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ORIGINAL ARTICLE

Effect of aprepitant administration on CINV caused by cisplatin multi-day chemotherapy and pharmacokinetics of docetaxel

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Abstract

Purpose To compare efficacy and safety of postponing administration of aprepitant and routine triple-antiemetic treatment for chemotherapy-induced nausea and vomiting in patients who received docetaxel and cisplatin multi-day chemotherapy treatment, and to evaluate the effect of aprepitant on docetaxel pharmacokinetics in the Chinese population.

Methods A total of 24 cancer patients (including 5 females and 19 males, 22–74 years old) received two cycles of high-emetic DP (docetaxel 75 mg/m^2 on day 1 + cisplatin 25 mg/m^2 on days 1–3) regimen. A randomized, two-period and cross-over study was applied for prevention of chemotherapy-induced nausea and vomiting. The patients in group A took aprepitant 125 mg on day 1 and 80 mg on days 2–3 (administered aprepitant 1 h before chemotherapy). In group B, the patients took aprepitant 125 mg on day 2, 80 mg on days 3–4, which was delayed 1 day than group A. Efficacy and safety in overall phase were evaluated within 5 days after initiation of chemotherapy. Simultaneously, the differences in the pharmacokinetic parameters of docetaxel between two different antiemetic treatments are compared.

Results The CR rate of delayed-phase nausea was compared between the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day administration treatment (group B), and the difference was statistically significant (16.7% vs 45.8% $P < 0.05$), despite there were similar for two groups in the CR rate of acute-phase nausea and vomiting, and delayed-phase vomiting. In two groups, the area under the docetaxel curve (AUC_{0-t} values) (mean ± SD) of docetaxel was 1134.21 ± 732.55 (ng h/mL) and 1080.94 ± 585.09 (ng h/mL), and the geometric means were 944.82 and 902.10 (ng h/mL), respectively. There was no significant difference in AUC values between the two antiemetic treatments ($P > 0.05$), as well as C_{max}, CL_z, $T_{1/2z}$, MRT and T_{max}.

Conclusions Delayed administration of aprepitant provided superior delayed-phase nausea protection for patients who received cisplatin-based chemotherapy in comparison with the routine triple-antiemetic treatment. In addition, in the routine triple-antiemetic treatment, aprepitant did not significantly affect the main pharmacokinetic parameters of docetaxel.

Keywords Docetaxel · Aprepitant · DP chemotherapy · CINV · Pharmacokinetic

Introduction

To date, despite significant advances in targeted therapy and immunotherapy, chemotherapy is still the primary strategy for malignancy with a tendency to spread throughout the body and advanced cancers that have metastasized. Nearly 70% cancer patients have undergone chemotherapy. If there were no effective interventions, the incidence of nausea and vomiting after chemotherapy would be as high as 70–80% [1], which was clinically called chemotherapy-induced nausea and vomiting (CINV). CINV not only reduces the patient's tolerance to chemotherapy, prevents the treatment from completing on time or even stops therapy [2], but also

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causes anorexia, nutritional deficiencies, and even water and electrolyte disorders [3], which directly affect the patients' short-term efficacy and quality of life. Highly emetogenic chemotherapy-caused CINV is more serious and more troublesome to prevent and control. Normally, chemotherapy drugs such as cisplatin and doxorubicin are limitedly used in high doses, which may affect the effect of treatments. It is a hot potato that how to further improve the control of CINV, especially for the multi-day prescription of high-vomiting chemotherapy.

A variety of neurotransmitters and their receptors is involved in the development of CINV. At present, a combination of peripheral, central, psychological and sensory factors is known to be associated with CINV, but the underlying mechanisms remain mostly unclear [1]. Numerous studies [4–6] have shown that considerations of classification, phase, chemotherapy regimens and differences between inter-individuals are the most important strategies to prevent CINV. Currently, for the nausea and vomiting in patients receiving moderate to high-emetic chemotherapy, the NCCN guidelines [7] recommend a combination of 5-HT3 receptor antagonist, dexamethasone and NK-1 receptor antagonist, and if necessary, combine olanzapine to form a quadruple antiemetic regimen. Although these treatments effectively enhance the control of acute-phase CINV, it still should pay more attention to the control of delayed-phase CINV [1, 8, 9]. Aprepitant is the first FDA-approved NK-1 receptor antagonist to prevent highly emetogenic chemotherapy-induced CINV [10], which is generally recommended on three consecutive days (days 1–3). In 2012, a phase III clinical study data [11] supported to alter the administration of aprepitant (days 3–7) in the triple-antiemetic treatment to prevent the occurrence of CINV, when cisplatin was administered for five consecutive days in the treatment of germ cell tumors. In 2013, Uchida et al. [12] found that for a multi-day chemotherapy regimen, aprepitant was effective for 5 days to prevent CINV, and no obvious adverse events (AEs) occurred. In the same year, Olver et al. [13] found that aprepitant was administrated for 7 days for superior preventions. Aprepitant was not approved for marketing in China until 2014. Chinese 2014 antiemetic guidelines [14] recommend aprepitant for the treatment of CINV associated with moderate- and high-emetic chemotherapy, but there were few studies on Chinese people. Hence, the optimal administration time and combination regimen of aprepitant for preventing CINV caused by cisplatin multi-day chemotherapy require further clinical studies to confirm.

