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REVIEW

Management of acute and delayed chemotherapy-induced nausea and vomiting: role of netupitant–palonosetron combination

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Purpose: The purpose of this review is to summarize and discuss the recently published data (both original studies and reviews) on the oral medication NEPA, consisting of netupitant (a neurokinin-1 receptor antagonist [NK1RA], 300 mg dose) and palonosetron (5-hydroxytryptamine [serotonin or 5HT] type 3 receptor antagonist [$5HT_3RA$], 0.5 mg dose), in the prevention of the acute and delayed nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy.

Methods: This review was based on the very limited number of available published trials consisting of two Phase III studies and one Phase II dose-selecting trial.

Results: These studies demonstrated some therapeutic benefits of NEPA over related chemotherapy-induced nausea and vomiting (CINV) prophylaxis management, as well as its beneficial safety profile. In particular, compared with single-dose 0.5 mg palonosetron, the complete response rates for all phases of CINV for the first cycle of highly emetogenic chemotherapy (with cisplatin), as well as anthracycline–cyclophosphamide-based moderately emetogenic chemotherapy, were significantly higher for single-dose NEPA. The high efficacy of NEPA in terms of prevention of CINV continued throughout repeated cycles of highly and moderately emetogenic therapies.

Conclusion: It is currently recommended that patients who are administered highly emetogenic chemotherapy regimens should obtain a three-drug combination consisting of NK1RA, $5HT_3RA$, and dexamethasone. The recently available oral combination of NEPA plus dexamethasone provides an additional pharmacological management option that could be considered in this scenario.

Keywords: chemotherapy-induced nausea and vomiting, palonosetron, netupitant, NEPA, safety, pharmacology, outcomes

Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most troublesome adverse events of chemotherapy and one that has substantial negative effects on patients, clinicians, and the entire health care system. Despite pharmacological prophylaxis, ~61% of patients undergoing moderately or highly emetogenic chemotherapy (MEC and HEC, respectively) experience CINV (34% acute, 58% delayed).[1] In addition, patients tend to underreport CINV and often minimize the problem of CINV, leading to suboptimal adherence to guidelines for CINV in significant percentages of the patients (overall 29%–57%).[2,3] In addition, it has been reported previously that, paradoxically, patients at highest risk for CINV were characterized by the highest incidence of guideline inconsistent prophylaxis.[2]

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In the past 2 decades, there has been substantial progress in the control of CINV related to the introduction of effective antiemetic agents, including the first- and second-generation serotonin (5-hydroxytryptamine [5HT]) type 3 receptor antagonists ($5HT_3$RAs; eg, ondansetron, granisetron, and palonosetron) and neurokinin-1 receptor antagonists (NK1RAs, eg, aprepitant, fosaprepitant, casopitant, and rolapitant).[4] An important benefit of the newer antiemetic agents appears to be associated with their prolonged pharmacological effect and consequently improved ability to control the delayed CINV, which can develop even several days after chemotherapy administration. In addition to pharmacotherapy, patient education regarding the timing, prevention, and treatment of CINV is another key component of successful management of CINV.

Use of CINV prophylaxis consistent with already published clinical practice guidelines is essential for attaining optimal CINV control. Both $5HT_3$RA and NK1RA comprise the backbone of standard CINV prophylaxis in the current practice of oncology. There are several evidence-based guidelines for CINV prophylaxis from different contemporary sources, including the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the American Society of Clinical Oncology. These guidelines generally recommend $5HT_3$RA plus corticosteroid for patients receiving MEC, and combination treatment with an NK1RA and $5HT_3$RA plus a corticosteroid for patients receiving HEC.[5–8] The current guidelines recommend palonosetron as the preferred $5HT_3$RA in patients receiving MEC.

It was suggested previously that the absence of the NK1RA in prevention of CINV in HEC might be identified as the main reason for the therapeutic failure of the prophylaxis.[9] In addition, the current therapy with oral aprepitant as an NK1RA might be relatively complex and inconvenient because of the need for repeated daily doses. This particular problem (ie, need for repeated redosing) has recently stimulated the development of different pharmaceutical formulations characterized by prolonged duration of action in CINV and the ability for convenient single-dose use. In October 2014, a fixed-dose oral combination containing the novel NK1RA netupitant and the second-generation, long-acting $5HTR_3$RA palonosetron (abbreviated NEPA) received approval by the US Food and Drug Administration (FDA). The combination of two longer-acting and effective antiemetic agents in a single, oral capsule may potentially help simplify CINV management. This article summarizes the recently published original studies and reviews on NEPA and discusses its role in the management of acute and delayed CINV.

