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Original Research Article

Protective effect of aprepitant against chemotherapy-induced nausea and vomiting in postoperative chemotherapy for gastric cancer

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Abstract

Purpose: *To investigate the clinical efficacy of aprepitant in the prevention of chemotherapy-induced nausea and vomiting (CINV) caused by schemotherapy after gastric cancer surgery, and associated factors, as well as adverse reactions to the drug.*
Methods: *A total of 100 postoperative gastric cancer patients in the Affiliated Cancer Hospital of Nanjing Medical University from January 2017 to January 2019, were randomly divided into control group (50 patients given dexamethasone + parlour SiQiong), and treatment group (50 patients given his minions horse temple + dexamethasone + parlour SiQiong). Recording of nausea and vomiting, as well as adverse reaction of patients, were started after 7 days of chemotherapy in patients.*
Results: *The total effective control of acute CINV in the control group was 82 %, while the total effective control of acute CINV in the study group was 94 %. Values of total effective control of DFS in the control and study groups were 70 and 86 %, respectively. The incidence of adverse reactions was similar in the two groups. There was a significant correlation between the anti-emetic effect of aprepitant and gastric surgery.*
Conclusion: *After gastric cancer surgery, combined treatment with aprepitant, palonosetron and dexamethasone prevents CINV induced by moderate emetogenic chemotherapy with orisaplatin. The combined treatment has good efficacy and can improve tolerance to, and compliance with chemotherapy.*

Keywords: *Aprepitant, Palonosetron; Acute chemotherapy-induced nausea and vomiting (CINV); Latency chemotherapy-induced nausea and vomiting (CINV), Nausea, Dexamethasone*

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is the most common adverse reaction to chemotherapy. It can lead to dehydration, electrolyte imbalance, malnutrition, poor psychological and social functioning of patients, non-adherence to chemotherapy, or even outright interruption of chemotherapy [1-4]. There are three types of nausea and vomiting caused by chemotherapy: acute nausea and vomiting, delayed nausea and vomiting, and anticipatory

nausea and vomiting, of which the first two are the most common. Acute nausea and vomiting refers to the nausea and vomiting of patients within 24 h after chemotherapy. The pathogenesis of nausea is different from that of vomiting. Therefore, the two processes may involve different pathways. However, their exact pathogenesis has not been fully understood. Thus, it is necessary to prevent and treat nausea and vomiting simultaneously in clinical practice. Since CINV is an inevitable problem for patients during chemotherapy, it is important to use effective anti-emetic drugs with low toxicity to solve this problem. The antiemetic drugs commonly used in clinical practice include dopamine receptor antagonist, glucocorticoid, 5-hydroxytryptamine receptor antagonist and NK-1 receptor antagonist [5]. The combination of 5-hydroxytryptamine receptor antagonist and glucocorticoid effectively prevents and controls CINV situation, but long-term use of 5-hydroxytryptamine receptor blocker adversely affects liver function. Moreover, glucocorticoid negatively impacts the immunity of patients. In 2003, aprepitant was the first NK-1 receptor blocker approved by FDP. Multiple clinical studies have confirmed that aprepitant has extensive anti-emetic effects, and does not increase the toxic and side effects associated with other drugs [6,7]. Therefore, the combination of aprepitant with glucocorticoid and 5-hydroxytryptamine has attracted much research attention.

In this study, 100 postoperative gastric cancer patients were included. Partial or total gastrectomy significantly reduces the tolerance of postoperative gastric cancer patients to chemotherapy and made them more prone to CINV, which is an important reason why postoperative adjuvant chemotherapy cannot be completed; it also affects the prognosis of patients. In this study, two antiemetic treatment schemes were established for comparison, so as to investigate the efficacy and adverse reactions of aprepitant in protecting gastric cancer from chemotherapy-mediated CINV. Moreover, the study was intended to analyze the correlation between the clinical and pathological characteristics of patients and the efficacy of aprepitant, and to investigate the pathological factors that affect the efficacy of aprepitant.

EXPERIMENTAL

Clinical profile of the patients

A total of 100 patients under postoperative platinum-based chemotherapy for gastric carcinoma of CINV in the Affiliated Cancer Hospital of Nanjing Medical University were enrolled from January 2017 - January 2019. Based on the anti-nausea treatment, patients were divided into control group (50 patients given dexamethasone + *parlour SiQiong*), and study group (50 patients who received *his minions horse temple* + dexamethasone + *parlour SiQiong*).

