

Aprepitant plus palonosetron versus dexamethasone plus palonosetron in preventing chemotherapy-induced nausea and vomiting in patients with moderate-emetogenic chemotherapy: A randomized, open-label, phase 3 trial

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Summary

Background Despite significant progress in the prevention of chemotherapy-induced nausea and vomiting (CINV) by using dexamethasone combined with palonosetron for patients who received moderate-emetogenic chemotherapy (MEC), some of these patients still suffer from CINV. We evaluated whether aprepitant combined with palonosetron can improve the efficacy in the prevention of CINV in patients receiving MEC.

Methods This was a single-centre, open-label, phase III, randomized controlled trial, which was done at the Sixth Affiliated Hospital of Sun Yat-sen University of China. The registered patients planned to receive mFOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil) but had not received any chemotherapy previously. The patients were randomized in a 1:1 ratio to the aprepitant group (aprepitant 125 mg orally on day 1, 80 mg on day 2-3) and the dexamethasone group (dexamethasone 10 mg intravenously on day 1, 5 mg on days 2 and 3), both groups with palonosetron 0.25 mg intravenously on day 1. The primary endpoint was the proportion of patients who achieved a complete response (CR), defined as the absence of vomiting and no use of rescue medications in the overall phase (0–120 h). The primary outcome and safety were assessed in the modified intention-to-treat population, which excluded all patients who used estazolam within 24 h before registration and those who refused to keep a diary documenting the severity of nausea, frequency of vomiting, and the use of rescue therapy. This trial is registered with ClinicalTrials.gov, NCT02909478.

Findings Between Sep 1, 2017, and Oct 23, 2019, 320 patients were enrolled, and 315 patients were evaluated. The proportion of patients who achieved CR was significantly higher with aprepitant than that noted with dexamethasone in the overall phase (88.8% vs. 74.2%; $P = 0.0010$; rate difference, RD 15%, 95% CI, 6% to 23%) and in the delayed phase (25–120 h), 90.6% vs. 75.5%, ($P < 0.0001$; RD 15%, 95% CI, 7% to 23%). No significant difference of CR rate was observed in the acute phase (0–24 h), 93.8% vs. 93.5%, ($P = 0.94$; RD 0%, 95% CI, -5% to 6%). In the overall phase, the incidence of insomnia ($P < 0.0010$), dyspepsia ($P = 0.038$), and flushing ($P = 0.0010$) reported by the patients was significantly higher in the dexamethasone group than that in the aprepitant group.

Interpretation Aprepitant combined with palonosetron is superior to dexamethasone combined with palonosetron in patients who received the MEC regimen mFOLFOX6 in terms of preventing CINV.

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Keywords: Chemotherapy-induced nausea and vomiting (CINV); Dexamethasone-free; Aprepitant; Palonosetron; Moderate-emetogenic chemotherapy (MEC)

Research in context

Evidence before this study

We searched PubMed for articles published between January 1, 2000, and August 31, 2021, with the terms “chemotherapy-induced nausea and vomiting (CINV)”, “Moderate Emetogenic Chemotherapy (MEC)”, “MEC”, “Dexamethasone (DEX)” and “Aprepitant”, with no language restrictions. American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend a combination of 5-hydroxytryptamine type 3 (5-HT₃) antagonists combined with DEX for patients receiving MEC. Antiemetic DEX administration on days 2 and 3 can be spared when combined with palonosetron in MEC. Aprepitant is a potent, orally bioavailable, selective neurokinin-1 receptor antagonists (NK-1 RA), which effectively antagonizes substance P that crosses the blood-brain barrier, leading to dramatic improvements in the prevention of CINV. Previous studies showed that the addition of aprepitant to an antiemetic regimen of 5-HT₃ antagonists and dexamethasone resulted in significantly better prevention of CINV in MEC. In addition, there is some evidence that dexamethasone has potential adverse effects.

Added value of this study

To our knowledge, the study was the first randomized, phase III study to compare aprepitant plus palonosetron versus dexamethasone plus palonosetron for the prevention of CINV in MEC. Our results showed the combination of aprepitant with palonosetron significantly improves antiemetic efficiency than the combination of dexamethasone with palonosetron in the mFOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil) regimen. The difference (15%) in complete response in the overall phase is a clinically meaningful improvement.

Implications of all the available evidence

Our findings showed that the combination of aprepitant with palonosetron in the absence of dexamethasone can be a better option for antiemetic therapy in MEC-mFOLFOX6. The study further supported that aprepitant combined with palonosetron can be selected to prevent CINV, as to reduce the potential drawback of dexamethasone.

