

Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting

An updated systematic review and meta-analysis

Tingting Qiu, MSc^{a,b,c}, Peng Men, PhD^{a,b}, Xiaohan Xu, MSc^{a,b}, Suodi Zhai, MD^{a,b,*}, Xiangli Cui, PhD^{c,*}

Abstract

Objective: To systematically evaluate the efficacy and safety of antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting (CINV) and provide updated information for clinical practice.

Methods: Pubmed, Embase, the Cochrane Library, and 3 Chinese literature databases were systematically searched. Randomized controlled trials comparing standard regimen (5-hydroxytryptamine-3 receptor antagonist and glucocorticoid) with aprepitant triple regimen (aprepitant plus the standard regimen) for preventing CINV were screened. Literature selection, data extraction, and quality evaluation were performed by 2 reviewers independently. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in the meta-analysis using RevMan 5.3 software.

Results: A total of 51 randomized controlled trials were finally included in the systematic review. Compared with the standard regimen, the aprepitant triple regimen significantly improved the complete response in the overall (OR 1.88, 95% CI 1.71–2.07), acute (OR 1.96, 95% CI 1.65–2.32) and delayed (OR 1.96, 95% CI 1.70–2.27) phases, regardless of emetogenic risk of chemotherapy. Aprepitant could also significantly enhance the proportions of patients who have no emesis, nausea, or use of rescue medication respectively in the overall, acute and/or delayed phases. Aprepitant was found to be associated with decreased risk of constipation (OR 0.85, 95% CI 0.74–0.97), but increased the incidence of hiccup (OR 1.26, 95% CI 1.05, 1.51). There were no statistically significant differences between the 2 groups on other safety outcomes.

Conclusion: The aprepitant triple regimen is effective for the prevention of CINV in patients being treated with moderately or highly emetogenic chemotherapy, and has a significant tendency to reduce the risk of constipation and increase the incidence of hiccup.

Abbreviations: 5-HT3RA = 5-hydroxytryptamine-3 receptor antagonist, CINV = chemotherapy-induced nausea and vomiting, CIs = confidence intervals, CR = complete response, FLIE = functional living index-emesis, HEC = highly emetogenic chemotherapy, MEC = moderate emetogenic chemotherapy, NK-1RA = neurokinin-1 receptor antagonists, ORs = odd ratios, RCT = randomized controlled trial.

Keywords: aprepitant, chemotherapy-induced nausea and vomiting, meta-analysis, systematic review

Editor: Jianxun Ding.

TQ and PM contributed equally to this work.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

^aDepartment of Pharmacy, Peking University Third Hospital, ^bInstitute for Drug Evaluation, Peking University Health Science Center, ^cDepartment of Pharmacy, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

* Correspondence: Suodi Zhai, No.49 North Garden Road, Haidian District, Beijing, China (e-mail: zhaisuodi@163.com), Xiangli Cui, No.95 Yong'an Road, Xicheng District, Beijing, China (e-mail: cui10@163.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Qiu T, Men P, Xu X, Zhai S, Cui X. Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting: an updated systematic review and meta-analysis. *Medicine* 2020;99:33(e21559).

Received: 19 November 2019 / Received in final form: 11 June 2020 /

Accepted: 3 July 2020

<http://dx.doi.org/10.1097/MD.00000000000021559>

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a series of common adverse reactions during chemotherapy, happening in 70% to 80% of treated patients.^[1–3] CINV can be classified into acute (within the first 24 hours after chemotherapy initiation) and delayed (24 to 120 hours post-chemotherapy) events. Nausea and vomiting can reduce patients' quality of life and treatment compliance, increase their fear for treatment, and even result in discontinuation of the anti-tumor therapy.

