Received: 23 April 2022 | Revised: 18 November 2022 | Accepted: 9 December 2022

DOI: 10.1002/cac2.12397

CANCER COMMUNICATIONS Open Access

ORIGINAL ARTICLE

Validation of different personalized risk models of chemotherapy-induced nausea and vomiting: results of a randomized, double-blind, phase III trial of fosaprepitant for cancer patients treated with high-dose cisplatin

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Abstract

Background: Highly emetogenic chemotherapy induces emesis in cancer patients without prophylaxis. The purpose of this study was to evaluate the efficacy and safety of a fosaprepitant-based triple antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with solid malignant tumors, determine risk factors and externally validate different personalized risk models for CINV.

Methods: This phase III trial was designed to test the non-inferiority of fosaprepitant toward aprepitant in cancer patients who were to receive the first cycle of single-day cisplatin chemotherapy. The primary endpoint was complete response (CR) during the overall phase (OP) with a non-inferiority margin of 10.0%. Logistic regression models were used to assess the risk factors of CR and no nausea. To validate the personalized risk models, the accuracy of the risk scoring systems was determined by measuring the specificity, sensitivity and area under the receiver operating characteristic (ROC) curve (AUC), while the predictive accuracy of the nomogram was measured using concordance index (C-index).

List of abbreviations: CINV, Chemotherapy-induced nausea and vomiting; AE, adverse effect; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; C-index, concordance index; NK1, neurokinin 1; RA, receptor antagonist; HT3, 5- serotonin; FDA, Food and Drug Administration; IWRS, interactive web response system; ECOG, Eastern Cooperative Oncology Group; CNS, central nervous system; VAS, visual analog scale; FLIE, Functional Living Index-Emesis; NIDL, no impact on daily life; SAEs, severe adverse events; ECGs, electrocardiograms; OP, overall phase; AP, acute phase; CR, complete response; DP, delayed phase; CI, confidence interval; ROC curve, receiver operating characteristic curve; C-index, concordance index; SS, safety set; FAS, full analysis set; PPS, per-protocol set..

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Funding information
Shandong Luoxin Pharmaceutical Group Stock Co., Ltd.

Results: A total of 720 patients were randomly assigned. CR during the OP in the fosaprepitant group was not inferior to that in the aprepitant group (78.1% vs. 77.7%, $P = 0.765$) with a between-group difference of 0.4% (95% CI, -5.7% to 6.6%). Female sex, higher cisplatin dose (≥ 70 mg/m^2), no history of drinking and larger body surface area (BSA) were significantly associated with nausea. The AUC for the acute and delayed CINV risk indexes was 0.68 (95% CI: 0.66-0.71) and 0.66 (95% CI: 0.61-0.70), respectively, and the C-index for nomogram CINV prediction was 0.59 (95% CI, 0.54-0.64). Using appropriate cutoff points, the three models could stratify patients with high- or low-risk CINV. No nausea and CR rate were significantly higher in the low-risk group than in the high-risk group ($P < 0.001$).

Conclusions: Fosaprepitant-based triple prophylaxis demonstrated non-inferior control for preventing CINV in patients treated with cisplatin-base chemotherapy. Female cancer patients without a history of alcohol consumption, with larger BSA and received high-dose cisplatin might be more vulnerable to CINV. Three personalized prediction models were well-validated and could be used to optimize antiemetic therapy for individual patients.

KEYWORDS
aprepitant, chemotherapy-induced nausea and vomiting, clinical trial, fosaprepitant, neurokinin-1 receptor antagonists, nomogram, nomogram, personalized risk model

1 | BACKGROUND

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse effect (AE) in the treatment of cancer that can reduce the quality of life and potentially impact the success of cytotoxic therapy by affecting patient compliance [1]. Chemotherapeutic agents can be divided into four emetogenic levels: high, moderate, low and minimal [2] On receiving highly emetogenic chemotherapy (HEC, including cisplatin) without adequate antiemetic treatment, > 90% of patients could experience CINV [2]. Therefore, a three-drug or four-drug combination comprising a neurokinin 1 (NK1) receptor antagonist (RA), a 5-serotonin (HT3)RA, and dexamethasone with or without olanzapine is recommended by clinical practice guidelines for patients receiving HEC [2, 3]. Aprepitant (Emend, Merck) was the first available NK1 RA approved by the Food and Drug Administration (FDA)in 2003 based on two prospective phase III trials, in which aprepitant demonstrated superior control of emesis in patients with HEC [4, 5]. Fosaprepitant is a phosphorylated analog of aprepitant with excellent water-solubility that can be rapidly converted to aprepitant after intravenous administration [6]. A large randomized, double-blinded study demonstrated that a single intravenous dose of fosaprepitant of 150 mg was non-inferior to a 3-day oral regimen of aprepitant in patients receiving their initial cycle of cisplatin-based (≥ 70 mg/m^2) chemotherapy [7].