with cancer who receive chemotherapy often have chemotherapy-induced nausea and vomiting (CINV). CINV exhibits a negative impact on patients' daily function and quality of life, leading to dose reductions and/or treatment interruption, which in turn results in poor prognosis.² To date, clinically effective prophylactics or therapeutics are available for the prevention or treatment of CINV, including 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists, dexamethasone (DEX), neurokinin-1 receptor antagonists (NK-1 RA), benzodiazepines, and antipsychotic agents.^{3,4} The effects of gabapentin, cannabinoid, and ginger are also being explored in the prevention of CINV.⁵ Cytotoxic drugs or combinations are divided into high (> 90%), medium (30–90%), low (10–30%), and very low (< 10%) risk levels according to emetogenicity, to guide the use of anti-emetic treatment.^{6,7} Patients receiving high emetic chemotherapy should receive combination therapy of NK-1 RA, 5-HT₃ antagonists, and dexamethasone, while patients receiving moderate-emetogenic chemotherapy (MEC), including the mFOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil) regimen, are recommended to use 5-HT₃ antagonists combined with dexamethasone.⁶

Although 5-HT₃ antagonist palonosetron combined with dexamethasone has promising efficacy in preventing CINV in patients who received the MEC regimen, approximately 30% of patients still suffer from CINV.⁸ Aprepitant is a potent, orally bioavailable, selective NK-1 receptor inhibitor, which effectively antagonizes substance P that crosses the blood-brain barrier, leading to dramatic improvements in the prevention of CINV.⁹ It significantly improves the efficacy in preventing CINV in the high-emetogenic chemotherapy (HEC) regimen when adding to 5-HT₃ antagonists, and dexamethasone. However, whether the preventive regimen containing NK-1 RA is needed in moderate emetic chemotherapy is still controversial.

Besides, checkpoint inhibitors (CPIs) have been widely used in the treatment of a variety of cancer types. The update of the 2020 Antiemetics American Society of Clinical Oncology (ASCO) guideline mentioned that, there is no evidence that corticosteroids should be avoided in antiemetic regimens when CPIs are administered in combination with chemotherapy.¹⁰ This study was designed in 2017, when several concerns were raised regarding the potential for concurrent use of corticosteroids in anti-emetic treatment to adversely affect the therapeutic efficacy of CPIs through their

Introduction

Nausea and vomiting are the most prevalent side effects of antineoplastic therapy.¹ An estimated 80% of patients

immunosuppressive effects.^{11,12} Moreover, the multi-period use of DEX could be associated with side effects, such as hyperglycemia, dyspepsia, insomnia, etc.¹³ A previous trial evaluating the efficacy of aprepitant in patients with moderate emetic chemotherapy indicated that this agent aided the prevention of CINV and reduced the use of DEX.¹⁴ However, no prospective randomized controlled study has been reported to confirm the effectiveness and safety of a dexamethasone-free antiemetic regimen.^{8,15,16} Therefore it is worth investigating whether NK-1 RA could be better than DEX in the moderate emetic regimen in terms of both efficacy and safety.

The objective of this phase III trial was to compare aprepitant plus palonosetron versus dexamethasone plus palonosetron for the prevention of CINV in patients with colorectal cancer who had received MEC-mFOLFOX6.

Methods

Study design and participants

This study was a single-centre, open-label, phase III randomized controlled trial. The study was conducted in the Sixth Affiliated Hospital of Sun Yat-sen University in China. Patients 18 years of age or older with colorectal cancer who were scheduled to be treated with their first course of the mFOLFOX6 regimen were eligible for enrollment in this study. Additional eligibility criteria included the following: European Cooperative Oncology Group (ECOG) performance status 0, 1, or 2; adequate organ function (i.e., hemoglobin ≥ 90 g/l without a history of blood transfusion within 14 days, absolute neutrophil count $\geq 1.5 \times 10^9/l$, platelet count $\geq 75 \times 10^9/l$, serum bilirubin $\leq 1.5 \times ULN$, ALT and AST $\leq 3.0 \times ULN$ without liver metastases, ALT and AST $\leq 5.0 \times ULN$ with liver metastases, serum creatinine $\leq 1 \times ULN$, endogenous creatinine clearance ≥ 60 ml/min), and general cognitive abilities.

We excluded patients who received olanzapine, phenothiazine, amifostine, or other cancer therapies within 4 weeks, and nausea or vomiting within 24 h before enrollment. Patients were also excluded if they had central nervous system diseases, gastro-intestinal obstruction, pregnancy or lactation, abdominal radiotherapy, alcohol dependence syndrome, alcohol abuse history, hypersensitivity to the study drug, uncontrolled diabetes, active HIV infection, infectious hepatitis, tuberculosis infections, uncontrolled infections, known cardiac arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the six months before enrollment. The manuscript adheres to CONSORT reporting guidelines.

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive either dexamethasone (control group) or

aprepitant (experiment group) plus palonosetron before chemotherapy. The randomization was done using a web-entry system, which required a personal account and password. The randomization was performed by an engineer without stratification factors and a balanced block. The clinical trial coordinator was in charge of enrolling patients and assigning them to treatment groups based on the allocation results. All participants provided written informed consent. The present study was approved by the Human Research Ethics Committee at the Sixth Affiliated Hospital of Sun Yat-Sen University and registered on ClinicalTrials.gov (NCT02909478).

