Fixed Combination Antiemetic

A literature review on prevention of chemotherapy-induced nausea and vomiting using netupitant/palonosetron

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BACKGROUND: Prevention of chemotherapy-induced nausea and vomiting (CINV) can be improved with guideline-consistent use of antiemetics. However, adherence to antiemetic guidelines remains often insufficient. Therefore, new strategies that improve adherence are needed.

OBJECTIVES: To review the latest antiemetic guideline recommendations and provide an update on the use of NEPA, a fixed combination antiemetic composed of the neurokinin-1 receptor antagonist (RA) netupitant and the 5-hydroxytryptamine-3 RA palonosetron (Akynzeo®).

METHODS: Analysis of the literature was performed, including guidelines, published literature, congress data on NEPA, and relevant articles on CINV.

FINDINGS: Nurses are in a unique position to promote guideline-consistent antiemetic prophylaxis and are central in the education of patients and caregivers. Thus, nurses’ continuous education on antiemetic treatments is key for the prevention and management of CINV. NEPA offers a simplified antiemetic therapy with the potential to increase guideline adherence.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV) is a common and distressing side effect for patients receiving highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) (Hesketh, 2009). Without adequate prophylaxis, greater than 90% of patients receiving HEC and 30%–90% of patients receiving MEC will experience CINV (Aapro et al., 2012). Consequences often include metabolic imbalance, nutrient depletion, and anorexia; impaired daily functioning and reduced quality of life; postponement or dose reduction of chemotherapy; and increased resource use and costs (National Comprehensive Cancer Network [NCCN], 2017; Viale, Grande, & Moore, 2012).

Oncology nurses have observed that clinical challenges, often manifested as obstacles to CINV prophylaxis, may be timely opportunities to provide education to patients, family members, and significant others involved in the ongoing care of patients receiving potentially emetogenic chemotherapy. Patient perceptions may affect the control of CINV. Some patients interpret nausea and vomiting as a positive response to chemotherapy and a sign that it is working. Many patients fear that a dose reduction or discontinuation of treatment will occur if CINV is reported to physicians and nurses, and others expect to suffer during chemotherapy and are concerned that reporting CINV would be interpreted as complaining. These perceptions represent excellent opportunities for nurses to provide comprehensive education regarding planned chemotherapy and all supportive care medications that can be administered (Salsman et al., 2012; Thompson, 2012).

The selection of antiemetic agents for CINV prevention is supported by evidence-based guidelines. The most relevant, up-to-date guidelines include those from the Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) (Roila et al., 2016), American Society of Clinical Oncology (ASCO) (Hesketh et al., 2017), and NCCN (2017). With guideline-consistent use of antiemetics, emesis can be prevented in the majority of patients (Jordan, Jahn, & Aapro, 2015). However, guidelines are not always followed; therefore, CINV remains a challenge for some patients (Aapro et al., 2012; Vidall et al., 2014). Additional antiemetic options are now available, such as netupitant/palonosetron (NEPA) (Akynzeo®) (Helsinn Healthcare SA, 2016),
an oral fixed combination of a highly selective neurokinin-1 receptor antagonist (NK1 RA) and a clinically distinct 5-hydroxytryptamine-3 receptor antagonist (5-HT3 RA) (Rojas et al., 2010; Stathis, Pietra, Rojas, & Slusher, 2012). NEPA is the first combination agent for antiemetic prophylaxis and targets two critical pathways associated with emesis in a single dose, simplifying the prophylactic regimen. Another NK1 RA, rolapitant (Varubi®), was also approved by the U.S. Food and Drug Administration ([FDA], 2015; Tesaro, Inc., 2018); with a half-life of about 180 hours, rolapitant can provide CINV protection in HEC- or MEC-treated patients in combination with other antiemetics (Rapport et al., 2015; Schwartzberg et al., 2015).

The current article reviews a summary of current guideline recommendations and the most recent NEPA data and discusses the role of nurses in CINV management and promotion of antiemetic guideline adherence.