In accordance with available guidelines, the prophylaxis and management of CINV are generally based on the emetogenicity of the chemotherapeutic regimen [2, 3]. However, risk factors for CINV can be treatment-specific or patient-specific. CINV is complicated by patient-related risk factors, such as younger age, female sex, a history of low alcohol intake, and a history of emesis during pregnancy [8]. Different personalized risk models for

CINV have been developed and validated. Two repeated-measure cycle-based models using numerical scoring systems (indexes), which were able to accurately identify patients at high risk for acute and delayed CINV prior to each cycle of chemotherapy, were proposed separately [9–11]. In 2017, a new repeated-measure prediction model based on a larger dataset was established [12]. To date, the three models have not been validated in patients receiving the initial cycle of HEC. Meanwhile, our group developed and validated a nomogram personalized estimate model in 2016, which could help estimate the individual risk of CINV development [13]. The second external validation of the nomogram model was conducted using this phase III study data.

Therefore, in this article, we report the findings of a multicenter, randomized, double-blinded, double-simulated, positive-control, phase III study on a fosaprepitant regimen in patients with solid malignant tumors receiving high-dose cisplatin. Moreover, in an exploratory analysis, we assessed the risk factors of CINV to identify individuals who should be offered a more rigorous prophylactic regimen. In addition, we also externally validated the personalized risk models.

2 | PATIENTS AND METHODS

2.1 | Study design

This phase III randomized, double-blind trial was designed to evaluate the efficacy and safety of intravenous fosaprepitant versus oral aprepitant in preventing CINV following HEC. Patients with solid malignant tumors who were to receive the first cycle of single-day cisplatin chemotherapy were enrolled, stratified by sex and randomly assigned in a 1:1 ratio to fosaprepitant (Luoxin Pharmaceutical Group Stock Co., Ltd., Linyi, Shandong, China) or aprepitant (MSD Pharmaceutical Co., LTD., Hangzhou, Zhejiang, China) combined with palonosetron (HaiRong Pharmaceutical Co., LTD., Yangtze River Pharmaceutical Group, Dujiangyan, Sichuan, China) and oral dexamethasone (Chenxin, Pharmaceutical Co., LTD., Jining, Shandong, China) groups. To maintain a double-blind, simulation agents of intravenous fosaprepitant, oral aprepitant and oral dexamethasone were used as matching placebos (Luoxin Pharmaceutical Group Stock Co., Ltd., Linyi, Shandong, China) (Supplementary Table S1). The matching placebos and the experimental drugs were identical in packaging and appearance. An interactive web response system (IWRS) was used for the randomization. The study protocol was approved by the ethics committee of Sun Yat-sen University Cancer Center and each participating institution, and all patients provided written informed consent. The study was conducted in accordance with the Good Clinical Practice guidelines and was registered with www.chinadrugtrials.org.cn (approved ID: CTR20170270)

2.2 | Patients

The key inclusion criteria for all cohorts were as follows: male and female patients ≥ 18 years old; diagnosed with solid malignancies by cytology or histology; chemotherapy-naive; planned to receive cisplatin (≥ 50 mg/m^2 for ≤ 3 h) containing regimen; life expectancy ≥ 3 months; and Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

Patients with the following conditions were excluded: vomiting and/or retching and nausea within 24 h prior to the randomization; allergic to the study drug; planned to receive abdominal or pelvic irradiation; scheduled administration of multiple-day moderately emetogenic chemotherapy (MEC) or HEC other than cisplatin in a single cycle; with comorbidities that do not allow them to take dexamethasone or require systemic glucocorticoid therapy; primary or metastatic central nervous system (CNS) malignancy; pregnant or breastfeeding; and serious uncontrolled disease affecting the liver, kidney, cardiovascular, respiratory, and endocrine systems, or CNS.

2.3 | Procedures and assessments

From the time of initiation of cisplatin infusion (0 h) until day 6 (120 h), patients completed a diary to record the severity of nausea, vomiting, and retching episodes and rescue medication. A 100-mm horizontal visual analog scale (VAS) was used to evaluate daily nausea severity. No nausea and no significant nausea were defined as a VAS score < 5 mm and a VAS score < 25 mm, respectively [14]. The Functional Living Index-Emesis (FLIE) questionnaire was completed on day 1 and day 6 to assess the impact of CINV on patients' daily lives. A total FLIE score > 108 and nausea/vomiting domain score > 54 indicated "no impact on daily life" (NIDL) [15]. Safety evaluations, including vital signs, AEs, severe adverse events (SAEs), electrocardiograms (ECGs) and general laboratory tests, were completed during clinical visits.

2.4 | Study endpoints

The primary efficacy endpoint was complete response (CR, no emesis with no use of rescue medication) within 120 h after initiation of cisplatin infusion (overall phase, OP). Secondary efficacy endpoints were as follows: CR in the

acute phase (AP) and delayed phase (DP), defined as 0-24 h (AP) and 25-120 h (DP) after chemotherapy initiation, respectively; no vomiting, no nausea, and no significant nausea during the acute, delayed, and overall phases; the proportion of patients with rescue medication; and FLIE scores during the OP. Safety was also assessed.

2.5 | Statistical analysis

The hypothesis was that the CR rate in the fosaprepitant arm during the OP would not be inferior to that in the aprepitant arm, with a non-inferiority margin of 10.0%. On the assumption that the percentage of patients with a CR in each arm would be 70.0% and a difference between treatment arms ≤ 10.0%, with a one-sided 0.025 significance level, 660 cases (330 cases per arm) were required to provide an 80.0% power for detecting the primary efficacy hypothesis. The sample size was increased to 720 cases (360 cases per arm) with an expected dropout rate of 8.0%.

