 2 days after last dose of chemotherapy)

[‡] Antiemetics should be given as a one-time dose (unless otherwise specified) an hour prior to chemotherapy administration, on the day of chemotherapy.

^a Dexamethasone dose listed is if used with NK₁ receptor antagonist. If NK₁ receptor antagonist is not used, dexamethasone dose is 20 mg on day of chemotherapy and 16 mg on subsequent days up to 2 days after last dose of chemotherapy.

2.2 Moderately Emetogenic Chemotherapy (MEC):

Dosing on days of chemotherapy [‡]	Dosing on subsequent days
Choose one 5-HT₃ receptor antagonist: Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV	No 5-HT ₃ RA recommended after day of chemotherapy
Dexamethasone 8 mg PO or 10 mg IV	No dexamethasone recommended after day of chemotherapy
OPTIONAL ON SUBSEQUENT CYCLES if inadequate control of CINV in previous cycle[£]:	
Aprepitant 125 mg PO on Day 1 then 80 mg PO on remaining days of chemotherapy	Aprepitant 80 mg PO daily (up to 2 days after last dose of chemotherapy)
OR Olanzapine 5 mg PO	Olanzapine 5 mg PO daily or 2.5 mg PO BID (up to 2 days after last dose of chemotherapy)

[‡] Antiemetics should be given as a one-time dose (unless otherwise specified) an hour prior to chemotherapy administration, on the day of chemotherapy.

[£] Consider olanzapine if patient experiences suboptimal control of nausea and NK₁ RA if patient experiences suboptimal control of emesis, after the first cycle.

3. High-dose Chemotherapy for Stem Cell Transplantation

Dosing on day of chemotherapy [‡]	Dosing on subsequent days
Choose one NK₁ receptor antagonist: Aprepitant 125 mg PO OR Fosaprepitant 150 mg IV OR NEPA (netupitant 300 mg + palonosetron 0.5 mg) PO	Aprepitant 80 mg PO daily (days 2 – 3) ^a if started on Day 1
Choose one 5-HT₃ receptor antagonist: Granisetron 2 mg PO or 1 mg IV OR Ondansetron 8 mg PO BID or 8 mg IV OR Palonosetron 0.25 mg IV or 0.5 mg PO	No 5-HT ₃ RA recommended after day of chemotherapy
Dexamethasone ^b 12 mg PO or 10 mg IV	Dexamethasone ^b 8 mg PO or 10 mg IV (days 2 – 3 or 4)

[‡] Antiemetics should be given as a one-time dose (unless otherwise specified) an hour prior to chemotherapy administration, on the day of chemotherapy.

^a Aprepitant is given on subsequent days only if used on day of chemotherapy. Do not give aprepitant on subsequent days if fosaprepitant or netupitant is given on day of chemotherapy.

^b Dexamethasone dose listed is if used with NK₁ receptor antagonist. If NK₁ receptor antagonist is not used, dexamethasone dose is 20 mg on day of chemotherapy and 16 mg on days 2 – 3 (or 4).

4. Oral Chemotherapy

Emetic Risk	Management
High to Moderate	Consider prophylaxis daily as per patient experience of CINV [*] <ul style="list-style-type: none"> 5-HT₃ Receptor Antagonist (granisetron 2 mg PO or ondansetron 8 mg PO BID)
Low to Minimal	No routine prophylaxis; PRN recommended <ul style="list-style-type: none"> Prochlorperazine 10 mg PO then q4-6h PRN OR Metoclopramide 10-20 mg PO then q4-6h PRN

^{*} Insufficient evidence to recommend routine prophylaxis; Consider if patient develops significant nausea or vomiting and re-assess routinely. Use clinical judgement for individual cases where primary prophylaxis may be warranted.

5. Breakthrough Nausea and/or Vomiting[†]

Examples may include the following [£]:

Drug	Dose
Domperidone	10 mg PO q4-6h PRN nausea and/or vomiting
Haloperidol	0.5-2 mg PO q4-6h PRN nausea and/or vomiting
Metoclopramide	10 mg PO q4-6h PRN nausea and/or vomiting
Olanzapine*	2.5 mg PO BID PRN nausea and/or vomiting
Prochlorperazine	10 mg PO 4-6h PRN nausea and/or vomiting

[†] Use caution when dopamine receptor antagonists (eg. Metoclopramide, haloperidol or prochlorperazine) or medications that cause sedation are given in combination with prophylactic olanzapine.

[£] Not a comprehensive list of agents for breakthrough nausea and vomiting.

* Preferred agent. If olanzapine given prophylactically for HEC or MEC, patients may be offered olanzapine (max daily dose suggested is 10 mg, due to sedation) or an agent of a different class.

Recommendations

High Emetic Risk Chemotherapy

Clinical Question 1: What is the optimal prevention strategy for nausea and vomiting with highly emetogenic chemotherapy (HEC; risk of emesis >90%) in adult patients who receive single day intravenous chemotherapy?

Recommendation 1.1:

Adults who receive HEC should be offered primary prophylaxis with a four-drug regimen consisting of a neurokinin-1 receptor antagonist (NK₁ RA), serotonin receptor antagonist (5-HT₃ RA), dexamethasone, and olanzapine. For patients at increased risk of sedation, clinical judgement should be used to determine the need for olanzapine, especially in patients at lower risk of CINV.

Summary of Evidence & Discussion

The recommendation to add olanzapine to the standard triple therapy for HEC regimens is a change from CCO's previous recommendations, which did not include olanzapine for primary prophylaxis.³ The decision to add olanzapine is based on evidence from a phase III randomized control trial (RCT) and a meta-analysis of ten RCTs that outline the benefit of using olanzapine to prevent nausea and vomiting in patients who receive highly emetogenic therapies.