Patients receiving highly emetogenic chemotherapy (HEC, eg, anthracycline and cyclophosphamide [AC] regimen) and moderate emetogenic chemotherapy (MEC, eg, carboplatin or oxaliplatin) are the major populations that suffering CINV,^[4] which can be prevented by prophylactic antiemetic agents. Glucocorticoids, most commonly dexamethasone, were first used for treating CINV in the early 1990s.^[5] Thereafter, the addition of 5-hydroxytryptamine-3 receptor antagonist (5-HT3RA) showed additional improvement in acute CINV, which acts by blocking the peripheral nervous pathways of gastrointestinal tracts.^[6]

Recent studies showed that the combination of the standard regimen (5HT3RA plus glucocorticoid) and neurokinin-1 receptor antagonists (NK-1RAs) could make greater advances

in preventing CINV. Currently, the National Comprehensive Cancer Network,^[7] the American Society of Clinical Oncology,^[8] and the Multinational Association of Supportive Care in Cancer/ European Society of Medical Oncology^[9] guidelines endorsed the use of NK-1RAs plus standard regimen in patients receiving HEC for preventing CINV. However, the American Society of Clinical Oncology and Multinational Association of Supportive Care in Cancer/ European Society of Medical Oncology guidelines did not recommend the addition of NK-1RA for MEC patients, while the National Comprehensive Cancer Network guideline recommended that an NK-1RA should be added to the standard regimen for select patients with additional risk factors or previous treatment failure with standard regimen alone. As for the Chinese guideline,^[10] NK-1RA was recommended to be selectively used in part of MEC patients.

Aprepitant is the first NK-1RA approved by the U.S. Food and Drug Administration for the prevention and treatment of CINV. In China, it's officially approved only for the prevention of CINV in HEC patients. There are some published systematic reviews^[11–13] on the prevention of CINV by aprepitant plus standard regimen. However, they primarily focused on a specific chemotherapy regimen, age group, or emetogenic risk group. Our research group previously performed a comprehensive evaluation of aprepitant on both HEC and MEC patients, regardless of chemotherapy regimen and age.^[14] A number of additional clinical trials investigating the correlations between aprepitant use and CINV prevention had been published and therefore a more comprehensive analysis was allowed. Thus we conducted an updated systematic evaluation to evaluate the efficacy and safety of antiemetic regimen with aprepitant in preventing CINV, so as to provide state-of-the-art evidence for clinical decision making.

2. Methods

This systematic review and meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions^[15] and is presented per the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline.^[16] It was registered on the International Prospective Register for Systematic Reviews (No. CRD 42019120574). This article was based on previously conducted studies and did not contain any studies with human participants or animals performed by any of the authors.

2.1. Search strategy and selection criteria

We systematically searched PubMed, Embase, the Cochrane Library, and 3 Chinese databases (China National Knowledge Infrastructure, Wangfang, and Chinese Biomedical Literature Database). The brand and generic drug names “aprepitant OR Emend” were used as search terms. Our previous evaluation searched the literature from inception to August 2015, so database search was limited between August 2015 and June 2018 for the current study. A manual search of reference lists of relevant reviews was additionally performed.

Two authors (TQ and PM) carried out the literature screening independently. The research questions and eligibility criteria for the systematic review conformed to the PICOS (participants, interventions, comparators, outcomes, and study design) approach. Studies meeting the following criteria were considered for inclusion:

- (1) Participants: malignant tumor patients who received HEC or MEC.
- (2) Interventions: aprepitant plus 5HT3RA and glucocorticoid (i.e. the aprepitant triple regimen) for the prevention of CINV.
- (3) Comparators: 5HT3RA and glucocorticoid (i.e. the standard regimen) for the prevention of CINV, with or without a placebo.
- (4) Outcomes:
 - Efficacy: complete response (CR, defined as no emesis and no use of rescue medication) in the overall (0 to 120 hours), acute and delayed phases; the proportion of patients who have no emesis, nausea, or use of rescue medication in the phases above; the Functional Living Index-Emesis (FLIE) score;
 - Safety: incidence of ≥ 1 adverse event, serious adverse event, discontinuation due to adverse events, febrile neutropenia, asthenia/fatigue, constipation, diarrhea, nausea, headache, hiccup, neutropenia, and anorexia.
- (5) Study design: randomized controlled trial (RCT).

Reviews, editorials, guidelines, and case reports were excluded. Considering the basic requirement of the publication quality, Chinese RCTs that not published on Source Journals for Chinese Scientific and Technical Papers and Citations were excluded.

