Journal of Hainan Medical University

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Comparison of nutritional status and inflammatory stress levels after gastric cancer patients with chemotherapy received palonosetron hydrochloride injection and tropisetron

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ARTICLE INFO

Article history:
Received 7 Jul 2016
Received in revised form 17 Jul 2016
Accepted 12 Jul 2016
Available online 24 Jul 2016

Keywords:
Gastric cancer
Palonosetron
Tropisetron
Inflammatory reaction
Stress reaction

ABSTRACT

Objective: To study the nutritional status and inflammatory stress levels after gastric cancer patients with chemotherapy received palonosetron and tropisetron. **Methods:** 94 patients with advanced gastric cancer undergoing FOLFOX4 intravenous chemotherapy in our hospital between May 2014 and March 2016 were selected and randomly divided into observation group (n=47) and control group (n=47) who received palonosetron and tropisetron for chemotherapy anti-emesis respectively. After four cycles of chemotherapy, serum samples were collected from two groups of patients to determine nutritional status, inflammatory reaction and stress reaction indexes. **Results:** After four cycles of chemotherapy, serum albumin (ALB), prealbumin (PAB), transferrin (TFN), immunoglobulin A (IgA), IgG and IgM content of observation group were significantly higher than those of control group (P<0.05). After four cycles of chemotherapy, serum Keap1 content of observation group was significantly higher than that of control group (P<0.05), while Nrf2, ARE, NQO1, HO-1, interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin-4 (IL-4) and IL-10 content were significantly lower than those of control group (P<0.05). **Conclusions:** Palonosetron has better antiemetic effect than tropisetron for gastric cancer patients with chemotherapy, and after chemotherapy, the nutritional status is better and the inflammatory stress level is lighter.

1. Introduction

Gastric cancer is one of the most common malignant tumors of digestive system in our country, it lacks early specific signs and symptoms, so the early diagnosis rate of gastric cancer is low, the majority of patients have developed to middle-advanced stage when diagnosed and have missed the timing of surgical resection, and intravenous chemotherapy is needed at this moment to kill tumor cells and prolong patients′ survival[1]. However, chemotherapeutic drugs can cause adverse reactions such as nausea and vomiting in patients with gastric cancer, which adversely affect the chemotherapy compliance and patients' nutritional status[2,3]. Therefore, chemical antiemetic treatment is an important auxiliary treatment in the chemotherapy process of patients with gastric cancer, and selecting rational antiemetic drugs can improve the antiemetic effect and guarantee the effect of chemotherapy. Palonosetron is a new generation of highly selective 5-hydroxytryptamine receptor antagonist, and compared with the first generation of 5-hydroxytryptamine receptor antagonist tropisetron, the drug has a stronger receptor affinity and longer half-life in the body, and has better treatment effect on acute vomiting and delayed vomiting than the tropisetron[4,5]. At present, there is no report about the effect of palonosetron and tropisetron on vicious vomiting caused by chemotherapy in patients with gastric cancer. In the following study, the nutritional status and inflammatory stress levels were compared after gastric cancer patients with chemotherapy received palonosetron and tropisetron.

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Fund project: Bayer Schering Youth Fund for Liver Cancer (No: Y-B-2011-008).

2. Materials and methods

2.1. Research subjects

94 patients with advanced gastric cancer undergoing FOLFOX4 intravenous chemotherapy in our hospital between May 2014 and March 2016 were selected as research subjects, and all patients were diagnosed with advanced gastric cancer by pathological examination and received FOLFOX4 chemotherapy. Random number table was used to divide the included patients into observation group and control group (n=47) who received different antiemetic treatment during chemotherapy respectively. Observation group received palonosetron for antiemetic treatment, including 32 male cases and 15 female cases that were (58.65±7.14) years old; control group received tropisetron for antiemetic treatment, including 30 male cases and 17 female cases that were (59.16±7.35) years old. The two groups of patients were not significantly different in general information (P>0.05).