For the primary endpoint, the proportions of patients with CR in the OP were calculated for the two treatment arms, and the difference in CR rates was also determined. The 95% confidence interval (CI) for the CR rates was calculated using the Clopper-Pearson method. The 95% CI for the difference in CR rates was calculated using the methodology of Newcombe [16]. Treatment comparisons for the secondary efficacy variables were made in a similar manner. Finally, in a post hoc analysis, logistic regression models were used to assess the impact of previously reported risk factors on CR and no nausea.

As for the validation of the three repeated-measure prediction models (Supplementary Table S2 and S3), the accuracy of the risk scoring system was determined by measuring the specificity, sensitivity and area under the receiver operating characteristic (ROC) curve (AUC) [9, 10]. The predictive accuracy of the nomogram was measured via a concordance index (C-index) as described previously [13]. A calibration plot was drawn to compare how well the predicted probabilities from the nomogram matched the actual probabilities. Bootstraps resample methods with 100 repetitions were used for these activities [13]. A ROC curve was used to determine the best cutoff value of the total point in the nomogram. Using the cutoff points defined by each model, the CR and no-nausea rates were compared between higher-risk and lower-risk groups for CINV by the chi-square test.

Statistical analyses were performed on the safety set (SS; all patients who received at least one dose of study treatment), full analysis set (FAS; all SS patients who had ≥ 1 efficacy assessment) and per-protocol set (PPS; all FAS patients who had no protocol violations that directly affected the primary endpoint). In addition, the primary and secondary efficacy endpoints were evaluated in the FAS and PPS. This analysis was performed by a statistician blinded to the study. Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patients' characteristics

A total of 804 patients from 34 research centers were screened, of whom 84 were excluded and 720 were stratified by sex and randomly assigned into two treatment arms (**Figure 1**). There were 709 patients in the SS, 706 in the FAS, and 649 in the PPS. In FAS, baseline demographic characteristics were balanced, and no significant differences were observed between the two treatment arms. Most patients were men, were older than 55 years, and had lung cancer (**Table 1**).

3.2 | Efficacy

In FAS, the CR rate was 78.1% (95% CI, 73.4%-82.3%) in the fosaprepitant arm and 77.7% (95% CI, 73.0%-81.9%) in the aprepitant arm, with a between-group difference of 0.4% (95% CI, -5.7% to 6.6%; $P = 0.765$) (Figure 2A). As the lower bound of the 95% CI for the difference in CR rate between the fosaprepitant and aprepitant arms was -5.7%, greater than the prespecified value of -10.0%, the fosaprepitant regimen was non-inferior to the aprepitant regimen with respect to CR in the OP. The study met its predefined primary endpoint. For secondary endpoints, the CR in the AP and DP was similar in the fosaprepitant and aprepitant arms (Figure 2A). The no vomiting, no nausea and no significant nausea rates during the OP, AP and DP were similar in these two arms (Figure 2B-D). Rescue medication was used during the OP by 8.2% (95% CI, 5.6%-11.6%) of patients in the fosaprepitant arm compared with 5.9% (95% CI, 3.7%-8.9%) in the aprepitant arm, with a between-group difference of 2.3% (95% CI, -1.5 to 6.2) (data not shown). For the FLIE assessment, the proportion of patients who reported NIDL for nausea, vomiting, and combined domains was similar between the fosaprepitant arm and aprepitant arm in the OP (Figure 2E).

3.3 | Tolerability

SS comprised 353 patients in the fosaprepitant arm and 356 in the aprepitant arm. The rate of AEs was 92.9% in the fosaprepitant arm and 91.3% in the aprepitant

