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Original Article

Therapeutic effects of palonosetron plus tropisetron on chemotherapy-induced nausea and vomiting

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Abstract: This study aims to observe the efficacy and toxicity of palonosetron plus tropisetron in preventing chemotherapy-induced nausea and vomiting (CINV). A total of 150 non-small cell lung cancer (NSCLC) patients undergoing cisplatin combined with docetaxel were included and divided into groups A, B and C. Group A received tropisetron (5 mg, n = 50), group B received palonosetron (0.25 mg, n = 50) and group C received tropisetron plus tropisetron (n = 50) before initiation of chemotherapy. The degree of nausea during the acute and delayed stages, adverse reactions, and safety after chemotherapy were observed. The complete remission rate (CRR) during the acute phase for groups A, B and C were 82.0%, 86.0% and 92.0%, respectively. There were no significant differences for the CRR among the three groups (P = 0.334, >0.05). The CRR for the delayed stage in group C (88.0%) was significantly higher compared with group A (52.0%) and group B (72.0%) (P<0.001). Meanwhile, the CRR of group B was significantly higher compared with group A (P = 0.039, <0.05). At least one adverse reaction was experienced in 60% patients in group A, 68.0% in group B and 64.0% in group C; no significant differences were observed. Moreover, the adverse reactions in the three groups were mild, generally well tolerated, and included headache, weakness, loss sleep and abdominal distension. Treatment of palonosetron plus tropisetron significantly prevents and improves chemotherapy induced delayed stage of CINV, without increasing the frequency or severity of adverse reactions, and without reducing tolerability.

Keywords: Palonosetron, tropisetron, nausea, vomiting, chemotherapy-induced nausea and vomiting

Introduction

In clinical practice, chemotherapy-induced nausea and vomiting (CINV) is the most frequently side effect in the cancer patients undergoing chemotherapy. CINV consistently and significantly decreases the life quality of patients, and subsequently decreases the adherence of patients to further therapy [1]. Currently, 5-HT3 receptor antagonists such as ondansetron, granisetron, and tropisetron are the first-line treatment for CINV [2]. The half-life of these drugs is typically several hours. Although the control rate of these drugs for CINV ranges from 50% to 70%, the effect on delayed vomiting control is limited, even with repeated drug treatment [3, 4]. Palonosetron is a novel and long-lasting 5-HT3 receptor antagonist. A previous study reported that the palonosetron is more effective in controlling delayed vomiting because it has a higher affinity to the receptors and a longer half-life [5-7]. However, the symptoms cannot be fully controlled in about 20% to 30% patients. Therefore, the safety and effectiveness of combining palonosetron with other anticathartic drugs are critical issues in chemotherapy in clinical practice. Until now, the use of a therapeutic strategy that combined two different 5-HT3 receptor antagonists has not been reported. In this study, we designed a prospectively randomized controlled clinical study of the safety and efficacy of palonosetron combined with tropisetron for the treatment of CINV.

Materials and methods

Patients

In this study, 150 patients who were diagnosed with non-small cell lung cancer (NLCLC) and received chemotherapy from May 2013 to

December 2014 were involved at Shandong Cancer Hospital. All of the patients provided consent to participate in the study. This study was approved by the ethics committee of the Shandong Academy of Medical Sciences, Jinan, China.

Inclusion criteria included the following: (1) NSCLC diagnosed by histopathology or cytology; (2) Age from 20 years to 70 years; (3) Received chemotherapy; (4) Karnofsky Performance Status (KPS) scores >70; (5) Normal blood routine, urine routine, and liver and kidney function before chemotherapy; (6) No complex complication of serious disorders.

Exclusion criteria included the following: (1) Previous treatment with antiemetics drugs within 24 h before chemotherapy; (2) Gastrointestinal tract obstruction; (3) Intracranial hypertension-induced vomit; (4) Central nervous system metastasis; (5) History of morphine for severe pain; (6) History of hypnotics or sedatives; (7) Chronic pharyngolaryngitis; (8) Intractable vomiting induced by psychiatric diseases.

