A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC)

L. Zhang1,2,3*, S. Lu4, J. Feng5, A. Dechaphunkul6, J. Chang7, D. Wang8, S. Chessari9, C. Lanzarotti10, K. Jordan11 & M. Aapro12

1State Key Laboratory of Oncology in South China, Guangzhou; 2Collaborative Innovation Center for Cancer Medicine, Guangzhou; 3Medical Oncology Department, Sun Yat-Sen University Cancer Center, Guangzhou; 4Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai; 5Medical Oncology, Jangsu Cancer Hospital, Nanjing, China; 6Division of Medical Oncology, Internal Medicine, Prince of Songkla University, Songkhla, Thailand; 7Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai; 8Cancer Center, Daping Hospital, Third Military Medical University, Chongqing, China; 9Corporate Clinical Development, Helsinn Healthcare, Lugano, Switzerland; 10Department of Medicine V, University of Heidelberg, Heidelberg, Germany; 11Department of Medicine V, University of Heidelberg, Heidelberg, Germany; 12Cancer Center, Clinique de Genolier, Genolier, Switzerland

*Correspondence to: Prof. Li Zhang, State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine; Medical Oncology Department, Sun Yat-Sen University Cancer Center, 651 Dongfeng East Road, Guangzhou 510060, China. Tel: +86-20-8734-2288; E-mail: zhangli@sysucc.org.cn

Background: Co-administration of multiple antiemetics that inhibit several molecular pathways involved in emesis is required to optimize chemotherapy-induced nausea and vomiting (CINV) control in patients receiving highly emetogenic chemotherapy (HEC). NEPA, a fixed combination of a highly selective NK1 receptor antagonist, netupitant (300 mg), and the pharmacologically distinct 5-HT3RA, palonosetron (PALO 0.50 mg), has shown superior CINV prevention compared with PALO in cisplatin and anthracycline/cyclophosphamide-based settings. This study is the first head-to-head comparison of NEPA versus an aprepitant (APR)/granisetron (GRAN) regimen.

Patients and methods: This randomized, double-blind phase III study conducted in Asia was designed with the primary objective to demonstrate non-inferiority of a single oral dose of NEPA compared with a 3-day oral APR/GRAN regimen in chemotherapy-naïve patients receiving cisplatin-based HEC. All patients also received oral dexamethasone (DEX) on days 1–4. The primary efficacy endpoint was complete response (CR: no emesis/no rescue medication) during the overall (0–120 h) phase. Non-inferiority was defined as a lower 95% CI greater than the non-inferiority margin set at −10%. Secondary efficacy endpoints included no emesis, no rescue medication, and no significant nausea (NSN).

Results: Treatment groups were comparable for the 828 patients analyzed: predominantly male (71%); mean age 54.5 years; ECOG 0–1 (98%); lung cancer (58%). NEPA demonstrated non-inferiority to APR/GRAN for overall CR [NEPA 73.8% versus APR/GRAN 72.4%, 95% CI (−4.5%, 7.5%)]. No emesis [NEPA 75.0% versus APR/GRAN 74.0%, 95% CI (−4.8%, 6.9%)] and NSN rates [NEPA 75.7% versus APR/GRAN 70.4%, 95% CI (−6.0%, 11.4%)] were similar between groups, but significantly more NEPA patients did not take rescue medication [NEPA 96.6% versus APR/GRAN 93.5%, 95% CI (0.2%, 6.1%)]. NEPA was well tolerated with a similar safety profile to APR/GRAN.
Conclusions: In this first study comparing NK1RA regimens and DEX, NEPA administered only on day 1 was non-inferior to a 3-day oral APR/GRAN regimen in preventing CINV associated with HEC.

Key words: CINV, netupitant, palonosetron, NEPA, aprepitant

Introduction

Advances in our understanding of the pathophysiology of CINV, identification of patient risk factors [1, 2], and development of new antiemetics have led to dramatic improvements in prevention of chemotherapy-induced nausea and vomiting (CINV) [3, 4]. With utilization of guideline-recommended antiemetic prophylaxis, CINV can now be prevented in the majority of patients [5, 6]. As a result, the quality-of-life of cancer patients has significantly improved and patients may avoid chemotherapy disruption or dose reductions [3].