A phase III RCT compared olanzapine 10 mg PO daily with placebo, in combination with dexamethasone, an NK₁ RA, and a 5-HT₃ RA, in patients receiving cisplatin (>70 mg/m²) or anthracycline/cyclophosphamide (AC) combination.⁴ Adding olanzapine significantly improved the proportion of patients with no nausea in the first 24 hours (74% versus 45%, P=0.002), the period of 25 – 120 hours (42% versus 25%, P=0.002), and the overall 120-hour period (37% versus 22%, P=0.002). Olanzapine also significantly improved the complete response rate (no emetic episodes and no use of rescue medication; CR) over all three periods: 86% versus 65% (P<0.001), 67% versus 52% (P=0.007), and 64% versus 41% (P<0.001), respectively.⁴

Additionally, a meta-analysis included ten RCTs of olanzapine used in the preventative setting in patients receiving either HEC or a mix of HEC and MEC. They found olanzapine to be superior in preventing emesis in the acute, delayed, and overall phases compared to prophylaxis with a 5-HT₃ RA (7 studies), or an NK₁ RA (3 studies), with or without dexamethasone.⁵ The absolute risk difference for no emesis between olanzapine-containing regimens and the comparator regimen for the acute, delayed, and overall phases were 9% (P=0.0007), 21% (P=0.0003), and 24% (P=0.0001), respectively. Olanzapine also significantly improved the endpoint of no nausea, but only in the delayed and overall phases, with an absolute risk difference of 24% (P<0.0001) for both phases.

Recommendation 1.2: Olanzapine

Adults who receive HEC should be offered olanzapine at a dose of 5 mg PO prior to chemotherapy, and 5 mg PO daily (or 2.5 mg PO bid) continued on days 2 to 4. For patients at increased risk of sedation, clinical judgement should be used to determine the need for olanzapine, especially in patients at lower risk of CINV.

Summary of Evidence & Discussion

While the evidence supporting the efficacy of olanzapine 10 mg as prophylaxis is robust, patient sedation can be a concern at this dose and has been reported as high as 73% in earlier RCTs when compared to 5-HT₃ RAs.⁶ Both NCCN and MASCC/ESMO guidelines acknowledge this concern and suggest a lower dose in certain patient populations.^{7,8} The decision to use a lower olanzapine dose in these recommendations differs from the ASCO 2017 guidelines⁹ and is based on phase II data showing comparable efficacy between 10 mg and 5 mg and safety data from several RCT and non-RCTs.

Yanai et al compared the efficacy of olanzapine 5 mg versus 10 mg in a phase II RCT of 153 cisplatin-treated patients receiving prophylaxis with aprepitant, palonosetron, and dexamethasone.¹⁰ Both groups met the primary endpoint for delayed emesis (24-120 hours), with CR rates of 77.6% (P=0.01) and 85.7% (P<0.001) in the 10 mg and 5 mg groups, respectively.¹⁰ The frequency of somnolence was 53.3% for olanzapine 10 mg and 45.5% for 5 mg. There were no discontinuations due to somnolence, and all events were grade 2 or lower.

The meta-analysis by Chiu et al also showed comparable results between olanzapine 5 mg and 10 mg in patients receiving HEC/MEC.⁵ The absolute risk difference for no emesis in the overall phase when compared to 5-HT₃ RA and dexamethasone prophylaxis was 34% (P<0.0001) and 22% (P<0.003) for 5 mg and 10 mg, respectively.

Data suggest that olanzapine-induced sedation is dose-dependent, is most notable earlier in therapy, and improved over time.^{4,10,11} In the Navari et al. trial there was an increase in sedation on day 2 compared with baseline (based on a 10-point visual analog scale), but sedation improved over days 3 to 5 despite patients continuing to receive olanzapine days 3 and 4.⁴ This suggests that tolerance to sedation may develop with continued dosing.

Rates of sedation may be underestimated in the current literature due to common reporting of only grade 3 or higher sedation. In the RCTs by Navari et al, sedation was not reported unless it was grade 3 or 4.^{4,12-14} However, grade 3 sedation is defined as difficulty to arouse and sedation that is grade 2 or lower may still have a significant impact on patients.

Considering the potential for sedation, several non-randomized trials have studied lower doses of olanzapine for prophylaxis. Sato et al prospectively added olanzapine 2.5 mg to standard triple therapy in breast cancer patients who experienced nausea or vomiting after their first cycle of chemotherapy with epirubicin and cyclophosphamide.¹¹ Somnolence (> grade 1) was noted in 27% of patients receiving olanzapine and similar to the Navari et al trial, the mean self-reported daytime sleepiness (reported on a scale of 0 to 5) decreased with continued use (from 1.9 to 0.4-0.9). Of the 45 patients evaluated in this study, 4 patients (8.9%) discontinued olanzapine due to somnolence.¹¹

In light of this evidence for lower doses of olanzapine and the benefit of reduced sedation, the addition of olanzapine 5 mg/day PO on days 1-4 to the standard triple therapy is recommended. Based on expert consensus of the working group, the option of splitting the dose of olanzapine to 2.5 mg PO bid may be offered to allow for omission of the second daily (usually daytime) dose, should significant sedation occur. A risk benefit analysis should be considered for patients at lower risk of CINV, and increased risk of sedation.

Recommendation 1.3: Palonosetron

Adults who receive HEC may be offered palonosetron as an alternative to other 5-HT₃ RA. One 5-HT₃ RA is not preferred over another based on the available evidence.