Trial grouping and treatment

The chemotherapy strategy was performed for the following procedures: 60-75 mg/m^2 docetaxel on the first day, 75 mg/m^2 cis-platinum on the first, second, and third days, with a 21-day treatment course interval. The patients were divided into 3 groups. The patients in group A were intravenously injected with 5 mg tropisetron on the first, second, and third days, 30 min before chemotherapy. The patients in group B were intravenously injected with 0.25 mg palonosetron on the first, second, and third days, 30 min before chemotherapy. The patients in group C were intravenously injected with 5 mg tropisetron and 0.25 mg palonosetron on the first, second, and third days, 30 min before chemotherapy. The injection time for every group was more than 39 seconds. When vomiting occurred two or more times during therapy, the patients were injected with 5 mg dexamethasone as adjunctive therapy.

Assessments

Signs and symptoms were recorded every day during the chemotherapy periods, including vomiting times, classification of vomit, adverse reactions to chemotherapy, and usage of the adjunctive drug dexamethasone. Vital signs, including body temperature, breathing frequency, pulse, blood pressure, were recorded pre- and post- chemotherapy. Physical and laboratory examinations, including liver function, kidney function, urine routine, blood routine, electrocardiogram (ECG) and serum electrolytes, were also performed before and after chemotherapy.

Gastrointestinal reaction classification

Gastrointestinal reactions were rated according to the following scale: 0 degrees = no nausea symptoms; 1 degree = appetite decrease and no change in eating habit; 2 degrees = feeding reduced, dehydration or malnutrition, and no obvious weight loss; 3 degrees = insufficient energy intake, or insufficient water (or other liquid) intake.

Vomiting classification

Vomiting was rated according to the following scale: 0 degree = no vomiting symptoms; 1 degree = 1 to 2 times in 24 hours; 2 degrees = 3 to 5 times in 24 hours; 3 degrees = more than 6 times in 24 hours, total parenteral nutrition, and hospital stay; 4 degrees = life threatening and in need of emergent treatment.

Evaluation criteria

The complete remission (CR) of acute vomiting was defined as no occurrence of vomiting 24 hours post chemotherapy without usage of salvage medications. The CR of delayed vomiting was defined as no occurrence of vomiting at all times post chemotherapy without usage of salvage medications. The improvement rate of nausea was calculated by degree of nausea $\leq$ 1.

Gastrointestinal adverse reactions

The gastrointestinal reactions and adverse reaction degrees were observed and evaluated according to the National Cancer Institute Chemotherapy Toxicity Classification standard (NCI-CTC) (4.0 version). NCI-CTC is categorized into degrees I through IV, and mainly evaluates occurrences of the coprostasis, abdominal distension, weakness and dizziness.

Table 1. Demographic and clinical characteristics of patients

	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	P
Age (mean ± SD)	59 (42-69)	59 (31-68)	52 (37-67)	
Gender				
Male	28 (56.0%)	28 (56.0%)	26 (52.0%)	0.898
Female	22 (44.0%)	22 (44.0%)	24 (48.0%)	
ECOG score				
1	28 (56.0%)	24 (48.0%)	26 (52.0%)	0.726
2	22 (44.0%)	26 (52.0%)	24 (48.0%)	
Chemotherapeutic strategy				
PP	34 (68.0%)	36 (72.0%)	38 (76.0%)	0.672
TP	16 (32.0%)	14 (28.0%)	12 (24.0%)	

Table 2. Comparison of complete response rates among the three groups of patients

		Acute stage of vomiting		Delayed stage of vomiting	
	n	Valid	Invalid	Valid	Invalid
Group A	50	82% (41/25)	18% (9/50)	52% (26/50)	48% (24/50)
Group B	50	86% (43/50)	14% (7/50)	72% (36/50)	28% (14/50)
Group C	50	92% (46/50)	8% (4/50)	88% (44/50)	12% (6/50)

Table 3. Comparison of nausea among all of three groups

	Grade 1	Grade 2	Grade 3
Group A	14 (28.0%)	24 (48.0%)	7 (14.0%)
Group B	24 (48.0%)	16 (32.0%)	4 (8.0%)
Group C	18 (36.0%)	14 (28.0%)	2 (4.0%)

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 13.0). Data were calculated as mean ± SD. The Chi-square test was used to analyze the classified variables. The Students' *t* test or non-parametric test were performed for data analysis. A *P*-value less than 0.05 was considered statistically significant.