In clinical practice, nearly 1/3 of AEs arise from drug–drug interactions (DDIs). Comorbidities occur frequently in tumor therapy, such as pain, venous thrombosis and epilepsy. The pharmacokinetics of patients with tumors is also discrepant, for drug absorption may drop due to mucositis or malnutrition, and excretion may decline because of liver and kidney function damages. Therefore, DDIs in cancer therapy are receiving increasing attention. Some studies [15, 16] have demonstrated that aprepitant could moderately inhibit CYP3A4 enzyme; so theoretically, aprepitant may affect the plasma concentration of drugs that are metabolized by the same pathway, such as the chemotherapy drugs docetaxel, paclitaxel, cyclophosphamide, and vincristine, and hormonal drugs such as dexamethasone. No clinically significant alterations in the pharmacokinetics or toxicity has been shown with aprepitant administered 1 h or 3 h before intravenously infused docetaxel among cancer patients in other countries [17, 18]. But it was unclear about the scientific mechanism. Moreover, studies indicated that a variety of factors may cause significant differences in the metabolic capacity of docetaxel among different ethnic groups, such as there were significant racial differences in the CYP3A4/5 gene polymorphism, especially the CYP3A5*3C allele, which had a high frequency of mutations in the Asian population, could cause the changes of metabolic enzyme function [19, 20]. Therefore, it is necessary to explore whether aprepitant affects the pharmacokinetics of docetaxel in Chinese population.

This study was designed to evaluate the efficacy and safety of postponing administration of the NK-1 receptor antagonist aprepitant in the prevention of docetaxel and cisplatin multi-day chemotherapy-caused CINV by altering routine administration of the aprepitant in the standard triple-antiemetic treatment, which was given on days 2–4 after start of chemotherapy. It also evaluated the effect of its pharmacokinetics on docetaxel in Chinese population at the meantime.

Materials and methods

Chemicals and reagents

Docetaxel (DTX, purity: 99.0%) and paclitaxel (PTX, purity: > 98.0%) were both purchased from HuNan HuaTeng Pharmaceutical Co. (ChangSha, China). Acetonitrile (HPLC grade) was obtained from Merck KGaA (Darmstadt, Germany). Water used in the experiment was deionized and purified by a Milli-Q system (Millipore, Bedford, MA, USA). Other solvents also were of the HPLC grade and commercially available.

Patient selection

Eligible patients met the following criteria: (1) the patient (aged 18 years or greater) was confirmed to have malignant tumor by histopathological examination, and no medical

treatments after diagnosis (chemotherapy, radiotherapy, molecular targeted therapy or immunotherapy, etc.); (2) could receive a multiple day-based highly emetogenic DP chemotherapy, and the doses of chemotherapy drugs and auxiliary drugs were the same in two groups; (3) neither diabetes nor peptic ulcer, neither serious organ failure nor immunodeficiency; (4) blood routine examination, function of liver and kidney, and electrolytes were normal; (5) neither vomiting within 24 h prior to chemotherapy, nor other antiemetics or sedatives were used. (6) No brain metastasis; (7) Nausea or vomiting were not caused by primary central nervous system malignancy, central nervous system metastases, gastrointestinal obstruction, radiotherapy or other factors; (8) signed informed consent.

The study has obtained approval from the appropriate ethical review boards, and then registered in the Chinese Clinical Trial Registry with the ID: ChiCTR1800016704.