Review of pharmacology, mode of action, pharmacokinetics of netupitant and palonosetron, and rationale for the combination

Delayed emesis (~24 hours after chemotherapy administration with agents such as cisplatin, carboplatin, cyclophosphamide, and doxorubicin) has been linked with the stimulation (by substance P) of neurokinin 1 receptors within the central and peripheral nervous systems. The $5HT_3$ receptors have been demonstrated to play a significant role in acute-onset CINV (1–6 hours after drug administration, generally resolved within 24 hours) to selectively stimulate the emetic response. Delayed CINV tends to be both more common than acute CINV and more resistant to CINV prophylaxis. The rationale behind the new developments in the pharmacological prophylaxis of CINV has, therefore, been directed toward preparations targeting these two pharmacological emetic pathways, aimed at providing single, cost-effective, and easy-to-use drug combinations that are relatively long-acting.

NEPA is the first commercially available pharmaceutical fixed-dose combination of two active antiemetic agents, which comprises a new, highly selective NK1RA, namely, netupitant, and a $5HT_3$RA, namely palonosetron. The results of the in vitro and in vivo pharmacological studies of netupitant (2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridine- 3-yl]-isobutyramide) demonstrated that it selectively inhibits binding of NK1 to NK1 receptors, but not to NK2 and NK3 receptors. Netupitant is characterized by high brain penetration; it is orally active and serves as a strong and selective NK1RA.[10] Based on the results of positron emission tomography (PET) studies, it was demonstrated that netupitant is an effective agent targeting human NK1 receptors.[11,12] It appears to have a high receptor occupancy level (90%) at the time of maximum plasma concentration, which is characterized by the long-lasting (96 hours) blockade of NK1 receptors in the human brain, even when given at a single oral dose. In addition to its high binding affinity to NK1 receptors, netupitant has a long half-life of 90 hours (compared to a 9- to 13-hour half-life of aprepitant).[10–12]

Palonosetron ((3aS)-2-[(S)-1-Azabicyclo-[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H benz[de]isoquinoline hydrochloride) is a second-generation $5HT_3$RA that has antiemetic activity at the central nervous system level and along the gastrointestinal tract.[13,14] Palonosetron has a longer half-life (40 hours) and higher binding affinity compared to

first-generation setrons, resulting in more effective $5HT_3$RA activity, from both pharmacologic and clinical points of view. It was also reported that receptor binding features of palonosetron are characterized by allosteric binding and positive cooperativity on the $5HT_3$ receptors when compared to binding with both granisetron and ondansetron.[10,15] It was also postulated that palonosetron triggers $5HT_3$ receptor internalization and produces long-lasting suppression of receptor function.[15] The described differences in binding and receptor function may contribute to clinically significant differences between palonosetron and the first-generation $5HT_3$RAs, including palonosetron's efficacy in preventing delayed CINV when compared to the first-generation receptor antagonists.[4] In addition, several studies have shown that palonosetron is characterized by high tolerability profile and achieves superior efficacy in preventing CINV compared with other $5HT_3$RA agents.[16–19]

In short, the antiemetic effect of NEPA appears to be due to its ability to inhibit cross talk between $5HT_3$ and NK1 receptors, as well as the inhibition of substance P signaling. Preclinical data demonstrated that NEPA synergistically enhanced and prolonged inhibition of the serotonin and substance P responses compared to either palonosetron or netupitant alone.[20,21]