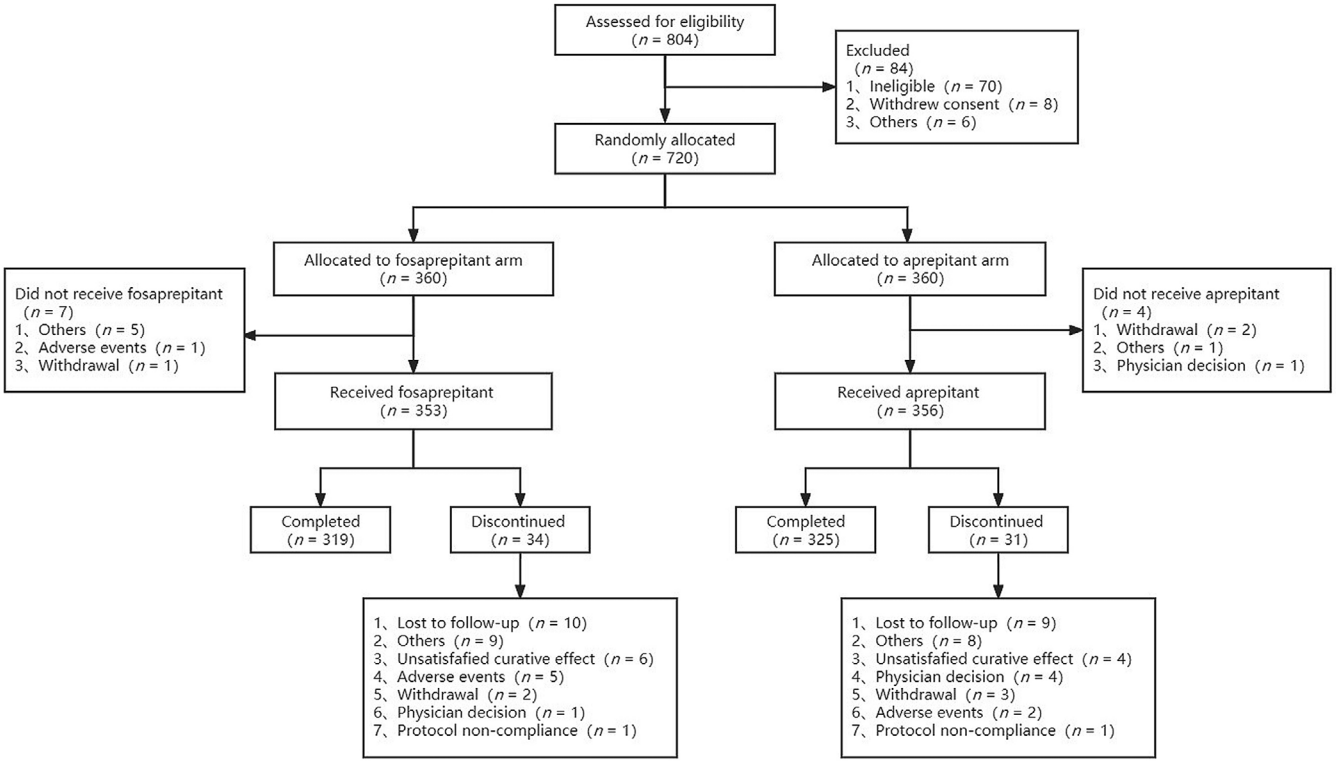

FIGURE 1 Study flowchart illustrating patients' randomization and group allocation for the Fosaprepitant and Aprepitant arms

arm. Serious treatment-related AEs for fosaprepitant were similar to those for aprepitant (0.6% vs. 0.3%). The commonly reported AEs (≥ 1% in at least one treatment arm) were constipation, hiccup, distension, dizziness, and increased alanine aminotransferase (ALT). There were no significant differences in the overall occurrence of AEs between the two treatment arms (Supplementary Table S4).

3.4 | Risk factors

Risk factors for our primary endpoint (CR) and no nausea in the OP were investigated in the exploratory analysis. The most commonly cited high-risk factors [8], including young age, female sex, limited or no regular alcohol intake and previous emesis (vomiting during pregnancy or motion sickness), were all assessed in the logistic regression analysis. Univariate analysis showed that sex (P = 0.002) and history of drinking (P = 0.003) were significantly associated with CR. However, the multivariate analysis indicated that only the female sex was a negative risk factor of CR (P = 0.039 Supplementary Table S5). In the univariate analysis for risk factors associated with no nausea in the OP, four prognostic factors were considered significant drivers of nausea: female sex (P < 0.001), younger age (P = 0.004), higher cisplatin dose (≥ 70 mg/m^2) (P < 0.001) and no history of drinking (P < 0.001). Comparatively, sex (P = 0.006), cisplatin dose (P < 0.001), body surface area (BSA, P = 0.016) and history of drinking (P < 0.001)were independently associated with nausea in the OP in multivariate analysis (Table 2).

3.5 | Model validation

Our study classified patients as high or low risk for CINV using various cutoff scores according to two repeated-measure cycle-based models described in a previous study [9, 10]. Logistic regression analysis revealed that patients at high risk were several times more likely to have a CINV event than patients at lower risk. (Table 3). The calculated risk scores and the probabilities for acute and delayed CINV events for each patient were used in a ROC analysis for further validation. The AUC for the acute and delayed risk indexes was 0.68 (95% CI: 0.66-0.71) and 0.66 (95% CI: 0.61-0.70), respectively, which supports the external validity of each prediction index (Supplementary Figure S1A-B). Moreover, using the cutoff point 9 for acute CINV and 28 for delayed CINV, no nausea and CR rate were significantly higher in the low-risk group than in the high-risk group (P < 0.001) (Supplementary Table S6 and S7).

In the nomogram model, CR, the primary endpoint of our study, was adopted as an indicator of the successful

TABLE 1 Demographic and baseline characteristics of the full analysis set (FAS)