Methods
From 2014–2015, two antiemetics, rolapitant and NEPA, were approved by the FDA (2014, 2015). NEPA was selected for an in-depth review because it is recommended by MASCC/ESMO, ASCO, and NCCN and because of its novelty as a combination antiemetic. Data on the preclinical and clinical development of NEPA were obtained from published literature in PubMed and from studies presented at international congresses from 2014–2016. Literature for the comprehensive background on the pathophysiology of CINV, antiemetic guideline adherence, and the role of nurses in CINV management was selected based on recent publications relevant to the focus of this review (Vidall et al., 2015).

Physiology of CINV
CINV physiology is complex and not fully understood. The current model suggests that effective prophylaxis requires inhibition of the central and peripheral pathways involved in CINV (Thompson, 2012) (see Figure 1). The peripheral pathway, located primarily in the gut, is associated with acute CINV and activated within 24 hours following chemotherapy (0–24 hours). This pathway is predominantly mediated by serotonin and is inhibited by 5-HT3 RAs (Hesketh, 2008). The central pathway is primarily associated with delayed CINV, starting more than 24 hours after chemotherapy (24–120 hours). This pathway is mainly mediated by substance P and inhibited by NK1 RAs (Hesketh, 2008). The two pathways are not mutually exclusive, and multiple neurotransmitters may have overlapping roles in acute and delayed CINV (Thompson, 2012).

Antiemetic Guidelines and Adherence
Updated guidelines assist healthcare professionals in administering optimal antiemetic prophylaxis. Once CINV occurs, the risk of experiencing CINV in subsequent chemotherapy cycles increases (Viale et al., 2012). Consequently, CINV management is focused on prevention rather than treatment. In the early 1990s, the introduction of first-generation 5-HT3 RAs, such as dolasetron (Anzemet®), granisetron (Kytril®), and ondansetron (Zofran®), transformed CINV prevention, particularly for acute emesis (Hesketh, 2004; Navari, 2013). However, their effectiveness in the management of delayed CINV was limited (Geling & Eichler, 2005). The addition of a corticosteroid, such as dexamethasone, was shown to increase the efficacy of 5-HT3 RAs and was recommended by international guidelines (Hesketh, 2004). The subsequent introduction of NK1 RAs, with the approval of the first-in-class aprepitant (Emend®) in 2003, represented a significant milestone in CINV prophylaxis, particularly for delayed CINV. Phase 3 trials showed improved CINV control with the addition of aprepitant to ondansetron plus dexamethasone (Hesketh, 2008; Hesketh et al., 2003; Poli-Bigelli et al., 2003). The general key evidence-based recommendations for antiemesis, defined in guidelines of MASCC/ESMO, ASCO, and NCCN, are the use of a 5-HT3 RA and dexamethasone on the day of chemotherapy (day 1) for prevention of CINV in patients receiving MEC; if necessary, patients may receive additional prophylaxis with dexamethasone on days 2 and 3 (Hesketh et al., 2017; NCCN, 2017; Roila et al., 2016) (see Table 1). The NCCN guidelines recommend the addition of an NK1 RA if further high-risk factors are present or if previous 5-HT3 RA plus dexamethasone treatment has failed (NCCN, 2017). For patients receiving anthracycline-cyclophosphamide (AC) or HEC, prophylaxis with either the triplet combination of an NK1 RA, a 5-HT3 RA, and dexamethasone (NCCN, 2017; Roila et al., 2016), or the four-drug regimen of olanzapine, an NK1 RA, a 5-HT3 RA, and dexamethasone (Hesketh et al., 2017; NCCN, 2017) is recommended. The NK1 RA, 5-HT3 RA, and dexamethasone triplet combination is also recommended by the MASCC/ESMO guidelines (Roila et al., 2016) for patients receiving carboplatin-based chemotherapy at
any dose. Administration of the triplet regimen is restricted only for patients receiving carboplatin administered at an area under the curve (AUC) of 4 mg/ml per minute or greater by ASCO and NCCN guidelines (Hesketh et al., 2017; NCCN, 2017).

Antiemetic guidelines recommendations categorize the risk of CINV by emetogenic potential of the antineoplastic agent only (e.g., HEC, MEC). Patient-related risk factors may also contribute to the likelihood of an emetic event, including younger age, female gender, low alcohol intake, anxiety, and history of motion sickness or nausea during pregnancy (Di Maio et al., 2013), and should also be considered. Prior to the administration of the initial cycle of chemotherapy, oncology nurses assess the patient to determine risk factors for CINV, looking specifically to identify patient-related risk factors that would need to be discussed with the physician and documented.