2.2. Treatment methods

Both groups of patients received FOLFOX4 chemotherapy after admission, and the method is as follows: oxaliplatin 100 mg/m^2, intravenous drip, on day 1, leucovorin calcium 200 mg/m^2, intravenous drip, on day 1, 5-fluorouracil 400 mg/m^2, intravenous drip, on day 1, and then 5-fluorouracil 2 400 mg/m^2, intravenous drip, for 46 h, 28 d as a treatment cycle, for four consecutive courses of treatment. During chemotherapy, observation group received palonosetron for antiemetic treatment: palonosetron hydrochloride injection (Chiatai Tianqing Pharmaceutical Group Co., LTD., approved by H20080716) 0.25 mg in 5 mL of normal saline injection, intravenous injection 15 min before chemotherapy; control group received tropisetron for antiemetic treatment during chemotherapy: tropisetron hydrochloride injection 0.25 mg in 5 mL of normal saline injection, intravenous injection 15 min before chemotherapy.

2.3. Biochemical index detection methods

After four cycles of chemotherapy, 5 mL of peripheral venous blood was collected from two groups and centrifuged to get serum, enzyme-linked immunosorbent assay kits were used to detect the albumin (ALB), prealbumin (PAB), transferrin (TFN), immunoglobulin A (IgA), IgG, IgM, interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin-4 (IL-4) and IL-10 content, and radiommunoprecipitation kits were used to determine Keap1, Nrf2, ARE, NQO1 and HO-1 content.

2.4. Statistical analysis

SPSS20.0 statistical software was used for analysis, measurement data was input in the software, then t test was used to analyze the differences between two groups and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Serum nutritional status indexes

After four cycles of chemotherapy, analysis of serum protein metabolism biochemical indexes ALB, PAB and TFN as well as serum immunoglobulin IgA, IgG and IgM between two groups of patients is shown in Table 1. Serum ALB, PAB and TFN content of observation group were significantly higher than those of control group (P<0.05). Serum IgA, IgG and IgM content of observation group were significantly higher than those of control group (P<0.05).

3.2. Serum stress molecule content

After four cycles of chemotherapy, analysis of serum stress molecules Keap1, Nrf2, ARE, NQO1 and HO-1 between two groups of patients is shown in Table 2. Serum Keap1 content of observation group was significantly higher than that of control group (P<0.05) while Nrf2, ARE, NQO1 and HO-1 content were significantly lower than those of control group (P<0.05).

Table 2

Comparison of serum stress molecules between two groups of patients (nmol/mL, n=47, $\bar{x}\pm s$).

Groups	Keap1	Nrf2	ARE	NQO1	HO-1
Observation group	9.42±1.05	4.69±0.57	3.26±0.42	2.18±0.32	1.69±0.18
Control group	6.58±0.86	7.61±0.89	5.58±0.74	3.37±0.41	2.77±0.35
t	7.948	6.891	8.684	8.228	7.698
P	<0.05	<0.05	<0.05	<0.05	<0.05

Table 1

Comparison of serum protein metabolism biochemical indexes and immunoglobulin between two groups of patients (n=47, $\bar{x}\pm s$).

Groups	ALB (g/L)	PAB (mg/L)	TFN (mg/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
Observation group	32.42±3.85	241.65±32.47	169.42±18.55	1.89±0.22	8.73±0.94	1.45±0.17
Control group	25.61±3.34	178.97±20.34	121.35±15.28	1.37±0.17	7.31±0.88	1.04±0.14
t	7.283	7.819	6.598	7.381	6.669	8.793
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

3.3. Serum inflammatory factor content

After four cycles of chemotherapy, analysis of serum inflammatory factors IFN-γ, TNF-α, IL-4 and IL-10 between two groups of patients is shown in Table 3. Serum IFN-γ, TNF-α, IL-4 and IL-10 content of observation group were significantly lower than those of control group (P<0.05).

Table 3
Comparison of serum inflammatory factors between two groups of patients (ng/mL, n=47, $\bar{x}\pm s$).

Groups	IFN-γ	TNF-α	IL-4	IL-10
Observation group	17.41±2.25	4.08±0.52	5.62±0.78	4.53±0.67
Control group	22.57±3.08	5.35±0.77	8.14±0.93	7.84±0.93
t	7.398	6.582	8.317	7.647
P	<0.05	<0.05	<0.05	<0.05