Both palonosetron and netupitant are eliminated by oxidative processes through the liver, but each of them is primarily metabolized by different cytochrome P450 (CYP) isoenzymes. Netupitant is metabolized through the CYP isoenzyme 3A4 (CYP3A4) (K_m: ~3–9 μM) to three major metabolites (M1, desmethyl derivative; M2, N-oxide derivative; and M3, OH-methyl derivative) and is principally excreted via the hepatic/biliary route.[22] Palonosetron is primarily metabolized through the CYP2D6 system, with minor involvement from the CYP1A2 and CYP3A4 systems. It is also excreted in urine as both its metabolite and the unchanged form in about equal proportion. Due to the different metabolic routes and excretion pathways, no interaction in elimination pathways between netupitant and palonosetron has been demonstrated.[23] The exposure to palonosetron, in terms of maximum plasma concentration (C_{max}) and area under the curve (AUC), was similar after administration of 0.75 mg palonosetron alone and in combination with 450 mg netupitant, suggesting that netupitant did not affect the pharmacokinetics of palonosetron. In general, these data indicate that exposure to palonosetron was slightly higher in subjects treated with palonosetron plus netupitant compared to palonosetron alone, but not significant according to bioequivalence standards (90% CI within the predefined no-effect limits of 80%–125%). Netupitant coadministration did not have any relevant effects on palonosetron metabolites.[24] The exposure to netupitant, in terms of C_{max} and AUC, was similar after administration of netupitant alone and in combination with palonosetron, demonstrating that palonosetron did not affect the pharmacokinetics of netupitant. Similarly, the pharmacokinetics of the netupitant metabolites was not affected by concomitant palonosetron administration.[24]

Efficacy studies, including comparative studies

The aim of the Phase II multicenter and randomized study[25] that was published in 2014 during the preapproval period was to identify the best dose combination for NEPA in adult patients receiving HEC chemotherapy with cisplatin. The dose of 0.5 mg of palonosetron was selected based on previous dose-ranging trials for palonosetron and was subsequently used for FDA approval of the 0.50 mg oral dose. A total of 694 patients were randomized to five different groups receiving palonosetron, three different oral doses of netupitant (100 mg, 200 mg, and 300 mg) coadministered with palonosetron 0.50 mg, or a 3-day course of aprepitant/ondansetron combination (as the additional exploratory arm). Dexamethasone was administered in all patients. Antiemetic efficacy measured as complete response (CR, defined as no CINV episodes and rescue medication) rates was higher in all NEPA dose groups compared with palonosetron alone during the delayed phase. It was also significantly higher for NEPA containing 300 mg netupitant during the acute phase. Moreover, this particular formulation was more effective than palonosetron alone during both acute and delayed phases for most of the measured secondary efficacy end points (eg, no vomiting, no significant nausea, and complete protection from CINV). The highest dose of netupitant in NEPA demonstrated gradual clinical benefits over the two lower NEPA doses for all secondary efficacy end points. It should also be noted that in a previous PET study,[12] the 300 mg netupitant dose was also the minimal dose tested that resulted in receptor occupancy of 90% in the striatum. Although no formal statistical comparison was made for the exploratory aprepitant/ondansetron arm of the study, the obtained results demonstrate similar CR rates between patients in the NEPA arm and those in the exploratory arm. The oral fixed combination of 300 mg netupitant and 0.50 mg palonosetron was subsequently developed and evaluated in the Phase III clinical development program.

The overall safety profile was similar among treatment groups in this study[12] and there was no evidence of a dose-related rise in the occurrence of adverse events for any NEPA group. The majority (95%) of all adverse events were of mild-to-moderate intensity. The most frequently observed adverse events consisted of hiccups and headache. Moreover, NEPA arms showed a safety profile similar to that of a combination of palonosetron and aprepitant, with a comparable incidence of adverse events and electrocardiogram (ECG) changes.

In the subsequently published results of the randomized and double-blind Phase III study, the efficacy and safety of a single oral dose of NEPA vs palonosetron, both administered with single-dose dexamethasone, were compared for the prevention of CINV in 1,449 patients receiving the first cycle of MEC with AC (cyclophosphamide with either doxorubicin or epirubicin).[26] In this study, NEPA was associated with higher CR rates after administration of chemotherapy than palonosetron alone during the acute phase (88.4% vs 85.0%; P=0.047), the delayed phase (76.9% vs 69.5%; P=0.001), and the full 120-hour period (74.3% vs 66.6%; P=0.001). NEPA was well tolerated, with a similar safety profile as palonosetron alone. Among the patients reporting adverse events, the most frequently observed adverse events included headache and constipation with mild-to-moderate intensity. Only five (0.7%) of the 940 NEPA-treated patients with observed severe adverse reactions experienced a serious management-related adverse event. No specific adverse events that would lead to discontinuation of the treatment were observed in this trial. It should be added here that after using NEPA in the first cycle of chemotherapy, its effectiveness was also compared with that of palonosetron in smaller groups of patients (76% completing at least four cycles). In this extension study, NEPA produced statistically significant better response (as measured by CR) when compared with palonosetron alone.[27]