Procedures

The patients in the experimental group were treated with NK-1 RA (125 mg on day 1, and 80 mg on days 2 and 3 orally). The patients in the control group were treated with dexamethasone (10 mg intravenously on day 1, 5 mg on days 2 and 3). All participants received 5-HT₃ receptor antagonists. Palonosetron was administered at 0.25 mg intravenously on the first day of chemotherapy. Dexamethasone sodium phosphate injection is approved with 4 mg/ml by Food and Drug Administration (FDA) while in China it is approved with 5 mg/ml. Due to the availability of the dexamethasone, dosage of dexamethasone was adjusted in this study. Although tropisetron was considered as the antiemetic drug in the study when the protocol was initially registered, palonosetron was used throughout the study because tropisetron was not available at the time the study commenced.

Demographic and medical data were recorded for all subjects. From the start of chemotherapy infusion on day 1 through the morning of day 6 (0–120 h), the patients recorded their responses in a diary every day, capturing information about the severity of nausea, frequency of vomiting, and the use of rescue therapy. Visual analog scales are psychometric instruments used for measuring the severity of nausea experienced by patients. A numerical rating scale of 0 to 10 was used, with 0 indicating the absence of symptoms and 10 indicating the worst possible symptom. The frequency of vomiting and the use of rescue therapy were evaluated based on the following criteria: 0, none; 1, once; 2, twice; 3, >2 times. Patients were also asked to document whether related adverse events of antiemetic medications occurred from day 1 to day 5, including insomnia, constipation, restlessness, dyspepsia, sweat, and flushing. They were asked to report “yes” or “no” without the grade. The patients received intravenous chemotherapy for a total of 3 days in the hospital. Diary records were collected every day. On days 4 and 5 following chemotherapy, the patients were contacted by phone to verify the appropriateness of the procedures.

Outcomes

The primary endpoint of the study was complete response, which was defined as the absence of emetic episodes and no use of rescue therapy during the overall phase (0–120 h from the initiation of chemotherapy). The secondary endpoints were the following: Complete response in the acute phase (0–24 h) and the delay phase (25–120 h), nausea score, time to first vomiting episode or use of rescue medication, frequency of rescue medication, and the adverse effect of antiemetic therapy. Among them, the severity of nausea can be judged by whether there is clinically significant nausea, which was defined as a nausea score of 3 or more according to previous studies.¹⁷ The number of days for clinically significant nausea, use of rescue medication, and the adverse effect for each patient were compared between groups. Besides, to analyse the changes in lymphocyte counts and peripheral lymphocyte subsets before and following the first cycle of chemotherapy, the numbers of participants who declined in the aforementioned lymphocytes were also compared between groups.

Statistical analysis

Based on the complete response proportions reported previously in patients treated with the two-drug combination of palonosetron (day 1) and dexamethasone (days 1–3) therapy, the proportion of patients who would achieve a complete response in the control group was assumed to be 80%.¹⁶ We considered a 13% increase in this proportion would be a clinically meaningful effect size. The sample size was estimated to be 316 patients in total, with a significance level of 5% in a two-sided test and a detection power of 90%.

The difference in the proportion of patients achieving a complete response during the acute/delay/overall phase between the different treatment arms was compared using a chi-squared test. For adjusted analyses, we used logistic regression. The estimates of the

median and the 95% CI were calculated for the period required for treatment failure in each group using the Kaplan-Meier method and the inter-group differences were analysed using the Cox proportional-hazards model. To compare the difference between clinically significant nausea, use of the rescue medicine, and adverse events, the difference in the duration of events between the two groups was evaluated by Mann-Whitney rank-sum test. All patients who received any type of treatment in this study were assessed for safety. The analysis of the primary and secondary endpoints was pre-specified. The subgroup analyses and the analysis of peripheral lymphocytes were specified post hoc. The comparison of the changes in lymphocyte counts and peripheral lymphocyte subsets was performed using the chi-square test. The univariate logistics regression was performed to evaluate the efficacy of different antiemetic therapy options among the subgroups, and the interaction terms were involved to analyse the impact of subgroup stratification factors on the antiemetic therapy.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study patients

From Sep 1, 2017, to Oct 23, 2019, 320 patients were enrolled (Figure 1). The modified intention-to-treat population excludes data for patients who used estazolam within 24 h before registration and who refuse to keep a diary. Among them, 164 patients were randomly assigned to the aprepitant group and 156 patients to the dexamethasone group. A total of 2 patients withdrew consent and 1 patient used estazolam within 24 h before

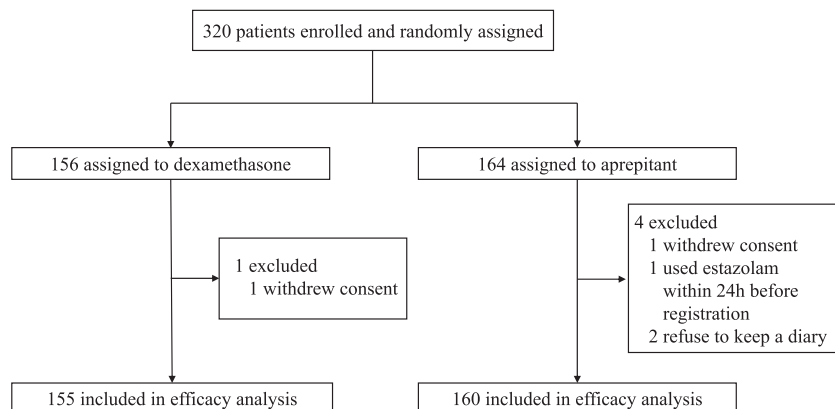


Figure 1. Trial profile.