Results

Patient demographics

A total of 150 patients were included in the study, with 50 patients in each group (Group A, B and C). The patients' age ranged from 31 to 69 years, and the median age was 57 years. The patients' characteristics, including age, gender, ECOG scores and chemotherapy strategy were not significantly different among the three groups (**Table 1**, P>0.05).

Major outcomes for complete remission rate

The complete remission rates (CRRs) for the acute phase of vomiting were 82.0% (41/50), 86.0% (43/50) and 92.0% (46/50) in groups A, B and C, respectively, with no significant difference among the three groups (**Table 2**, *P* = 0.334, >0.05). However, the CRRs for the delayed phase of vomiting were 52.0% (26/50), 72.0% (36/50) and 88.0% (44/50) in groups A, B and C, respectively. There were significant differences among the groups (**Table 1**, P<0.001).

Secondary outcomes for complete remission rate

The total CRR for the delayed phase of vomiting in group A (tropisetron, 72.0%) was significantly lower compared with group B (palonosetron, 52.0%) (**Table 2**, P = 0.039, <0.05). The CRR of group C (palonosetron combining tropisetron, 88.0%) was significantly higher versus group A (52.0%, P<0.001) and group B (72.0%, P = 0.046, <0.05) (**Table 2**).

Vomiting time and salvage treatment rates

The average vomiting times in groups A, B and C were 101.84 ± 70.10, 120.72 ± 65.15 and 141.6 ± 53.56 hours, respectively. Although there were no significant differences among the three groups, the vomiting time of group C was numerically longer compared to groups A and B (P = 0.067, >0.05).

Twenty-eight patients in group A (48.0%), 20 in group B (40.0%) and 14 in group C (28.0%) received salvage treatments; there were no significant differences between groups (P = 0.171, >0.05). The average salvage times (2.32 ± 3.97, 1.44 ± 2.35 and 1.20 ± 2.32 for groups A, B and C, respectively) were not significantly different among the three groups (P = 0.385, >0.05).

There were 45 cases of nausea in group A, 44 cases in group B and 34 cases in group C, with no significant differences among the three groups (**Table 3**, P = 0.059, >0.05).

Table 4. Adverse reactions in three groups.

	Group A	Group B	Group C	P
Weakness	16 (32.0%)	16 (32.0%)	10 (20.0%)	>0.05
Loss sleep	2 (4.0%)	2 (4.0%)	4 (8.0%)	>0.05
Abdominal distension	16 (32.0%)	12 (24.0%)	10 (20.0%)	>0.05
Coprostasis	18 (36.0%)	28 (56.0%)	24 (48.0%)	>0.05

Adverse reactions

A total of 60.0%, 68.0% and 64.0% of patients in groups A, B and C experienced more than one adverse reaction. Most of the most common adverse reactions- constipation, weakness and abdominal distension-were grades 1 and 2. There were no significant differences in the occurrence of adverse reactions among the three groups (**Table 4**, $P = 0.477$, >0.05).

Laboratory examinations and ECGs indicated no significant variations among the three groups.

Discussion

In the present study, there were no significant differences among the three groups in preventing acute vomiting caused by chemotherapy strategy. However, we also found that the effect of combined palonosetron and tropisetron on chemotherapy strategy-induced delay phase of vomiting was significantly higher compared to palonosetron or tropisetron treatment alone. Furthermore, the frequency of adverse reactions was not increased significantly compared to palonosetron or tropisetron treatment alone.