Characteristic	Fosaprepitant arm	Aprepitant arm	*P* values[Φ]
Total cases	352	354	
Sex [cases (%)]			**1.000**
Male	261 (74.1)	263 (74.3)	
Female	91 (25.9)	91 (25.7)	
Age [years; median (range)]	59 (21-82)	59 (24-80)	0.813
< 55 years [cases (%)]	120 (34.1)	124 (35.0)	
≥ 55 years [cases (%)]	232 (65.9)	230 (65.0)	
Cisplatin dose [cases (%)]			0.853
< 50 mg/m^2	12 (3.4)	12 (3.4)	
50-70 mg/m^2	209 (59.4)	203 (57.3)	
≥ 70 mg/m^2	131(37.2)	139 (39.3)	
Tumor site [cases (%)]			0.304
Lungs	239 (67.9)	245 (69.2)[#]	
Urogenital	36 (10.2)	24 (6.8)[*]	
Digestive	58 (16.5)	69 (19.5)[#]	
Others	19 (5.4)	16 (4.5)[*]	
BSA [m^2; median (range)]	1.65 (1.04-2.03)	1.65 (1.22-2.15)	0.429
History of drinking [cases (%)]			0.587
Yes	137 (38.9)	130 (36.7)	
No	215 (61.1)	224 (63.3)	
History of motion sickness [cases (%)]			0.504
Yes	5 (1.4)	3 (0.8)	
No	347 (98.6)	351 (99.2)	
History of VP in female[§] [cases (%)]			0.103
Yes	11 (3.1)	4 (1.1)	
No	80 (22.7)	87 (24.6)	

Abbreviation: VP, vomiting during pregnancy; BSA, body surface area.

[#]one subject in the aprepitant arm had both respiratory and digestive tumors.

*one female in the aprepitant arm was diagnosed with genital tumor and tumors with an unknown primary site.

[§]the total number of females was 91 in our study.

[Φ]*P-values* were calculated with the *t*-test or the chi-square test.

prevention of CINV. The variables defined in our previous work, including sex (females stratified by history of vomiting during pregnancy), age, history of drinking, history of motion sickness, BSA, emetogenicity of chemotherapy and antiemetic regimens, were evaluated in this study [13]. The nomogram is shown in Supplementary Figure S2. Figure 3A shows that the actual CINV corresponded closely to the predicted development. The calibration plot for the probability of CINV showed a good agreement between the prediction by nomogram and actual observation. The C-index for CINV prediction was 0.59 (95% CI, 0.54-0.64) (Figure 3A). The AUC of the nomogram model was 0.59 (95% CI 0.47-0.70) (Figure 3B). Using the cutoff value of the total point (136 determined by the ROC curve, the no-nausea rate and CR rate were significantly higher in the low-risk group than in the high-risk group ($P < 0.001$; Figure 3B and Table 4).

As for the repeated-measure prediction model published in 2017 [12], the area under the ROC curve for CINV risk indexes was 0.55 (95% CI: 0.50 -0.60) (Supplementary Figure S1C) using the data of our study. Since most predictive factors for the risk score in this model were based on information from patients who had undergone prior treatment cycles (Supplementary Table S3), it would not be suitable for patients receiving first-line chemotherapy.

4 | DISCUSSION

The current study was a randomized, double-blind, phase III clinical trial to evaluate the antiemetic efficacy and safety profile of a fosaprepitant regimen in patients receiving cisplatin-based chemotherapy. The fosaprepitant regimen was found to be non-inferior to the aprepitant

TABLE 2 Risk factors associated with no nausea in the overall phase

Risk factors	Subgroups	*n*	No nausea		Univariate analysis		Multivariate analysis	
			n (%)	*n* (%)	OR (95%CI)	*P* Value	OR (95%CI)	*P* Value
Regimen	Fosaprepitant vs. Aprepitant	706	183 (52.0)	179 (50.6)	1.059 (0.788-1.422)	0.705	1.058 (0.777-1.441)	0.719
Sex and VP	Male vs. Female without VP vs. Female with VP	706	-	-	-	**<0.001**		**0.006**
	Female without VP vs. Male	691	66 (39.5)	294 (56.1)	0.511 (0.358-0.729)	**<0.001**	0.599 (0.394-0.912)	**0.017**
	Female with VP vs. Male	539	2 (13.3)	294 (56.1)	0.120 (0.027-0.539)	**0.006**	0.154 (0.033-0.721)	**0.018**
Age (year)	≥55 vs. < 55	706	255 (55.2)	107 (43.9)	1.577 (1.154-2.156)	**0.004**	1.192 (0.850-1.672)	0.308
Cisplatin dose (mg/m^2)	< 50 vs.50-70 vs. 70	706	-	-	-	**<0.001**		**<0.001**
	50-70 vs. < 50	436	232 (56.3)	17 (70.8)	0.531 (0.216-1.308)	0.169	0.555 (0.222-1.387)	0.208
	≥ 70 vs. < 50	294	113 (41.9)	17 (70.8)	0.297 (0.119-0.739)	**0.009**	0.291 (0.115-0.739)	**0.009**
BSA	≥ 1.651 vs. < 1.651	706	182 (50.8)	180 (51.7)	0.965 (0.718-1.297)	0.814	0.667 (0.480-0.926)	**0.016**
History of drinking	No vs. Yes	706	195 (44.4)	167 (62.5)	0.479 (0.351-0.653)	**<0.001**	0.546 (0.384-0.777)	**<0.001**
History of motion sickness	No vs. Yes	706	359 (51.4)	3 (37.5)	1.765 (0.419-7.442)	0.439	1.342 (0.285-6.326)	0.710

Abbreviation: VP, vomiting during pregnancy; N, number of patients; BSA, body surface area; OR, odds ratio.