2.2. Data extraction and quality assessment

Data extraction was collected and arranged by researchers using a collection form. Study and patients characteristics, intervention details, as well as outcome measures mentioned earlier, were extracted. Corresponding authors were contacted for data not available within studies, or when outcomes were presented in an unsuitable format for data synthesis. The data was first extracted by 2 authors and cross-checked.

Two authors independently assessed the quality of included studies. Discrepancies were resolved by discussion or through consultation with the third reviewer. The potential risks of bias in RCTs were assessed according to the criteria developed using the Cochrane risk of bias tool.

2.3. Statistical analyses

Outcomes were pooled using Review Manager 5.3 software (RevMan, Cochrane, London). Dichotomous data were presented as odds ratios (ORs). For continuous data, estimates were pooled using the inverse variance methodology to calculate weighted mean differences. All results were estimated from each study with 95% confidence intervals (CIs). Heterogeneity was assessed using the chi-square test and the I^2 statistic. If I^2 was no more than 50%, a fixed-effect model with the Mantel-Haenszel method was used; otherwise, the random-effect model was adopted. If the extracted data was not sufficient for a quantitative meta-analysis, a narrative approach was conducted to summarize the study-specific results. Potential publication biases of CR in the overall, acute and delayed phases as primary outcomes were assessed by drawing funnel plots.

To explore any potential risk factors that might affect the CR results, 4 prespecified subgroup analyses were conducted, according to patient's age, 5HT3RA treatment time length, race, emetogenic risk of chemotherapy and whether glucocorticoid dose was adjusted in the intervention group.

Table 1
Subgroup analyses for complete response.

Subgroups	ORs, 95% CIs, and P values		
	overall CR	acute CR	delayed CR
Age			
Children and adolescents	3.05 ^{1.93, 4.83} $P < .001$	1.95 ^{0.61, 6.25} $P = .26$	2.42 ^{1.05, 5.57} $P = .04$
Adults	1.84 [1.67, 2.03] $P < .001$	1.90 [1.60, 2.26] $P < .001$	1.93 [1.66, 2.23] $P < .001$
5-HT3RA treatment time length			
Intervention and control: 1 day	2.04 [1.80, 2.33] $P < .001$	1.88 [1.59, 2.22] $P < .001$	2.19 [1.92, 2.50] $P < .001$
Intervention and control: more than 1 day	2.16 [1.45, 3.22] $P < .001$	3.88 [2.11, 7.15] $P < .001$	2.78 [0.81, 9.51] $P = .10$
Intervention: 1 day; control: more than 1 day	1.54 [1.31, 1.80] $P < .001$	1.63 [1.12, 2.38] $P = .01$	1.43 [1.22, 1.68] $P < .001$
Race			
Asian	1.76 [1.51, 2.05] $P < .001$	1.52 [1.22, 1.89] $P < .001$	1.83 [1.51, 2.20] $P < .001$
Non-asian	1.87 [1.66, 2.12] $P < .001$	1.96 [1.69, 2.29] $P < .001$	1.87 [1.51, 2.31] $P < .001$
Emetogenic risk of chemotherapy			
HEC	2.08 [1.81, 2.38] $P < .001$	2.12 [1.68, 2.68] $P < .001$	2.28 [1.99, 2.62] $P < .001$
MEC	1.60 ^{1.37, 1.87} $P < .001$	1.66 ^{1.09, 2.54} $P = .02$	1.41 ^{1.20, 1.65} $P < .001$
Dexamethasone dose in the intervention group			
Adjusted	1.77 [1.59, 1.97] $P < .001$	1.73 [1.42, 2.09] $P < .001$	1.70 [1.47, 1.96] $P < .001$
Not adjusted	2.17 [1.73, 2.74] $P < .001$	2.70 [1.84, 3.97] $P < .001$	2.53 [1.90, 3.35] $P < .001$

5-HT3RA = 5-hydroxytryptamine-3 receptor antagonist, CIs = confidence intervals, CR = complete response, HEC = highly emetogenic chemotherapy, MEC = moderate emetogenic chemotherapy, ORs = odds ratios.