registration. Two patients refused to keep a diary. Therefore, the data from 315 patients (160 in the aprepitant group and 155 in the dexamethasone group) were analysed. No substantial differences were found between the two groups in terms of age, sex, BMI, family history, smoking history,

comorbidities, the dosage of chemotherapy drugs, and the type of treatment (Table 1). Moreover, vomiting risk indicators, including feeling nauseous, vomiting, being easily drunk, motion sickness, pregnancy response, and sensitivity to odor were evaluated before chemotherapy (Table 1).^{18–21}

	Dexamethasone N = 155	Aprepitant N = 160	Total N = 315
Age (years)			
Median	56 (29-81)	55 (25-74)	56 (25-81)
< 45	127 (81.9)	127 (79.4)	254 (80.6)
≥ 45	28 (18.1)	33 (20.6)	61 (19.4)
Sex— no. (%)			
Male	86 (55.5)	104 (65)	190 (60.3)
Female	69 (44.5)	56 (35)	125 (39.7)
BMI			
Median (range)	22.03 (14.27-33.25)	21.94 (15.42-31.23)	22.04 (14.27-33.25)
Family history— no. (%)			
No	151 (97.4)	155 (96.9)	306 (97.1)
Yes	4 (2.6)	5 (3.1)	9 (2.9)
Smoking— no. (%)			
No	129 (83.2)	127 (79.4)	256 (81.3)
Yes	26 (16.8)	33 (20.6)	59 (18.7)
Complications— no. (%)			
No	130 (83.9)	136 (85.0)	266 (84.4)
Yes	25 (15.8)	24 (15.0)	49 (15.6)
Chemotherapeutic drug— dose (mg)			
Median (range)			
OXA	140 (100-170)	140 (100-175)	
5-FU	4500 (3500-5500)	4500 (3500-5500)	
Treatment type— no. (%)			
Neoadjuvant	59 (38.1)	72 (45.0)	132 (41.6)
Adjuvant	84 (54.2)	74 (46.3)	158 (50.2)
First-line	12 (7.7)	14 (8.8)	26 (8.3)
Nausea— no. (%)			
No	153 (98.7)	156 (97.5)	309 (98.1)
Yes	2 (1.3)	4 (2.5)	6 (1.9)
Vomit—no. (%)			
No	153 (98.7)	159 (99.4)	312 (99.0)
Yes	2 (1.3)	1 (0.6)	3 (1.0)
Easy drunk— no. (%)			
No	99 (63.9)	102 (63.7)	201 (63.8)
Yes	56 (36.1)	58 (36.3)	114 (36.2)
Motion sickness— no. (%)			
No	123 (79.4)	135 (84.4)	258 (81.9)
Yes	32 (20.6)	25 (15.6)	57 (18.1)
Pregnancy response— no. (%)			
No	141 (91.0)	152 (95.0)	293 (93.0)
Yes	14 (9.0)	8 (5.0)	22 (7.0)
Sensitive to odor— no. (%)			
No	133 (85.8)	133 (83.1)	266 (84.4)
Yes	22 (14.2)	27 (16.9)	49 (15.6)

Table 1: Baseline demographic and clinical characteristics.

BMI, body mass index; OXA, oxaliplatin; 5-FU, 5-fluorouracil

Efficacy

During the overall period, the proportion of patients in the aprepitant group who achieved complete response was significantly higher than that of the dexamethasone group (88.8% vs. 74.2%; $P = 0.0010$). After adjusting for baseline characteristic, including age, sex, smoking, easy drunk (ie, never drinking or getting drunk easily), motion sickness, sensitive to odor and treatment type, the antiemetic therapy still had effect on CINV control, with statistically significant P value (OR, 0.387, 95% CI, 0.201 to 0.745; $P = 0.0050$) (Appendix p1). Easy drunk refers to never drinking or getting drunk easily. Figure 2 indicates the results of subgroup analysis for the primary endpoint used. The analysis indicated that females, patients aged less than 45 years old, being easily drunk, sensitive to odor, and those receiving neoadjuvant chemotherapy may benefit the most from the aprepitant group (Appendix p2). Interaction P values showed no evidence of interaction of treatment effect with a subgroup of patients. (Figure 2, Appendix p2). At different assessment periods, the aprepitant and the dexamethasone groups exhibited different rates of complete response as follows: In the acute phase, 93.8% vs.

93.5%, ($P = 0.94$); in the delayed phase, 90.6% vs. 75.5%, ($P < 0.0001$) (Table 2).

