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Original Article

Phase II clinical trial of palonosetron combined with tropisetron in preventing chemotherapy-induced nausea and vomiting

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Abstract: The purpose of the study was to evaluate the efficacy and toxicity of palonosetron combined with tropisetron in preventing chemotherapy-induced nausea and vomiting. A total of 82 non-small cell lung cancer patients undergoing Docetaxel combined with Cisplatin were randomly divided into group A and group B. The patients were received palonosetron combined with tropisetron (group A, n = 42) or tropisetron alone (group B, n = 40) before initiation of chemotherapy. The nausea degree, antiemetic efficacy and safety after chemotherapy were evaluated. Patients were administered for rescue therapy if needed. Results showed no significant difference in complete remission rate (CRR) during acute phase (0-24 h post chemotherapy) between group A and group B (90.48% versus 75%, P > 0.05). The CRR of group A during delayed (24-120 h post chemotherapy) and overall phases (0-120 h post chemotherapy) were 83.33% and 78.57%, higher than group B (50% and 42.50%, P < 0.05). AS for the improvement rate of nausea during delayed phase, group A is better than group B (57.14% versus 35%, P < 0.05). The adverse drug reactions of two groups were mild and generally well tolerated, including headache, constipation and abdominal distension, and no statistically significant differences were observed. In conclusions, compared to tropisetron alone, the therapy of palonosetron plus tropisetron is more effective and safer in controlling of nausea and vomiting induced by high emetic risk chemotherapy.

Keywords: Palonosetron, tropisetron, nausea, vomiting

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect in the treatment of tumor patients, which would severely impact the life quality of patients and decrease the therapeutic effect and compliance of patients [1]. 5-HT3 receptor antagonists are clinically used at present, which has made some progresses in the prevention and controlling of CINV. However, there are still some defects in 5-HT3 receptor antagonists in the treatment of delayed vomiting caused by highly emetogenic chemotherapy drugs [2]. As one of the short-effect 5-HT3 receptor antagonists, tropisetron could effectively control about 70% of acute-CINV [3], but its effect on delayed vomiting was not evident [1]. Palonosetron, the second generation of long-time 5-HT3 receptor antagonists, is more effective on delayed vomiting for its higher affinity on receptors and longer half-life [4]. But there are still some patients who continuously present gastrointestinal reaction and the single-drug controlling rate has no breakthrough. Delayed CINV is still the bottleneck of the efficacy of antianacathartic drugs. So far the combined application of the two 5-HT3 receptor antagonists has not been reported, and our study focused on the therapeutic effect of palonosetron plus tropisetron versus tropisetron alone on the prevention of CINV.

Materials and methods

Patient selection

Inclusion criteria: Non-small cell lung cancer patients diagnosed by histopathology or cytolo-

Table 1. Baseline demographic and clinical characteristics

	Group A (n = 42)	Group B (n = 40)
Age (mean ± SD)	55.76 ± 9.26	57.35 ± 8.50
Gender n (%)		
Male	19 (45.24%)	22 (55.00%)
Female	23 (54.76%)	18 (45.00%)
ECOG score		
1	22 (52.38%)	23 (57.50%)
2	20 (47.62%)	17 (42.50%)
Alcohol use		
Yes	15 (35.71%)	17 (42.50%)
No	27 (64.29%)	23 (57.50%)
Chemotherapeutic history		
Non-naive	24 (57.14%)	25 (62.50%)
Naive	18 (42.86%)	15 (37.50%)

Table 2. Comparison of complete response rates between the two groups of patients

	Group A n (%)	Group B n (%)	*P* value
Acute phase (0-24 h)	38 (90.48%)	30 (75.00%)	0.063
Delayed phase (24-120 h)	35 (83.33%)	20 (50.00%)	0.001
Overall phase (0-120 h)	33 (78.57%)	17 (42.50%)	0.001

Table 3. Comparison of the improvement rates of nausea between two groups

	Group A n (%)	Group B n (%)	*P* value
Acute phase (0-24 h)	32 (76.19%)	14 (35.00%)	0.044
Delayed phase (24-120 h)	24 (57.14%)	26 (65.00%)	0.266

gy; Age between 20 to 70 years; Patients accepted chemotherapy with docetaxel plus cis-platinum; Normal in blood routine, urine routine, liver and kidney function, electrolyte and electrocardiogram before chemotherapy; Patients with good compliance and have assigned the informed consent; Patients with ECOG grade ≤ 2.

