ANTICANCER RESEARCH *37*: 6831-6837 (2017)
doi:10.21873/anticanres.12144

Control of Nausea Based on Risk Analysis in Patients with Esophageal and Gastric Cancer Who Received Cisplatin-based Chemotherapy

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Abstract. *Background: Cisplatin is commonly used for esophageal and gastric cancer, but has a high emetic risk. Although the control of vomiting is favorable, nausea is still poorly controlled in patients receiving cisplatin-based regimens. The present study was designed to determine the risks for cisplatin-induced nausea. The effect of olanzapine, an antipsychotic drug, as an antiemetic for patients with risk of poor control of nausea was subsequently examined. Patients and Methods: The prevalence of antiemetic medication and the control of nausea and vomiting were retrospectively examined in patients with esophageal or gastric cancer receiving the first cycle of cisplatin-based chemotherapy. Risks for nausea were analyzed by multivariate logistic regression analysis, in which threshold for age and cisplatin dose wer assessed by receiver operating characteristic curve analysis. Results: A total of 186 patients received cisplatin-based regimens during January 2011 and December 2016. Guideline-consistent antiemetic medication was administered to all patients. Although the rate of no vomiting was high (93%), the rate of non-significant (grade 2 or more) nausea was insufficient (64%) during the overall period. Risk analysis showed that cisplatin dose of 50 mg/m^2 or more and female gender were significant risks for nausea. Addition of olanzapine, but not of prochlorperazine, to the standard antiemetic medication was effective in suppressing nausea in patients who experienced nausea in the first cycle. Conclusion: Being female and cisplatin doses at 50 mg/m^2 or more were demonstrated to increase risk for nausea. Addition of olanzapine to the standard medication was effective in preventing nausea in high-risk patients with esophageal and gastric cancer.*

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Key Words: Cisplatin, esophageal cancer, gastric cancer, nausea, risk analysis, olanzapine.

Cisplatin is commonly used for esophageal and gastric cancer, however, the agent has high emetic risk, classified as highly emetic chemotherapy. Ohtsu *et al*. demonstrated in patients with advanced gastric cancer that 5-fluorouracil (5-FU) plus cisplatin led to a significantly higher tumor response rate and longer median progression-free survival but not overall survival as compared with 5-FU alone (1). Koizumi *et al*. also reported in phase 3 study comparing the effect of S-1 alone and its combination with cisplatin in patients with advanced gastric cancer that the combination was superior to S-1 alone in prolonging median progression-free survival (HR: 0.57; $p<0.0001$) as well as median overall survival (HR: 0.77; $p=0.04$) but led to more severe adverse drug reactions, including nausea and vomiting (2). Thus, oral fluoropyrimidine and cisplatin combination chemotherapy is currently used as the first-line treatment option for unresectable advanced gastric cancer. On the other hand, Bang *et al*. reported in patients with human epidermal growth factor receptor 2 (HER2)-positive gastric or gastro-oesophageal junction cancer that addition of trastuzumab (monoclonal antibody to HER2) to chemotherapy led to ignificantly longer median overall survival than chemotherapy alone (3). Thus, oral fluoropyrimidine, cisplatin and trastuzumab combination chemotherapy is currently regarded as the standard chemotherapy for HER2-positive gastric cancer.

On the other hand, cisplatin with 5-FU regimen is recommended as neoadjuvant chemotherapy for stage II/III thoracic esophageal cancer and unresectable progressive recurrent esophageal cancer (4, 5).

Cisplatin is classified as chemotherapy with high emetic risk (HEC) in several guidelines for prevention of chemotherapy-induced nausea and vomiting (CINV) (6-9).