An algorithm has been developed by a panel of experts, and the following factors were identified as predictors of risk of CINV (Dranitsaris et al., 2017):
- Patient age younger than 60 years
- Anticipatory nausea and vomiting
- History of morning sickness
- Less than seven hours of sleep the night before chemotherapy
- CINV in a prior cycle of chemotherapy
- Use of AC- or platinum-based chemotherapy

**FIGURE 1.**
**THE ROLE OF NK1 AND 5-HT3 RECEPTOR ANTAGONISTS IN EFFECTIVE PREVENTION OF CINV**

5-HT3—5-hydroxytryptamine-3; CINV—chemotherapy-induced nausea and vomiting; GI—gastrointestinal; NK1—neurokinin-1; RA—receptor antagonist

**Note.** From “Optimizing Treatment Outcomes in Patients at Risk for Chemotherapy-Induced Nausea and Vomiting” by N. Thompson, 2012, Clinical Journal of Oncology Nursing, 16, p. 310. Copyright 2012 by Oncology Nursing Society. Adapted with permission.
Patient use of nonprescribed antiemetics at home

Cycle of chemotherapy (lower risk of CINV after the first cycle)

Based on these risk factors, a scoring algorithm was developed to select the most suitable antiemetic regimen for each individual patient. The algorithm can be accessed at http://cinvrisk.org.

AC-based chemotherapy, historically considered a MEC regimen, has been classified as HEC (Hesketh et al., 2017; NCCN, 2017; Roila et al., 2016).

**Table 1.** Guideline recommendations for antiemetic use with moderately emetogenic, highly emetogenic, and anthracycline-cyclophosphamide–based chemotherapy

<table>
<thead>
<tr>
<th>Guideline</th>
<th>MEC</th>
<th>HEC</th>
<th>AC Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American Society of Clinical Oncology</strong> (Hesketh et al., 2017)</td>
<td><strong>Day 1</strong></td>
<td><strong>Days 2–3</strong></td>
<td><strong>Day 1</strong></td>
</tr>
<tr>
<td>PALO + DEX, if carboplatin AUC is 4 mg/ml per minute or greater; NEPA + DEX or NK,RA (APR/FOS/ROL) + 5-HT,RA + DEX</td>
<td>DEX (can be added if using agents with a known risk for delayed nausea and vomiting; not including carboplatin AUC 4 mg/ml per minute or greater)</td>
<td>NEPA + DEX + OLZ or NK,RA (APR/FOS/ROL) + 5-HT,RA + DEX + OLZ</td>
<td>DEX (if APR 125 mg is used on day 1, then use once-daily APR 80 mg on days 2–3)</td>
</tr>
<tr>
<td><strong>Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology</strong> (2016) (Roila et al., 2016)</td>
<td>5-HT,RA + DEX</td>
<td>DEX; if an agent with a known potential for delayed CINV is used (e.g., oxaliplatin, doxorubicin, cyclophosphamide), consider use of DEX on days 2–3; otherwise, no routine prophylaxis is recommended. If carboplatin (any dose): APR; if APR 125 mg is used on day 1, then use once-daily APR 80 mg on days 2–3.</td>
<td>NEPA + DEX or NK,RA (APR/FOS/ROL) + 5-HT,RA + DEX or NK,RA (APR/FOS/ROL) + 5-HT,RA + DEX + OLZ (in patients with high risk of nausea)</td>
</tr>
<tr>
<td><strong>National Comprehensive Cancer Network</strong> (2017)</td>
<td>NEPA + DEX (with or without lorazepam, and with or without either an H₂ blocker or a proton pump inhibitor) or 5-HT,RA + DEX with or without NK,RA (APR/FOS/ROL) (an NK,RA should be added for patients with additional risk factors or previous treatment failure)</td>
<td>DEX or 5-HT,RA monotherapy (no 5-HT,RA required if PALO or GRAN [extended-release injection or transdermal patch] is given on day 1; with or without lorazepam, and with or without either an H₂ blocker or a proton pump inhibitor; if APR was included on day 1, then it should be given with or without DEX on days 2–3; if OLZ is given on day 1, also administer on days 2–4)</td>
<td>NEPA + DEX or NK,RA (APR/FOS/ROL) + 5-HT,RA + DEX or OLZ (with or without lorazepam, and with or without either an H₂ blocker or a proton pump inhibitor; if APR was included on day 1, also administer on days 2–3; if OLZ is given on day 1, also administer on days 2–4)</td>
</tr>
</tbody>
</table>