The control group comprised 27 males and 23 females, with mean age of 39.5±2.5 years. In the study group, there were 20 males and 30 females, with men age of 43.1 ± 2.9 years. The patients with gastric cancer received chemotherapy every 3 weeks, and the specific chemotherapy was moderate emetogenic regimen containing orisaplatin, oxaliplatin combined with sergione (SOX), oxaliplatin combined with capecitabine (XELOX), oxaliplatin combined with paclitaxel (TP), and oxaliplatin combined with docetaxel (DP). The doses were: oxaliplatin: 130mg/m^2 day1, and sergio: 80 mg/m^2 bid dL-14; capecitabine 1000 mg/m^2 *bid* dL - 14; paclitaxel: 175 mg/m^2 dL, and docetaxel: 75 mg/m^2 dL. This research was registered at Chinese Clinical Trial Registry (approval no. ChiCTR-OPN-15006601) and was conducted according to the guidelines of Declaration of Helsinki promulgated in 1964, as amended in 1996 [8].

Inclusion and exclusion criteria

Inclusion criteria: (1) patients aged 18 years old or above; (2) patients newly treated or who did not receive radiotherapy or chemotherapy 6 months before the study; (3) patients whose ECOG physical strength scores were 0-2 points; (4) patients with expected duration of platinum-containing chemotherapy of more than 2 weeks, and (5) patients who signed written informed consent.

Exclusion criteria: (1) patients who had other complications, e.g. leukopenia and thrombocytopenia; (2) patients who had other diseases prone to CINV, such as hypocalcemia, intestinal obstruction, and central nervous system metastasis; (3) patients who received radiotherapy, chemotherapy and other treatments within the previous 6 months, and (4) diabetic patients with elevated blood glucose control.

Antiemetic regimen

The anti-emetic drugs received by the patients were: oral 125 mg aprepitant 1h before day 1 of chemotherapy, and oral 80 mg in the morning of day 2 and day 3 of chemotherapy. Intravenous

infusion of palonosetron (0.25 mg/dL), and dexamethasone (5 mg/dL) was performed 30 min before chemotherapy.

Assessment of antiemetic effect

The degree of control of acute and delayed CINV in the two groups was recorded. Acute CINV referred to nausea and vomiting that occurred within 24 h of chemotherapy, while delayed CINV referred to nausea and vomiting that occurred 24 h after chemotherapy. The NCI-CTCAE 4.0 standard has classified nausea and vomiting into grades 0 - V, with grade 0 as the lightest and grade V as the most serious [9]. In the present study, absence of acute and delayed CINV (level 0) was designated complete control (CC). Level Ⅰ acute and delayed CINV was classified as partial control (PC), but acute and delayed CINV at level Ⅱ was classified as uncontrollable (UC) [10]. The total control efficiency was calculated as shown in Equation 1 where TCE is total control efficiency, CC is complete control, PC is partial control and N is total number of patients.

$$TEC = \frac{(CC + PC) \times 100}{N} \quad \ldots\ldots\ldots\ldots (1)$$

Statistical analysis

Statistical analysis was performed using SPSS 20 software. Count data is represented as n (%). Two-group comparison was done using χ^2 test. Measurement data are expressed as mean ± SD. Comparison between groups was carried out with *t*-test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Clinical characteristics of the patients

The gender, age, ECOG score, stage, differentiation degree, surgical methods and case distribution of chemotherapy regimens of the two groups were analyzed using χ^2 test. The comparison reveled no significant differences in the various clinicopathological characteristics between the two groups ($p > 0.05$), indicating that the two groups were comparable (Table 1).

Comparative anti-emetic efficacy

The cases of complete control of acute nausea and vomiting in the control group and the study group were 26 and 36, while cases of partial control were 15 and 11; and uncontrolled cases were 9, and 3, respectively. Total effective control in the control group and the study group were 82 and 94 %, respectively. The total effectiveness of control of acute nausea and vomiting in the two groups was comparable ($p > 0.05$). In the control group and the study group, there were 23 and 35 cases of delayed nausea and vomiting; 12 and 8 cases of partial control; and 15 and 7 cases of uncontrolled nausea and vomiting, respectively. The total effectiveness of control in the two groups were 70 and 86 %, respectively. The total effectiveness of control of acute nausea and vomiting in the two groups differed significantly ($p < 0.05$). These results are shown in Table 2.

Risk factors for clinical efficacy of aprepitant in the prevention of nausea and vomiting

As shown in Table 3, subgroup analysis was conducted on clinical characteristic factors, and the results showed that the anti-emetic effect of aprepitant was not significantly correlated with gender, age, ECOG score, stage ($p > 0.05$).

