Quality of Life Effects of an Oral Fixed Combination of Netupitant and Palonosetron in Chemotherapy-Induced Nausea and Vomiting Prevention: Real-World Evidence in Patients with Breast Cancer Receiving Anthracycline-Cyclophosphamide-Based Chemotherapy

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Keywords

NEPA · Netupitant · Palonosetron · Chemotherapy-induced nausea and vomiting · Antiemetic · Real-world · Breast cancer

Abstract

Introduction: In a prospective non-interventional study involving 2,173 patients, we showed that use of the oral fixed combination of netupitant 300 mg and palonosetron 0.5 mg (NEPA) for prevention of chemotherapy (Ctx)-induced nausea and vomiting has beneficial effects on the quality of life (QoL) of patients with various types of cancers receiving highly or moderately emetogenic Ctx. Here, we report on the effects on QoL, effectiveness, and tolerability of NEPA in patients with breast cancer exposed to anthracycline-cyclophosphamide (AC)-based Ctx. **Methods:** This is a post hoc subanalysis of a prospective non-interventional study in 1,197 patients with breast cancer receiving up to 3 cycles of doxorubicin or epirubicin plus cyclophosphamide and NEPA.

NEPA administration was per the summary of product characteristics. **Results:** In cycle 1 of Ctx, a large proportion of patients (84%) reported “no impact on daily life” (NIDL) due to vomiting; 53% of patients reported NIDL due to nausea. The complete response rate was 86/88/81% in the acute/delayed/overall phase in cycle 1, and NEPA was well tolerated throughout the study. **Conclusion:** The real-world beneficial effects of NEPA prophylaxis on QoL were confirmed for patients with breast cancer receiving AC. NEPA was effective with a good safety profile in this patient population in clinical practice.

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Published by S. Karger AG, Basel

Introduction

Anthracycline-cyclophosphamide (AC)-based chemotherapy (Ctx) was introduced for breast cancer treatment in the 1970s and has been widely associated with nausea, vomiting, and hair loss [1]. Ctx-induced

nausea and vomiting (CINV) negatively impacts patients' quality of life (QoL), with nausea associated with early treatment discontinuation in patients with breast cancer [2, 3]. Optimal CINV management has been shown to improve the QoL and survival of patients with cancer [4].

For Ctx of early breast cancer, international guidelines recommend an anthracycline, typically doxorubicin or epirubicin, combined with cyclophosphamide followed or preceded by taxanes (paclitaxel or docetaxel) [5, 6]. AC is currently ranked as highly emetogenic Ctx (HEC) [7–9], and international CINV guidelines recommend prophylaxis comprising both a neurokinin-1 receptor antagonist (NK₁RA) and a 5-hydroxytryptamine-3 (5-HT₃) RA with obligatory addition of dexamethasone, and the possibility to add olanzapine for specific patients. In addition to the emetogenic potential of Ctx, patient- and disease-related factors, for example age <60 years, receiving cycle 1 or 2 of Ctx, anticipatory CINV, experiencing CINV in the previous cycle, use of non-prescribed agents in the previous cycle, platinum-anthracycline-based Ctx [10], and female gender [11], among others, can increase the CINV risk. While these risk factors for CINV have shown utility for therapy selection and are recognized in all antiemetic guidelines [12], they are usually not considered for development of antiemetic recommendations. Given that patients with breast cancer often have additional risk factors, such as being female and young (25% are <50 years old), they are at particular risk of CINV [5, 6].

Low adherence to antiemetic guidelines in routine clinical practice is frequent and leads to suboptimal CINV control [13–15]. Factors such as low prescription rates and errors during home administration contribute to non-adherence [14, 16]. Hence, use of complex antiemetic regimens is likely to impose a barrier to guidelines adherence [17]. The 3 approved oral NK₁RAs, aprepitant, rolapitant (no longer marketed in EU), and the oral fixed combination of the NK₁RA netupitant (300 mg) and the 5-HT₃RA palonosetron (0.5 mg) (NEPA), differ in complexity of their administration schedules, in terms of number of doses, number of days, and doses of corticosteroids [18, 19].