Evidence-based antiemetic guidelines [7–9] for patients receiving highly emetogenic chemotherapy (HEC) consistently recommend co-administration of a triplet antiemetic regimen of a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist (RA), a neurokinin-1 (NK1) RA and a corticosteroid, such as dexamethasone (DEX). The American Society of Clinical Oncology (ASCO) has also recently recommended the addition of olanzapine to this triplet regimen [7].

Despite evidence demonstrating that CINV control is optimized when guideline recommendations are followed [5, 6], guidelines are often inadequately adhered to in clinical practice. This may, in part, be due to perceived complexity of some of the multimodal antiemetic regimens, as the NK1RAs, 5-HT3RAs, and corticosteroid components each have differing doses/schedules from 1 to 4 days post-chemotherapy initiation. Simpler, less frequent dosing regimens have been shown to result in better compliance across a variety of therapeutic classes [10].

NEPA was developed as an oral fixed combination of the highly selective NK1RA, netupitant (300 mg), and the clinically [4] and pharmacologically [11] distinct 5-HT3RA, palonosetron (0.5 mg). The simultaneous targeting of two critical antiemetic pathways, in unison with the single dose administration results in a convenient antiemetic offering long-lasting protection from CINV.

Pivotal clinical studies have demonstrated superiority of oral NEPA plus DEX over oral palonosetron plus DEX in preventing CINV during the acute (0–24 h), delayed (25–120 h), and overall (0–120 h) phases following both cisplatin- [12] and anthracycline-cyclophosphamide (AC)-based chemotherapy [13, 14]. In addition, NEPA was shown to be efficacious over multiple cycles in patients receiving either HEC or moderately emetogenic chemotherapy (MEC) [15].

These studies supported the registration of oral NEPA in the United States (US) and Europe (EU) [16, 17], with NEPA becoming the first alternative NK1RA (containing compound) and the first antiemetic fixed combination. Subsequently, the next NK1RA, oral rolapitant, was approved [18]. An intravenous fixed combination of NEPA (fosnetupitant 235 mg and palonosetron 0.25 mg) is currently under evaluation by the US Food & Drug Administration (FDA). Thus far, none of the NK1RAs have been compared in head-to-head trials, as all registration studies were conducted with a 5-HT3RA/DEX comparative control.

Herein we report the results of a Phase III study of a single dose of NEPA plus DEX compared with a standard 3-day regimen of aprepitant plus granisetron (APR/GRAN) plus DEX, in patients receiving cisplatin-based chemotherapy. The objective was to demonstrate, in the first head-to-head comparison study, non-inferiority of NEPA to APR/GRAN in preventing CINV associated with HEC. The study was designed in collaboration with the China FDA (CFDA) as a registration study for oral NEPA in China.

Patients and methods

Study design

This was a phase III, multicenter, randomized, double-blind/double-dummy, single initial cycle, parallel group international study. Patients were randomized at 46 enrolling sites in 4 countries (30 in China, 5 Taiwan, 3 Thailand, and 8 Korea) between February 2014 and August 2015.

The trial protocol was approved by institutional review board/independent ethics committees and all patients provided written informed consent before treatment initiation. The study was conducted in compliance with the Code of Ethics for the CFDA, Good Clinical Practice, the principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines.

Patients

Inclusion/exclusion criteria were similar to those in the original oral NEPA pivotal trials [12, 13, 15]. Eligible patients were ≥18 years, naive to chemotherapy, and scheduled to receive their first course of cisplatin-based (≥50 mg/m2) chemotherapy (as monotherapy or in combination with other chemotherapy) for the treatment of a confirmed solid tumor malignancy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2.

Patients were not eligible if they were scheduled to receive: (i) MEC or HEC from days 2 to 5 following cisplatin, (ii) moderately or highly emetogenic radiotherapy within 1 week before day 1 or between days 1 and 5, or (iii) a bone marrow or stem-cell transplant. Additional exclusion criteria included: receipt of medication with antiemetic effect <24 h of day 1; vomiting, retching or mild nausea <24 h before day 1; serious cardiovascular disease history or predisposition to cardiac conduction abnormalities except for incomplete right bundle branch block; or chronic use of select CYP3A4 inducers <4 weeks or a substrate or inhibitor <1 week before day 1.

