Antiemetic regimen with aprepitant in the prevention of chemotherapy-induced nausea and vomiting
An updated systematic review and meta-analysis

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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-HT\textsubscript{3}RA = 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

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\textsuperscript{[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,\textsuperscript{[4]} which can be prevented by prophylactic antiemetic agents. Glucocorticoids, most commonly dexamethasone, were first used for treating CINV in the early 1990s.\textsuperscript{[5]} Thereafter, the addition of 5-hydroxytryptamine-3 receptor antagonist (5-HT\textsubscript{3}RA) showed additional improvement in acute CINV, which acts by blocking the peripheral nervous pathways of gastrointestinal tracts.\textsuperscript{[6]}

Recent studies showed that the combination of the standard regimen (5HT\textsubscript{3}RA 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 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.
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 phases (OR 1.70–2.27, P < .001). Compared with the standard regimen, the aprepitant triple regimen significantly improved the proportion of patients who have no nausea event during the overall (OR 1.53, 95% CI 1.31–1.80, P < .001) and delayed phases (OR 1.68, 95% CI 1.51–1.89, 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...
Table 2
Meta-analysis results of safety outcomes.

| Safety outcomes                          | Studies | Participants | ORs, 95% CIs and P values |
|-----------------------------------------|---------|--------------|---------------------------|
| Asthenia/fatigue                         | 30      | 6657         | 0.99 [0.80, 1.23] P=.91   |
| Constipation                             | 35      | 7455         | 0.85 [0.74, 0.97] P=.01   |
| Diarrhea                                 | 23      | 6132         | 1.02 [0.87, 1.21] P=.79   |
| Nausea                                   | 13      | 4999         | 1.12 [0.95, 1.33] P=.18   |
| Anorexia                                 | 14      | 4670         | 0.90 [0.76, 1.07] P=.23   |
| Headache                                 | 12      | 3209         | 0.85 [0.68, 1.06] P=.14   |
| Hiccup                                   | 24      | 5003         | 1.26 [1.05, 1.51] P=.01   |
| Febrile neutropenia                      | 11      | 4934         | 1.07 [0.77, 1.48] P=.70   |
| Discontinuation due to adverse event     | 11      | 5453         | 1.39 [0.93, 2.06] P=.11   |
| Serious adverse event                   | 13      | 6033         | 1.15 [0.95, 1.38] P=.15   |
| More than 1 adverse event               | 10      | 6421         | 0.97 [0.85, 1.11] P=.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.⁶¹ 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.⁶²

The first and second generations 5HT3RAs are proved to be associated with a small number of patients experiencing mild headache, diarrhea, or constipation.⁶⁰ 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 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.

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