Oral NEPA is the only available fixed-combination antiemetic and is approved for cisplatin-based HEC as well as AC-based HEC and moderately emetogenic Ctx (MEC; including carboplatin-based regimens) [20]. For patients receiving AC, a single dose of oral NEPA is administered with dexamethasone (12 mg) on the day of Ctx, providing effective protection covering the overall period (0–120 h) post-Ctx [19, 21]. In a phase 3 study including patients with breast cancer who received AC ($n = 1,412$), oral NEPA-dexamethasone was significantly superior to palonosetron-dexamethasone for CINV control and had a

good tolerability profile [21, 22]. Importantly, significantly more patients in the NEPA group reported “no impact on daily life” (NIDL) due to nausea and vomiting [21]. In addition, a subanalysis from a second phase 3 safety trial in patients receiving HEC and MEC showed that NEPA-dexamethasone provided better CINV control in the subset of 39 patients with breast cancer compared with the overall population [22]. Recently, the safety of both the oral and intravenous NEPA formulations [20] was described in a phase 3 study ($n = 402$) in patients with breast cancer receiving AC. Both formulations had a favorable safety profile with no treatment-related injection-site adverse events (AEs) and high antiemetic efficacy. Importantly, most patients in both groups reported NIDL due to nausea and vomiting [23].

Clinical trials have shown that collection of patient-reported outcomes regarding CINV can contribute to improved QoL and survival [4]. We conducted a non-interventional study in 2,173 patients throughout Germany to evaluate QoL in patients receiving antiemetic prophylaxis with NEPA for HEC and MEC under real-world conditions [24]. NEPA-based prophylaxis had a positive effect on the QoL of patients receiving HEC and MEC and was effective with a good tolerability profile in the real-world setting.

Herein, we report a post hoc subanalysis evaluating the effect of NEPA on the QoL of patients with breast cancer treated with AC who participated in the non-interventional study. NEPA effectiveness and safety were also analyzed.

Methods

Study Design

This is a post hoc analysis of a prospective non-interventional study conducted at 162 centers throughout Germany from September 2015 to March 2018 [24]. The primary endpoint was QoL in patients with breast cancer treated with AC who received NEPA antiemetic prophylaxis in daily practice. Secondary endpoints were NEPA effectiveness and safety.

Patients provided signed informed consent before enrollment, in compliance with the Declaration of Helsinki. The study was conducted in accordance with the German Medicines Act (Arzneimittelgesetz), and the Supreme Federal Authority, the Association of Accredited Physicians (Kassenärztliche Bundesvereinigung), the Central Federal Association of Statutory Health Insurance Funds (GKV-Spitzenverband), and the Association of Private Health Insurers (Verband der Privaten Krankenversicherung) were notified by OnkoDataMed GmbH (study No. CTU 130 K).

Patients and Procedures

Patients were recruited between September 2015 and September 2017. Male and female adults (≥ 18 years of age) with breast cancer scheduled to receive NEPA prophylaxis for CINV associated with AC were included in this subanalysis. Patients receiving Ctx other than AC for breast cancer were excluded. Details on patient eligibility were described previously [24].

Fig. 1. Relative frequencies of patients experiencing no influence on daily life activities due to nausea, vomiting, or combined nausea and vomiting, by cycle: subanalysis population. NIDL, no impact on daily life.

Table 1. Patient demographics and baseline characteristics: sub-analysis population

Parameter	Overall population (n = 1,197)
Gender, n (%)	
Female	1,188 (99.2)
Male	9 (0.8)
Age, years	
Mean (SD)	54.6 (9.3)
Median (range)	52.5 (26–79)
<60 years, n (%)	782 (65.8)
≥60 years, n (%)	415 (34.9)
Tumor type, n (%)	
Breast	1,197 (100)
ECOG PS, n (%)	
0	864 (72.2)
1	294 (24.6)
2	39 (3.3)
Therapy type, n (%) ^a	
Adjuvant	644 (53.8)
Neoadjuvant	533 (44.5)
Palliative	15 (1.3)
Emetic risk of chemotherapy, n (%) ^b	
AC HEC	1,197 (100)
Number of patients per cycle, cycle 1/2/3 ^b	1,192/1,155/1,125
Anticipatory CINV of patients in cycle 1/2/3, n (%) ^{b,c}	
Nausea	97/89/117 (8.5/8.0/11.1)
Vomiting	11/3/1 (1.0/0.3/0.1)