For the nausea evaluation, there was no significant difference in the duration of clinically significant nausea between the two groups ($P = 0.40$) (Table 3). In addition, no significant difference in the proportion of clinically significant nausea and no differences in the nausea score between the two groups each day was noted (Appendix p 3). What's more, patients were asked to report the frequencies of vomiting and rescue medications used for nausea or vomiting each day in the Nausea and Vomiting Daily Diary Questionnaire according to the following score categories: none, one, two, and more than two. Similarly, there was no significant difference in the number of days of using the use of rescue drugs between the two groups ($P = 0.78$) (Table 3). No significant differences were noted in the use of rescue drugs between the two groups on days 1–5 (Appendix p 4). On days 2–4, the patients in the dexamethasone group reported significantly higher vomiting events than those in the aprepitant group (Appendix p 5). Treatment failure was defined as the occurrence of vomiting or the use of rescue medication.

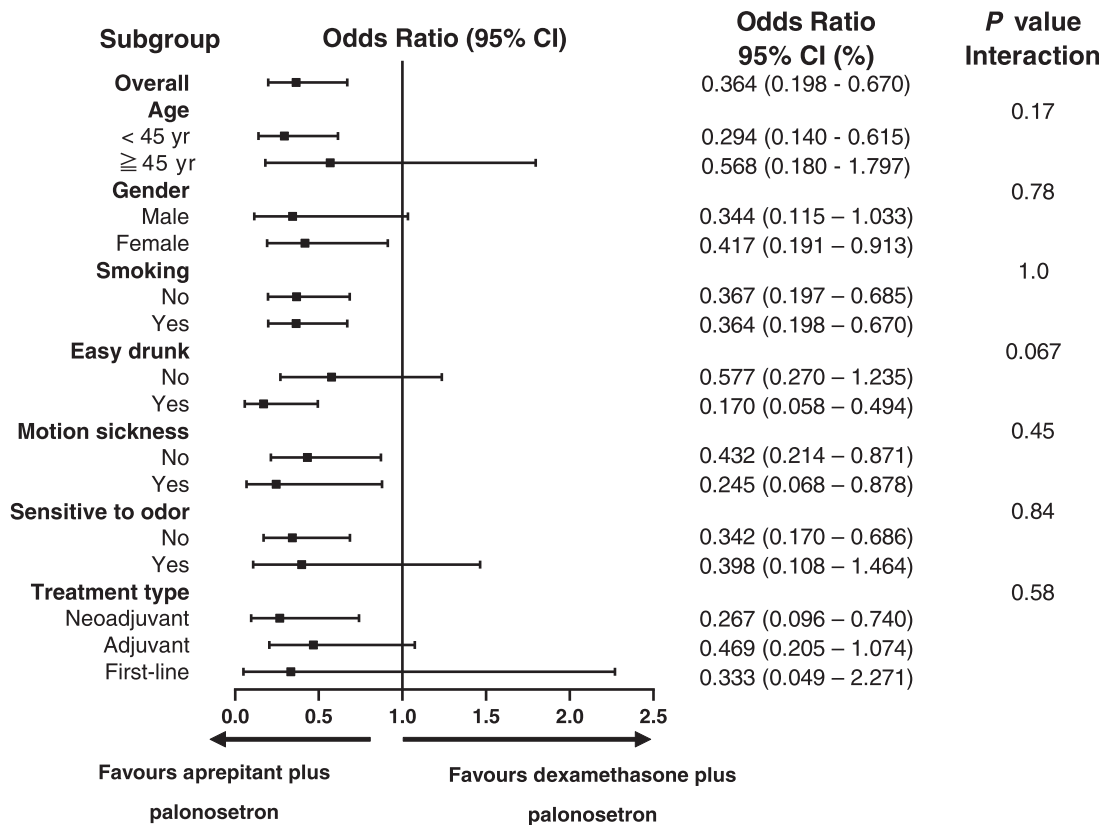


Figure 2. Complete response in Key Subgroups of Patients

Shown are odds ratios for complete response with the aprepitant group as compared with the dexamethasone group in subgroups.

P-value: The interaction terms were involved to analyse the impact of subgroup stratification factors on antiemetic therapy.

	Aprepitant (n = 160)		Dexamethasone (n = 155)		Rate difference (RD)	P-value
	No. (%)	95% CI	No. (%)	95% CI		
Complete response						
Overall	142(88.8%)	82.9% to 93.2%	115 (74.2%)	66.6% to 80.9%	15% (6% to 23%)	0.0010
(0–120 h)						
Acute	150(93.8%)	88.9% to 97.0%	145 (93.5%)	88.4% to 96.8%	0% (-5% to 6%)	0.94
(0–24 h)						
Delayed	145 (90.6%)	85.0% to 94.6%	117 (75.5%)	68.0% to 82.0%	15% (7% to 23%)	<0.0001
(25–120 h)						

Table 2: Results of complete response (CR) rates.
Complete response: no emetic episodes and no use of rescue therapy.