S-HT,RA—5-hydroxytryptamine-3 receptor antagonist; AC—anthracycline/cyclophosphamide; APR—aprepitant; AUC—area under the curve; CINV—chemotherapy-induced nausea and vomiting; DEX—dexamethasone; FOS—fosaprepitant; GRAN—granisetron; HEC—highly emetogenic chemotherapy; MEC—moderately emetogenic chemotherapy; NEPA—netupitant/palonosetron; NK,RA—neurokinin-1 receptor antagonist; OLZ—olanzapine; PALO—palonosetron; ROL—rolapitant.
Roila et al., 2016). Patients who receive AC are mostly patients with breast cancer, usually (but not always) young and female, and at a higher risk of developing CINV. Findings have demonstrated that the emetogenicity of carboplatin might be underestimated (Jordan et al., 2015), and prophylaxis with the NK,RA, 5-HT,RA, and dexamethasone combination is now recommended in the guidelines (Hesketh et al., 2017; NCCN, 2017; Roila et al., 2016).

Despite studies showing that adherence to guidelines can reduce the incidence of CINV (Aapro et al., 2012), guidelines are often not followed. Adherence has been found to be suboptimal in oncology practices in Europe and the United States (Aapro et al., 2012; Gilmore et al., 2014; Navari & Aapro, 2016). In addition, a multinational study revealed that only 38% of patients adhere to physicians’ and oncology nurses’ guidelines when self-administering antiemetic medication at home (Vidall et al., 2015). A potential reason for the low adherence may be that antiemetic regimens are often complex. For example, some of the dosing schemes for regimens based on NK,RA involve the following regimens (NCCN, 2017):

- **Aprepitant-based regimens:** Aprepitant plus 5-HT,RA plus dexamethasone (day 1) and aprepitant (days 2–3) plus once-daily dexamethasone (days 2–4 in HEC; days 2–3 in MEC)
- **Rolapitant-based regimens:** Rolapitant (two tablets) plus 5-HT,RA plus dexamethasone (day 1), and 5-HT,RA (days 2–3 in MEC [Schwartzberg et al., 2015]) plus twice-daily dexamethasone (days 2–4 in HEC; days 2–3 in MEC)
- **NEPA-based regimens:** NEPA plus dexamethasone (day 1) and once-daily dexamethasone (days 2–4 in HEC; days 2–3 in MEC)

Another relevant factor is the prescribing behavior of the clinician, which can be difficult to change (Jordan, Gralla, Jahn, & Molassiotis, 2014). Oncology nurses in the United States have reported “physicians’ preference” as the main barrier to following guideline recommendations (Clark-Snow, Affronti, & Rittenberg, 2018). An effective method for facilitating change and improving guideline adherence is feedback from patients on their CINV outcomes (Jordan et al., 2014).

**Role of Nurses in Managing Patients With CINV**

Effective management of any symptom or cluster of symptoms requires that multiple dimensions of the patient’s symptom experience, strategies, and outcomes are considered, including communication, education, assessment, and monitoring with the use of effective and validated tools (Braun et al., 2012; Rieger & Yarbro, 2003; Shepard & Kelvin, 1999).

Oncology nurses, as part of an interprofessional team, are uniquely positioned to facilitate the implementation of strategies for effective CINV prevention and management. Their responsibilities include assessing CINV risk, educating patients and caregivers, administering antiemetic therapy, evaluating treatment, and providing feedback to the medical team when changes in treatment are warranted (Viale et al., 2012). Nurses must also be aware of their institutional guidelines and local protocols and pay attention to updates. In settings where interprofessional care is provided, oncology nurses may assist in designing individual treatment plans and defining institutional practice guidelines (Thompson, 2012). In addition, tools that facilitate communication between patients and oncology professionals, such as the validated MASCC Antiemesis Tool (MAT) (www.mascc.org/mat) (Molassiotis et al., 2007), can be used to assist with treatment decisions and support oncology nurses with CINV assessment. The MAT can be an important addition to an individual patient’s treatment plan. Patients are given a clear verbal and written explanation of what nausea and
vomiting are and the importance of documenting the occurrence of episodes of nausea and vomiting during the acute and delayed periods. Patients may refer to the MAT as a reminder to take antiemetics as prescribed during the delayed period (one to two days after administration of chemotherapy). The information gathered by nurses from this tool will provide valuable insight regarding the effectiveness of individual antiemetic regimens and of any potential changes that may be needed for the following treatment cycles. Patient diaries may also be used if the MAT is not available.