AC, anthracycline-cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting; ECOG PS, Eastern Cooperative Oncology Group performance status; HEC, highly emetogenic chemotherapy.

^a Patients receiving multiple therapies at cycles 1, 2, and 3 could be assigned to multiple categories.

^b Patients not documented in the electronic case report form were excluded.

^c Nausea and vomiting directly before the start of chemotherapy.

NEPA was administered as per the summary of product characteristics, i.e., one oral NEPA dose 1 h before the start of each AC cycle combined with 12 mg of dexamethasone. The study did not influence physicians' clinical practice and did not modify patients' treatment.

Assessments

For QoL, the impact of nausea and vomiting on daily life was measured using the Functional Living Index-Emesis (FLIE) questionnaire, which was completed by patients on days 1–5 of each cycle. Individual patients' data were collected in electronic case report forms during 3 Ctx cycles. Details on QoL, effectiveness, and safety assessments were described previously [24].

Statistical Analysis

No statistical analyses were performed. Descriptive statistics for demographic, QoL, effectiveness, and safety data are presented. Analysis and handling of missing data of FLIE questionnaires were described previously [24]. Complete response (CR) was defined as no emesis and no need for additional rescue medication. No significant nausea (NSN) was defined as no or mild nausea (grade 1) according to Common Terminology Criteria for Adverse Events version 4.03. Patients were stratified by age (<60 vs. ≥60 years). QoL and effectiveness were analyzed for each group.

Results

Patients

Among the 2,173 patients included in the final analysis of the non-interventional study [24], a total of 1,430 (66%) had breast cancer, of whom 1,197 (84%) received AC and constituted the subanalysis population. Most patients were female (99%) and the median age was 52.5 years (range 26–79), with 66% younger than 60 years (Table 1; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000514891). For 54/45/1% of patients, AC was administered in the adjuvant/neoadjuvant/palliative settings, respectively.

Table 2. Effectiveness outcomes by chemotherapy cycle

Parameter	Cycle 1	Cycle 2	Cycle 3
CR ^a			
Acute	86.0	86.9	88.3
Delayed	88.2	87.2	86.0
Overall	81.0	81.7	81.1
No emesis ^b			
Acute	94.2	95.1	96.2
Delayed	97.1	96.7	96.9
Overall	92.8	93.5	94.4
No significant nausea ^c			
Acute	69.1	73.9	76.0
Delayed	72.7	71.5	70.1
Overall	60.1	61.8	62.4
No nausea ^c			
Acute	43.3	47.1	49.8
Delayed	39.7	40.8	41.6
Overall	31.1	33.6	35.7
No rescue medication ^d			
Acute	90.2	90.3	91.6
Delayed	90.1	89.0	88.6
Overall	85.6	85.4	86.0

Values are the percentage of patients. CR, complete response.

^a Number of evaluable patients in cycles 1/2/3 by phase: acute, 1,120/1,092/1,047; delayed, 1,093/1,067/1,023; overall, 1,075/1,055/1,023.

^b Number of evaluable patients in cycles 1/2/3 by phase: acute, 1,120/1,092/1,047; delayed, 1,093/1,067/1,023; overall, 1,075/1,055/1,013.

^c Number of evaluable patients in cycles 1/2/3 by phase: acute, 1,130/1,102/1,057; delayed, 1,119/1,093/1,044; overall, 1,103/1,085/1,038.

^d Number of evaluable patients in cycles 1/2/3 by phase: acute, 1,162/1,159/1,163; delayed, 1,150/1,111/1,066; overall, 1,150/1,111/1,066.