The guidelines recommend using the combination of dexamethasone, 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist and neurokinin-1 (NK_1) receptor antagonist for prevention of CINV associated with HEC (6-9). It has been shown that adherence to the antiemetic guideline leads to an improvement of the control of CINV (10-17). Tamura *et al*. reported in patients receiving HEC that vomiting can be controlled by adhering to the antiemetic guideline, in which the rate of control is 94% for acute vomiting and 89% for delayed vomiting (18). However, the control of nausea was not sufficient (79% for acute nausea and 51% for delayed nausea). Oyama *et al*. also reported difficulty in controlling cisplatin-induced nausea (CIN) irrespective of prior antiemetic treatment with 5-HT_3 antagonist, dexamethasone, and aprepitant in patients with gastric cancer (67% for nausea) (19). Recently, Navari *et al*. showed that olanzapine, an atypical antipsychotic drug, effectively prevents nausea when used in combination with dexamethasone, aprepitant or fosaprepitant, and 5-HT_3 antagonist in patients receiving cisplatin (≥70 mg/m^2) or cyclophosphamide-doxorubicin combination, in which the rate of control of nausea during the overall period was 37% for the olanzapine-treated group and 22% for the placebo-treated group (20).

In the present study, we examined the risk of CIN in patients with esophageal or gastric cancer who received their first cycle of cisplatin-based chemotherapy. Subsequently, the effect of addition olanzapine to the standard antiemetic premedication in the next chemotherapy cycle on the control of nausea was investigated in patients who experienced nausea in the first cycle of chemotherapy.

Patients and Methods

Patients. The subjects of the present study were a total of 186 patients who received their first cycle of cisplatin-based chemotherapy for esophageal or gastric cancer during January 2011 and December 2016.

The present study was carried out in accordance with the guidelines for the care for human study adopted by the Ethics Committee of the Gifu Graduate School of Medicine, and notified by the Japanese Government (approval no. 22-156 of the Institutional Review Board). In view of the retrospective nature of the study, the need for the informed consent of participants was not mandated. Data were obtained from medical record and were coded anonymously.

Antiemetic medication and evaluation of the control of CINV. All patients received the standard antiemetic medication consisting of the combination of 5-HT_3 receptor antagonist such as granisetron (3 mg/day, intravenously, on day 1), dexamethasone (9.9 mg/day, intravenously, on day 1 and 4-8 mg/day, orally, on days 2-4) and NK1 receptor antagonist such as aprepitant (125 mg, orally, on day 1 and 80 mg/day, orally, on days 2 and 3). The primary end-point was the control of significant (grade≥2) nausea during overall period. The control of vomiting and the complete response (no vomiting and no rescue treatment) were also checked during acute (within 24 hours), delayed (24-120 hours), and overall (0-120 hours) periods.

Table I. *Demographics of patients*.

Characteristic	
Number of patients	186
Gender (male/female)	148/38
Age (minimum-maximum), years	65.2 (31-83)
Type of cancer	
Gastric cancer	101 (54, 3%)
Esophageal cancer	85 (45.7%)
Chemotherapy regimen (cisplatin dose)	
Docetaxel+5-FU+cisplatin (40 mg/m^2)	79 (42.5%)
Docetaxel+5-FU+cisplatin (70 mg/m^2)	6 (3.2%)
Docetaxel+S-1+cisplatin (60 mg/m^2)	33 (17.7%)
Docetaxel+S-1+cisplatin (40 mg/m^2)	4 (2.2%)
S-1+cisplatin (60 mg/m^2)	28 (15.1%)
5-FU+cisplatin (80 mg/m^2)	15 (8.1%)
Capecitabine+cisplatin (80 mg/m^2)	12 (6.5%)
Irinotecan+cisplatin (30 mg/m^2)	9 (4.8%)

5-FU: 5-Fluorouracil. Data are the mean±S.D, or absolute number, with percentage.

Risk analysis for nausea in the overall period. Demographics of patients who received their first cycle of cisplatin-based chemotherapy were compared between patients who experienced significant nausea and those who did not during overall period. Subsequently, risk factors for significant nausea were examined by univariate and multivariate logistic regression analyses. The cut-off value for age or cisplatin dose was assessed by the Youden index method in the receiver operating characteristic curve (ROC) analysis, in which the Youden index was calculated as the maximum value of (sensitivity+specificity−1), according to methods described elsewhere (21).