Understanding the pathophysiology of CINV and the available antiemetic medications can improve patient care and outcomes. Knowledge of patient history and risk factors and the emetogenic potential of chemotherapy are essential when addressing the antiemetic needs of individual patients.

**NEPA**

NEPA is the first fixed combination antiemetic, composed of netupitant and palonosetron, and is administered in a single oral capsule on the day of chemotherapy (Rojas et al., 2010; Stathis et al., 2012). NEPA was first approved by the FDA in the United States in 2014 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy, including but not limited to HEC (FDA, 2014; Helsinn Healthcare SA, 2016). In 2015, NEPA received approval in the European Union for the prevention

### TABLE 3.

**EFFICACY OF NEPA PLUS DEX VERSUS ORAL PALO PLUS DEX**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>NEPA + DEX (N = 136)</th>
<th>ORAL PALO + DEX (N = 135)</th>
<th>NEPA + DEX (N = 724)</th>
<th>ORAL PALO + DEX (N = 725)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>98.5*</td>
<td>89.7</td>
<td>88.4**</td>
<td>85</td>
</tr>
<tr>
<td>Delayed</td>
<td>90.4***</td>
<td>80.1</td>
<td>76.9****</td>
<td>69.5</td>
</tr>
<tr>
<td>Overall</td>
<td>89.6*</td>
<td>76.5</td>
<td>74.3****</td>
<td>66.6</td>
</tr>
<tr>
<td><strong>No emesis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>98.5*</td>
<td>89.7</td>
<td>90.9**</td>
<td>87.3</td>
</tr>
<tr>
<td>Delayed</td>
<td>91.9</td>
<td>80.1</td>
<td>81.8****</td>
<td>75.6</td>
</tr>
<tr>
<td>Overall</td>
<td>91.1*</td>
<td>76.5</td>
<td>79.8****</td>
<td>72.1</td>
</tr>
<tr>
<td><strong>No significant nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>98.5***</td>
<td>93.4</td>
<td>87.3</td>
<td>87.9</td>
</tr>
<tr>
<td>Delayed</td>
<td>90.4***</td>
<td>80.9</td>
<td>76.9**</td>
<td>71.3</td>
</tr>
<tr>
<td>Overall</td>
<td>89.6***</td>
<td>79.4</td>
<td>74.6**</td>
<td>69.1</td>
</tr>
<tr>
<td><strong>Complete protection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>97*</td>
<td>87.5</td>
<td>82.3</td>
<td>81.1</td>
</tr>
<tr>
<td>Delayed</td>
<td>84.4***</td>
<td>73.5</td>
<td>67.3****</td>
<td>60.3</td>
</tr>
<tr>
<td>Overall</td>
<td>83</td>
<td>69.9</td>
<td>65.8**</td>
<td>57.9</td>
</tr>
</tbody>
</table>

DEX—dexamethasone; NEPA—netupitant/palonosetron; PALO—palonosetron

* p ≤ 0.01 from logistic regression versus PALO, not adjusted for multiple comparisons with exception of complete response overall; ** p ≤ 0.05 from two-sided Cochran-Mantel-Haenszel test including treatment, age class, and region as strata; *** p ≤ 0.05 from logistic regression versus PALO, not adjusted for multiple comparisons with exception of complete response overall; **** p ≤ 0.01 from two-sided Cochran-Mantel-Haenszel test including treatment, age class, and region as strata.

Note. Complete response consists of no emesis and no rescue medication. No significant nausea consists of a visual analog scale score of less than 25 mm on a scale from 0 (no nausea) to 100 (as bad as possible). Complete protection consists of complete response and no significant nausea.