Quality of Life

FLIE questionnaires from 1,027/1,005/964 (86/87/86%) patients were analyzed in cycles 1/2/3, respectively. In cycle 1, NIDL due to vomiting was reported by 84% of patients, 53% of patients reported NIDL due to nausea, and 64% of patients had NIDL due to combined nausea and vomiting. These rates were maintained with a slight numeric increase in subsequent cycles (Fig. 1).

Nausea and vomiting had a greater impact on the daily life of patients <60 vs. ≥60 years (online suppl. Fig. 1). NIDL due to nausea, vomiting, and combined domains improved consistently from cycle 1 to 3 in both age categories, with the largest numeric improvements observed in younger patients.

Effectiveness

In cycle 1, the CR rate was 86, 88, and 81% in the acute (0–24 h), delayed (24–120 h), and overall (0–120 h) periods post-Ctx; these high response rates were maintained

in cycles 2 and 3 (Table 2). The rate of no emesis in the acute, delayed, and overall periods was ≥93% during the 3 cycles. Both NSN and no nausea rates increased numerically across cycles in all phases, except for NSN in the delayed phase. In cycle 1, rescue medication was needed for 10, 10, and 14% of patients in the acute, delayed, and overall phases, respectively, and the low rates were maintained in cycles 2 and 3. CR and NSN outcomes were consistently higher in the group of patients ≥60 vs. <60 years throughout the cycles (online suppl. Fig. 2, 3).

The effectiveness of NEPA prophylaxis was rated as “very good” or “good” by the vast majority of physicians (>86%) and patients (>84%) in all 3 Ctx cycles analyzed (online suppl. Fig. 4). The perceptions of NEPA effectiveness by both patients and treating physicians were similar in patients <60 and ≥60 years (online suppl. Fig. 5).

Safety

In total, 386 (32%) patients reported treatment-emergent AEs during the study period, with 116 (10%) experiencing NEPA treatment-related AEs (Table 3). The most common treatment-related AEs were fatigue (5%) and constipation (4%). Among 71 (6%) patients reporting serious AEs, the toxicity was considered to be related to NEPA in 5 (0.4%) patients. Specifically, diarrhea (grade 4), febrile neutropenia (grade 3), and serotonin syndrome leading to depression and suicide attempt (grade 4) occurred in 1 patient each, with all patients recovering within 3–5 days; 1 patient with constipation grade 1 recovered after 43 days and 1 patient with pancytopenia (grade 3) was recovering at the time of the safety report. No deaths or other relevant safety signals related to NEPA were reported.

Discussion

Patients with breast cancer are generally highly susceptible to CINV, due to patient- and Ctx-related risk factors, for example they are mainly female, of young age, and receiving AC [5, 6, 10, 11, 25]. This post hoc subgroup analysis from a prospective non-interventional study in patients with various tumor types receiving HEC/MEC treatment aimed to evaluate the effects of NEPA prophylaxis specifically in patients with breast cancer receiving AC treatment [24].

NEPA prophylaxis was evaluated in a total of 1,197 patients with diverse demographic and disease characteristics under routine clinical practice conditions. Most patients were female (99%) and the median age was 52.5 years (66% of patients were <60 years). QoL (the primary endpoint) outcomes revealed that CINV was generally well controlled in cycle 1. Vomiting had NIDL for most patients (84%), whereas a lower proportion of patients reported NIDL due to nausea (53%); 64% of patients had