Table 1: Clinical profile of patients

Variable	Control group (n=50)	Study group (n=50)	*P*-value
Gender			
Male	27 (54%)	20 (40%)	0.2292
Female	23 (46%)	30 (60%)	
Age (years)			
< 60	36 (72%)	31 (62%)	0.3952
≥ 60	14 (28%)	19 (38%)	
ECOG score			
0	38 (76%)	29 (58%)	0.0881
1	12 (24%)	21 (42%)	
Stage			
Ⅰ-Ⅱ	9 (18%)	15 (30%)	0.2414
Ⅲ-Ⅳ	41 (82%)	35 (70%)	
Degree of differentiation			
Poorly differentiated	11 (22%)	19 (38%)	0.1259
Medium and high differentiation	39 (78%)	31 (62%)	
Surgical procedure			
Total gastrectomy	5 (10%)	7 (14%)	0.4896
Proximal Gastrectomy	19 (38%)	21 (42%)	
Distal gastrectomy	27 (54%)	22 (44%)	
Chemotherapy regimens			
SOX	16 (32%)	22 (44%)	0.3363
XELOX	17 (34%)	14 (28%)	
TP	8 (16%)	10 (20%)	
DP	9 (18%)	4 (8%)	

Table 2: Control of nausea and vomiting between the two groups

Group	Acute CINV					Delayed CINV				
	CC	*PC*	*UC*	*Total effectiveness of control*	*P-value*	*CC*	*PC*	*UC*	*Total effectiveness of control*	*P-value*
Control	26	15	9	82%	0.073	23	12	15	70%	0.045
Study	36	11	3	94%		35	8	7	86%	

*CC = complete control; PC = partial controls; UC = uncontrolled

Table 3: Correlation analysis between clinical characteristics and antiemetic effect of patients

Variable	Treatment group	Full control	Partial control
Gender			
Male	20 (40%)	12 (60%)	3 (15%)
Female	30 (60%)	24 (80%)	8 (26.7%)
χ^2	-	2.381	0.952
P	-	0.123	0.329
Age (year)			
< 60	31 (62%)	26 (83.9%)	6 (19.4%)
≥ 60	19 (38%)	10 (52.6%)	5 (26.3%)
χ^2	-	1.188	0.333
P	-	0.276	0.564
ECOG score			
0	29 (58%)	20 (69%)	7 (24.1%)
1	21 (42%)	16 (76.2%)	4 (19%)
χ^2	-	0.315	0.184
P	-	0.574	0.668
Stage			
Ⅰ-Ⅱ	15 (30%)	9 (60%)	3 (20%)
Ⅲ-Ⅳ	35 (70%)	27 (77.1%)	8 (22.9%)
χ^2	-	1.531	0.050
P	-	0.216	0.823

Table 4: Correlation analysis between clinical characteristics and antiemetic effect of patients

Variable	Treatment group	Full control	Partial control
Degree of differentiation			
Poorly differentiated	19 (38%)	8 (42.1%)	2 (10.5%)
Medium and high differentiation	31 (62%)	28 (90.3%)	9 (29%)
χ^2	-	3.024	2.351
P	-	0.082	0.126
Surgical procedure			
Total gastrectomy	7 (14%)	4 (57.1%)	0 (0)
Proximal gastrectomy	21 (42%)	14 (66.7%)	2 (9.5%)
Distal gastrectomy	22 (44%)	18 (81.8%)	8 (36.4%)
χ^2	-	6.968	6.872
P	-	**0.031**	**0.032**
Chemotherapy regimen			
SOX	22 (44%)	17 (77.3%)	5 (22.7%)
XELOX	14 (28%)	11 (78.6%)	3 (21.4%)
TP	10 (20%)	6 (60%)	2 (20%)
DP	4 (8%)	2 (50%)	1 (25%)
χ^2	-	2.278	0.054
P-value	-	0.517	0.997

Risk factors for clinical efficacy of aprepitant in the prevention of nausea and vomiting

As shown in Table 4, subgroup analysis was conducted on clinical characteristic factors, and the results showed that the anti-emetic effect of aprepitant was not significantly correlated with degree of differentiation and chemotherapy regimen of the patients ($p > 0.05$), but was significantly correlated with method of gastric surgery ($p < 0.05$).

DISCUSSION

It was proposed in 1997 that chemotherapy drugs trigger vomiting reflexes by interaction with

chemoreceptors through a variety of signal transduction pathways, thereby producing the adverse reactions of CINV in patients [11]. Moreover, studies have revealed that the stimulatory effect of chemotherapy drugs on the mucosa of the digestive tract also plays an important role in the occurrence of CINV [12]. This may be related to poor selectivity of chemotherapy drugs, since they destroy both malignant tumor cells and normal tissue cells. It has been reported that 5-HT3 is a neurotransmitter related to the CINV induced by chemotherapy [9]. The use of 5-HT3 receptor antagonists for anti-emetic treatment commenced in the 1990s, and a well-known glucocorticoid was added to almost every antiemetic treatment scheme. Thus, the combination of 5-HT3 with glucocorticoid is one of the most widely used anti-emetic schemes in clinical practice. The use of standard 5-HT3 in combination with dexamethasone as antiemetic regimen resulted in control of CNIV in about 80% of patients with acute CINV [13].