Statistical analyses. Data were analyzed by using SPSS version 22 (IBM Corp., Armonk, NY, USA). For comparison of the demographics of patients between the two groups, *t*-test was used for parametric analysis and chi-square test or Mann–Whitney *U*-test was for non-parametric analysis. The rate of no significant nausea and the rate of no vomiting were compared by Kruskal-Wallis test followed by Scheffe's test for multiple comparison, or by McNemar test for comparison between the paired two groups. Differences with a *p*-value less than 0.05 were considered significant.

Results

Demographics of patients. Demographics of patients were shown in Table I. Among 186 patients, there were 139 (74.7%) over the age of 60 years. There were 92 patients (49.5%) treated with doses of cisplatin less than 50 mg, 61 patients (32.8%) treated with more than 50 mg but less than 70 mg, and 33 patients (17.7%) treated with more than 70 mg. The average cisplatin dose was 52.8 mg/m^2.

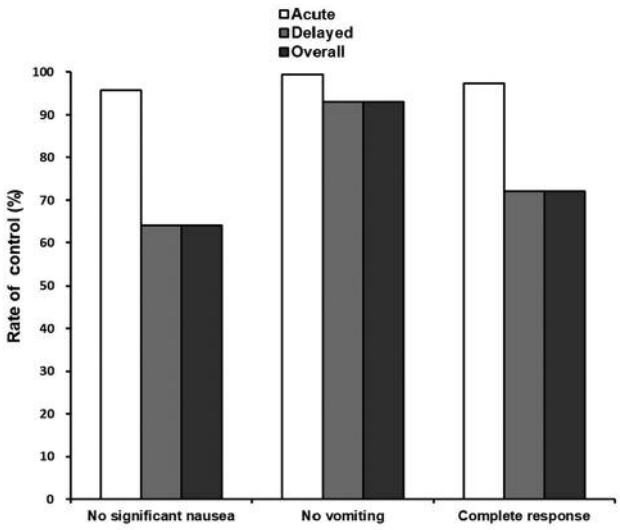

Figure 1. *Rate of no significant nausea, no vomiting, and the complete response during acute, delayed and overall treatment period in patients with esophageal or gastric cancer who received cisplatin-based chemotherapy.*

Control of CINV. The rate of no significant nausea, the rate of no vomiting and the complete response are shown in Figure 1. The control of CINV during the acute period was favorable. Although the rate of no vomiting during the delayed period was favorable, the rate of no significant nausea and the complete response rate during delayed periods were worse.

Comparison of demographics between patients with significant nausea and those without it. To determine the risk for cisplatin-induced nausea, demographics of patients were compared between patients who had significant (grade≥2) nausea and those who did not. As shown in Table II, significant differences in gender ($p<0.001$), drinking habit ($p=0.018$), and cisplatin dose ($p=0.004$) were observed between the two groups, with more female patients, habitual drinkers, and those treated with a higher cisplatin dose more frequently experiencing significant nausea.

Risk factors for CIN. The cut-off values for age and cisplatin dose were 66.5 years and 50 mg/m^2, respectively, as determined by ROC curve analysis. The area under curves (AUC) for age and cisplatin dose were 0.512 (95% confidence interval: 0.424-0.600) and 0.608 (0.522-0.695), respectively. Considering clinical utility, the cut-off age was set 65 years. As shown in Table III, a univariate logistic regression analysis indicated that cisplatin dose at ≥50 mg/m^2 ($p=0.018$) and female gender ($p=0.026$) were found to be significant risks for CIN. A multivariate logistic regression analyses also showed that both were significant risk factors for CIN ($p=0.022$ and $p=0.003$, respectively).