Table 3. Summary of AEs by chemotherapy cycle and overall

	Cycle 1 (n = 1,192)	Cycle 2 (n = 1,155)	Cycle 3 (n = 1,125)	Overall (n = 1,197)
Treatment-emergent AEs	286 (24.0)	225 (19.5)	137 (12.2)	386 (32.2)
Treatment-related AEs ^a	81 (6.8)	55 (4.8)	28 (2.5)	116 (9.7)
Serious AEs	3 (0.3)	2 (0.2)	0 (0)	71 (5.9)
Serious treatment-related AEs ^b	3 (0.3)	2 (0.2)	0 (0)	5 (0.4)
Treatment-related AEs ^a leading to death	0 (0)	0 (0)	0 (0)	0 (0)
Treatment-related AEs ^a in >1% of patients				
Fatigue	38 (3.2)	9 (0.8)	8 (0.7)	54 (4.5)
Constipation	33 (2.8)	22 (1.9)	4 (0.4)	52 (4.3)
Insomnia	25 (2.1)	9 (0.8)	1 (0.1)	35 (2.9)
Nausea	10 (0.8)	14 (1.2)	10 (0.9)	25 (2.1)
Headache	9 (0.8)	6 (0.5)	3 (0.3)	17 (1.4)

Data are presented as the number of patients with AEs (%). AE, adverse event.

^a Considered by the investigator as treatment related.

^b Five treatment-related serious AEs were reported: diarrhea, constipation, serotonin syndrome, febrile neutropenia, and pancytopenia, occurring in 1 patient each.

NIDL due to combined nausea and vomiting. Overall, QoL outcomes were maintained in subsequent cycles, showing a slight but consistent improvement in all domains. These results nearly mirror our previous report of the whole population receiving various HEC regimens [24], including the patients receiving AC presented in this subanalysis (86%), cisplatin-based regimens (13%), and AC for other solid tumors (1%). Our results suggest that the benefit of NEPA on QoL outcomes may be generalized to various HEC regimens. Notably, our real-world results are in line with previous observations from randomized controlled trials in Ctx-naïve patients with breast cancer (online suppl. Table 2) [22, 23].

Similarly, the antiemetic effectiveness of NEPA in terms of rates of CR, no emesis, and no need for rescue medication was high and comparable with that reported for the overall population [24]. These outcomes also align with previous reports from randomized phase 3 clinical trials in patients with breast cancer receiving AC (online suppl. Table 3) [22, 23, 26, 27].

Antiemetic effectiveness in terms of NSN was lower than that observed in randomized controlled trials, especially in the acute phase. Enrollment of Ctx non-naïve patients, who have a higher likelihood of added comorbidities and are excluded from controlled trials, may partially account for this difference. Nevertheless, NSN and no-nausea rates in this analysis were slightly lower compared with the overall population receiving HEC/MEC [24]. This highlights the high prophylactic needs and special challenge for nausea control in patients with breast cancer receiving AC [28, 29]. While delayed nausea can occur in 73–82% of women with breast cancer receiving mostly AC in the absence of an NK₁RA-based prophylaxis [28], NEPA-dexamethasone is the only NK₁RA regimen that

has shown a consistent benefit in nausea control versus prophylaxis with 5-HT₃RA-dexamethasone [21, 22, 30].

The antiemetic effects of NEPA are extended to patients who are at higher risk for CINV and generally excluded from clinical trials, including those with anticipatory nausea (8%) and those non-naïve to Ctx who may have experienced CINV previously, which may account for the slight differences observed between randomized controlled trials and the present study. Of note, 66% of patients were <60 years of age, and, as expected, both QoL and effectiveness outcomes were lower in this age group compared with patients ≥60 years.

Recent studies have analyzed the effectiveness of aprepitant-based prophylaxis in the real world. In a retrospective study including 1,247 Ctx-naïve patients receiving AC for breast cancer, prophylaxis with aprepitant-palonosetron-dexamethasone resulted in no CINV events in 61% of patients [31]. While a direct comparison of effectiveness between studies cannot be done, our analysis showed an overall 81% CR rate in patients naïve and non-naïve to Ctx. The more complex administration schedule of aprepitant-based regimens, which require home administration of aprepitant on days 2 and 3 after Ctx and dexamethasone on days 2–4 [32], may be more difficult to implement in the real world than NEPA.

In the present analysis, antiemetic effectiveness of NEPA was ranked mostly as “very good” both by physicians and patients in the 3 Ctx cycles analyzed. Contrary to previous reports, our study showed a good correlation between patients’ and physicians’ perceptions [16].