Treatment

Patients were stratified by gender and randomly assigned (1:1) to receive either NEPA or APR/GRAN treatment (supplementary Table S1, available at Annals of Oncology online). Granisetron 3 mg is the registered dose in China.

Group 1:

Day 1: NEPA (300 mg netupitant and 0.5 mg palonosetron) plus DEX 12 mg

Days 2–4: DEX 8 mg daily
**Assessments**

During days 1–5 (0–120 h), each patient completed a diary, capturing emetic episodes, severity of nausea and rescue medications intake. An emetic episode was defined as any episode of vomiting or retching or combined vomiting/retching. Severity of nausea was evaluated using a 100-mm horizontal visual analog scale (VAS) ranging from ‘no nausea’ (0 mm) to ‘nausea as bad as it could be’ (100 mm). The Functional Living Index-Emesis (FLIE) questionnaire [nine nausea-specific (nausea domain) and nine vomiting-specific (vomiting domain) items] was used to assess the impact of CINV on patient’s daily life. Responses were marked on a 100-mm VAS with anchors of 1 and 7. Patients completed this questionnaire on days 2 and 6 [19]. The proportion of patients with scores reflecting ‘no impact on daily life’ (NIDL) during the acute/delayed and overall phases. FLIE scores reflecting NIDL during the acute/delayed phases was also evaluated as a secondary ‘quality-of-life’ endpoint. Safety was assessed by collection of adverse events, vital signs, physical examination, clinical laboratory tests, and electrocardiograms (predose, and 5, 24, and 120 postdose).

**Results**

**Analyzed patient population**

A total of 834 patients were randomized into the study (N = 417/group); 81% of patients were from China, and 12% from Thailand. Four patients randomized to NEPA and one patient to APR/GRAN did not receive study treatment and were therefore excluded from the safety/FAS populations. One additional NEPA-treated patient did not receive the protocol-required HEC and was also excluded from the FAS population. Consequently, 829 (413 NEPA/416 APR/GRAN) and 828 (412 NEPA/416 APR/GRAN) represented the safety and FAS efficacy populations, respectively (supplementary Figure S1, available at Annals of Oncology online).

Baseline characteristics were similar between treatment groups (Table 1). The population was predominantly males (71%); lung cancer was the most common (58%) cancer type.

**Efficacy**

For the primary efficacy endpoint, NEPA demonstrated non-inferiority to APR/GRAN with overall CR rates of 73.8% and 72.4%, respectively (95% CI: −4.5%, 7.5%) (Figure 1).

Daily rates of patients with CINV events (experiencing emesis and/or use of rescue medication) remained between 13% and 15% for APR/GRAN and declined from 16% to 8% over the 5 days for NEPA. The difference between treatment groups (8.0% NEPA and 13.9% APR/GRAN, 95% CI: 1.7%, 10.2%) reached statistical significance on day 5 (Figure 2).

**Table 1. Patient baseline and disease characteristics (safety population)**

| Characteristic          | NEPA + DEX (N = 413) | APR/GRAN + DEX (N = 416) | Overall (N = 829) |
|-------------------------|----------------------|--------------------------|-------------------|
| **Gender**              |                      |                          |                   |
| Male                    | 292 (70.7%)          | 297 (71.4%)              | 589 (71.0%)       |
| Female                  | 121 (29.3%)          | 119 (28.6%)              | 240 (29.0%)       |
| **Age (years), mean (SD)** | 54.6 (9.63)         | 54.5 (10.24)             | 54.6 (9.93)       |
| **Race**                |                      |                          |                   |
| Asian                   | 413 (100.0%)         | 416 (100.0%)             | 829 (100.0%)      |
| **BMI (kg/m²), mean (SD)** | 22.49 (3.337)      | 22.85 (3.435)            | 22.67 (3.389)     |
| **ECOG performance status** |                      |                          |                   |
| 0                       | 175 (42.5%)          | 171 (41.1%)              | 346 (41.8%)       |
| 1                       | 231 (56.1%)          | 236 (56.7%)              | 467 (56.4%)       |
| 2                       | 7 (1.7%)             | 9 (2.2%)                 | 16 (1.9%)         |
| **Most common (>5%) cancer types** |                  |                          |                   |
| Lung                    | 254 (61.5%)          | 229 (55.0%)              | 483 (58.3%)       |
| Head and neck           | 24 (5.8%)            | 31 (7.5%)                | 55 (6.6%)         |
| **Cisplatin**           | 412 (99.8%)          | 416 (100%)               | 828 (99.9%)       |
| Dose <70 mg/m²          | 161 (39.0%)          | 177 (42.5%)              | 338 (40.8%)       |
| Dose ≥70 mg/m²          | 251 (60.8%)          | 239 (57.5%)              | 490 (59.1%)       |
| **Most common (>5%) concomitant chemotherapy** | |                          |                   |
| Gemcitabine             | 123 (29.8%)          | 93 (22.4%)               | 216 (26.1%)       |
| Pemetrexed              | 69 (16.7%)           | 79 (19.0%)               | 148 (17.9%)       |
| Docetaxel               | 67 (16.2%)           | 68 (16.3%)               | 135 (16.3%)       |
| Etoposide               | 58 (14.0%)           | 53 (12.7%)               | 111 (13.4%)       |
| Fluourouracil           | 27 (6.5%)            | 32 (7.7%)                | 59 (7.1%)         |