TABLE 3 Detailed analysis of the risk scoring system of the two repeated-measure cycle-based models for acute and delayed CINV

Score cut point	CINV rate	Sensitivity[#]	Specificity[*]	Correctly classified	OR[§] (95% CI)
Acute CINV					
≥ 7	4.2%	97.8%	19.6%	24.7%	2.5 (0.6-11.0)
≥ 9	8.1%	69.6%	60.2%	60.8%	3.5 (1.4-8.6)
≥ 11	30.8%	23.9%	89.9%	85.6%	2.2 (0.8-6.1)
Delayed CINV					
> 20	6.9%	72.2%	58.1%	60.6%	7.8 (2.3-26.6)
> 24	6.9%	72.2%	58.1%	60.6%	7.8 (2.3-26.6)
> 28	8.1%	61.9%	64.5%	64.0%	3.5 (1.4-8.7)

Abbreviation: CINV, chemotherapy-induced nausea and vomiting; OR, odds ratio; CI, confidence interval.

[#]the proportion of patients who had a CINV event and were classified as high risk.

*the proportion of patients who did not have a CINV event and were classified as low risk.

[§]risk of a moderate to severe CINV event in patients determined to be at high- vs low-risk by the respective scoring systems.

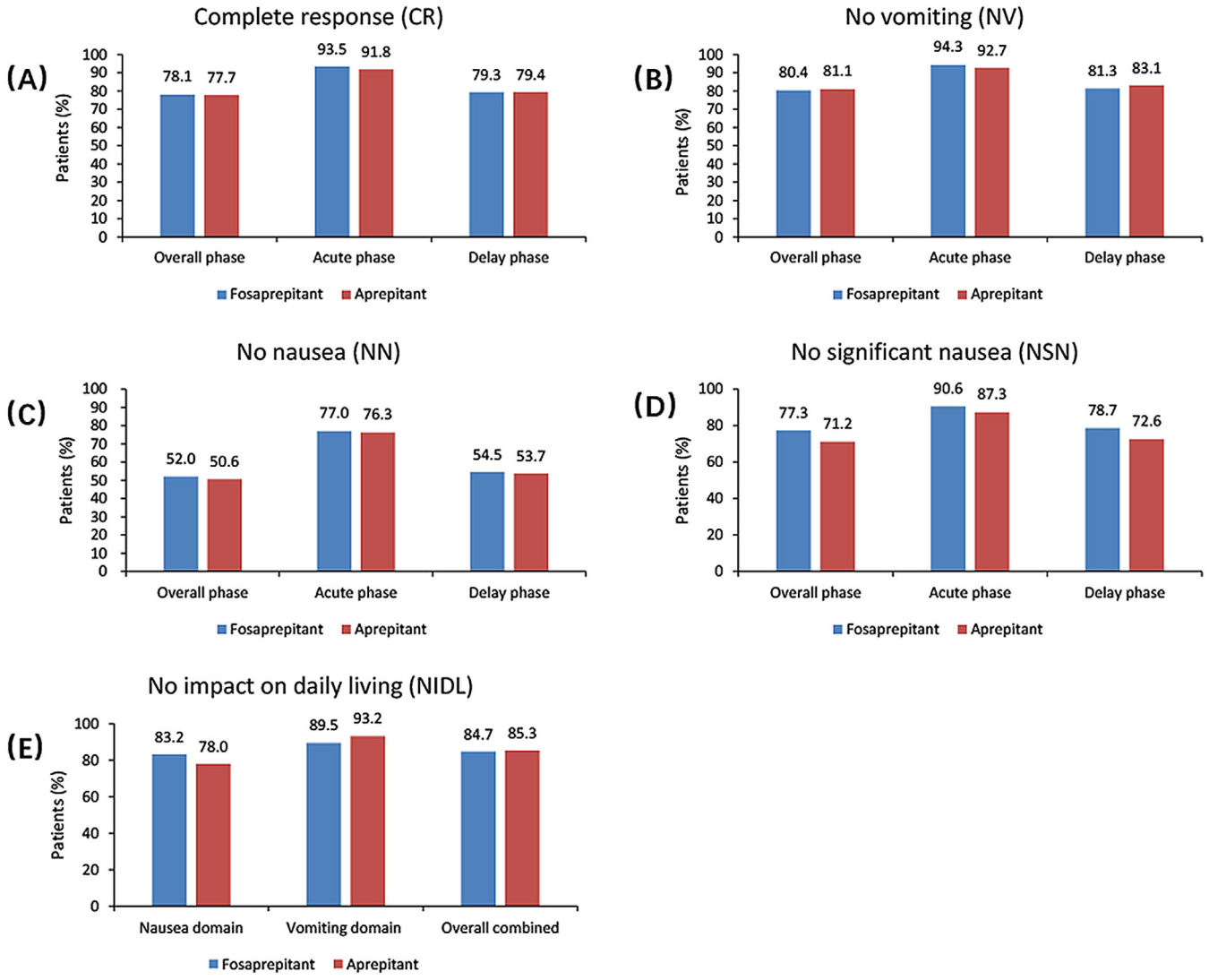

FIGURE 2 Bar graph showing the percentage of patients achieving (A) CR (B) NV (C) NN (D) NSN (E) NIDL based on FLIE in the overall phase. Overall phase, 0 to 120 hours after initiation of chemotherapy. Acute phase, 0 to 24 hours after initiation of chemotherapy. Delayed phase, 25 to 120 hours after initiation of chemotherapy. Abbreviation: CR, complete response; NV, no vomiting; NN, no nausea; NSN, no significant nausea; NIDL, no impact on daily living; FLIE, Functional Living Index-Emesis