Chemotherapy-induced nausea and vomiting always triggers metabolic disturbance, nutrient loss, apocleisis, and other problems. The above complications could strongly affect the adherence of patients to further therapy, thereby decreasing the probability of prolonging the survival period. Currently, the main mechanism and pathway have not been fully clarified. A previous study reported that the vomiting center and chemoreceptor trigger zone (CTZ) are the most important structural foundation for the occurrence of vomiting [8]. The neurotransmitters that cause nausea and vomiting mainly include dopamine, histamine, 5-HT and substance P ect. A previous study demonstrated that different types and stages of CINV involve different dominant neurotransmitters and receptors [9]. The acute stage of CINV mainly occurs 24 hour after chemotherapy and is mediated by 5-HT, which subsequently triggers nausea and vomiting [10, 11]. Therefore, 5-HT receptor inhibitors could prevent the occurrence of acute CINV occurrence in clinical practice [12]. However, the delayed stage of CINV mainly occurs 24 to 120 hours post chemotherapy, via a mechanism that is not clearly defined and may be associated with 5-HT, dopamine and substance P [13-16].

Another study reported that tropisetron, which has a half-life of only 8 hours [11], is a competitive 5-HT3 receptor antagonist in the central and peripheral nervous systems [10]. A pharmacokinetics study illustrated that palonosetron's affinity is significantly higher compared with the first generation of the 5-HT antagonists, with a half-life as long as 40 hours [17]. Palonosetron does not only have highly allosteric interaction with the 5-HT3 receptor, but can also continuously block the signal crosstalk of 5-HT3/NK1, which contributes to the vomiting reaction induced by substance P in delayed phase [18, 19]. Therefore, in this study, we attempted to investigate whether a combination of drugs could increase affinity and selectivity to the 5-HT3 receptor.

The CRRs of acute vomiting for palonosetron plus tropisetron versus tropisetron versus palonosetron alone were 82.0%, 86.0% and 92.0%, respectively. Although no significant differences were found, we also discovered that the CRR of the combination group was noticeably higher than the single-drug treatment group. This result suggests that palonosetron plus tropisetron could significantly improve the symptoms of acute vomiting. However, the sample size of this study is also small. Future studies with a larger patient population may demonstrate significant results.

The CRR of palonosetron plus tropisetron for delayed vomiting was 88.0%, which was significantly higher compared with the CRR of tropisetron alone (52.0%) and palonosetron alone (72.0%) ($P<0.05$). Considering the high frequency of chemotherapy-induced vomiting, prevention of delayed vomiting is critical for the successful process of chemotherapy. Although a few large randomized, double-blind clinical trials reported a CRR of palonosetron on the delayed phase of vomiting of up to 70% (6, 8, 9)

[5, 6, 8, 9, 20], 30% of patients did not have satisfactory anti-nausea and anti-vomiting effects. We analyzed the results and found that the CRR in the combined group was significantly higher compared with the tropisetron or palonosetron alone groups, and the combined group also significantly decreased the severity of nausea in patients; these findings suggest that palonosetron plus tropisetron is superior and more effective in controlling of CINV.

Moreover, the present study also showed that palonosetron plus tropisetron could significantly prolong the vomiting control time and decrease the frequency of vomiting. Although no statistical difference was found among the three groups, there was a trend suggesting that the combined group was better than the single-drug group, which further supported the superiority of the combined group in controlling CINV.

Regarding adverse reactions or toxicity, the toxic reactions in the three groups mainly included coprostasis, abdominal distension, weakness and dizziness, all of which were grade 1 or 2; there were no grade 3 or 4 reactions. Only a few patients present with mild headache,sleep loss; most had very light symptoms.

Although we have reported some of the important results, there are also some limitations in the present study. Firstly, patients with poor chemotherapy for CINV were more likely to experience nausea and vomiting symptoms than those with previous good control. Secondly, some patients were not chemotherapy-naïve, and the CINV data of previous treatments in those patients were not included in our statistical analyses. Thirdly, the sample size of patients in this study was small.

Conclusions

Treatment with palonosetron plus tropisetron significantly prevents and improves the chemotherapy-induced delayed stage of CINV, without increasing the frequency of adverse reactions; the tolerability to treatment good. The strategy of combining palonosetron with tropisetron is a potential and promising therapeutic method for controlling CINV, and may be valuable and feasible in clinical practice.

Disclosure of conflict of interest

None.

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