Exclusion criteria: Patients with gastrointestinal tract obstruction; Patients who had vomited or received antiemetics within 24 h before chemotherapy; Patients with central nervous system metastasis or intracranial hypertension-induced vomit; Patients with chronic pharyngolaryngitis; Patients with long time use of morphine for severe pain; Patients had long time use of hypnotics or sedative; Patients with intractable vomiting induced by psychiatric disorders.

Study design

From January 2013 to June 2014, patients who met the inclusion and exclusion criteria at Shandong Cancer Hospital were collected and analyzed with random control trail. The common chemotherapy regimens were 60-75 mg/m^2 docetaxel at the first day, with a total of 75 mg/m^2 cis-platinum given at the first, second and third days, 21 days for every cycle. Patients were randomized grouped into group A and B. Patients in group A were intravenously injected with 25 mg palonosetron HCl 30 min before chemotherapy at the first and third days, and 5 mg tropisetron were intravenously injected at the first, second and third days 30 min before chemotherapy; Patients in group B were given 5 mg tropisetron similar with group A. All patients received 10 mg dexamethasone, patients with two or more times of vomit during therapy were given salvage treatments.

The symptoms and signs of patients were recorded daily within 6 days after chemotherapy, which included the vomiting times in each day (classification of vomit: vomit at a time; vomit for several times with no more than 1 min of response duration; several times of retching for no more than 5min of duration; several times of retching for no more than 5 min of duration plus vomit more than once with no more than 1 min of response duration), the grade of nausea and vomiting, first time of vomiting, the use of salvage medications, the adverse reactions presented during therapy (such as headache, constipation, abdominal distension), and laboratory examinations including liver and kidney function, blood routine, urine routine, serum electrolytes, electrocardiogram, etc.

Evaluation index and criterion

The major endpoint of our study was the complete remission (CR) rate of acute and delayed phase, which was defined as no occurrence of vomiting after chemotherapy without the use of salvage medications. The secondary endpoint included CR rate of both phase, vomiting con-

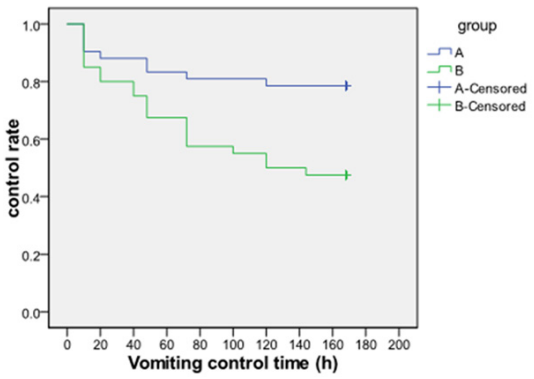

Figure 1. Kaplan-Meier plot of vomiting control time.

trol time, mean times of vomiting, rate of salvage treatments, rate of improved nausea, rate of occurrence of adverse reactions. The improvement rates of nausea was calculated by degree of nausea ≤ 1. The degree of gastrointestinal reactions and adverse reactions were evaluated according to the NCI-CTC (3rd edition) standard.

Statistical analysis

All analyses were performed using the software SPSS version 13.0. The chi-square test was used to assess the classified variables, and the measurement data was indicated as median or mean ± SD. The t test or non-parametric test was performed for data analysis. Subgroup analysis was performed using chi-square test and the vomiting control time was assessed using log-rank test. *P* values < 0.05 were considered statistically significant

Results

Characteristics of the patients

A total of 82 patients were recruited in our study. Of these patients, 42 patients were in group A and 40 patients were grouped into B. The patients' characteristics are shown in **Table 1**. There were no significant differences in terms of the gender, age, ECOG grade, drinking history, and chemotherapy history (P > 0.05).