Treatment

Study protocol

A prospective, randomized and self-crossing control trial with a 3-week washout period was carried out; 24 cancer patients who were treated with a high-vomiting DP chemotherapy (docetaxel 75 mg/m^2 on day 1 + cisplatin 25 mg/m^2 on days 1–3) were randomly divided into two antiemetic regimen groups: groups AB and groups BA. Before each chemotherapy cycle, the patients were examined and evaluated whether they could undergo chemotherapy in accordance with comprehensive diagnosis. Patients would not take other antiemetic medications other than those in the experimental design within the first 1–5 days of chemotherapy. However, if there was an antiemetic failure (vomiting > 5 times/24 h, continuous vomiting within 1 min counted one vomiting), other antiemetic, sedative, hormone and other drugs could be administrated for salvage treatment. The administration of DP chemotherapy for all patients is same, and the docetaxel intravenous infusion duration time was 1 h on day 1. Figure 1 summarizes the doses and administrative sequences of major chemotherapeutic drugs and antiemetics. Patients in group A took oral aprepitant 125 mg once a day on day 1, 80 mg on days 2–3 (administered before docetaxel intravenous infusion). And in group B, the patient delayed 1 day to take aprepitant, which was that patients took aprepitant 125 mg on day 2, 80 mg on days 3–4. Patients are allowed to get other antiemetic drugs including palonosetron 0.25 mg on day 1 and day 3, and dexamethasone on four consecutive days. To better control the experimental variables, the administration of other adjuvant drugs for chemotherapy was kept at the same level.

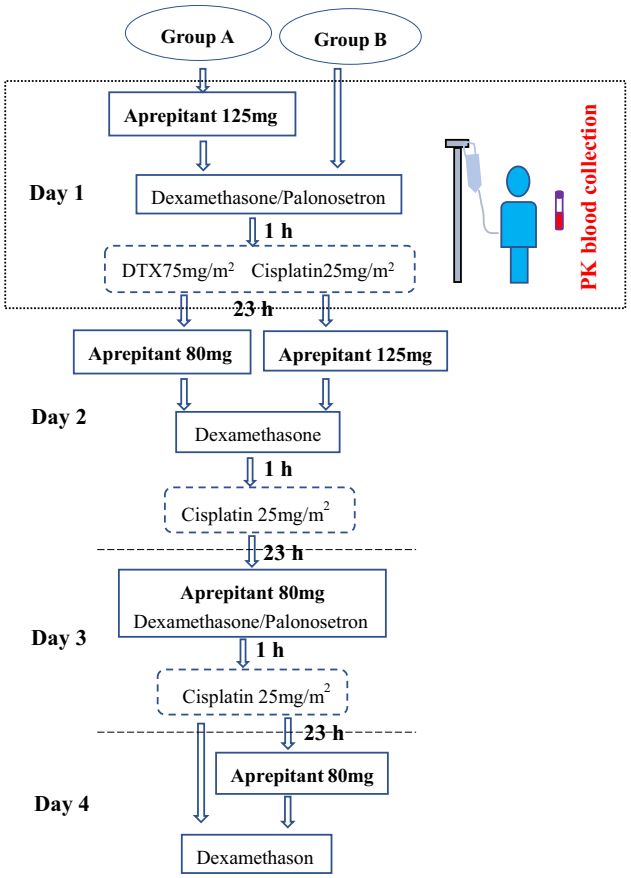

Fig. 1 Administration (dosage and sequence) of major chemotherapeutic drugs and antiemetic between the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day treatment (group B). The dotted box: chemotherapy drugs; solid box: antiemetic drug; Collecting pharmacokinetic blood samples on the first day of chemotherapy. Aprepitant, dexamethasone and palonosetron are taken simultaneously

Efficacy and safety assessments

During the first 120 h (5 days) after the administration of chemotherapy, patients recorded all events of CINV and use of rescue medication in a daily diary. Complete remission (CR) was defined as no vomiting (nausea) and treated in the absence of rescue medication, which was the grade 0 in the nausea and vomiting grading criteria, and where the proportion of all evaluable patients is the CR rate. The patients who underwent DP chemotherapy were evaluated for the following efficacy endpoints: CR in the overall phase (0–120 h), CR in the acute phase (24 h), and CR in the delayed phase (> 24–120 h). The patients were observed for the occurrence of major AEs to assess the safety of therapy, while closely monitored the appearance of CINV. The incidence and severity of AEs were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3 for the safety population.