Summary of Evidence & Discussion

There are no changes to CCO's previous antiemetic recommendations regarding preference of any particular 5-HT₃ RA over another. The evidence for this recommendation has been discussed in depth in the CCO 2013 Antiemetic Report.³ A review of the literature since then was conducted and 2 phase III trials were found comparing palonosetron to granisetron in patients receiving HEC. Kubota et al. concluded that palonosetron was more effective than granisetron for the prevention of nausea in the delayed and overall phase – with an absolute difference in no nausea of 6.9% for the overall phase ($p=0.0117$) – but they did not show any difference in the primary endpoint of no nausea in the acute phase (0-24 hours).¹⁵ Additionally, this study did not include an NK₁ RA as is standard for HEC prophylaxis. Suzuki et al. compared palonosetron to granisetron in combination with dexamethasone and aprepitant. They were also unable to show a difference in the primary endpoint of CR in the acute phase, and while palonosetron was numerically superior in the overall phase (0-120 hours), this superiority was not statistically significant.¹⁶ This is reflective of previous evidence showing majority of the benefit with palonosetron is beyond 24 hours, when combined with dexamethasone.¹⁷ Although palonosetron may possess slight superiority it is not clear if this is due to its longer half-life in comparison to other 5-HT₃ RAs.

Recommendation 1.4: NEPA

For adults who receive HEC, the combination agent, NEPA (NK₁ RA, netupitant/ 5-HT₃ RA, palonosetron) is a reasonable alternative to an NK₁ RA plus a 5-HT₃ RA.

Summary of Evidence & Discussion

NEPA is a new agent (marketed in 2017 in Canada) and was not reviewed in the CCO 2013 Antiemetic Report.³ It is available as a single capsule containing netupitant 300 mg and palonosetron 0.5 mg.¹⁸ NEPA has been evaluated in a randomized, double blind, dose-ranging study in 694 cisplatin-treated patients.¹⁹ Three different doses of netupitant (100 mg, 200 mg, and 300 mg) in combination with oral palonosetron 0.5 mg were compared to palonosetron 0.5 mg alone given on day 1. An exploratory arm of aprepitant plus ondansetron was also included. All arms received dexamethasone on days 1-4. All NEPA doses had statistically superior overall CR rates compared to palonosetron, with netupitant 300 mg numerically displaying the greatest benefit of the NEPA arms (87.4% NEPA₁₀₀, 87.6% NEPA₂₀₀, 89.6% NEPA₃₀₀ vs. 76.5% with palonosetron $p \leq 0.05$).¹⁹ In comparison, the overall CR rate in the aprepitant/ondansetron group was 86.6% but there was no formal comparison between this and the NEPA groups. In the acute phase, only the NEPA₃₀₀ group was significantly superior to palonosetron alone, which led to the adoption of the current dose.

A randomized, phase III trial found similar results when comparing NEPA to palonosetron, in combination with dexamethasone, in 1455 patients receiving AC.²⁰ NEPA was superior in acute, delayed and overall phases compared to palonosetron alone, with a CR rate of 74.3% vs. 66.6% ($P=0.001$) in the overall phase. The groups had comparable adverse effect rates. In addition, NEPA has been shown to be efficacious over multiple cycles in patients receiving HEC or MEC.^{21,22}

Zhang et al. conducted a randomized, phase III trial to demonstrate non-inferiority of NEPA compared to standard HEC prophylaxis with aprepitant/granisetron (APR/GRAN), in patients receiving cisplatin.²³ All patients received dexamethasone from days 1 to 4. NEPA demonstrated non-inferiority to APR/GRAN with overall CR rates of 73.8% and 72.4%, respectively. Adverse event rates were also similar (NEPA 58.1%, APR/GRAN 57.5%).²³ Another trial by Aapro et al. found the rates of adverse events between NEPA and palonosetron to be similar, with the most common side effects including headache and constipation ($\geq 2\%$), and QT prolongation (1.6%).²²

The evidence supports NEPA as an efficacious alternative to 5-HT₃ RA / NK₁ RA combinations in patients receiving HEC and has the added benefit of being a one-day, single capsule dose.

Recommendation 1.5: Dexamethasone with Anthracycline plus Cyclophosphamide (AC)

Adult patients who receive an anthracycline plus cyclophosphamide for a breast cancer indication should receive a four-drug regimen as part of HEC prophylaxis. If palonosetron is the 5-HT₃ RA used, dexamethasone does not need to continue after day 1. If other 5-HT₃ RAs are used for AC, the need for dexamethasone beyond day 1 is uncertain. Clinicians may choose to limit dexamethasone to day 1, especially when intolerance to steroids, or comorbid conditions exist that make minimizing corticosteroid use desirable.

Summary of Evidence & Discussion

The reclassification of AC chemotherapy (specifically, breast cancer AC regimens) as highly emetogenic was discussed in the 2013 CCO Antiemetic Report.³ Although the recommendations for acute CINV remain unchanged in this update, several trials suggest that limiting dexamethasone to day 1 may be sufficient in some patients receiving AC regimens.

Roila et al. evaluated aprepitant compared to dexamethasone for the prophylaxis of delayed CINV. They randomized 551 breast cancer patients receiving AC chemotherapy to receive either dexamethasone 4 mg bid or aprepitant 80 mg on days 2-3 after receiving a combination of palonosetron 0.25 mg, aprepitant 125 mg and dexamethasone 8 mg on day 1.²⁴ The CR for the delayed phase (days 2-5) were identical between the two groups (79.5%) but patients in the dexamethasone group experienced significantly more insomnia and heartburn.

In a 2018 phase III RCT, dexamethasone on day 1 was shown to be non-inferior to dexamethasone days 2-3 when combined with an NK₁ RA and palonosetron in 396 patients receiving cisplatin or AC. Overall CR rates were 44% vs. 46.9% respectively, with a risk difference of 2.9% (95% CI, 212.6% to 6.8%; P = 0.007). These results are supported by phase III single vs. multi-day dexamethasone trials, that did not include an NK₁ RA.^{25,26} A multi-center, non-inferiority, RCT in breast patients receiving AC, showed no difference in CR rates between one day of dexamethasone and 3 days (53.6% vs 53.7%, respectively) when given with palonosetron.²⁶ Similarly, no statistically significant differences were observed between one-day and 3-day CR rates in a comparable non-inferiority trial (67.5% vs. 71.1%, respectively in overall phase).²⁵ In addition, the day 1 only schedule of dexamethasone is consistent with the administration of dexamethasone in earlier NK₁ RA trials for NEPA²⁰ and aprepitant.²⁷

Since all of the evidence surrounding single-day dexamethasone is in combination with palonosetron, a recommendation cannot be made to limit dexamethasone to day 1 only, in breast cancer patients receiving AC chemotherapy, if other 5-HT₃ RA are used. Clinicians should use their clinical judgement when situations exist that make steroid-sparing desirable.