*Median cisplatin dose was 73 mg/m² in the NEPA group and 72 mg/m² in the APR/GRAN group. APR, aprepitant; GRAN, granisetron; SD, standard deviation; BSA, body surface area; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.*
Response rates for the secondary efficacy endpoints during the acute phase slightly favored NEPA with the exception of no emesis, where slightly higher rates were seen for APR/GRAN (Table 2). During the delayed and overall phases response rates favored NEPA for no emesis, NSN, and no rescue use, while no nausea rates were slightly higher for APR/GRAN. No rescue medication rates were significantly higher for NEPA during the delayed and overall phases (Table 2). Metoclopramide was the most common rescue medication, used by 2.7% of NEPA patients and 5.0% of APR/GRAN patients, while all other rescue medications were used by <1% of patients.

A higher proportion of NEPA-treated patients reported NIDL due to nausea (nausea domain), vomiting (vomiting domain), or both (overall domain) during the acute and delayed phases; this was significant for the nausea domain during the delayed phase (Figure 3).

### Safety

The incidence of AEs was comparable between the two treatment groups (NEPA 58.1%, APR/GRAN 57.5%). The most common TRAEs were constipation (NEPA 8.0%, APR/GRAN 6.3%) and hiccups (NEPA 2.7%, APR/GRAN 1.4%). Among the patients reporting AEs, the majority (90%) reported events of mild/moderate intensity, with more severe AEs in the APR/GRAN group (10.8% versus NEPA 8.7%). There were two patients with serious
TRAEs in each group (NEPA: (i) atrial fibrillation and (ii) chest pain/hypotension/decreased heart rate/non-responsiveness (concomitant medication included amifostine); APR/GRAN: (i) increased alanine aminotransferase and (ii) pancreatitis. While the patient experiencing the chest pain/hypotension event recovered within an hour of NEPA treatment, this was the only AE leading to discontinuation from study. There were no deaths in the NEPA group, while four patients treated with APR/GRAN died due to unrelated AEs. Changes from baseline in 12-lead ECGs were rare and similar.

Table 2. Secondary endpoints: no emesis, no significant nausea, and no rescue medication rates

| Endpoint                              | NEPA + DEX (N = 412) | APR/GRAN + DEX (N = 416) | Risk difference (95% CI) |
|---------------------------------------|-----------------------|---------------------------|--------------------------|
| No emesis                             | 85.2%                 | 87.5%                     | −2.2% (−6.9%, 2.4%)      |
| Acute                                 | 79.4%                 | 76.2%                     | 3.3% (−2.4%, 8.9%)       |
| Delayed                               | 75.0%                 | 74.0%                     | 1.1% (−4.8%, 6.9%)       |
| Overall                               |                       |                           |                          |
| No nausea                             | 89.8%                 | 87.3%                     | 2.6% (−1.7%, 6.9%)       |
| Acute                                 | 78.2%                 | 72.8%                     | 5.4% (−0.4%, 11.2%)      |
| Delayed                               | 75.7%                 | 70.4%                     | 5.4% (−0.6%, 11.4%)      |
| Overall                               |                       |                           |                          |
| No nausea                             | 68.9%                 | 67.8%                     | 1.2% (−5.1%, 7.5%)       |
| Acute                                 | 53.2%                 | 54.3%                     | −1.1% (−7.9%, 5.7%)      |
| Delayed                               | 49.3%                 | 51.4%                     | −2.1% (−8.9%, 4.7%)      |
| Overall                               |                       |                           |                          |
| No rescue use                         | 98.8%                 | 98.3%                     | 0.5% (−1.2%, 2.1%)       |
| Acute                                 | 97.6%                 | 94.7%                     | 2.9% (0.2%, 5.5%)*       |
| Delayed                               | 96.6%                 | 93.5%                     | 3.1% (0.2%, 6.1%)*       |
| Overall                               |                       |                           |                          |