3. Results

3.1. Baseline characteristics and risk of bias

The selection process for articles included in the systematic review is shown in Supplemental Digital Content (Figure S1, Available at: <http://links.lww.com/MD/E662>). From the 1625 citations identified by the literature searching and from other sources, 25 trials^[17–41] met the inclusion criteria for inclusion. A total of 51 RCTs^[17–67] were finally included in the systematic review.

A total of 11217 patients were enrolled. According to the emetogenic risk of chemotherapy, patients in 30 trials received HEC, 17 received MEC, 3 received HEC and MEC, while 1 trial did not report. Most of the patients in the intervention groups were treated with aprepitant for 3 days. See Supplemental Digital Content (Table S1, <http://links.lww.com/MD/E667>) for detailed information.

The risk of bias summary is shown in Supplemental Digital Content (Figure S2, <http://links.lww.com/MD/E663>), and an assessment of the risk of bias for each of the studies selected is shown in Supplemental Digital Content (Figure S3, <http://links.lww.com/MD/E664>). Random sequence generation was adequate in 35 trials, and allocation concealment was adequately described in 11 trials. 4 trials were considered to be at high risk of performance and detection bias. All studies were judged to be at low risk of attrition, reporting, and other bias.

3.2. Prevention of CINV

Compared with the standard regimen, the aprepitant triple regimen significantly improved CR in the overall (OR 1.88, 95%

CI 1.71–2.07, $P < .001$), acute (OR 1.96, 95% CI 1.65–2.32, $P < .001$) and delayed (OR 1.96, 95% CI 1.70–2.27, $P < .001$) phases [Supplemental Digital Content (Figure S4, Available at: <http://links.lww.com/MD/E665>)]. The results of the subgroup analyses were shown in Table 1. Aprepitant triple regimen still retained the advantages against the standard regimen on CR in most subgroups. Compared with the standard regimen, the aprepitant triple regimen significantly improved the proportion of patients who have no emesis event during the overall (OR 2.50, 95% CI 2.16–2.91, $P < .001$), acute (OR 2.09, 95% CI 1.76–2.49, $P < .001$), and delayed phases (OR 2.49, 95% CI 2.14–2.89, $P < .001$). It significantly improved the proportion of patients who have no nausea event during the overall (OR 1.53, 95% CI 1.13–1.75, $P < .001$) and delayed phases (OR 1.50, 95% CI 1.30–1.74, $P < .001$), but not in the acute phase (OR 1.18, 95% CI 0.97–1.43, $P = .09$). The aprepitant triple regimen significantly improved the proportion of patients who have no use of rescue medication in the overall phase (OR 1.45, 95% CI 1.26–1.68, $P < .001$), while data for acute and delayed phases was not reported. Significant publication biases of primary outcomes (CR in the overall, acute or delayed phases) were not found by drawing funnel plots [see Supplemental Digital Content (Figure S5, Available at: <http://links.lww.com/MD/E666>)].

3.3. FLIE score

A total of 8 studies reported the results of the FLIE score.^[23,33,34,49,50,57,59,65] Meta-analysis was not performed due to the inconsistency among reporting types of the results. The FLIE scores of the aprepitant triple regimen were higher than

Safety outcomes	Studies	Participants	ORs, 95% CIs and P values
Asthenia/fatigue	30	6657	0.99 [0.80, 1.23] <i>P</i> = .91
Constipation	35	7455	0.85 [0.74, 0.97] <i>P</i> = .01
Diarrhea	23	6132	1.02 [0.87, 1.21] <i>P</i> = .79
Nausea	13	4999	1.12 [0.95, 1.33] <i>P</i> = .18
Anorexia	14	4670	0.90 [0.76, 1.07] <i>P</i> = .23
Headache	12	3209	0.85 [0.68, 1.06] <i>P</i> = .14
Hiccup	24	5003	1.26 [1.05, 1.51] <i>P</i> = .01
Febrile neutropenia	11	4934	1.07 [0.77, 1.48] <i>P</i> = .70
Discontinuation due to adverse event	11	5453	1.39 [0.93, 2.06] <i>P</i> = .11
Serious adverse event	13	6033	1.15 [0.95, 1.38] <i>P</i> = .15
More than 1 adverse event	10	4621	0.97 [0.85, 1.11] <i>P</i> = .64

CIs = confidence intervals, ORs = odd ratios.

those of the standard regimen, and the FLIE questionnaire results showed that significantly more patients in the aprepitant group reported minimal or no impact of CINV on daily life, compared with patients in the control groups.