The period to treatment failure in the dexamethasone group was significantly shorter than that of the aprepitant group (hazard ratio [HR] 2.365, [95% CI 1.356–4.126]; $P = 0.0020$; [Figure 3](#)).

Adverse effects of the anti-emetic regimen

Since the adverse events were reported by the patients themselves, this study only reported the overall incidence of adverse events and did not conduct a grade assessment of the adverse events. In the overall phase, the incidence of antiemetic medication-related adverse events, including insomnia ($P < 0.0010$), dyspepsia ($P = 0.038$), and flushing ($P = 0.0010$) reported by patients was significantly higher in the dexamethasone group than that noted in the aprepitant group, but not for constipation ($P = 0.084$), restlessness ($P = 0.26$), and sweat ($P = 0.40$) ([Table 3](#)). The symptoms reported by patients in daily life between the two groups are shown in the appendix p 6.

The changes in the number of peripheral blood cells before and following the first cycle of chemotherapy were analysed (appendix p 7). Analyses were performed for the proportion of patients with a decline in lymphocyte count, the ratio of CD3+T, CD3+CD4+T, and CD3+CD8+T lymphocytes, and natural killer (NK) cells (CD3-CD16+/CD56+), the data showed that non-significant differences were observed between the two groups. Although the ratio of B cells (CD3-CD19+) to lymphocytes was observed more frequently in the dexamethasone group, the difference was not statistically significant (58.6% vs. 45%, $P = 0.066$).

Discussion

The present randomized, controlled, open-label, phase 3 study indicated that the application of NK-1 RA combined with 5-HT₃ receptor antagonists was more effective in the prevention of nausea and vomiting than the application of 5-HT₃ receptor antagonists combined with dexamethasone in patients without chemotherapy history who received MEC.

This is the first randomized control trial, which provided strong evidence regarding the contribution of aprepitant and palonosetron without dexamethasone in the prevention of CINV in the MEC-mFOLFOX6 regimen. In recent years, several clinical studies have explored the effects of reducing the use of dexamethasone in the treatment of anti-CINV. Yuka et al. compared the effects of dexamethasone administration on day 1 with those noted following administration of this compound on days 1 to 3 and those noted following the combined treatment of the patients with NK-1 RA and palonosetron for HEC and found that the CR rates were similar for the overall period in both treatment arms.²² In the antiemetic study of MEC, palonosetron combined with dexamethasone on day 1 was not inferior to dexamethasone on days 1 to 3.⁸ At present, the Multinational Association of Supportive Care in the Cancer/European Society for Medical Oncology and National Comprehensive Cancer Network guidelines states that the administration of DEX on days 2 and 3 can be spared for MEC. However, whether the prophylactic regimen containing NK-1 RA should be used to prevent CINV in MEC remains controversial. A recent prospective study has demonstrated that the combination of aprepitant with palonosetron and dexamethasone provided antiemetic efficacy in women patients with high-risk vomiting undergoing FOLFOX or FOLFIRI chemotherapy regimen.²³ However, all these studies contained dexamethasone in the antiemetic regimen. Indeed, our results showed the combination of aprepitant with palonosetron significantly improves antiemetic efficiency than the combination of dexamethasone with palonosetron in the mFOLFOX6 chemotherapy regimen. In the present study, the CR rates in the experimental and the control groups were lower than those of the expected estimate. The main reason for the lower CR rate may be due to the high percentage (80%) of the patients being at a younger age. In addition, patients with unresected primary lesions are still at risk of intestinal obstruction. In addition, the gastrointestinal symptom is a common postoperative complication. The complete response rate of the two-drug combination of palonosetron (day 1

Item/number of days	Dexamethasone N (%)	Aprepitant N (%)	P-value*
Clinically significant nausea			0.40
0	99 (63.9)	97 (60.6)	
1	11 (7.1)	10 (6.3)	
2	14 (9.0)	17 (10.6)	
3	16 (10.3)	12 (7.5)	
4	7 (4.5)	6 (3.8)	
5	8 (5.2)	18 (11.3)	
Rescue medication			0.78
0	143 (92.3)	149 (93.1)	
1	6 (3.9)	5 (3.1)	
2	5 (3.2)	3 (1.9)	
3	0 (0)	2 (1.3)	
4	0 (0)	1 (0.6)	
5	1 (0.6)	0 (0)	
Insomnia			<0.0010
0	111 (71.6)	144 (90.0)	
1	15 (9.7)	5 (3.1)	
2	11 (7.1)	4 (2.5)	
3	6 (3.9)	2 (1.3)	
4	6 (3.9)	2 (1.3)	
5	6 (3.9)	3 (1.9)	
Constipation			0.084
0	86 (55.5)	108 (67.5)	
1	10 (6.5)	6 (3.8)	
2	19 (12.3)	10 (6.3)	
3	15 (9.7)	13 (8.1)	
4	11 (7.1)	5 (3.1)	
5	14 (9.0)	18 (11.3)	
Restlessness			0.26
0	139 (89.7)	149 (93.1)	
1	4 (2.6)	3 (1.9)	
2	2 (1.3)	4 (2.5)	
3	2 (1.3)	1 (0.6)	
4	5 (3.2)	1 (0.6)	
5	3 (1.9)	2 (1.3)	
Dyspepsia			0.038
0	123 (79.4)	141 (88.1)	
1	8 (5.2)	3 (1.9)	
2	8 (5.2)	7 (4.4)	
3	7 (4.5)	3 (1.9)	
4	5 (3.2)	4 (2.5)	
5	4 (2.6)	2 (1.3)	
Sweat			0.40
0	124 (80.0)	133 (83.1)	
1	9 (5.8)	13 (8.1)	
2	8 (5.2)	3 (1.9)	
3	3 (1.9)	5 (3.1)	
4	5 (3.2)	3 (1.9)	
5	6 (3.9)	3 (1.9)	
Flushing			0.0010
0	137 (88.4)	157 (98.1)	
1	8 (5.2)	2 (1.3)	
2	5 (3.2)	1 (0.6)	
3	1 (0.6)	0 (0)	
4	1 (0.6)	0 (0)	
5	3 (1.9)	0 (0)	