4. Discussion

FOLFOX4 is the common intravenous chemotherapy regimen for patients with malignant digestive tract tumor, and the regimen is based on platinum-based chemotherapeutic drugs, aided by leucovorin calcium and 5-fluorouracil, and can effectively kill cancer cells and prolong patients' survival time. The most common adverse reactions of platinum-based chemotherapeutic drugs are digestive tract reactions characterized by repeated nausea and vomiting during chemotherapy, and patients with severe gastrointestinal adverse reactions are unable to tolerate nausea and vomiting symptoms and have to terminate chemotherapy, which causes adverse effects on the prognosis. The mechanism for platinum-based chemotherapeutic drugs to cause nausea and vomiting is to activate the digestive tract and chromaffin cells to release neurotransmitter 5-HT, and 5-HT can be combined with 5-HT_3 receptor and then transmit the excitation from the vagus nerve into the vomiting center, and cause symptoms of nausea and vomiting[6–8]. Therefore, 5-HT_3 receptor antagonist is the most common antiemetic drug used during chemotherapy. Palonosetron is a new generation of 5-HT_3 receptor antagonist, and compared with the first generation of 5-HT_3 receptor antagonist tropisetron, the drug has the biggest advantages of strong receptor affinity and short drug half-life, and can more durably and effectively antagonize 5-HT_3 receptor and alleviate the symptoms of nausea and vomiting. Studies have reported that for patients with lung cancer, the antiemetic effect of palonosetron is better than that of tropisetron during platinum-based chemotherapy[9]. At present, it is not yet clear about the difference in antiemetic effect between palonosetron and tropisetron for patients with gastric cancer during platinum-based chemotherapy.

In the study, in order to define the antiemetic effect of palonosetron and tropisetron for gastric cancer patients with chemotherapy, the nutritional status of patients after chemotherapy was analyzed at first in the study. The most direct influence of chemotherapy-induced nausea and vomiting on patients with gastric cancer is to lead to poor nutritional status, vomiting during chemotherapy can affect the patients′ eating and nutrition intake, and the malignant tumors continuously consume the nutrients in the patients, which will gradually result in malnutrition[10,11]. ALB, PAB and TFN are the most common indexes to reflect the protein consumption and nutritional status in the body, and chronic inadequate nutrient intake and excessive consumption will cause the massive protein consumption and lead to the negative nitrogen balance in the body[12]. In the study, the analysis of serum nutrition indicators after two groups of patients received different antiemetic drugs showed that serum ALB, PAB and TFN content of observation group were significantly higher than those of control group (P<0.05). This means that palonosetron is with more ideal antiemetic effect than tropisetron, and during chemotherapy, patients are with less protein consumption and better nutritional status. Vomiting-induced negative nitrogen balance will not only affect the albumin and ferritin metabolism, but can also affect the immunoglobulin IgA, IgG and IgM synthesis and suppress immune function. Further analysis of the above immunoglobulin content showed that serum IgA, IgG and IgM content of observation group were significantly higher than those of control group (P<0.05). This further confirms the superior antiemetic effect of palonosetron for gastric cancer patients with chemotherapy, and patients are with less immunoglobulin consumption during chemotherapy.

Persistent nausea and vomiting is a strong source of stress for the body, and therefore, chemotherapy-induced nausea and vomiting will not only affect the patients' nutritional status, but can also cause the oxidative stress reaction in the body. Keap1-Nrf2-ARE is an important signaling pathway that regulates the oxidative stress in the body, and Keap1 can negatively adjust the transcription factor function of Nrf2, and inhibit the combination between Nrf2 and its reaction element as well as the expression of downstream antioxidant enzymes AQO-1 and HO-1[13,14]. In the process of oxidative stress caused by nausea and vomiting, the negatively regulatory effect of Keap1 on Nrf2-ARE is weakened and the effect of Nrf2-ARE on regulating the expression of antioxidant enzymes is enhanced, which alleviates the oxidative stress reaction through AQO-1 and HO-1[15]. In the study, the analysis of the effect of different antiemetic drugs on Keap1-Nrf2-ARE pathway showed that serum Keap1 content of observation group was significantly higher than that of control group (P<0.05) while Nrf2, ARE, NQO1 and HO-1 content were significantly lower than those of control group (P<0.05). This means that using palonosetron to stop vomiting can reduce the oxidative stress caused by vomiting, and the compensatory activation of Nrf2-ARE significantly reduces. The inflammation caused by nausea and

vomiting is mainly characterized by increased pro-inflammatory factor secretion and compensatory anti-inflammatory factor secretion, IFN-γ and TNF-α are the pro-inflammatory factors secreted by Th1 cells, and IL-4 and IL-10 are the anti-inflammatory and immunosuppressive factors secreted by the Th2 cells[16,17]. In the study, analysis of the content of above pro-inflammatory and anti-inflammatory factors showed that serum IFN-γ, TNF-α, IL-4 and IL-10 content of observation group were significantly lower than those of control group ($P<0.05$). This means that using palonosetron to stop vomiting can relieve the inflammation caused by vomiting.