Pharmacokinetic methods

Determination of plasma concentration

The plasma concentration of docetaxel was determined by LC–MS/MS. Briefly, the blood sample was extracted by liquid–liquid extraction, and the process was as follows: frozen plasma was thawed and an aliquot of 100 µL plasma was spiked with 50 µL (400.0 ng/mL) of paclitaxel as an internal standard. Then, 1 mL of tert-butyl methyl ether was added. After mixing and centrifugation at 12,000 rpm for 5 min at 4 °C, the organic layer was separated and evaporated to dryness in a vacuum concentration system. The residue was reconstituted with 50 µL of acetonitrile–water (85:15, v/v) solution; then, the supernatant was transferred into a sample vial for analysis by LC–MS/MS after centrifugation.

The chromatography separation was performed using a waters UPLC system equipped with a Xtimate™ C_{18} column (2.1 × 150 mm, 3.0 µm. Welch Materials, MD, USA), protected by a pre-column frit (4.0 × 3.0 mm, 3.0 µm). The mobile phase was acetonitrile/water containing 0.1% formic acid (85:15, v –/– v) at a flow rate of 0.250 mL/min. Docetaxel and paclitaxel were detected by multiple reaction monitoring (MRM) under MS positive ion mode as the following *m/z*: 808.5 → 527.6 (docetaxel), 854.8 → 286.6 (paclitaxel). The LC–MS/MS method was verified by method validation that the standard curve ranging from 10 to 2000 ng/mL of docetaxel, and the intra- and inter-assay RSD of quality control samples were ranging from 4.8 to 9.4%.

Pharmacokinetic studies

Blood samples for measurement of docetaxel concentrations were collected just pre-dose (0 h) and at 0.5, 1.0, 1.17, 1.5, 2, 3.5, 6, 11, and 25 h after docetaxel infusion. As we know, when administered by body surface area, the pharmacokinetic of docetaxel was significantly different, and the difference in clearance between individuals was as high as seven times or more. So the pharmacokinetic parameters were determined by statistical moment analysis from the concentration–time profile in plasma. The main pharmacokinetic parameters of docetaxel for this study were AUC_{0-t}, $AUC_{0-\infty}$ and plasma clearance (CL_z), and other parameters such as C_{max}, T_{max}, MRT_{0-t}, $MRT_{0-\infty}$ and $T_{1/2z}$ were provided for information purposes only.

Statistical methods

All these statistical analyses were conducted by statistical program SPSS 10.0 and DAS.3.3.0. Measurement data are expressed as mean ± standard deviation (SD). The incidences of nausea and vomiting were recorded as frequencies (*n*) and percentages (%). In this study, to compare the CR rate of CINV and frequency of toxicity caused by DP, chemotherapy regimens between the two groups were both applied by chi-square or Fisher's exact tests. P value < 0.05 was considered be statistically significant and was not adjusted for multiplicity. The pharmacokinetic data of docetaxel from the different administration treatments were analyzed simultaneously using a non-compartmental model to fit the main parameter values. The individual AUC, C_{max} and CL date for docetaxel were natural log transformed and then evaluated with an analysis of variance (ANOVA) model. The significance of the sequence, period, treatment and subject-within-sequence effects was tested. Descriptive statistics were provided by treatment for MRT, T_{max} and $T_{1/2}$, which were analyzed with the Wilcoxon rank sum test.

Results

Patients

Twenty-four cancer patients enrolled in the trial, and whose performance status score ≤ 1. The median age of patients was 52 years (22–74 years old), and the number of male patients were close to four times that of female (79.2% vs 20.8%). The most common types of malignant disease included lung cancer (approximately 41.7%), nasopharyngeal carcinoma (approximately 41.7%) and esophageal cancers (12.5%), and maxillary sinus cancer accounted for 2% of the proportion. All eligible people took docetaxel at a single dose of 75 mg/m^2 on day 1 and cisplatin at multiple doses of 25 mg/m^2 on days 1–3. And the patients received two antiemetic treatments in admission sequence.