Note. Acute phase was 0–24 hours, delayed phase was 25–120 hours, and overall phase was 0–120 hours.

Note. The NEPA + DEX (N = 136) and Oral PALO + DEX (N = 135) columns are based on information from Hesketh, Rossi, et al., 2014, and the NEPA + DEX (N = 724) and Oral PALO + DEX (N = 725) columns are based on information from Aspro et al., 2014.
of acute and delayed nausea and vomiting associated with cisplatin-based HEC and MEC (Helsinn Healthcare SA, 2017).

Netupitant
Netupitant is an orally active, potent, and selective NK₁RA (Rizzi et al., 2012). Positron-emission tomography imaging and pharmacokinetic studies have demonstrated that netupitant has a long terminal half-life (about 90 hours), a high receptor occupancy (90% or greater) in most of the tested brain regions, and a long duration of occupancy (Spinelli et al., 2014).

Palonosetron
Palonosetron is a second-generation 5-HT₃RA that has a longer plasma half-life (about 40 hours) and higher receptor-binding affinity compared with first-generation 5-HT₃RAs. Palonosetron exhibits allosteric interactions and positive cooperativity, and triggers 5-HT₃ receptor internalization (Navari, 2010). In addition, palonosetron may inhibit cross-talk in 5-HT₃/NK₁ receptors (Rojas et al., 2010; Statthil et al., 2012). In a phase 3 trial, palonosetron plus dexamethasone was superior in delayed CINV control as compared to granisetron plus dexamethasone (Saito et al., 2009). A pooled analysis of four randomized phase 3 trials showed that palonosetron was significantly better at preventing CINV as compared to first-generation 5-HT₃RAs ondansetron, dolasetron, or granisetron in the overall (51% versus 40%, p < 0.0001) and delayed (57% versus 45%, p < 0.0001) phases (Schwartzberg, Barbour, et al., 2014). Palonosetron is safe and well tolerated and does not have significant cardiotoxicity (Gonullu, Demircan, Demirag, Erdem, &
Yucel, 2012). Palonosetron treatment was shown to result in better adherence to chemotherapy and fewer treatment delays in HEC- or MEC-treated patients as compared to other 5-HT₃RAs (Palli, Grabner, Quimbo, & Rugo, 2015).

**Drug–Drug Interactions**

Similar to aprepitant, netupitant is a moderate inhibitor of CYP3A4, and interactions with CYP3A4 substrates have been reported (Lanzarotti & Rossi, 2013). Dexamethasone is a CYP3A4 substrate, and increased exposure with netupitant has been observed (Lanzarotti & Rossi, 2013); therefore, the dose of dexamethasone was reduced when coadministered with NEPA in the pivotal clinical trials (Aapro et al., 2014; Gralla et al., 2014; Hesketh, Rossi, et al., 2014). The systemic exposure to docetaxel, etoposide, and cyclophosphamide (also metabolized primarily by CYP3A4) was higher after coadministration with NEPA than with palonosetron alone (Helsinn Healthcare SA, 2016). Drug–drug interactions of netupitant with other CYP3A4 substrates, including ifosfamide, imatinib, irinotecan, paclitaxel, vinblastine, vincristine, and vinorelbine, have not been fully investigated. Caution and monitoring are advised for patients receiving NEPA and CYP3A4-metabolized chemotherapy agents.

**NEPA Clinical Data**

In three randomized, double-blind phase 2 and 3 studies, NEPA (netupitant 300 mg plus palonosetron 0.5 mg) has been shown to be highly effective in CINV prophylaxis in the acute, delayed, and overall phases following HEC or MEC (Aapro et al., 2014; Gralla et al., 2014; Hesketh, Rossi, et al., 2014) (see Table 2).

**Phase 2 Pivotal Dose-Ranging Study**

A phase 2 dose-ranging study was conducted to determine the most appropriate clinical dose for NEPA (Hesketh, Rossi, et al., 2014) in 694 patients undergoing cisplatin-based HEC.