Table 3: Duration of clinically significant nausea, rescue, and adverse events in the Dexamethasone group and the Aprepitant group.

Clinically significant nausea: No nausea scores of 3 or more on a scale from 0 to 10.

P-value*: The difference in the duration of events between the two groups was evaluated by Mann-Whitney rank-sum test.

only) and dexamethasone (days 1–3) in patients receiving MEC was approximately 74.2%. The observed differences in the proportions of the patients achieving a complete response between the aprepitant and dexamethasone groups were 14.6 percentage points for the overall phase and 15.1 percentage points for the delayed phase, however, generally close in the acute period. The analysis of the composition of the complete response indicated no significant differences in the distribution of vomiting times between the two groups on day 1, whereas the vomiting times were significantly higher in the delayed period in the dexamethasone group compared with those of the aprepitant group. Furthermore, no significant differences were noted in the frequency of rescue drugs between the two groups. However, it can be found that the use of rescue drugs on days 3–5 in the dexamethasone group was slightly higher than that in the aprepitant group. This may be related to the difference in the pathogenesis of CINV in the acute and delayed phases. CINV is complicated and its mechanism has not yet been fully elucidated. CINV is regulated by the following two key pathways: One is the central (brain) pathway and the other is the peripheral (gastrointestinal) pathway.²⁴ Acute CINV refers to the reaction occurring within 0–24 h of chemotherapy, which is mainly controlled by the peripheral (gastrointestinal) pathway and involves mainly the neurotransmitter 5-HT.^{25–27} Delayed CINV occurs within 24–120 h following chemotherapy, which is mainly controlled by the central pathway, and the neurotransmitter involved is substance P.^{27–29} Both groups in the present study were treated with the second generation 5-HT receptor antagonist palonosetron on the first day, which exhibits both competitive binding and allosteric interactions with the 5-HT₃ receptor. Palonosetron indicates high effectiveness and safety compared with those of the older 5-HT₃ antagonists in preventing vomiting.^{30–32} This may also explain the finding that the aprepitant group was identical to the dexamethasone group in the acute phase and more efficient than the latter in the delayed phase. Subgroup analysis indicated that the female, age < 45 years, easily drunk subjects, the sensitivity to odor, and the patients receiving neoadjuvant chemotherapy may benefit from the aprepitant group. Some studies have shown that these people are more prone to vomiting, the benefit for the primary endpoint in patients receiving aprepitant is most likely related to the characteristics of the population.^{18–21} As we can see in the result, no interaction effect was observed, which indicated no obvious effect of subgroup factors on the treatment effect.

In terms of nausea, the proportion of clinically significant nausea in the aprepitant group was numerically slightly higher than that noted in the dexamethasone group, but there was no significant difference in the proportion of clinically significant nausea between the two groups. The results were consistent with previous

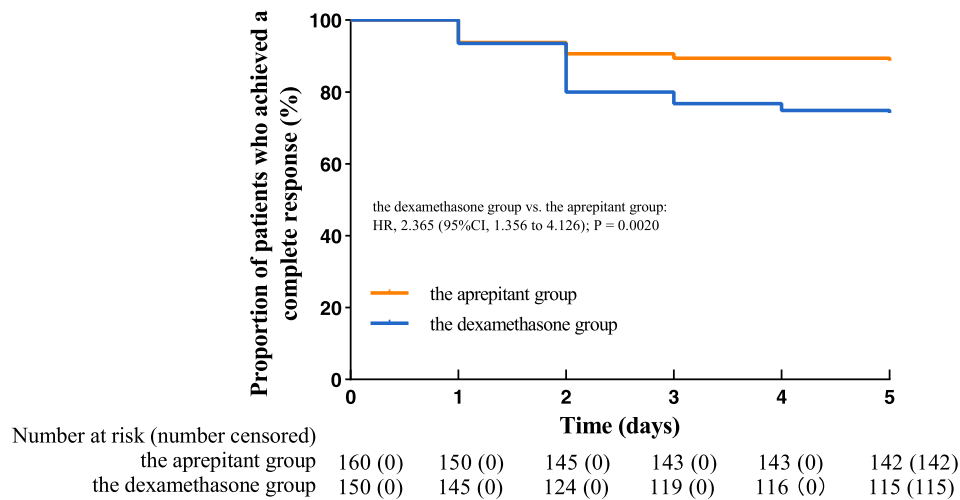


Figure 3. Kaplan-Meier plot showing time to treatment failure in two groups.