Moderate Emetic Risk Chemotherapy

Clinical Question 2: What is the optimal prevention strategy for nausea and vomiting with moderately emetogenic chemotherapy (MEC; risk of emesis 30% - 90%) in adult patients who receive single day intravenous chemotherapy?

Recommendation 2.1: MEC regimens excluding carboplatin AUC \geq 5

Adults who receive MEC, excluding carboplatin regimens with an area under the curve (AUC) \geq 5, should be offered primary prophylaxis with a 5-HT₃ RA and dexamethasone, on day 1. Olanzapine or an NK₁ RA may be added, as prophylaxis, to subsequent cycles if the patient experiences suboptimal control of CINV. Clinicians should continue to assess patient response throughout chemotherapy treatment in order to optimize the

use of these agents; consider adding olanzapine if the patient experiences suboptimal control of nausea and NK₁ RA if the patient experiences suboptimal control of emesis.

Recommendation 2.2: Carboplatin AUC ≥ 5

Adults who receive chemotherapy regimens with carboplatin AUC ≥ 5, should be offered primary prophylaxis with an NK₁ RA in addition to a 5-HT₃ RA and dexamethasone. Olanzapine may be added, as prophylaxis, to subsequent cycles if the patient experiences suboptimal control of CINV.

Summary of Evidence & Discussion

The option of adding olanzapine for suboptimal control of nausea or emesis in MEC is a new CCO recommendation.³ Refer to Recommendation 1.1 for details of the evidence surrounding the use of olanzapine for the prevention of CINV in HEC. The majority of the evidence for olanzapine as prophylaxis is in patients receiving HEC. The meta-analysis by Chiu et al.⁵, discussed earlier, included 4 studies that contained MEC, but it did not include any MEC only studies. Only one study in the meta-analysis separated patients by emetogenic potential so the authors were unable to evaluate this emetic risk subgroup in the preventative setting. A small phase II trial by Navari et al. evaluated the efficacy results of olanzapine, in combination with palonosetron and dexamethasone, in patients receiving MEC separately from those receiving HEC.²⁸ The CR for patients receiving MEC overall (0-120 hours) was 72%, but only 50% of what were classified as MEC patients, received non-AC chemotherapy, confounding the interpretation of a true MEC subgroup. Despite the methodological limitations with these studies, the Working Group recognizes that there may be benefit in adding olanzapine for certain patients when a combination of a 5-HT₃ RA and dexamethasone has failed to control CINV. However, due to the limited data and the propensity for causing sedation, this recommendation remains an option for subsequent cycles only. The addition of optional olanzapine for MEC differs from ASCO, which does not recommend the use of olanzapine prophylaxis for MEC due to the sparsity of evidence, but it is in line with the NCCN guidelines, which provide an olanzapine-palonosetron-dexamethasone combination as one of the options for prophylaxis of MEC.⁷

The option of adding NK₁ RA for suboptimal control of nausea or emesis in MEC is not a new recommendation to the CCO guidelines.³ The use of an NK₁ RA in patients who were treated with carboplatin (AUC ranging from 5-6) was evaluated in six RCTs, in both gynecological and non-gynecological settings.²⁹⁻³⁴ All six trials evaluated an NK₁ RA (5 out of 6 used aprepitant; one used rolapitant³⁴) plus a 5-HT₃ RA and dexamethasone. Three of the trials were placebo controlled.^{29,33,34} In four of the six RCTs, an NK₁ RA significantly improved CR rates throughout the overall phase.^{29,30,32,34} The remaining two RCTs demonstrated a numerically superior CR rate for the NK₁ RA groups, but it was not statistically significant.^{31,33} These trials demonstrated the benefit of including an NK₁ RA in the primary prophylaxis of carboplatin-based regimens. The cut-off of AUC ≥ 5 reflects the doses used in the above trials – all except one post-hoc analysis, specified carboplatin doses of AUC of 5 or 6. This differs from the ASCO guidelines which recommend adding an NK₁ RA to the prophylaxis regimen for patients treated with carboplatin AUC ≥ 4.⁹

The first double-blind trial evaluating the role of NK₁ RA for oxaliplatin specifically, compared casopitant to placebo plus ondansetron and dexamethasone in 710 patients receiving oxaliplatin-based therapies.³⁵ Casopitant did not improve CINV control for the overall (86% casopitant vs. 85% placebo; P=0.7273), acute (97% casopitant vs. 96% placebo), or delayed phases (86% casopitant vs. 85% placebo).³⁵ In contrast, a phase III trial by Nishimura et al. compared aprepitant to placebo, in combination with a 5-HT₃ RA and dexamethasone, in patients receiving FOLFOX or XELOX. They found that significantly more patients in the aprepitant group experienced no vomiting in the overall and delayed phases (95.7% versus 83.6%; P<0.0001 and 95.7% versus 84.7%; P<0.0003, respectively).³⁶ Due to the conflicting evidence of these 2 large randomized trials, no recommendation can be made about the use of NK₁ RA for primary prophylaxis in patients treated with oxaliplatin-based therapies. However, the Working Group acknowledged that this, or olanzapine, would be reasonable options in patients with suboptimal control of nausea with a 5-HT₃ RA and dexamethasone. This differs from the NCCN guidelines, which recommend adding an NK₁ RA to a 5-HT₃ RA and dexamethasone for patients receiving MEC regimens that are associated with a higher risk for emesis, including oxaliplatin.⁷

Recommendation 2.3: Palonosetron

Adults who are treated with MEC may receive palonosetron as an alternative to other 5-HT₃ RAs. One 5-HT₃ RA is not preferred over another based on the available evidence.