TABLE 4 No nausea and CR rate in the low- and high-risk groups using the cutoff value of total point determined by the ROC curve of the nomogram model

Variables	Low-risk group	High-risk group	Total	*P* Value
	n	*n*	*N*	
Nausea	114	230	344	
No nausea	192	170	362	
Total	306	400	706	
No nausea rate	62.7% (192/306)	42.5% (170/400)		$P < 0.001$
No CR	47	109	156	
CR	259	291	550	
Total	306	400	706	
CR rate	84.6% (259/306)	72.8% (291/400)		$P < 0.001$

Abbreviation: CR, complete response; ROC, receiver operating characteristic.

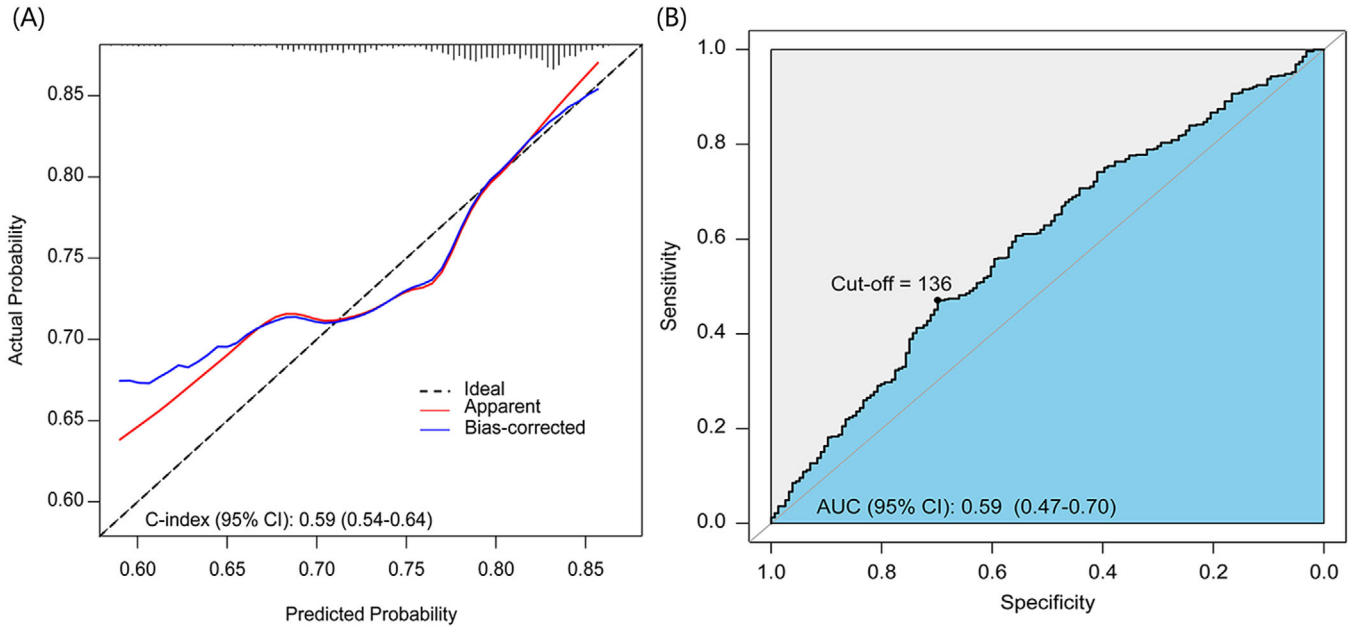

FIGURE 3 Predictive accuracy of nomogram measured by calibration plots and ROC curve. (A) Calibration plots of the nomogram model. The X-axis represents the predicted CINV probabilities estimated by the nomogram, and the Y-axis is the actual rates of CINV development. The dashed straight line means the ideal reference line where predicted CINV corresponds to the actual outcome. (B) ROC curve of the nomogram model. The cutoff value of the total point was determined by the ROC curve as 136. Abbreviation: CINV, chemotherapy-induced nausea and vomiting; ROC, receiver operating characteristic; C-index, concordance index; AUC, area under the (ROC) curve; CI, confidence interval

regimen, and the clinical trial met its predefined primary endpoint. The efficacy findings of the current study were consistent with those of previous phase III trials on fosaprepitant regimens in patients treated with cisplatin-based chemotherapy [7, 17].