Table II. *Comparison of patient demographics between patients with significant nausea and those without nausea.*

Characteristic	Patients with nausea	Patients without nausea	*p*-Value
Number of patients	67	119	
Female (%)	23 (34.3%)	16 (13.4%)	<0.001[a]
Age (minimum-maximum)	64.5 (31-83)	65.4 (34-83)	0.476[b]
Laboratory data*			
Aspartate aminotransferase (U/l)	25±17	26±22	0.871[c]
Alanine aminotransferase (U/l)	22±22	23±22	0.821[c]
Creatinine clearance (ml/min)	86.3±30.1	80.7±26.8	0.205[c]
Total-bilirubin (mg/dl)	0.56±0.21	0.62±0.34	0.105[c]
Neutrophil count (n/μl)	4578±2705	4349±1891	0.542[c]
Leukocyte count (n/μl)	6740±3031	6552±2224	0.659[c]
Hemoglobin (g/dl)	12.5±1.7	12.4±1.8	0.87[c]
Platelet count (n/μl)	26.7±8.7	26.3±7.5	0.744[c]
Type of cancer, n (%)			
Gastric	31 (46.3%)	49 (41.1%)	0.501a
Esophageal	36 (53.7%)	70 (58.9%)	
Patients with previous therapy, n (%)	11 (16.4%)	17 (14.3%)	0.696[a]
With smoking history	26 (38.8%)	61 (51.2%)	0.102[a]
Habitual drinker	3 (4.5%)	17 (14.3%)	0.018a
Obesity (BMI≥25 kg/m^2)	7 (10.4%)	17 (14.3%)	0.746[a]
Low body weight (BMI<18.5 kg/m^2)	15 (22.4%)	35 (29.4%)	0.300[a]
Cisplatin dose (mg/m^2)	57.3±16.5	50.6±13.9	0.004[a]

BMI: Body mass index. *Mean±S.D, or absolute number percentage. [a]Chi-square test, [b]Mann-Whitney *U*-test, [c]*t*-test.

Relationship between the number of risk factors and the rate of no significant nausea. As shown in Figure 2, the rate of no significant nausea decreased as the number of risk factors increased (1 risk factor *versus* no risk factor: $p=0.0055$), and 42.5% (2 risk factors *versus* no risk factor: $p=0.0084$).

Comparison of antiemetic effects of olanzapine and prochlorperazine added to the standard antiemetic medication in patients who had previous nausea. Among 67 patients who had nausea during the first cycle of chemotherapy, 53 patients (79.1%) had either or both risk factors female gender and cisplatin dose at ≥50 mg/m^2. Of 53 patients who had either one or two risk factors and previous experience of significant nausea, 13 were treated with olanzapine (5 mg/day, before sleep on days 1-4) and seven patients with prochlorperazine (15 mg/day, three times a day on days 1-5), in addition to the standard three-drug antiemetic medication before the second cycle of chemotherapy. As shown in Figure 3A, the rate of no significant nausea during

Table III. *Univariate and multivariate logistic regression analyses for the risk of cisplatin-induced significant nausea in patients with esophageal or gastric cancer.*

	Univariate analysis			Multivariate analysis		
Factor	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Cisplatin ≥50 mg/m^2	2.092	1.133-3.862	0.018	2.087	1.112-3.918	0.022
Female	3.147	1.512-6.551	0.026	3.140	1.490-6.617	0.003
Age under 65 years	1.193	0.645-2.207	0.574			
Non habitual drinker	2.447	0.783-7.647	0.124			

overall period was significantly elevated from the first to the second cycle for olanzapine ($p<0.01$) and non significantly for prochlorperazine. Similarly, as shown in Figure 3B, the complete response was significantly improved almost 3-fold ($p<0.001$) by olanzapine but not by prochlorperazine (in which control in fact declined non significantly).

Discussion

In the present study, the control of both nausea (95.7%) and vomiting (99.5%) were favorable during the acute period of cisplatin-based chemotherapy in patients with esophageal or gastric cancer. Moreover, the rate of no vomiting was also high (93.0%) during delayed period. However, the rate of no significant nausea during delayed period was still insufficient (64.0%). Tamura *et al*. reported that in patients receiving HEC or moderate emetic risk chemotherapy (MEC) that the incidence of nausea was 20.8% during the acute period and 49.4% during the delayed period in 1,195 patients receiving HEC (18). Oyama *et al*. also reportedthat the rate of no nausea in gastric cancer patients receiving cisplatin (60 mg/m^2) and S-1 (80 mg/m^2) was 92.4% during the acute period and 66.0% during the delayed period (19). Therefore, our data were generally consistent with their data.