All NEPA doses were superior to palonosetron for the primary endpoint of complete response (no emesis, no rescue medication) during the overall phase following chemotherapy. Overall, complete response was experienced by 87.4%, 87.6%, and 89.6% of patients, respectively, in the NEPA₃₀₀ (p = 0.018), NEPA₂₀₀ (p = 0.017), and NEPA₁₀₀ (p = 0.004) arms, compared with 76.5% of patients in the oral palonosetron arm (Hesketh, Rossi, et al., 2014). NEPA₃₀₀ also demonstrated significantly higher efficacy versus oral palonosetron for complete response during the acute and delayed phases, and for no emesis, no significant nausea, and complete protection (complete response plus no significant nausea) (Aapro et al., 2014; Hesketh, Rossi, et al., 2014) (see Table 3). Although no formal comparisons were performed, NEPA₃₀₀ had numerically higher response rates for all of the efficacy endpoints compared with the exploratory aprepitant plus ondansetron plus dexamethasone arm. NEPA₃₀₀ consistently showed significant superiority versus oral palonosetron for all efficacy endpoints (Aapro et al., 2014; Hesketh, Rossi, et al., 2014) and was, therefore, selected as the dose for phase 3 studies.

Across groups, the overall incidence, type, frequency, and intensity of treatment-emergent adverse events were comparable. Most (95%) treatment-emergent adverse events were grade 1 or 2 (per the Common Terminology Criteria for Adverse Events [CTCAE]). Treatment-related adverse events occurred in 15.4% of NEPA₃₀₀ and 12.5% of oral palonosetron–treated patients, the most frequent being hiccups (5.1% versus 3.7%).

**FIGURE 3.** PROPORTION OF PATIENTS WHO REPORTED NO EFFECT ON QUALITY OF LIFE DURING THE OVERALL (0–120 HOURS) PHASE BASED ON FUNCTIONAL LIVING INDEX–EMESIS ASSESSMENT

<table>
<thead>
<tr>
<th>Domain</th>
<th>NEPA + DEX (N = 724)</th>
<th>PALO + DEX (N = 725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>71.5</td>
<td>65.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>90.1</td>
<td>84.4</td>
</tr>
<tr>
<td>Overall</td>
<td>78.5</td>
<td>72.1</td>
</tr>
</tbody>
</table>

Note. Data were based on full analysis set (N = 1,449). For these data, p values were 0.015 for the nausea domain, 0.001 for the vomiting domain, and 0.005 for the overall combined domain.

Phase 3 Clinical Data

A phase 3 study was conducted in 1,455 patients receiving AC-based chemotherapy (Aapro et al., 2014) to compare NEPA with oral palonosetron (0.5 mg). After cycle 1, patients could continue in a multiple-cycle extension phase, receiving the same treatment on day 1 of each cycle.

NEPA showed significantly higher complete response rates during the acute, delayed, and overall phases in cycle 1, as compared to oral palonosetron (Aapro et al., 2014).

NEPA was also superior to oral palonosetron for no emesis in the acute, delayed, and overall phases, and for no significant nausea and complete protection in the delayed and overall phases (Aapro et al., 2014). In addition, higher overall complete response rates for NEPA were sustained during cycles 2–4 (Aapro, Karthaus, et al., 2017) (see Figure 2).

To assess the effect of CINV on quality of life, patients completed the Functional Living Index–Emesis questionnaire on day 6 (Aapro et al., 2014; Lindley et al., 1992; Martin et al., 2003). As shown in Figure 3 (Aapro et al., 2014), significantly more NEPA-treated patients reported no impact on daily living for the individual nausea and vomiting domains, compared with oral palonosetron–treated patients, specifically for all items included in the vomiting domain and within the nausea domain for items regarding impact on daily functioning, personal hardship, and performing leisure activities (Jahn, Jordan, & Rizzi, 2014b). A greater proportion of NEPA-treated patients also reported no impact on daily living for the combined domains (Aapro et al., 2014). The higher nausea control associated with NEPA treatment was correlated with a quality-of-life benefit (Jahn, Jordan, & Rizzi, 2014a).

The overall incidence, type, frequency, and intensity of adverse events were comparable between the two groups. Most (85%) treatment-emergent adverse events were CTCAE grade 1 or 2 (Aapro et al., 2014). The incidence of treatment-emergent adverse events was 8.1% for NEPA- and 7.2% for oral palonosetron–treated patients, with headache (3.3% versus 3%) and constipation (2.1% in each arm) being the most common. During multiple cycles of AC-based chemotherapy, the type and incidence of adverse events were similar for both arms (Aapro, Karthaus, et al., 2017).