Summary of Evidence & Discussion

There has been no change to CCO's previous antiemetic recommendations regarding preference to any particular 5-HT₃ RA over another for MEC. The evidence for this recommendation was discussed in the CCO 2013 Antiemetic Report.³ In 2014, a meta-analysis was conducted comparing palonosetron to other 5-HT₃ RAs in CINV prophylaxis.¹⁷ Of the 16 trials reviewed, only three concentrated on MEC regimens alone, and two of those three trials included patients who were treated with AC (considered MEC at the time of the trial, but have since been reclassified to HEC).^{37,38} The third, a crossover trial in a small population of 30 patients, found no statistically significant difference in the acute or delayed phase CR rates between palonosetron and ondansetron when given with dexamethasone.³⁹ Given the evidence, it is still uncertain whether palonosetron is superior to other 5-HT₃ RAs in the prevention of CINV in patients treated with MEC regimens and palonosetron is not preferred over other agents in this class.

Recommendation 2.4: Dexamethasone duration

For adults treated with oxaliplatin- or carboplatin-based regimens, there is insufficient evidence to recommend dexamethasone beyond day 1 for prevention of CINV.

Summary of Evidence & Discussion

This recommendation has not changed from CCO's previous 2013 Antiemetic Report but differs slightly from ASCO and MASCC/ESMO guidelines.^{3,8,9} The lack of

randomized, controlled trials evaluating dexamethasone duration in MEC was the basis for this distinction.

One open-label phase III trial evaluated single-day dexamethasone compared to dexamethasone days 1-3 in MEC that excluded AC.⁴⁰ All patients received palonosetron 0.75 mg on day 1 and 73% of patients received oxaliplatin-based treatment, while 12% received carboplatin-based regimens. There was no difference between one day of dexamethasone and 3 days in the overall CR rate (66.2% and 63.6% for day 1 and days 1-3, respectively ie. a 2.5% difference 95% CI -7.8%-12.8%, p value for non-inferiority test = 0.0004).

Although there were no further studies identified assessing dexamethasone duration in MEC, two large, prospective, antiemetic trials in carboplatin-based regimens reported satisfactory delayed phase CR rates (63.6% and 82.3%) with single-day dexamethasone (in combination with a 5-HT₃ RA and NK₁ RA).^{34,41} In carboplatin-based studies that used multiple-day dexamethasone (days 1-3) as part of triple therapy, the CR rates for the delayed phase were comparable, ranging from 62% to 90%.³¹⁻³³ A similar trend can be observed with oxaliplatin-based antiemetic trials.⁴²⁻⁴⁴

Without convincing evidence supporting the continuation of dexamethasone after day 1 in patients receiving carboplatin- and oxaliplatin-based regimens, and with the propensity to reduce steroid use whenever possible, a recommendation cannot be made to continue dexamethasone routinely in these patients. However, similar to the ASCO, NCCN and MASCC/ESMO guidelines, the Working Group recognizes that in some situations extending dexamethasone may be warranted and clinicians are to use their clinical judgement to determine when this would be appropriate.

Low and Minimal Emetic Risk Chemotherapy

Clinical Question 3: What is the optimal prevention strategy for nausea and vomiting with low (LEC; risk of emesis 10% - 30%) and minimally emetogenic chemotherapy (risk of emesis < 10%) in adult patients who receive single day intravenous chemotherapy?

Recommendation 3.1: Adults who receive LEC should be offered a single dose of dexamethasone prior to chemotherapy.

Recommendation 3.2: Adults who receive minimally emetogenic chemotherapy should not be routinely offered antiemetic prophylaxis.

Summary of Evidence & Discussion

There has been no change to CCO's recommendations for LEC and minimally emetogenic chemotherapy. ASCO's decision to add a 5-HT₃ RA as an alternative to dexamethasone for LEC was based on an informal consensus with low quality of evidence.⁹ As there is no new evidence to suggest a change to the recommendations, the consensus of the Working Group was to maintain the current recommendation for LEC.

High dose chemotherapy for stem cell transplantation

Clinical Question 4: What is the optimal prevention strategy for nausea and vomiting in adult patients who receive high-dose chemotherapy for stem cell transplantation (SCT)?

Recommendation 4: Adults who receive high-dose chemotherapy for SCT should be offered a three-drug antiemetic regimen of an NK₁ RA, a 5-HT₃ RA and dexamethasone.

Summary of Evidence

This is a new CCO recommendation; prophylaxis for high dose chemotherapy for SCT was not discussed in the previous report.³ This recommendation is based on three randomized, placebo-controlled trials in the setting of transplant that all found better control of vomiting when aprepitant was added, regardless of the high-dose chemotherapy studied.⁴⁵⁻⁴⁷ Schmitt et al. compared aprepitant with placebo, along with granisetron and dexamethasone, in 362 patients receiving high-dose melphalan conditioning for autologous transplant.⁴⁵ Aprepitant significantly improved the outcomes of overall CR (58% vs. 41%, $p=0.0042$), no vomiting (78% versus 65%, $P=0.0036$) and no major nausea (94% versus 88%, $P=0.026$).⁴⁵ Additionally, Stiff et al. compared aprepitant to placebo, plus ondansetron and dexamethasone, in patients treated with ablative preparative regimens.⁴⁶ Aprepitant significantly increased the percentage of patients who did not experience vomiting (73.3% versus 22.5%, $P<0.001$), however there was no significant difference in no nausea observed.⁴⁶ Finally, Svanberg et al. compared aprepitant with placebo plus tropisetron and betamethasone in patients receiving high-dose chemotherapy prior to SCT.⁴⁷ Aprepitant significantly improved the outcome of no vomiting (83% versus 36%, $P=0.0001$), but similar to Stiff et al., there was no difference in nausea.⁴⁷

With regards to safety, Stiff et al found no difference between aprepitant and placebo groups for regimen-related toxicity, time to engraftment, or transplantation outcome.⁴⁶ Based on these 3 trials, the addition of aprepitant resulted in less vomiting in patients receiving high dose chemotherapy and SCT. This recommendation parallels the ASCO and MASCC/ESMO guidelines.^{8,9}

Multiple-day Cisplatin

Clinical Question 5: What is the optimal prevention strategy for nausea and vomiting in adult patients who receive multiple-day intravenous chemotherapy?