3.4. Safety outcomes

There were no significant differences between the aprepitant triple regimen and standard regimen for most outcomes (Table 2), except for constipation and hiccup. The aprepitant group had a significant tendency to reduce the risk of constipation (OR 0.85, 95% CI 0.74–0.97, *P* = .01) and increase the incidence of hiccup (OR 1.26, 95% CI 1.05–1.51, *P* = .01).

4. Discussion and conclusion

The primary efficacy results of our systematic review and meta-analysis were consistent with previous studies. Compared to the standard regimen, the aprepitant triple regimen significantly improved the CR in the overall, acute, and delayed phases. Regardless of the emetogenic risk of chemotherapy, the aprepitant triple regimen consistently improved the prevention of CINV in the overall, acute, and delayed phases. This provides evidence for the recommended aprepitant for cancer patients receiving MEC.

The results of subgroup analyses enriched the knowledge of aprepitant treatment. The OR estimates of CR in the children and adolescents subgroups were larger than those in the adult group. A previous study has shown that younger patients had a higher risk of CINV.^[68] The results suggested that the benefit of aprepitant combination in children and adolescents may be more remarkable; however, the result in the acute phase was not statistically significant. Also, when 5HT3RA was used for more than 1 day in both the aprepitant and standard regimen groups, aprepitant significantly improved CR in the overall and the acute phases, but not in the delayed phase. These results may be partially explained by the relatively small population size of the available trials. Meanwhile, the mechanisms of CINV in acute or delayed phases are quite different. Serotonin mediates the early CINV process that occurs within 8 to 12 hours following chemotherapy, after which time substance P acting at NK receptors becomes the dominant mediator of vomiting.^[69]

The first and second generations 5HT3RAs are proved to be associated with a small number of patients experiencing mild headache, diarrhea, or constipation.^[70] Our result showed that the addition of aprepitant was able to lower the risk of constipation. Hiccups are often observed in patients treated with cisplatin-based chemotherapy. A previous cluster analysis^[71] indicated that aprepitant was not a major risk factor for the onset of hiccups. However, the meta-analysis showed an opposite result. More large-scale trials are still required to further investigate the issue.

However, there are still some limitations in this study. Firstly, a few trials included in the meta-analysis were found to have a possible unclear or high risk of bias in some domains. This potential bias may reduce the credibility of the corresponding results. Interpretations of these findings must be made with caution. Secondly, the adverse events were generally not reported as primary endpoints in the included RCTs. Definitions of adverse events used in the included RCTs were not specifically stated, which could mean some inconsistency across studies. Also, our analyses were based on trial-level, rather than patient-level, data. Detailed information, such as the exact time of constipation occurrence, or any dechallenges or rechallenges, was not reported.

In conclusion, aprepitant triple regimen not only effectively improves the prevention of CINV in both highly and MEC patients, but also reduces the incidence of constipation. However, more attention to the increased risk of hiccup should be paid.

Author contributions

Conceived and designed the study: XC SZ TQ PM XX. Performed the study: TQ PM. Analyzed the data: TQ PM. Wrote the paper: TQ PM. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

References

- [1] Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT₃ receptor antagonists. *Support Care Cancer* 1994;2:286–92.
- [2] De Boer-Dennert M, de Wit R, Schmitz PI, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT₃ antagonists. *Br J Cancer* 1997;76:1055–61.
- [3] Passik SD, Kirsh KL, Rosenfeld B, et al. The changeable nature of patients' fears regarding chemotherapy: implications for palliative care. *J Pain Symptom Manage* 2001;21:113–20.
- [4] Navari RM. Management of chemotherapy-induced nausea and vomiting: Focus on newer agents and new uses for older agents. *Drugs* 2013;73:249–62.
- [5] Grunberg SM, Slusher B, Rugo HS. Emerging treatments in chemotherapy-induced nausea and vomiting. *Clin Adv Hematol Oncol* 2013;11(2 suppl 1):1–8.
- [6] Rojas C, Slusher BS. Pharmacological mechanisms of 5-HT₃ and tachykinin NK₁ receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur J Pharmacol* 2012;684:1–7.
- [7] National Comprehensive Cancer Network. *Antiemesis* 2019;1:2019.
- [8] Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J Clin Oncol* 2016;34:381–6.
- [9] Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol* 2016;27(suppl 5):v119–33.