Another phase 3 study evaluated the safety of NEPA during multiple cycles of HEC and MEC (Gralla et al., 2014). The efficacy of NEPA was also described. Patients were randomly assigned in a 3:1 ratio to NEPA or to a control arm (three-day oral aprepitant regimen with oral palonosetron [0.5 mg] on day 1). Overall, 413 randomized patients completed 1,961 chemotherapy cycles, with 75% of patients completing at least four cycles (Gralla et al., 2014); in the first cycle, 76% of patients received MEC, and 24% received HEC. NEPA was well tolerated, with a similar incidence of treatment-emergent adverse events as in the aprepitant plus palonosetron arm during the first cycle of chemotherapy (65% versus 62%, respectively). The majority of treatment-emergent adverse events were CTCAE grade 1 or 2, and toxicity did not increase over multiple cycles. Treatment-emergent adverse events occurred in 5% and 3% of the NEPA- and aprepitant plus palonosetron–treated patients, respectively, during cycle 1, and in 10% and 6% of patients, respectively, during the entire study period. Overall, the most frequent treatment-emergent adverse events in the NEPA arm were constipation (3.6%) and headache (1%).

The overall complete response rates for NEPA were high (81%–91%) and maintained across cycles (Aapro, Karthaus, et al., 2017; Gralla et al., 2014). In the overall population, there was a small but consistent numeric advantage (2%–7%) for NEPA over aprepitant plus palonosetron in each cycle.

Combined Trial Analyses

Post-hoc subanalyses combining data from the three pivotal studies have shown the following:

- Complete response rates for NEPA were generally higher in older patients (aged 65 years or older) than the overall population (Aapro, Jordan, et al., 2017).
- In patients receiving cisplatin-based HEC, NEPA consistently showed a numerically higher absolute benefit (about 13%) compared with oral palonosetron for female patients and/or patients aged older than 55 years (Hesketh, Jordan, & Gralla, 2014).
- In patients of the phase 2 (cisplatin-based) and phase 3 (AC-based) studies, NEPA was shown to significantly improve nausea control compared with oral palonosetron, particularly in the delayed phase and for cisplatin-treated patients (Schwartzberg, Aapro, et al., 2014).

Implications for Nursing

Nurses are in a unique position to enhance the supportive care of patients by promoting guideline-recommended antiemetic prophylaxis. Maintaining an open dialogue with the patient’s physician and other interprofessional team members is vital to discuss and make recommendations for antiemetic regimens when needed. The use of standardized order sets, either in electronic or paper format, by physicians and nurses might also improve adherence. In addition, nurses have an ideal platform for improving communication regarding patients’ concerns and experiences. The provision of ongoing patient education and assessments and the creation of care plans that meet patient needs can ensure optimal CINV prophylaxis.
Conclusion
Nonadherence to antiemetic guidelines recommendations results in suboptimal CINV control (Aapro et al., 2012). Consequently, newly incorporated strategies to improve guideline-consistent use of antiemetics are needed. Increasing nurses’ knowledge of antiemetic guidelines and of the proper use of newly incorporated antiemetic medications is key to providing optimal CINV control in patients with cancer.

New antiemetics may also contribute to guideline adherence by providing a simplified treatment alternative. NEPA, a fixed combination agent, has been incorporated into antiemetic guidelines (Hesketh et al., 2017; NCCN, 2017; Roila et al., 2016). In clinical trials, NEPA plus dexamethasone was superior to oral palonosetron plus dexamethasone in preventing emesis and nausea during the entire emetic risk period (Aapro et al., 2014; Hesketh, Rossi, et al., 2014). In addition to offering guideline-based prophylaxis, NEPA has also been shown to reduce the impact of CINV on patients’ functioning (Aapro et al., 2014; Jahn et al., 2014a, 2014b). NEPA’s administration as a single oral dose before chemotherapy offers the possibility for reducing the pill burden for healthcare providers and patients. As a result, the more convenient NEPA schedule can help to reduce the burden of care for patients with cancer and may lead to better adherence to therapy.

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