Recommendation 5.1:

Adults who receive multiple-day chemotherapy regimens should be offered the antiemetic agents appropriate for the chemotherapy agent(s) with the highest emetic risk on the day of chemotherapy, and for up to 2 days after completion of chemotherapy.

Recommendation 5.2:

Adults who receive 5-day cisplatin regimens should be offered a four-drug antiemetic regimen consisting of aprepitant, a 5-HT₃ RA, dexamethasone, and olanzapine. Aprepitant, dexamethasone, and olanzapine should be continued for up to 2 days after chemotherapy.

Summary of Evidence & Discussion

Multiday chemotherapy presents additional challenges due to the complex overlap of acute and delayed CINV after the first day of chemotherapy. In addition, most antiemetic studies have been conducted with single-day chemotherapy and there is limited evidence for patients receiving multiday chemotherapy.

The addition of an NK₁ RA to a 5-HT₃ RA and dexamethasone combination for multiple-day cisplatin regimens was discussed in the 2013 CCO Antiemetic Report and parallels the ASCO and MASCC/ESMO recommendations.^{3,8,9} This recommendation was based on a phase III RCT of patients who received a 5-day cisplatin regimen for testicular cancer.⁴⁸ The addition of aprepitant, days 3-7, to a 5-HT₃ RA (other than palonosetron) and dexamethasone combination, significantly improved the CR in the acute phase (47% vs. 15%, p<0.001) and delayed phase (63% vs. 35%, p<0.001). This is supported by non-randomized phase II trials that reported 58-90% control of emesis with triple therapy (NK₁ RA, 5-HT₃ RA and dexamethasone) when given with multiple-day chemotherapy.⁴⁹⁻⁵¹ Additionally, a meta-analysis of this RCT and another from 2007 showed an odds ratio (OR) of 3.56 in favour of triplet antiemetic regimens with NK₁ RA (95% CI 1.77-7.15; p=0.0004) in patients treated with 5-day cisplatin.⁵²

Despite the benefit of an NK₁ RA in multiple day cisplatin regimens, the optimal antiemetic regimen schedule still remains unclear. The RCT by Albany et al. used a 5-day aprepitant schedule that began on day 3 but only gave dexamethasone on days 1 and 2, (5-HT₃ was given days 1-5).⁴⁸ Joshi et al. randomized patients treated with 5-day cisplatin to receive aprepitant or placebo days 1-3 plus ondansetron day 1 only and dexamethasone days 1-7.⁵³ Of the phase II studies mentioned, in patients receiving 5-day cisplatin, NK₁ RA was given on days of chemotherapy (days 1-5) or continued 2 days post-chemotherapy (days 1-7), 5-HT₃ RA was given days 1-5 (unless palonosetron) and dexamethasone was given during and for 2-3 days after chemotherapy.⁴⁹⁻⁵¹ Taking into consideration the variability in duration of NK₁ RA in the literature, the Working Group recommends giving an NK₁ RA for the duration of, as well as up to 2 days after completion of 5-day cisplatin treatment. In contrast, 5-HT₃ RA were solely administered during the 3- and 5-day cisplatin treatment in the phase II-III studies identified^{48,50,51,53-55}, therefore 5-HT₃ RA is recommended on days of treatment only.

The preferred NK₁ RA is aprepitant, based on the existing evidence with aprepitant and the lack of evidence available for other agents in that class (fosaprepitant and NEPA) in multiple-day regimens. The MASCC/ESMO guidelines similarly recommend aprepitant as the agent of choice for patients receiving multiple-day cisplatin therapy for germ cell tumors. As mentioned above, the two phase III trials in 5-

day cisplatin both compared aprepitant to placebo.^{48,53} One phase II trial evaluated fosaprepitant in a small population of 54 patients.⁵⁵ The CR rate was only 24.1%, significantly lower than that of aprepitant in a similar study.⁴⁸ There have been no studies identified evaluating NEPA in multiple-day cisplatin regimens. Due to the paucity of evidence with these agents, a recommendation cannot be made for fosaprepitant or NEPA as alternatives to aprepitant with multiple-day chemotherapies.

The data is limited for the use of palonosetron beyond day 1 in multiple-day chemotherapy. One multi-center phase II study in Japan showed CR rates of 78-90% over multiple courses when palonosetron on day 1 was combined with aprepitant and dexamethasone in testicular germ cell patients.⁵⁰ Palonosetron 0.75 mg was given on day 1 only, aprepitant days 1-5 and dexamethasone days 1-8. This dose of palonosetron, however, is higher than the standard dose used in North America. The authors estimated one dose would be sufficient for the 5-day treatment based on the long half-life of the drug (37-48 hours).⁵⁶ When used in lower doses (0.25 mg), palonosetron was shown to be effective and well tolerated when given on days 1, 3 and 5 in combination with dexamethasone with 5-day cisplatin therapy.⁵⁷ Among the other multiple-day studies, neither of the two phase III trials in 5-day cisplatin regimens previously discussed included palonosetron in their antiemetic regimens.^{48,53} Two of the phase II studies in 5-day cisplatin included palonosetron, one of which was in combination with fosaprepitant and yielded low CR rates.⁵⁵ Although evidence is insufficient to recommend palonosetron beyond day 1, palonosetron on days 1, 3 and 5 may be a reasonable option in multiple-day chemotherapy based on the long half-life of the drug, but further studies are required to validate this approach.