- [10] Yu SY, Yin JL, Qin SK, et al. Tumor treatment related vomiting prevention guide (2014 edition). *Chin Clin Oncol* 2014;19:263–73.
- [11] Di Maio M, Baratelli C, Bironzo P, et al. Efficacy of neurokinin-1 receptor antagonists in the prevention of chemotherapy-induced nausea and vomiting in patients receiving carboplatin-based chemotherapy: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2018;124:21–8.
- [12] Chapell R, Aapro MS. Efficacy of aprepitant among patients aged 65 and over receiving moderately to highly emetogenic chemotherapy: a meta-analysis of unpublished data from previously published studies. *J Geriatr Oncol* 2013;4:78–83.
- [13] Abdel-Rahman O. Neurokinin-1 inhibitors in the prevention of nausea and vomiting from highly emetogenic chemotherapy: a network meta-analysis. *Ther Adv Med Oncol* 2016;8:396–406.
- [14] Zhang MM, Xu XH, Zhai SD. Health technology assessment on aprepitant to control chemotherapy induced nausea and vomiting. *China Health Insurance* 2016;11:50–6.
- [15] Higgins J, Green SE (2011) *Cochrane handbook for systematic reviews of interventions* version 5.1.0. Available at: <http://handbook-5-1.cochrane.org/> Accessed 22 November 2017.
- [16] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- [17] An N, Lan H, Zhang M, et al. Clinical research on aprepitant for the prevention of nausea and vomiting due to EP regimen chemotherapy in small-cell lung cancer patients. *Med J West China* 2018;30:242–5.
- [18] 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;25:1340–6.
- [19] Kusagaya H, Inui N, Karayama M, et al. Evaluation of palonosetron and dexamethasone with or without aprepitant to prevent carboplatin-induced nausea and vomiting in patients with advanced non-small-cell lung cancer. *Lung Cancer* 2015;90:410–6.
- [20] Yahata H, Kobayashi H, Sonoda K, et al. Efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen: a multicenter, placebo-controlled, double-blind, randomized study in patients with gynecologic cancer receiving paclitaxel and carboplatin. *Int J Clin Oncol* 2016;21:491–7.
- [21] Kim JE, Jang JS, Kim JW, et al. Efficacy and safety of aprepitant for the prevention of chemotherapy-induced nausea and vomiting during the first cycle of moderately emetogenic chemotherapy in Korean patients with a broad range of tumor types. *Support Care Cancer* 2016;25:1–9.
- [22] Bubalo J, Mulverhill K, Meyers G, et al. A randomized, placebo-controlled pilot trial of aprepitant combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients undergoing cyclophosphamide-based conditioning regimens prior to hematopoietic stem cell transplant (HSCT). *Bone Marrow Transplant* 2018;53:1010–8.
- [23] Ishido K, Higuchi K, Azuma M, et al. Aprepitant, granisetron, and dexamethasone versus palonosetron and dexamethasone for prophylaxis of cisplatin-induced nausea and vomiting in patients with upper gastrointestinal cancer. *Anticancer Drugs* 2016;27:884–90.
- [24] Aridome K, Mori SI, Baba K, et al. A phase II, randomized study of aprepitant in the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapies in colorectal cancer patients. *Mol Clin Oncol* 2016;4:393–8.
- [25] Kaushal P, Atri R, Soni A, et al. Comparative evaluation of triplet antiemetic schedule versus doublet antiemetic schedule in chemotherapy-induced emesis in head and neck cancer patients. *Ecanermediscalscience* 2015;9:567.
- [26] Sugimori Y, Ota T, Ujihira T, et al. A phase II randomised study to evaluate the efficacy of aprepitant plus palonosetron for preventing delayed-phase CINV associated with TC therapy in gynaecological cancer. *J Obstet Gynaecol Res* 2017;43:1454–9.
- [27] Song Z, Wang H, Zhang H, et al. Efficacy and safety of triple therapy with aprepitant, ondansetron, and prednisone for preventing nausea and vomiting induced by R-CEOP or CEOP chemotherapy regimen for non-Hodgkin lymphoma: a phase 2 open-label, randomized comparative trial. *Leuk Lymphoma* 2017;58:816–21.