However, the regimen was not too effective in a majority of patients with delayed CINV [14-16]. Therefore, delayed CINV is still a problem that needs urgent solution. Currently, many clinical studies have confirmed that NK-1 receptor blocker has a good effect in preventing the occurrence of delayed CINV.

Aprepitant, an NK-1 receptor antagonist, blocks the action of NK-1 and suppresses CINV through a central mechanism [17]. Poli *et al* conducted a controlled study on treating CINV in combination with aprepitant and standard antiemetic regimen in 500 patients undergoing high-dose cisplatin chemotherapy. The results showed that 82.8 and 68.4 % of aprepitant group and control groups reached the end point of complete response during the observation period of acute CINV, respectively, and in the observation period of delayed CINV, the proportion of complete response end points in aprepitant group and control group was 67.7 and 46.8 % respectively [18]. Campos *et al* [19] found that aprepitant combined with dexamethasone and 5-HT3 receptor blockers had greater advantages in preventing the occurrence of delayed CINV than dexamethasone combined with 5-HT3 receptor blockers. Oyama *et al* [20] published a study in 2013 on CINV caused by chemotherapy in patients with gastric cancer treated by aprepitant combined with granisetron and dexamethasone, the results showed that the proportion of the overall observation period, acute CINV stage and delayed CINV stage of gastric cancer patients who reached the end point of complete response was 88.7%, 98.1% and 88.7, respectively. About half of the patients in the study had varying degrees of anorexia, but no drug rescue was needed. This study suggested that aprepitant combined with granisetron and dexamethasone can effectively prevent CINV caused by moderate vomiting chemotherapy in patients with gastric cancer.

All gastric cancer patients in our study received a moderately vomiting regimen containing olanzapine. The results showed that the total effective control rate of acute CINV in the study group and the control group were 94 and 82 %, respectively, and the total effective control rate of delayed CINV was 86% and 70%, respectively. The total effective control rate of acute CINV in the study group was higher than that in the control group, but the difference between the two groups was not statistically significant ($p > 0.05$), while the total effective control rate of delayed CINV was statistically significant $p < 0.05$). The results suggested that the efficacy of palonosetron combined with dexamethasone in the treatment of acute CINV was excellent enough, the therapeutic effect was not significantly improved after the addition of aprepitant, but the therapeutic effect on delayed CINV was significantly improved after the addition of aprepitant. The result is consistent with the above research results. On the other hand, there was no significant difference in the incidence of adverse reactions between the two groups, indicating that aprepitant did not increase drug-related adverse reactions and was highly safe [21]. Therefore, it can be reasonably recommended that paronosetron combined with dexamethasone in the clinical treatment of chemotherapy-mediated acute CINV in gastric cancer patients, and effective control of delayed CINV with aprepitant after 24 h of chemotherapy.

In addition, this study analyzed the correlation between patients' gender, age, ECOG score, tumor stage, differentiation degree, surgical method, chemotherapy regimen and the antiemetic efficacy of aprepitant. It was found that there was a significant correlation between the operative method and the antiemetic effect of aprepitant ($p < 0.05$). In patients with distal gastric resection, the effect of CC and PC of CINV was higher than that of total and proximal gastric resection. It may be because of the patients with total gastrectomy or proximal gastric resection, the physiological structure of the stomach and the surrounding anatomical position are changed, the function of storing food is lost and the mechanism of self-regulation is lacking, the tolerance is reduced, then CINV is more likely to occur. On the other hand, total gastrectomy also affects the absorption and

absorption of aprepitant. Therefore, the difference in surgical methods affects the antiemetic effect of aprepitant. For patients who underwent total gastrectomy or proximal gastrectomy, adequate intensity of vomiting should be given at the beginning of chemotherapy.

Limitation of the study

The number of cases in this study was small, and patients were not followed up for a long time. Long-term efficacy of aprepitant in CINV patients has not been documented.

CONCLUSION

The prevention of CINV by aprepitant combined with palonosetron and dexamethasone shows high effectiveness, especially significantly reducing the incidence of delayed CINV with mild side effects, which improves the tolerance of gastric cancer patients to moderate emetogenic chemotherapy and provides more effective antiemetic treatment for the majority of gastric cancer patients.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

All work was done by the author named in this article and the authors accept all liability resulting from claims which relate to this article and its contents. Ning Sun designed the study and interpreted the results. Ning Sun, Yan Zhang, Chenchen Li, Xiaoming Wang, Renhong Guo collected data and drafted the manuscript. Ning Sun performed the experiments.

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