The addition of olanzapine to the antiemetic regimen for patients receiving multiple-day cisplatin is also largely based on the classification of 5-day cisplatin regimens as HEC and the new recommendation for olanzapine in patients receiving single-day HEC. A 2018 observational study of 40 lung patients receiving 3-day cisplatin, showed promising results when olanzapine 5 mg was given days 0-5, in combination with ondansetron and dexamethasone, reporting CR rates of 70% - 82.5%.⁵⁴ Somnolence was observed in 35% of patients (Grade 1) but none were severe and there were no discontinuations due to somnolence.

Cannabinoids

Clinical Question 6: What is the role of cannabinoids in the prevention or treatment of chemotherapy-induced nausea and vomiting?

Recommendation 6:

Due to the lack of high quality clinical trials, no recommendation can be made to incorporate synthetic or non-synthetic cannabinoids as part of standard antiemetic therapy. If a cannabinoid is used, it should be after optimal therapy (including combination therapy with a 5-HT₃ RA, NK₁ RA, dexamethasone and olanzapine) has failed to provide adequate control of nausea and vomiting. If used, patients should be guided to access products with consistent concentrations.

Summary of Evidence & Discussion

The evidence remains insufficient to make a recommendation regarding use of cannabinoids for CINV. Numerous studies have examined the antiemetic effects of oral cannabinoids, such as nabilone, in the treatment of CINV with variable results. Although earlier meta-analyses showed cannabinoids to have similar efficacy compared with prochlorperazine and metoclopramide, studies were often of poor quality design and did not reflect the current chemotherapy and antiemetic treatment regimens – for example not including 5-HT₃ RA and NK₁ RA.^{58–60}

A 2015 meta-analysis reviewed 23 trials from 1975 to 1991 comparing oral cannabinoids to conventional antiemetics, mainly prochlorperazine, for MEC and HEC regimens.⁵⁹ They found that there was no difference in nausea and/or vomiting, but participants were 3-4 times more likely to withdraw due to adverse events with cannabinoids. However, the quality of the trials analyzed ranged from low to moderate, and lacked comparison to the newer antiemetic drugs that are now standard therapy. The authors concluded that although cannabis-based medication may have benefits in refractory CINV, methodological limitations of the trials limit their conclusion and further research with newer anti-emetics would likely modify their conclusions.⁵⁹

Breakthrough Nausea and Vomiting

Clinical Question 7: What is the optimal treatment for adult patients who experience nausea and vomiting secondary to chemotherapy, despite optimal prophylaxis (breakthrough)?

Recommendation 7.1:

Adult patients who experience CINV despite optimal prophylaxis and did not receive olanzapine prophylactically, should be offered olanzapine 5 mg daily or 2.5 mg bid in addition to the standard antiemetic regimen.

Recommendation 7.2:

Adult patients who experience CINV despite optimal prophylaxis and have already received olanzapine, may be offered olanzapine 5 mg bid (for a total of 10 mg/day) or a drug of a different class in addition to continuing the standard antiemetic regimen.

Summary of Evidence & Discussion

The recommendation for breakthrough treatment of CINV is new to the CCO guidelines. Evidence regarding breakthrough CINV is limited, with little high quality evidence available to support or refute the use of several agents commonly used in the breakthrough setting. However, there is evidence that supports the use of olanzapine in breakthrough CINV. Navari et al conducted a phase III, double-blind RCT to study olanzapine in patients who developed breakthrough CINV despite standard prophylaxis for HEC (dexamethasone, palonosetron, and fosaprepitant).¹³ They compared olanzapine 10 mg orally daily for 3 days with metoclopramide 10 mg orally three times daily for 3 days. The proportion of patients who had no emesis over the 72 hour

observation period in those who received olanzapine and metoclopramide were 70% and 31% ($P < 0.01$), respectively. Similarly, reports of no nausea over the same period were 68% and 23% ($P < 0.01$) respectively.¹³ This is the recommended olanzapine dose in MASCC/ESMO guidelines for breakthrough CINV.⁸ These results are supported by non-randomized studies of olanzapine in the breakthrough setting. A phase II, open label study of olanzapine for breakthrough in 46 patients receiving a HEC regimen found the CR of breakthrough emesis, retching, and nausea control to be 60.9%, 71.7%, and 50.0%, respectively after 24 hours.⁶¹ Additionally, a retrospective chart review from 2013 to 2015 found that olanzapine in the breakthrough setting improved nausea in 88% of cases, and vomiting in 21% of cases.⁶² Furthermore, a meta-analysis by Chiu et al, including three RCTs of olanzapine in the breakthrough setting, found olanzapine improved the endpoint of no emesis when compared to other antiemetic interventions.⁵ Of the three RCTs analyzed in this meta-analysis, one included patients receiving HEC only (Navari et al, addressed above), while two included patients receiving MEC only. The absolute risk difference in no emesis between olanzapine and other antiemetic intervention arms was 36% ($P < 0.00001$).⁵ Similar to olanzapine in the prophylactic setting, sedation may be a concern with the use of olanzapine for breakthrough CINV. Navari et al reported no cases of grade 3 or 4 toxicities and no significant difference between metoclopramide and olanzapine in terms of adverse effects, whereas the retrospective chart review by Chiu et al found drowsiness in 42% of patients (grade not reported).^{13,62} These results demonstrate that olanzapine is likely safe to use in this setting, however sedation can be a concern, and should be monitored when using olanzapine as breakthrough treatment.

Current guidelines recommend doses of olanzapine ranging from 5 mg to 10 mg daily for breakthrough nausea and vomiting. NCCN, recommends olanzapine 5 mg to 10 mg daily as one of several potential options for treating breakthrough CINV.⁷ As mentioned previously, studies of olanzapine in the prophylactic setting found comparable efficacy between the 5 mg and 10 mg doses. The optimal dose of olanzapine for the treatment of breakthrough CINV is unclear due to the heterogeneity of studies. The recommendation of a 5 mg daily dose is based on the body of evidence for olanzapine in the prophylactic setting and the consensus of the Working Group.