- [28] Guo XY, Zheng RJ, Li JY, et al. Effect analysis of Aprepitant for chemotherapy patients with lung cancer. *Clin Pulm Med* 2015;20:2153–6.
- [29] Jiang M, Chi F, Zeng Y. Efficacy of aprepitant in treatment of chemotherapy-induced nausea and vomiting in patients with advanced breast cancer. *Clinical Misdiagnosis and Mistherapy* 2017;30:95–8.
- [30] Jiang M, Chi F, Wu R. Efficacy of aprepitant in preventing chemotherapy-induced nausea and vomiting in patients with breast cancer. *Practical Pharmacy And Clinical Remedies* 2017;20:293–7.
- [31] Kang YX, Min J, Zhang DW, et al. Clinical observation of Aprepitant combined with Tropisetron in the prevention of nausea and vomiting caused by high vomiting chemotherapy regimen. *Modern Oncol* 2016;24:1926–48.
- [32] Meng N, Zhu Q, Li YM, et al. Clinical effect of aprepitant on chemotherapy-induced nausea and vomiting patients with lung cancer. *Guangxi Medical Journal* 2018;40:112–5.
- [33] Meng WJ, Wang X, Jia YS, et al. Efficacy and safety evaluation on aprepitant in prevention of nausea and vomiting induced by highly emetogenic chemotherapy. *J Jilin Univ (Med Edit)* 2016;42:331–5.
- [34] Pan GH, Xu Y, Hu SS, et al. Clinical observation of triple therapy with aprepitant, ondansetron and dexamethasone on prevention of adjuvant chemotherapy induced nausea and vomiting for post-operative patients with rectal carcinoma. *Chin J Pharmacoevidemiol* 2017;11:725–8.
- [35] Qi J. Aprepitant as secondary prevention in moderate-severe vomiting caused by AC chemotherapy for breast cancer. *J Pharm Pract* 2017;35:158–60.
- [36] Su J, Luo Y, Zhu YH, et al. Clinical observation of aprepitant combined with tropisetron and dexamethasone in the prevention of vomiting induced by cisplatin chemotherapy. *J Hunan Normal Univ (Med Sci)* 2016;13:60–3.
- [37] Tian X, Wu LN, Hu TY, et al. Clinical research on aprepitant for the prevention of nausea and vomiting due to paclitaxel and cisplatin chemotherapy in lung adenocarcinoma patients. *Practical Pharmacy And Clinical Remedies* 2016;19:1152–5.
- [38] Tian X, Xuan Y, Hu TY, et al. Clinical observation of NK1 receptor antagonist aprepitant for the prevention of nausea and vomiting induced by pf chemotherapy regimen with head and neck cancer. *J Med Res* 2016;45:49–53.
- [39] Yan Y, Ren Y. The observation of multipathway blocking the effect of nausea and vomiting induced by chemotherapy in breast cancer. *Mondrn Oncol* 2017;25:68–71.
- [40] Yu HQ, Chen HY, Ren RM, et al. Therapeutic effect of aprepitant triple regimen on patients receiving high emetogenic chemotherapy. *Chin J Integr Med* 2016;25:274–6.
- [41] Zhao GF, Xiong J, Ye T, et al. Clinical observation of aprepitant in the antiemetic treatment of doxorubicin and ifosfamide regimen induced vomiting. *J Clin Oncol* 2017;23:802–6.
- [42] Albany C, Brames MJ, Fausel C, et al. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a Hoosier Oncology Group study. *J Clin Oncol* 2012;30:3998–4003.
- [43] Bakhshi S, Batra A, Biswas B, et al. Aprepitant as an add-on therapy in children receiving highly emetogenic chemotherapy: a randomized, double-blind, placebo-controlled trial. *Support Care Cancer* 2015;23:3229–37.
- [44] Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol* 2001;19:1759–67.
- [45] Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003;97:2290–300.
- [46] De Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol* 2003;21:4105–11.
- [47] Gore L, Chawla S, Petrilli A, et al. Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability. *Pediatr Blood Cancer* 2009;52:242–7.
- [48] Herrstedt J, Muss HB, Warr DG, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and