NEPA was well tolerated under real-world conditions in patients with various comorbidities, many of whom required concomitant medication, and the safety profile was in line with that from pivotal trials [21, 23]. It is note-

worthy that common AEs occurring during Ctx were categorized as NEPA related by the investigator.

The potential for cardiac toxicity limits the cumulative dose of anthracyclines for treatment of breast cancer and restricts the choice of concomitant medication [33]. While cardiac toxicity is a class AE of first-generation 5-HT₃RA [18], the second-generation 5-HT₃RA palonosetron included in NEPA is not associated with cardiotoxic effects [19]. Accordingly, the frequency of clinically relevant cardiotoxic events was low (0.7%) in this analysis.

In conclusion, this post hoc analysis demonstrates that prophylaxis with NEPA in patients with breast cancer receiving AC is associated with favorable effects on QoL and is effective with a good safety profile in the real-world setting as previously observed in pivotal trials, supporting the use of NEPA in this population in daily clinical practice.

Acknowledgments

The authors thank the volunteers, investigators, and study teams. We thank Dr. Silvia Olivari from Helsinn Healthcare SA for her contributions in the development of the manuscript. Editorial support and medical writing assistance were provided by Iratxe Abarrategui, PhD, CMPP, from Aptitude Health, The Hague, the Netherlands, funded by RIEMSER Pharma GmbH, Berlin, Germany. The authors are fully responsible for all content and editorial decisions for this manuscript.

Statement of Ethics

Patients provided signed informed consent before enrollment, in compliance with the Declaration of Helsinki. The study was conducted in accordance with the German Medicines Act (Arzneimittelgesetz), and the Supreme Federal Authority, the Association of Accredited Physicians (Kassenärztliche Bundesvereinigung), the Central Federal Association of Statutory Health Insurance Funds (GKV-Spitzenverband), and the Association of Private Health Insurers (Verband der Privaten Krankenversicherung) were notified by OnkoDataMed GmbH (study No. CTU 130 K).

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Conflict of Interest Statement

J.S.: honoraria, travel expenses, RIEMSER Pharma GmbH. C.M.K.: honoraria, Amgen, Eli Lilly, Novartis, Mundipharma, Pfizer, PharmaMar, RIEMSER, Roche, Tesaro; consulting or advisory role, Amgen, Axios, Eli Lilly, Hilotherm, Mundipharma, NewCo, Novartis, Pfizer, RIEMSER, Roche, Tesaro; research funding, AstraZeneca, Axios, MSD Sharp & Dohme (Merck), NewCo, Novartis, Pfizer, PharmaMar, RIEMSER, Seattle Genetics, Immunomedics; travel, accommodations, expenses, Amgen, Hexal, Immunomedics, Pfizer, PharmaMar, Tesaro, Teva Oncology. C.H.: advisory board, AstraZeneca, Lilly, Pfizer, Roche. S.B.: lectures, studies and support for congress participation, Amgen, Roche, Novartis, Pfizer, Riemsler, Lilly, Clovis, GSK, Onkovois, AstraZeneca, MSD. M.H.: honoraria, Pfizer, AstraZeneca, iOMEDI-CO, MMF, Amgen; research funding, RIEMSER, Indivumed. J.K.-S. and D.R.: nothing to disclose. E.F.: RIEMSER employee. M.K.: ad board, travel grant, Helsinn Healthcare, RIEMSER Pharma GmbH.

Funding Sources

The study described within this paper was sponsored by RIEMSER Pharma GmbH, Berlin, Germany. RIEMSER Pharma GmbH also participated in the writing, review, and approval of the manuscript.

Author Contributions

J.S., C.M.K., C.H., S.B., M.H., J.K.-S., D.R., and M.K. participated in the conceptualization of the study, investigation, preparation of the original draft, and manuscript review and editing. E.F. participated in the conceptualization of the study, project administration and supervision, preparation of the original draft, and manuscript review and editing.

Availability of Data

Individual patient-level data will not be shared.

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