*P < 0.05; based on CMH test with gender as stratifying variable.
APR, aprepitant; GRAN, granisetron; DEX, dexamethasone; NSN, no significant nausea.

Discussion

While the current antiemetic armamentarium offers the potential to prevent CINV in the majority of patients, events including hospitalization do occur. Simplifying the multi-drug regimens may be appealing to clinicians and patients and may enhance compliance with antiemetic guideline recommendations. The standard aprepitant regimen requires co-administration of a 5-HT3 RA (in this study IV GRAN 30 min before chemotherapy) on day 1 and oral APR 60 min before chemotherapy on day 1 with subsequent oral doses 24 and 48 h later. As a combination of a highly selective NK1RA, netupitant, and the clinically superior 5-HT3RA, palonosetron, NEPA conveniently packages two classes of antiemetics recommended by guidelines in the HEC/high risk MEC settings in a single oral dose administered 60 min before chemotherapy. In clinical practice NEPA could either be taken at home or at the clinic/hospital before chemotherapy.

Aprepitant, the first NK1RA in the class has been long available with well-established efficacy and safety in various HEC and MEC settings including cisplatin-, carboplatin-, and AC-based chemotherapies [20]. Similarly, NEPA/DEX demonstrated unequivocal superiority over palonosetron/DEX in preventing CINV in pivotal trials in the HEC/AC settings, leading to its approval in the USA/Europe [12, 13, 15]. With the most recent approval of rolapitant, the third-in-class NK1RA, clinicians have three NK1RA-containing options for patients at most risk for CINV. Recently, a network meta-analysis showed that all three
NK1,RAs have similar antiemetic effects [21]. However, thus far, no NK1-containing regimens have been directly compared with each other.

For NEPA registration in China, the CFDA requested that NEPA demonstrate comparable efficacy to a standard aprepitant and 5-HT3RA (granisetron) containing regimen. Thus, this phase III study in patients receiving cisplatin-based HEC was designed to demonstrate non-inferiority of a single dose of NEPA to a standard 3-day aprepitant/granisetron regimen, both groups in combination with DEX as recommended by antiemetic guidelines. This study was also the first head-to-head comparison study of NK1-containing regimens. For the primary efficacy endpoint of overall CR, NEPA was non-inferior to APR/GRAN. For secondary efficacy endpoints of no emesis and NSN, delayed and overall rates were numerically but not significantly higher for NEPA. In addition, significantly more patients treated with NEPA did not need to use any rescue medication during the delayed and overall phases. Daily rates of CINV events (emesis/rescue use) did not change substantially throughout days 1–5 for APR/GRAN; however, rates for NEPA declined numerically over time and were significantly lower on day 5, again suggesting a benefit for delayed CINV.

The slightly higher response rates for NEPA were reflected in a quality of life benefit, with a correspondingly greater proportion of patients with no impact on their functioning due to nausea during the delayed phase, when CINV control is most challenging. While this difference is small, it is encouraging that NEPA demonstrated some potential to improve quality of life.

The efficacy findings seen in the current study were consistent with those in two NEPA registration trials [12, 15] where NEPA, although not statistically compared, was shown to be at least as effective as an exploratory APR/ondansetron regimen [12] and an exploratory APR/palonosetron regimen [15].

NEPA was well tolerated with a comparable adverse event profile to APR/GRAN. The majority of AEs were mild/moderate in intensity, unrelated to study treatment, and typical for a cancer population undergoing chemotherapy. There were no cardiac safety concerns for either treatment.