Analysis of the major endpoint

As shown in **Table 2**, the CRR of the acute phase of vomiting were 90.48% and 75% in group A and B, which showed no significant difference (P > 0.05). For delayed phase, the CRR were 83.33% and 50% for patients in group A and B, respectively, and significant difference was found between the two groups (P < 0.05).

Analysis of the secondary endpoint

The total CRR of group A and B were 78.57% and 42.50%, in which group was significantly higher than group B (P < 0.05). The median vomiting control time in group A was significantly longer than group B based on log-rank test, (168 h versus 132 h, P = 0.005, **Figure 1**). The mean times of vomiting were 0.95±2.33 and 1.50 ± 2.14 per patient in the two groups (P = 0.015). Nine patients in group A (21.43%) and 14 in group B (35%) received salvage treatments, and revealed no significant difference (P = 0.171). As shown in **Table 3**, the improvement rates of nausea between two groups presented no significant difference in acute phase, but remarkable difference was found in delayed phase (57.14% versus 35%, P = 0.044). Stratification analysis revealed that gender, history of drinking, history of chemotherapy did no significantly influence the CRR in the two groups (P > 0.05). However, the CRR could be influenced by age, and patients > 60 years old had a higher rate of CRR than young patients (**Table 4**).

A total of 62.5% and 64.29% of patients in group A and B presented more than one adverse reactions and most of them were in grade I. The common adverse reactions were constipation, headache, and abdominal distension, and no significant difference of the occurrence of adverse reactions was observed between two groups (P > 0.05). As shown in **Table 5**, of adverse reactions, constipation was the most common and the occurrence of constipation in patients older than 60 was 14.29% and 12.5%, respectively (P > 0.05). The laboratory examination and ECG showed no significant variations.

Discussion

Our research is the first clinical report about the combined use of long-time and short-time 5-HT3 receptor antagonist in China. In this study, a total of 82 non-small cell lung cancer patients who received high emetic risk chemotherapy were included in our randomized controlled trail, and results suggest that palonose-

Table 4. The complete response rates of patients with different clinical characteristics

	Group A					Group B				
	n	Acute phase	P	Delayed phase	P	n	Acute phase	P	Delayed phase	P
Gender										
Male	19	19	> 0.05	17	> 0.05	22	20	0.028	13	> 0.05
Female	23	19		18		18	10		7	
ECOG score										
1	22	15	> 0.05	19	> 0.05	23	18	> 0.05	12	> 0.05
2	20	13		16		17	12		8	
Age										
> 60	17	16	> 0.05	17	0.049	16	15	0.062	12	0.01
< 60	25	22		18		24	15		8	
Alcohol use										
Yes	15	15	> 0.05	13	> 0.05	17	14	> 0.05	9	> 0.05
No	27	23		22		23	16		11	
Chemotherapeutic history										
Non-naive	24	22	> 0.05	20	> 0.05	25	20	> 0.05	15	> 0.05
Naive	18	16		15		15	10		5	

Table 5. Comparison of adverse events between the two groups of patients

	Group A		Grou B		*P* value
	n	%	n	%	
Headache	3	7.14%	2	5%	> 0.05
Constipation	8	19.05%	7	17.5%	> 0.05
Abdominal distension	2	4.76%	1	2.5%	> 0.05

tron plus tropisetron were more effective and safe on clinical controlling of CINV.