Based on above discussion, it is believed that palonosetron has better antiemetic effect than tropisetron for gastric cancer patients with chemotherapy, and it can relieve the malnutrition and inflammatory stress caused by chemotherapy-induced vicious vomiting.

References

[1] Cao J, Qi F, Liu T. Adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis. *Scand J Gastroenterol* 2014; **49**(6): 690-704.

[2] Nazari M, Taghizadeh A, Orafaei H, et al. Nausea and vomiting in Iranian Traditional Medicine based on Avicenna's viewpoint. *Electron Physician* 2015; **7**(2): 1047-1053.

[3] Lorenzen S, Spörl S, Lordick F. Incidence and treatment of chemotherapy-induced nausea and emesis in gastrointestinal cancer. *Z Gastroenterol* 2014; **52**(8): 821-830.

[4] Simino GP, Marra LP, Andrade EI, et al. Efficacy, safety and effectiveness of ondansetron compared to other serotonin-3 receptor antagonists (5-HT3RAs) used to control chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2016; **9**(9): 1183-1194.

[5] Ma Y, Su L, Liu L, et al. Phase II clinical trial of palonosetron combined with tropisetron in preventing chemotherapy-induced nausea and vomiting. *Int J Clin Exp Med* 2015; **8**(5): 7989-7994.

[6] Goto A, Kotani H, Miyazaki M, et al. Genotype frequencies for polymorphisms related to chemotherapy-induced nausea and vomiting in a Japanese population. *J Pharm Health Care Sci* 2016; **21**(2): 16.

[7] Janicki PK. Management of acute and delayed chemotherapy-induced nausea and vomiting: role of netupitant-palonosetron combination. *Ther Clin Risk Manag* 2016; **2**(12): 693-699.

[8] Kiernan J. Genetic influence on chemotherapy-induced nausea and vomiting: a narrative review. *Oncol Nurs Forum* 2016; **43**(3): 389-393.

[9] Gao W, Liu LX, Xu J, et al. Palonosetron prevents the nausea and vomiting caused by platinum-based chemotherapeutic drugs for lung cancer: clinical observation. *Jiangsu Med J* 2014; **40**(24): 3021-3023.

[10]Kanda M, Mizuno A, Tanaka C, et al. Nutritional predictors for postoperative short-term and long-term outcomes of patients with gastric cancer. *Medicine (Baltimore)* 2016; **95**(24): e3781.

[11]Hsieh MC, Wang SH, Chuah SK, et al. A prognostic model using inflammation- and nutrition-based scores in patients with metastatic gastric adenocarcinoma treated with chemotherapy. *Medicine (Baltimore)* 2016; **95**(17): e3504.

[12]Liu BZ, Tao L, Chen YZ, et al. Preoperative body mass index, blood albumin and triglycerides predict survival for patients with gastric cancer. *PLoS One* 2016; **11**(6): e0157401.

[13]Yang L, Palliyaguru DL, Kensler TW. Frugal chemoprevention: targeting Nrf2 with foods rich in sulforaphane. *Semin Oncol* 2016; **43**(1): 146-153.

[14]Bao J, Li J, Li D, et al. Correlation between expression of NF-E2-related factor 2 and progression of gastric cancer. *Int J Clin Exp Med* 2015; **8**(8): 13235-13242.

[15]Kawasaki Y, Ishigami S, Arigami T, et al. Clinicopathological significance of nuclear factor (erythroid-2)-related factor 2 (Nrf2) expression in gastric cancer. BMC Cancer 2015; 15(15): 5.

[16]Elimova E, Wadhwa R, Shiozaki H, et al. Molecular biomarkers in gastric cancer. *J Natl Compr Canc Netw* 2015; **13**(4): 19-29.

[17]Namikawa T, Munekage E, Munekage M, et al. Evaluation of systemic inflammatory response biomarkers in patients receiving chemotherapy for unresectable and recurrent advanced gastric cancer. *Oncology* 2016; **90**(6): 321-326.