No nausea was reported by 52.0% (95% CI, 46.6%-57.3%) of patients in the fosaprepitant arm compared with 50.6% (95% CI, 45.2% to 55.8%) in the aprepitant arm in the OP in our trial (Figure 2C). The no-nausea rate in the OP of previous phase III clinical studies on fosaprepitant, rolapitant and NEPA was also around 50%, which was significantly lower than the CR rate [7, 18, 19]. As nausea is not as well controlled as vomiting, the treatment of nausea should be further investigated in clinical trials. Furthermore, the pathophysiology of nausea is less understood, and it is unclear whether the same neurotransmitters and receptors are responsible for emissaries related to nausea [20]. As the addition of olanzapine to triple prophylaxis for a patient receiving HEC proved to be effective in preventing both emesis and nausea [21], the four-drug regimen is currently recommended by various international guidelines [2, 3].

Except for the type of treatment, the onset, severity, and duration of nausea and vomiting vary depending on individual patient susceptibility [22]. It is important to identify individuals prone to CINV so that a more rigorous prophylactic regimen can be adopted [20]. Therefore, we assessed the patient's specific risk factors and validated different personalized risk models for CINV. As the control of nausea deserves more attention, we analyzed the risk factors of nausea in addition to that of CR and chose "no nausea" as a reliable index [23].

Only sex was found to be a risk factor for CR in the OP phase in multivariate analysis (Supplementary Table S5), which means that the three-drug antiemetic regimen could eliminate all the other risk factors for CR. Sex was also found to be the only risk factor for vomiting in MEC with the prophylactic aprepitant-based three-drug antiemetic regimen in a subgroup risk factor analysis of the SENRI trial [24]. However, the female sex, higher dose of cisplatin ($\geq$ 70 mg/m^2), no history of drinking and larger BSA were still independently associated with a higher incidence rate of nausea in the OPin multivariate analysis. Adult patients with these risk factors could be offered an NK1RA- and olanzapine-based four-drug combination as recommended by the guideline [2] and may be candidates for future clinical trials. To our knowledge, this is the first CINV risk factor analysis based on a phase III clinical trial in which all patients receiving high-dose DDP chemotherapy were treated with NK1RA triple prophylaxis.

Two separate repeated-measure cycle-based models were well-validated, and so was our nomogram model using this phase III clinical trial data. Using the appropriate cutoff points of the three models, high-risk and

low-risk groups with different CR and no-nausea rates can be well defined ($P < 0.001$). The three models can be used to identify individuals receiving first-line cisplatin-based chemotherapy who are prone to CINV. Meanwhile, risk model-guided antiemetic prophylaxis should be explored in prospective clinical trials as in the prior phase III study [11], which could facilitate the assessment of individual risk and thus improve the personalized management of CINV. In addition, as mentioned above, nausea is not as well controlled as vomiting. It may be necessary to figure out new drugs and more efficient personalized prediction models for nausea in the future to achieve better management.

There were some limitations of the study. First, the compliance of fosaprepitant (intravenous) and aprepitant (oral) may be different when used for a long time, which may affect the efficacy of antiemetic therapy. Further evaluation of the long-term compliance and efficacy of the two drugs are required. Second, all the risk factors and personalized prediction models were based on clinical characteristics. Biomarkers for CINV and the genetic and molecular mechanisms were worth exploring.

In conclusion, our study indicated that a single-dose intravenous fosaprepitant-based triple prophylaxis was well tolerated and demonstrated non-inferior control of CINV compared to the aprepitant-based triple regimen in patients treated with cisplatin-based chemotherapy. Females with no history of alcohol intake and larger BSA who receive high doses (≥ 70 mg/m^2) of cisplatin might be more vulnerable to chemotherapy-induced nausea. Three personalized prediction models were well validated using the data of our study. They could be used to optimize antiemetic therapy for patients at high risk of CINV and prevent the occurrence of nausea and vomiting.

AUTHOR CONTRIBUTIONS

Li Zhang was the leading principal investigator of this study. Yuanyuan Zhao, Bing Zhao, Gang Chen, Yinlan Chen, Zijun Liao, Haiming Zhang, Weineng Feng, Yinyin Li, Heng Weng, Weidong Li, Yuefen Zhou, Biyong Ren, Yanda Lu, Jianhua Chen, Zhenteng Liu, Zhenzhong Su and Wenliang Wang conducted the study and collected the data. Yuanyuan Zhao, Bing Zhao and Gang Chen analyzed the data and interpreted the results. Yuanyuan Zhao and Li Zhang also contributed to manuscript drafting and editing. All authors agreed to be responsible for all aspects of the study and approved the final manuscript.

ACKNOWLEDGMENTS

We thank the patients, their families and all the institutions and investigators who participated in this study. We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

COMPETING INTERESTS

ZTL, ZZS, and WLW are employees of Luoxin Pharmaceutical Group Co., Ltd. All the other authors declare no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The datasets obtained and analyzed during the present study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee Review Board approved the study protocol at each site, and all patients provided written informed consent. The study was conducted in accordance with the Good Clinical Practice guidelines and was registered with www.chinadrugtrials.org.cn (approved ID: CTR20170270)

CONSENT FOR PUBLICATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhao Y, Zhao B, Chen G, Chen Y, Liao Z, Zhang H, et al. Validation of different personalized risk models of chemotherapy-induced nausea and vomiting: results of a randomized, double-blind, phase III trial of fosaprepitant for cancer patients treated with high-dose cisplatin. Cancer Communications. 2022;1–11. https://doi.org/10.1002/cac2.12397