CINV prevention effects

Table 1 summarizes and compares the CR rate of overall, acute- and delayed-phase CINV in both the routine antiemetic treatment (group A) and the aprepitant delayed 1-day administration treatment (group B). In the present study, few patients experienced vomiting in the overall phase; it was observed the CR rate was similar between the two groups. Among patients who received the aprepitant delayed 1-day administration treatment, a higher proportion of patients (20.8% of absolute benefit) versus the routine antiemetic treatment experienced no significant nausea in the overall phase, although the differences of CR rate did not reach statistical significance (37.5% vs 16.7%; $P = 0.104$). Similarly, the CR rate of acute-phase nausea between the routine antiemetic treatment and the aprepitant delayed 1-day administration treatment was 91.7% (22/24) and 95.8% (23/24), respectively, and the difference was not statistically significant ($P > 0.05$). However, a significant higher proportion of patients in the aprepitant delayed 1-day

Table 1 CR of CNIV in patients with the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day administration treatment (group B) [number of cases (CR rate %)]

CINV	Treatment A ($N=24$)	Treatment B ($N=24$)	Absolute benefit[a] (%)	P value
Nausea				
Overall phase	4 (16.7)	9 (37.5)	20.8	0.104[b]
Acute phase	22 (91.7)	23 (95.8)	4.1	1.000[c]
Delayed phase	4 (16.7)	11 (45.8)	29.1	0.029[b]
Vomiting				
Overall phase	24 (100)	24 (100)	0.0	1.000
Acute phase	24 (100)	24 (100)	0.0	1.000
Delayed phase	24 (100)	24 (100)	0.0	1.000

[a]Group B vs group A (control group)

[b]Pearson chi square: $n \geq 40$, the number of $T < 5$ is less than 20% and there is no theoretical number less than 1

[c]Continuity correction: $n \geq 40$, the number of $T < 5$ is more than 20% and there is no theoretical number less than 1

administration treatment vs the routine triple-antiemetic treatment achieved a CR of delayed-phase nausea in the delayed phase (45.8% vs 16.7%; $P < 0.05$).

Safety

The safety population (all 24 patients enrolled into the trial who received group A or B) was used for the safety and tolerability. The degree of AEs in patients was mild and self-limiting, and there was no treatment termination due to serious AEs. Table 2 presents the number and proportions of patients who reported different types and levels of AEs after each treatment visit. The mostly reported AEs in patients with the two groups included constipation, anemia, dizziness, fatigue, and hiccups. There were 48 AEs in the aprepitant delayed 1-day treatment compared to the 43 AEs of the routine triple-antiemetic treatment. Additionally, one patient developed severe III° myelosuppression during treatment, and which was appropriately given a leukocyte-raising drugs after evaluation. The patient's AEs were well controlled before discharge. The frequency of constipation was the highest, compared 17 times (70.8%) for the group A with 18 times (75%) for the group B, followed by anemia (25% vs 41.7%) and fatigue (16.7% vs 29.2%), and finally dizziness and hiccup were with the lowest probability. All data in terms showed a comparison in the incidence rate of AEs proved no significant difference between two groups ($P > 0.05$).

Docetaxel pharmacokinetics

Figure 2 shows docetaxel AUC_{0-t} values between the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day administration treatment (group B), the AUC_{0-t} values (mean ± SD) of docetaxel were 1134.21 ± 732.55 (ng h/mL) and 1080.94 ± 585.09 (ng h/mL), and the geometric means were 944.82 and 902.10 (ng h/mL), respectively. The reference range between the dotted lines represented the therapeutic window; the result indicated that the AUC_{0-t} values of most patients in the two treatments were not in the therapeutic window, which needs more attention. Figure 3 shows the individual docetaxel $AUC_{0-\infty}$ values between the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day treatment (group B). And the difference

Table 2 The occurrence of clinical adverse events in groups A and B [number of cases (% of patients)]

Adverse events	Treatment A ($N=24$)	Treatment B ($N=24$)	P value
Most common adverse events			
Anemia	6 (25)	10 (41.7)	0.221
Fatigue	4 (16.7)	7 (29.2)	0.303
Hiccup	4 (16.7)	2 (8.3)	0.663
Constipation	17 (70.8)	18 (75)	0.745
Dizziness	1 (4.2)	2 (8.3)	1.000
Serious adverse events			
III° myelosuppression	1 (4.2)	1 (4.2)	1.000
Adverse events occurred in overall phase			
Total	43	48	–