The CRR of acute vomiting for palonosetron plus tropisetron versus tropisetron alone were 90.48% and 75% respectively. Although no significant statistical difference was found, we observed that the CRR of combination group was 15.48% higher the single-drug group (P = 0.063), which suggested that palonosetron plus tropisetron had a trend to significantly improve the acute vomiting (**Table 2**) Studies containing more patients are needed to demonstrate it. In our study, cis-platinum used in the chemotherapy regimen caused decreased incidence of acute vomiting and increased delayed vomiting in divided doses. The CRR of palonosetron plus tropisetron on delayed vomiting was 83.33%, which was significantly improved compared with tropisetron alone. Delayed vomiting is one of the most important factors that influence the process of chemotherapy. Previous studies showed that CRR of granisetron, ondansetron and tropisetron (first generation of 5-HT3 receptor antagonists) were 55.5%, 48.5% and 48.5%, respectively [5]. For patients treated with high emetic risk chemotherapy, more than half of them continuously appeared nausea and vomiting [1, 6-10]. In our study, the CRR tropisetron of alone on delayed phase was 50%, which was consistent with previous studies. Although randomize double-blind clinical trials had reported that the CRR of palonosetron on delayed phase was 42%~80% [11-15], which significantly improved the delayed vomiting compared with first generation of antiemetics, 20%~50% of patients did not get a satisfactory anti-nausea effect. In spite of palonosetron alone group was not set in our study, compared with previous studies, the CRR of palonosetron plus tropisetron was not only higher than tropisetron, but also higher than palonosetron. For overall phases, the CRR of combined group was 78.57%, which was significant higher than tropisetron, indicating that palonosetron plus tropisetron was superior in controlling of CINV. The combined group could also significantly decrease the nausea degree of patients.

Our study proved that palonosetron plus tropisetron was much better than tropisetron alone on controlling of nausea and vomiting in acute, delayed and even overall phase. Tropisetron is the competitive 5-HT3 receptor antagonist of peripheral neurons and central nervous system [16], and the half-life is 8 h [17]. Pharmacok-

inetics has shown that the affinity of palonosetron is 30~100 times higher than the first generation of 5-HT3 receptor antagonists, and the plasma half-life is 40 h [18]. Different from the first generation drugs, palonosetron is not only highly allosteric interact with 5-HT3 receptor, it could also continuously inhibit the function of 5-HT3 receptor and block the signal crosstalk of 5-HT3/ NK1, which contributes to the vomiting reaction induced by substance P in delayed phased [19, 20]. The molecular pharmacological specificity of palonosetron determines its high response rate to acute and especially delayed CINV. We presumed that the combined use of drugs could increase the selectivity and affinity to 5-HT3 receptor. More studies are needed to confirm the synergistic effect and its exact molecular mechanisms. Subgroup analysis revealed that younger patients were more likely to develop nausea and vomiting compared to older patients,, which suggested that age could be one of the risk factors of CINV though its molecular mechanisms remain uncertain. Inconsistent with previous studies, our data showed that gender, history of drinking and history of chemotherapy were not correlated with CINV, which might be due to the small sample of patients in subgroups [12, 21]. Meanwhile, our study also proved that palonosetron plus tropisetron could significantly prolong the vomiting controlling time and decrease the frequency of vomiting. Although no statistical difference was found between two groups, there was a trend that the combined group was better than the single-drug group, which further verified the superiority of combined group on controlling CINV.

For toxicity, the occurrence of toxic reaction in combined group was similar with tropisetron, the addition of drug did not increase the adverse reactions though only a few patients presented mild headache, constipation and abdominal distension. Constipation was the most common adverse reaction in our study. Subgroup analysis revealed that older patients were more likely to occur constipation, which might be due to the reduced renal excretion function, liver detoxification capacity and gastrointestinal functions.

There are some limitations in our study. Patients with previous poor control of CINV were more likely to present nausea and vomiting compared to those with previous good control [22]. In our study, some patients were not the first time to receive chemotherapy and the CINV data of previous treatments were not included in our statistics, which might cause the deviation of our results. In addition, small sample of the patients and the lack of palonosetron group were also disadvantages of study.

In conclusion, the combined use of palonosetron and tropisetron could significantly improve the chemotherapy induced gastrointestinal reactions, revealed better the curative effect than tropisetron, showed no increased side effect, and the tolerance of patients were good. The combined use of palonosetron and tropisetron is a promising regimen for controlling of chemotherapy induced nausea and vomiting, which is valuable in clinical treatments.

Disclosure of conflict of interest

None.

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