studies.^{33,34} David et al. investigated the addition of aprepitant to dexamethasone combined with ondansetron for the prevention of CINV in MEC, which also did not improve overall nausea or significant nausea.³⁴ This might be explained in part that nausea is a subjective feeling, and the underlying mechanisms of its regulation are currently unknown. It is suggested that substance P plays a more important role in the mechanism of vomiting than nausea, and additional neurotransmitters may be involved in the mechanism of nausea development. Therefore, nausea is rarely used as the primary endpoint in this type of clinical trial while composite endpoints, such as the absence of emetic episodes and no use of rescue therapy, are favored as the primary endpoints in clinical trials.³⁵ It is noted more and more attention is paid to the assessment of nausea. At present, inadequately controlled nausea remains a major problem in many patients. A study has shown that gabapentin may reduce nausea in the both acute and delayed phases.³⁶ Other antipsychotic agents such as olanzapine may also control nausea. Gabapentin or olanzapine might be considered to be combined with the current experimental drugs to achieve better control of nausea in further study.

The study further supported that aprepitant combined with palonosetron can be selected to prevent CINV, as to reduce the potential drawback of dexamethasone. Firstly, the incidence of adverse events was higher in the dexamethasone group than in the aprepitant group, such as insomnia. Furthermore, dexamethasone is one of the most widely used glucocorticoids in tumor treatment, with a high binding affinity to the glucocorticoid receptor. Glucocorticoids are considered to be one of the lymphocyte death-inducing factors, and immature B cells are more sensitive to glucocorticoid-induced apoptosis.^{37,38} B cells express glucocorticoid

receptors throughout their developmental process, and glucocorticoid receptors exert an intrinsic role in B cell survival and homeostasis.^{39,40} B lymphocytes are an important part of the immune system required for regulating humoral immunity. They can differentiate into plasma cells under antigen stimulation, synthesize, and secrete immunoglobulins to exert powerful immune effects. In the dexamethasone group, the decreasing trend of the proportion of B cells in the total lymphocyte count indicated that this compound may exert a damaging effect on humoral immunity. Further in-depth analysis of the immune cell subgroups is required since the current study only explored the changes caused by dexamethasone on peripheral lymphocytes. The ASCO guidelines update in 2020 state that there is no evidence that dexamethasone should be removed from antiemetic regimens when receiving systemic therapy including CPDs. However, a dexamethasone-free antiemetic regimen can reduce the concerns of some clinicians.

One limitation of the present study was that the efficacy and effects of only one cycle of chemotherapy were investigated, instead of assessing the dexamethasone-free regimen in multiple cycles. Secondly, this was a single-centre, open-label trial. Due to the limitations of conditions, we failed to get placebos of aprepitant and dexamethasone with similar appearance. Although the study was not a double-blind study, the outcomes of the study were evaluated and filled in diaries by the patients, which to some extent, reduced the bias of the researchers. What's more, only the code of the patients, but not the grouping information were presented in the diaries. Thirdly, the lack of grading of adverse effects may be a limitation in determining adverse events. Because the data were recorded in diaries by the patients themselves, only "yes or no" were set on the diaries, the

grading of adverse effects were absent. Fourth, the lack of stratification at randomization was also a limitation of this study. After adjusting for the baseline characteristics, the antiemetic therapy was still had effect on CINV. Lastly, the combination of aprepitant and palonosetron exhibited no superior effects on the prevention of nausea. This requires further investigation. These issues should be considered in future clinical trials.

In conclusion, the combination of aprepitant with palonosetron in the absence of dexamethasone can be a better option for antiemetic therapy in MEC and would be of great significance in the era of immunotherapy.

Contributors

YC, ZHW contributed to trial design, statistical analysis, the initial draft of the manuscript. LSS, CLS contributed to data management and statistical analysis. JWZ, HBH, WWL, YC, XYX, JYL, and QZ recruit patient and collected data. YHD contributed to trial conception and design and are responsible for the decision to submit the manuscript for publication. YC, ZHW, LSS, and CLS contributed equally. YC, ZHW and YHD had full access to and verify the data, and take responsibility for the integrity of the data and adherence to the study protocol. All authors contributed to data collection and interpretation, and revision of the manuscript for important content.

Declaration of interests

All authors declare no competing interests.

Data sharing statement

The study protocol is provided in the supplementary appendix. Anonymized participant data will be made available with publication, upon requests directed to the corresponding author (dengyanh@mail.sysu.edu.cn). Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit.

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Supplementary materials

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