A limitation of this study was the predominance of male patients, with females representing only 29% of the study population. Gender is a well-established risk factor, with females at greater risk for CINV. In two recent identically designed rolapitant trials, the difference in proportions of males/females in the studies was deemed as a potential factor that may have contributed to differing antiemetic efficacy in the studies [22]. As gender was balanced for the NEPA and APR/GRAN groups within this study, this should not have influenced these results.

As the majority of the patients in the NEPA pivotal trials were Caucasian, this study raises the question as to whether similar antiemetic efficacy would be seen in Asian and Caucasian populations. Additional studies would be needed to determine this; however, it is reassuring that a comparison of the pharmacokinetic profiles of netupitant and palonosetron in Chinese and Caucasian patients show differences considered as not clinically meaningful [23].

In conclusion, our study indicated that as a combination antiemetic targeting two antiemetic pathways with a single dose administered only once per cycle, NEPA offers a convenient and simplified prophylactic antiemetic that is at least as effective as a 3-day aprepitant regimen with granisetron.

Acknowledgements

The authors thank the clinical investigators, patients, and site personnel who participated in this study. Editorial and medical writing assistance was provided by Jennifer Vanden Burgt, an independent Medical Affairs consultant, Minneapolis, MN and funded by Helsinn Healthcare SA, Lugano, Switzerland.

Funding

Helsinn Healthcare, SA, Lugano, Switzerland who provided the study drugs and the funding for this study (no grant number applies).

Disclosure

LZ: consultant for MSD; research funding from Helsinn, Lilly, and MSD; SL: consultant for Boehringer and Roche; speaker’s bureau for Lilly; travel reimbursed by Hutchison and Medipharm Limited; JC: medical advisor for QuintilesIMS; SC: employee of Helsinn Healthcare; CL: employee of Helsinn Healthcare; KJ: consultant for Helsinn Healthcare, Merck, MSD and Tesaro; travel reimbursed by MSD; MA: consultant/investigator for Helsinn Healthcare, Merck and Tesaro. All remaining authors have declared no conflicts of interest.

References

1. Dranitisas G, Molassiotis A, Clemens M et al. The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. Ann Oncol 2017; 28(6): 1260–1267.
2. Hu Z, Liang W, Yang Y et al. Personalized estimate of chemotherapy-induced nausea and vomiting: development and external validation of a nomogram in cancer patients receiving highly/moderately emetogenic chemotherapy. Medicine 2016; 95(2): e2476.
3. Navari R, Aapro M. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med 2016; 374(14): 1356–1367.
4. Saito M, Aogi K, Sekine I et al. Palonosetron plus dexamethasone for prevention of CINV during chemotherapy: double-blind, double-dummy, randomised comparative phase III trial. Lancet Oncol 2009; 10(2): 115–124.
5. Aapro M, Molassiotis A, Dicato M et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). Ann Oncol 2012; 23(8): 1986–1992.
6. Gilmore JW, Peacock NW, Gu A et al. Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE study. J Oncol Pract 2014; 10(1): 68–74.
7. Hesketh PJ, Kris MG, Basch E et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2017; 35(28): 3240–3261.
8. Roila F, Molassiotis A, Herrstedt J et al. 2016 MASCC and ESMO guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting in advanced cancer patients. Ann Oncol 2016; 27(5): v119–v133.
9. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology: Antiemesis [v2. March 28, 2017]; https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf (3 November 2017, date last accessed).
10. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23: 1296–1310.
11. Rojas C, Raje M, Tsukamoto T, Slusher BS. Molecular mechanisms of 5-HT\textsubscript{3} and NK\textsubscript{1} receptor antagonists in prevention of emesis. Eur J Pharmacol 2014; 722: 26–37.
12. Hesketh PJ, Rossi G, Rizzi G et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. Ann Oncol 2014; 25(7): 1340–1346.
13. Aapro M, Rugo H, Rossi G et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol 2014; 25(7): 1328–1333.
14. Aapro M, Karthaus M, Schwartzberg L et al. NEPA, a fixed oral combination of netupitant and palonosetron, improves control of chemotherapy-induced nausea and vomiting (CINV) over multiple cycles of chemotherapy: results of a randomized, double-blind, phase 3 trial versus oral palonosetron. Support Care Cancer 2017; 25(4): 1127–1135.
15. Gralla RJ, Bozjak SM, Hontsa A et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 2014; 25(7): 1333–1339.