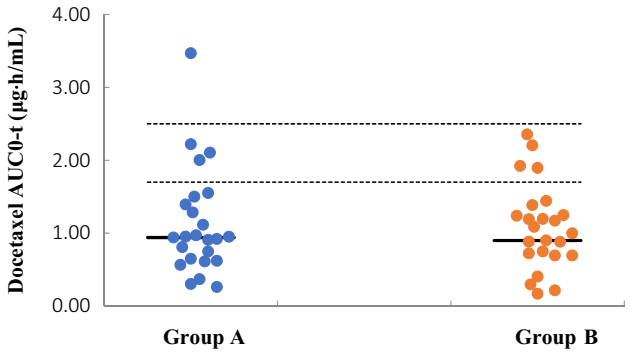

Fig. 2 Docetaxel AUC_{0-t} values between the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day administration treatment (group B). The dotted line indicates a well-referenced target AUC value for which the balance between efficacy and toxicity is optimal, ranging from 1.7 to 2.5 μg h/mL. Short solid lines represent geometric means

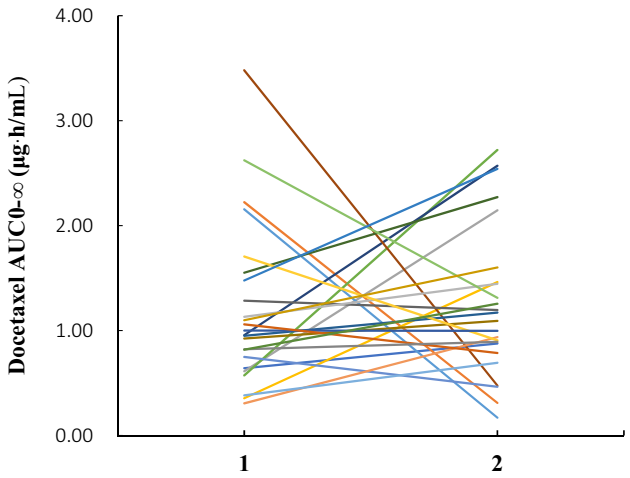

Fig. 3 The individual docetaxel $AUC_{0-\infty}$ values between the routine triple-antiemetic treatment (group A) and the aprepitant delayed 1-day treatment (group B). 1 (group A); 2 (group B)

in pharmacokinetic parameters of docetaxel between the two combination therapies is listed in Table 3. The results indicated that following group A and group B, the $AUC_{0-\infty}$ values of docetaxel were 1203.50 (ng·h /mL) and 1262.63 (ng·h /mL) with the difference of 105% (A/B), respectively. The difference of the average residence time (MRT_{0-t}), plasma clearance (CL_z), and the peak concentration (C_{max}) was all 104%. The median time to reach peak concentration (T_{max}) and the half time ($T_{1/2z}$) of docetaxel was 0.82 h and 4.48 h when docetaxel was given with group A, and 0.73 h and 9.07 h when docetaxel was given with group B. The interaction results showed it did not reach statistical significance with drug effects, sequence effects or period effects for the studied pharmacokinetic parameters of docetaxel between two groups.

Discussion

Chemotherapy regimen and inter-individual differences are the most critical factors affecting the frequency and extent of CINV. Accurate assessments of CINV high-risk patients before treatment are particularly important to improve individualized treatment and quality of life. Studies [21] have reported that female patients (younger than 55 years old), with low alcohol intake, poor physical condition and severe vomiting during pregnancy, are more likely to develop CINV. Although foreign studies [22] have indicated that aprepitant can enhance the antiemetic effect of 5-HT3 receptor antagonist and dexamethasone, domestic clinical studies [23] have shown that the addition of aprepitant does not improve the prevention of acute CINV in Chinese. In theory, the delayed administration of aprepitant in this experiment does not affect the preventive effect on acute CINV. This study used a prospective, randomized, and cross-over study method to better exclude the effects of factors such as gender, age, disease, chemotherapy sensitivity, and compliance

Table 3 The difference in pharmacokinetic parameters of DTX between the two combination therapies (mean ± S.D)

Parameters	Group A ($N=24$)	Group B ($N=24$)	Difference (A/B %)	P value
AUC_{0-t} (ng h/mL)	1134.21 ± 732.55	1080.94 ± 585.09	105	0.831
$AUC_{0-\infty}$ (ng h/mL)	1203.50 ± 770.01	1262.63 ± 722.04	96	0.846
MRT_{0-t} (h)	2.07 ± 1.49	1.94 ± 1.32	104	0.864
$MRT_{0-\infty}$ (h)	3.53 ± 3.59	7.06 ± 10.44	74	0.424
CL_z (L/h/m^2)	89.28 ± 57.50	92.85 ± 89.15	104	0.846
T_{max} (h)	0.82 ± 0.26	0.73 ± 0.25	115	0.233
C_{max} (ng/mL)	1025.62 ± 579.63	1002.10 ± 526.48	104	0.858
$T_{1/2z}$[a] (h)	4.48 ± 4.55	9.07 ± 12.05	71	0.290