The safety and efficacy of NEPA over repeated cycles of chemotherapy were studied in the second available Phase III trial.[28,29] This multicenter and double-blind study aimed to assess the safety and the efficacy of NEPA in preventing CINV over repeated cycles of HEC or MEC in chemotherapy-naïve patients. Patients with breast cancer treated with AC chemotherapy were not enrolled into the study. In this study, NEPA was compared to oral aprepitant plus oral palonosetron 0.50 mg for CINV prevention in 412 patients treated with chemotherapy for tumors over multiple cycles of chemotherapy. All patients received dexamethasone based on emetogenicity of chemotherapy. Antiemetic efficacy measured using CR rates was high for both treatment groups and was retained throughout the cycles of chemotherapy. NEPA demonstrated a small but consistent numerical improvement in CR rates (2%–7%) over aprepitant and palonosetron during each chemotherapy cycle. The efficacy in both groups in the acute phase was similar. The CR rates during the delayed phase of each cycle were similar to those in the overall phases, with differences ranging from 2% to 6%. In the overall population, CR rates in the overall phase were similar in the first chemotherapy cycle (81% in the NEPA group vs 76% in the control arm). The reported control of nausea was also similar in both study groups: 84%–92% in all cycles for NEPA and 81%–87% for the control group.

The majority of observed adverse events were of mild-to-moderate intensity, and 25.0% and 32.7% of patients experienced severe chemotherapy-related adverse effects with NEPA and aprepitant combined with palonosetron, respectively. Among all reported severe adverse effects, the most common were neutropenia (11.7% NEPA, 10.6% control) and leukopenia (4.5% NEPA, 4.8% control). There was no indication of increased frequency of adverse effects with repeated cycles. The fraction of patients who presented with drug-related adverse effects was relatively low in both groups (10.1% NEPA, 5.8% with control). The most frequent adverse effects observed for NEPA included constipation (3.6%) and headache (1.0%). There were no serious abnormalities in ECG or left ventricular ejection fraction at the end of the study, with small changes in both groups.

Safety and tolerability

The reported adverse events in all three reported studies were as expected for $5HT_3$RA and NK1RA agents. NEPA had an adverse event profile similar to that of oral palonosetron and an aprepitant-based regimen.[25–29] A comprehensive review of the safety profile for NEPA from the previously cited clinical studies indicates that treatment-emergent side effects were generally similar for NEPA, oral palonosetron, and oral aprepitant groups, including the percentage of patients reporting adverse effects that were considered to be treatment related. There were no deaths in the clinical program that were considered to be related to the NEPA treatment. The most frequent adverse events included headache, fatigue, and constipation. In addition, a similar frequency of cardiac adverse effects was reported in each treatment group during all cycles of treatment. In summary, it has been indicated that the safety profile for NEPA is consistent with that expected for these drug classes, with the type and incidence of adverse effects also being as expected for a diverse cancer population

treated with cytotoxic chemotherapy. Neither netupitant nor palonosetron have shown any effects on corrected QT intervals in individual clinical trials. In addition, administration of a single dose of NEPA (netupitant/palonosetron: 200 mg/0.5 mg and supratherapeutic dose of 600 mg/1.5 mg) to healthy volunteers did not have clinically significant effects on ECG (ie, no changes in QT, QTc, QRS interval, PR interval, and heart rate).[30]

Place in therapy

The FDA approved NEPA in October 2014 for the prevention of acute and delayed CINV related to initial and repeat courses of chemotherapy, including but not limited to HEC. NEPA has been available as a single capsule to be administered before each cycle of chemotherapy. The approval was based on Phase II and III studies (listed earlier) in patients undergoing MEC and HEC treatment. The listed NEPA benefits include a convenient dosage form, dual mechanism of action, and favorable side effect profile. In the US market, NEPA (Akynzeo®) has been distributed and marketed under license from Helsinn Healthcare. In addition, the same combination of netupitant and palonosetron (Akynzeo, Helsinn Birex) has been recommended for approval in Europe in 2015 for use in the prevention of CINV (both HEC and MEC). In addition, the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a favorable opinion about NEPA, with similar indication for its use as specified by the FDA.