- emesis over multiple cycles of moderately emetogenic chemotherapy. *Cancer* 2005;104:1548–55.
- [49] Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin - The Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;21:4112–9.
- [50] Hu Z, Cheng Y, Zhang H, et al. Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial. *Support Care Cancer* 2014;22:979–87.
- [51] Ito Y, Karayama M, Inui N, et al. Aprepitant in patients with advanced non-small-cell lung cancer receiving carboplatin-based chemotherapy. *Lung Cancer* 2014;84:259–64.
- [52] Kang HJ, Loftus S, Taylor A, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:385–94.
- [53] Maehara M, Ueda T, Miyahara D, et al. Clinical efficacy of aprepitant in patients with gynecological cancer after chemotherapy using paclitaxel and carboplatin. *Anticancer Res* 2015;35:4527–34.
- [54] Nasu R, Nann ya Y, Kurokawa M. A randomized controlled study evaluating the efficacy of aprepitant for highly/moderately emetogenic chemotherapies in hematological malignancies. *Int J Hematol* 2015;101:376–85.
- [55] Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group. *N Engl J Med* 1999;340:190–5.
- [56] Nishimura J, Satoh T, Fukunaga M, et al. Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. *Eur J Cancer* 2015;51:1274–82.
- [57] Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97:3090–8.
- [58] Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. *Support Care Cancer* 2010;18:423–31.
- [59] Schmitt T, Goldschmidt H, Neben K, et al. Aprepitant, granisetron, and dexamethasone for prevention of chemotherapy-induced nausea and vomiting after high-dose melphalan in autologous transplantation for multiple myeloma: results of a randomized, placebo-controlled phase III trial. *J Clin Oncol* 2014;32:3413–20.
- [60] Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. *Ann Oncol* 2006;17:1000–6.
- [61] Stiff PJ, Fox-Geiman MP, Kiley K, et al. Prevention of nausea and vomiting associated with stem cell transplant: results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. *Biol Blood Marrow Transplant* 2013;19:49–55.
- [62] Svanberg A, Birgegård G. Addition of aprepitant (Emend) to standard antiemetic regimen continued for 7 days after chemotherapy for stem cell transplantation provides significant reduction of vomiting. *Oncology* 2015;89:31–6.
- [63] Takahashi T, Hoshi E, Takagi M, et al. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. *Cancer Sci* 2010;101:2455–61.
- [64] Tanioka M, Kitao A, Matsumoto K, et al. A randomised, placebo-controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy. *Br J Cancer* 2013;109:859–65.
- [65] Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005;23:2822–30.
- [66] Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. *Breast Cancer Res Treat* 2009;113:529–35.
- [67] Ding RM, Wang P, Tian Y, et al. Clinical observation of aprepitant on nausea and vomiting caused by FAC chemotherapy regimen for breast cancer. *Chin J Diffic and Compl Cas* 2015;14:45–8.
- [68] Warr DG, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of phase 3 trial of aprepitant in patients receiving adriamycin-cyclophosphamide-based chemotherapy. *Supportive Care* 2011;19:807–13.
- [69] Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer* 2003;39:1074–80.
- [70] Navari RM. The safety of antiemetic medications for the prevention of chemotherapy-induced nausea and vomiting. *Expert Opin Drug Saf* 2016;15:343–56.
- [71] Asano H, Watanabe M, Kawaguchi A, et al. A search for the risk factors for hiccups and evaluation of antiemetic therapy in CDDP-based chemotherapy, using cluster analysis. *Gan To Kagaku Ryoho* 2013;40:1031–6.