$T_{1/2z}$ 0.693/Zeta, Zeta is the slope of the c–t curve tail segment

[a]$T_{1/2z}$ is the elimination$T_{1/2}$ calculated by the statistical moment method

on the results, and increased the credibility of the results and reduced the number of samples required for the study. The results suggest to alter the usual administration of aprepitant (group B) to increase the CR rate of delayed nausea caused by cisplatin 3-day chemotherapy (48.8% vs 16.7%), and the difference is statistically significant ($P < 0.05$). In the prevention of acute-phase nausea, vomiting and delayed-phase vomiting, the two regimens were similar in effects, and the differences were not statistically significant. It indicated that the delayed administration of aprepitant did not affect the acute-phase CINV caused by DP chemotherapy, which was consistent with the domestic market research of aprepitant (79. 4% vs 79.3%, $P = 0.9$) [23]. It is worthy of clinical further research.

The AEs of two regimens were generally the same, showing self-limiting and safe tolerance. Further analysis showed that the most common AEs between two groups were constipation and anemia, although there was no statistical difference ($P > 0.05$). It may be associated with the combination of chemotherapy drugs and antiemetic drugs.

DDIs may occur in any processes of pharmacokinetics, with metabolic factors accounting for up to about 40% [24] and having the greatest impact. At the same time or at a certain stage, two or more drugs may be administered in combination to produce a compound effect, which may enhance the efficacy of the drug or reduce the side effects, and may also weaken the efficacy or cause some toxic and side effects. Therefore, the characteristics of the drug should be fully utilized in combination, and the pharmacological effects of various drugs should be exerted to achieve the best efficacy and the lowest toxicity. The results show that aprepitant has no clinically important or statistically significant effects on any of the pharmacokinetics parameters of docetaxel in the routine triple-antiemetic treatment, which was consistent with the results of two foreign studies [17, 18].

But it is worth that no matter which period of patients, the AUC value is mostly lower than the reference range of therapeutic window reported at home and abroad [25–28], and some patients have a large difference in AUC values (AUC_{0-t} range from 0.170 to 3.470 μg h/mL). What is more regrettable is that there is no optimal docetaxel AUC to maximize efficacy and minimize toxicity, whether at home or abroad. Evaluate the short-term efficacy by reducing the tumor diameter after chemotherapy, or take repeated trials and groping methods to find a better treatment. This is not only time consuming and laborious, but it may also increase the chance of side effects, and may even delay the disease or develop resistance. As a monitoring tool, therapeutic drug monitoring can provide an objective indicator for judging the condition of a drug in vivo by monitoring blood concentration in real time, providing a reference for individualized drug delivery. The pharmacokinetic results of docetaxel in this study showed that the AUC difference was as high as 20 times in docetaxel between individuals. It is worth further research.

As we all know, docetaxel is mainly metabolized by CYP3A4/5. The mutation rate of CYP3A5 varies among races, among which CYP3A5*3 has a mutation frequency of 77.6% in Caucasians, 70.6% in Blacks, and 71–85% in Asian [19, 20]. In this experiment, the mutation frequency of docetaxel CYP3A5*3 gene was 78.57%, which was consistent with the literature reports. In theory, the systemic exposure of docetaxel will raise, but we found that docetaxel AUC is lower than the AUC reported in the previous two studies, and the CL value is higher than the latter; the best explanation may be the reason for the low dose. Moreover, the presence of variable expression ratios of CYP3A4/5 in difference ethnic populations may result in different DDIs between docetaxel and aprepitant, so it may relate to the difference in systemic exposure of docetaxel between inter-individuals. After the preliminary statistical analysis, the docetaxel AUC value was not associated with CYP3A5*3/*3. Of course, because of limited trial data, future well-designed and powerful randomized, clinical trials are warranted.

In conclusion, delayed administration of aprepitant did not prevent acute-phase CINV caused by DP 3-day chemotherapy, but to some extent improved the preventive effect of delayed-phase nausea caused by DP 3-day chemotherapy. In addition, in the standard triple protocols, aprepitant does not significantly affect the main pharmacokinetic parameters of docetaxel in Chinese people.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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