Delayed CINV continues to represent a frequent adverse effect of HEC, AC MEC, and MEC treatment in cases without use of anthracyclines and cyclophosphamide (non-AC MEC). In the most recent systematic review, van der Vorst et al[9] evaluated the efficacy of two or more antiemetic strategies in the prevention of delayed CINV induced by treatment with non-AC MEC. Included randomized clinical trials reported outcomes on palonosetron, aprepitant, casopitant, NEPA, olanzapine, and megestrol acetate. This review concluded that superiority of palonosetron over first-generation $5HT_3$ receptor antagonists when used alone for the prevention of acute and delayed CINV after non-AC MEC has not been proven. In addition, it appears that the addition of an NK1RA to first-generation $5HT_3$RA does not significantly improve the incidence of delayed CINV after non-AC MEC, while NEPA shows highly effective increase of CR rates. An advantage of NEPA is that a single capsule only needs to be administered on Day 1 of each chemotherapy cycle, which has the potential to improve adherence to CINV prevention guidelines.

It should be noted that at the present time, the number of original studies for NEPA is extremely limited (ie, only three of them) and the number of reviews (including this article) is dramatically larger (>15 at present).[31–43] Obviously, more original studies will need to be performed to adequately determine the role of NEPA in therapy as well as to determine which patient population will benefit most from its use. In addition, whether NEPA simplifies therapy for the patient by decreasing the number of individual components prescribed, which, in turn, might improve adherence to the medication, should also be evaluated using a prospective design.

It should be also added here that NEPA is one of many new developments in the pharmacological treatment of delayed CINV. The new agents in the list include the new oral long-acting NK1RA rolapitant and the transdermal patch containing granisetron. Rolapitant (Varubi™; half-life of 180 hours) has recently been approved for use, in combination with other antiemetic agents, for the prevention of delayed CINV.[44] An additional benefit of rolapitant over other NK1RAs is that no dosage adjustment for dexamethasone is required. A novel transdermal formulation of granisetron (the granisetron transdermal delivery system – Sancuso®) has been developed to deliver granisetron continuously over 7 days. This preparation might also offer a convenient alternative route for continuously delivering granisetron for up to 7 days, which is as effective as oral granisetron.[45,46] New data have also recently been published on the psychotropic drug olanzapine. Olanzapine is a relatively inexpensive drug, but, so far, no evidence of its effectiveness and safety profile in CINV has been reported.[47]

Cost considerations

The value of NEPA addition to CINV management will be influenced by, among others, the cost and effectiveness over other antiemetic options. Formal cost-effectiveness analyses of NEPA are not yet available. The final out-of-pocket cost might therefore differ according to the insurance plan. From the health care payer perspective, it might be predicted, however, that NEPA might potentially dominate (ie, be less costly and more effective) over aprepitant plus palonosetron in patients receiving HEC and palonosetron alone in patients treated with MEC.

Limitations

The reported clinical experience with NEPA has so far been very limited. A total of three studies have been published (one for Phase II and two for Phase III, as well as associated

abstracts for different symposia), and the results of these studies have been summarized herein. In addition, several recent reviews have summarized new information already available about NEPA.[29–43] There are so far no other published studies describing the clinical experience with NEPA beyond the studies supporting the approval process.

Conclusion

It is currently recommended that patients who are administered HEC (including anthracycline plus cyclophosphamide) should obtain a three-drug combination consisting of NK1RA, $5HT_3$RA, and dexamethasone. The recently available oral combination of NEPA plus dexamethasone is an additional pharmacological management option that could be considered in this scenario. More studies are needed to adequately determine both the role of NEPA in therapy as well as which patients will most benefit from its use.

Disclosure

The author reports no conflicts of interest in this work.

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