For patients who receive olanzapine as part of their antiemetic prophylaxis regimen, the choice of breakthrough is not as clear. Although common in practice and theoretically sound, the principle of adding an agent with a different mechanism of action for breakthrough CINV, is not supported by clinical evidence. Olanzapine is supported by RCTs in the breakthrough setting. The addition of 5 mg/day for breakthrough nausea and vomiting to prophylactic doses would provide a total daily dose of 10 mg, in line with doses studied in earlier trials.^{4,12} Caution should be taken in patients at risk of sedation and modifications made to the antiemetic regimen as necessary.

Other options for breakthrough nausea and vomiting include metoclopramide, haloperidol, prochlorperazine, and domperidone. These agents are recommended options for use in breakthrough nausea and vomiting in the NCCN guidelines.⁷ While these agents have historically been used to treat breakthrough CINV, there is no high

quality data to support or refute their use. Caution should be exercised when dopamine receptor antagonists are used in combination with olanzapine due to the risk of extrapyramidal symptoms. Caution should be exercised with olanzapine and other medications that may cause sedation (eg. benzodiazepines) due to the possibility of potentiating sedation.

Oral Chemotherapy

Clinical Question 8: What is the optimal prevention strategy for nausea and vomiting in adult patients who receive single day oral chemotherapy?

Recommendation 8: There is insufficient evidence to recommend routine antiemetic prophylaxis prior to an oral chemotherapy. In the event that a patient develops significant nausea or vomiting, consider initiating a routine prophylactic antiemetic agent. Clinical judgement should be used for individual cases where primary prophylaxis may be warranted.

Summary of Evidence & Discussion

To date, prevention of CINV from oral chemotherapy remains substantially empirical. The level of evidence regarding antiemetic prophylaxis for oral chemotherapy is low overall. Three small, phase II trials of patients receiving temozolomide for glioblastoma evaluated the value of various prophylactic antiemetics on CINV. Two of these trials assessed the efficacy or safety of a single dose of palonosetron, and the other a more complex regimen of palonosetron, aprepitant and dexamethasone.^{63–65} Affronti et al. studied the safety of weekly palonosetron in patients receiving 6 weeks of temozolomide concomitant with radiotherapy. CR rates, which were a secondary endpoint, ranged from 67-79% for the 6 weeks with a tolerable toxicity profile for palonosetron (most common AE constipation; 29% Grade 1-2).⁶⁴ In the phase II study by Rozzi et al., CR rates of 91% were observed over the 7-day period with a single dose of palonosetron in patients receiving multi-day temozolomide, however most of the patients enrolled were receiving daily doses of corticosteroids.⁶³ Twenty one patients receiving concomitant temozolomide and radiotherapy were enrolled in the study by Matsuda et al. to receive weekly palonosetron and multiple-cycle aprepitant in addition to a single dose of dexamethasone.⁶⁵ The percentage of patients with complete response in the overall period was 76.2%. Although these studies suggest that routine antiemetics may be effective in preventing CINV with oral chemotherapy such as temozolomide, overall trial quality is low due to lack of randomization, lack of comparators, and small subject sample size. In addition to the lack of high quality RCTs, the evidence for primary prophylaxis of oral chemotherapy-induced nausea and vomiting is complicated by factors such as concomitant radiation therapy and underreporting of emesis in non-antiemetic studies if nausea and vomiting are not monitored, or over reporting based on disease-related factors. For example, a study by Shepherd et al. evaluating the efficacy of erlotinib compared to placebo in 731 advanced stage lung cancer patients reported an incidence of emesis of around 25% for both the treatment (erlotinib) and placebo groups.⁶⁶ This makes it difficult to interpret the true emetogenicity of oral chemotherapy.

The NCCN guidelines for oral chemotherapy prophylaxis recommend a daily 5-HT₃ RA prior to oral chemotherapy for high to moderate emetic risk treatments and antiemetics as needed for low to minimal emetic risk chemotherapy.⁷ If nausea and/or vomiting were to occur, antiemetics would subsequently be given daily. This recommendation is similar to that of NCCN and is likewise based on consensus of the Working Group. However, due to insufficient evidence, the addition of routine prophylaxis to high-moderate emetic risk oral chemotherapy should also be based on patient-specific risk factors.

Acknowledgements

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Appendix 1:

[Changes to Emetic Risk of Chemotherapy Regimens in Adults](#)

A list of regimens that had a change in emetic risk classification since the 2013 Antiemetic Report.

Appendix 2:

[Emetic Risk of Single Intravenous Agents in Adults](#)

A list of all IV agents in the CCO Drug Formulary and their emetogenic classification.

Appendix 3:

[Emetic Risk of Single Oral Agents in Adults](#)

A list of all oral agents in the CCO Drug Formulary and their emetogenic classification.

Appendix 4: Abbreviations

Abbreviation	Explanation
5-HT ₃ RA	Serotonin (5-HT ₃) Receptor Antagonist
AC	Anthracycline (ex. doxorubicin or epirubicin) plus Cyclophosphamide combination regimens
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BID	Twice daily
CCO	Cancer Care Ontario
CINV	Chemotherapy-Induced Nausea and Vomiting
CIV	Continuous Intravenous Infusion
CR	Complete Response
ESMO	European Society of Medical Oncology
HEC	High Emetic Risk Chemotherapy
IV	Intravenous
LEC	Low Emetic Risk Chemotherapy
MASCC	Multinational Association of Supportive Care in Cancer
MEC	Moderate Emetic Risk Chemotherapy
NCCN	National Comprehensive Cancer Network
NEPA	Fixed-dose Netupitant and Palonosetron combination
NK ₁ RA	Neurokinin-1 Receptor Antagonist
PO	By mouth
PRN	As needed
RCT	Randomized Controlled Trial
SCT	Stem Cell Transplantation

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