In the present study, patients were all treated with the guideline-consistent antiemetic medication for HEC consisting of the combination of 5-HT_3 receptor antagonist (day 1), dexamethasone (days 1-4) and an NK_1 receptor antagonist aprepitant (days 1-3). The three-drug antiemetic medication seemed to be insufficient for the control of delayed nausea in a particular population of patients. In this respect, it is conceivable that more careful and personalized antiemetic medication is required to control nausea based on the risk factors for CIN. Therefore, we determined in the present study the risk factors for nausea in patients receiving cisplatin-based chemotherapy. In our data, the percentage of females (34.3% *versus* 13.4%, $p<0.001$) and the dose of cisplatin (57.3±16.5 mg/m^2 *versus* 50.6±13.9 mg/m^2, $p=0.004$) were significantly higher, while the percentage of habitual drinkers (4.5% *versus* 14.3%, $p=0.018$) was significantly lower in patients with nausea than in those without. The cut-off values for age and cisplatin dose as assessed by ROC analysis were 66.5 years and 50 mg/m^2, respectively. The multivariate logistic regression indicated that both female gender and cisplatin doses at 50 mg/m^2 and higher were significant risk factors for CIN. The present data were consistent with our previous data in 779 patients receiving the first cycle of different emetic risk categories of chemotherapy for various cancer types showing that female gender (odds ratio: 1.615, 95% confidence interval: 1.022-2.552; $p=0.04$) was a significant risk for nausea (22). A number of studies have also demonstrated that being female is a risk factor for CINV associated with cisplatin (23-25).

It was notable that cisplatin was fond to be highly emetogenic when used at doses of 50 mg/m^2 and higher, since there has been little evidence suggesting the relationship between the dose of cisplatin and its emetogenic property. Interestingly, in the National Comprehensive Cancer Network (NCCN) 2005 antiemetic guideline, anticancer drugs are categorized based on the emetic risk into five categories (levels 1-5) and cisplatin at doses of 50 mg/m^2 and higher is classified as level 5 (HEC), while cisplatin at doses lower than 50 mg/m^2 are classified as level 4 (MEC). Therefore, our present data do support the basis of the dose of cisplatin as HEC defined by NCCN 2005. In contrast, Hesketh *et al*. reported in patients receiving the first cycle of chemotherapy containing cisplatin at doses of 70 mg/m^2 that cisplatin at 80 mg/m^2 and higher was associated with an increased risk for reduction in complete response (OR: 1.149, 95% CI: 1.005-1.314, $p=0.033$) (26). Thus, the cut-off dose of cisplatin was different between our data and those reported by Hesketh *et al*. (26). This may be explained by the difference in the indicator of antiemesis (no nausea or complete response). In addition, doses of cisplatin administered were different between the two groups: 30 mg/m^2 to 80 mg/m^2 in the present study and 70 mg/m^2 and more in theirs.

In any case, care should be taken to avoid delayed nausea in female patients with esophageal or gastric cancer who receive cisplatin at 50 mg/m^2 or higher.

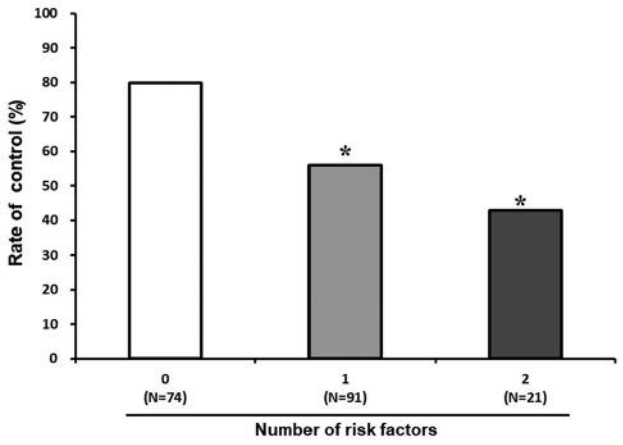

Figure 2. *Relationship between the number of risk factors and the rate of no significant nausea in patients receiving cisplatin-based chemotherapy. Risk factors were female gender and a dose of cisplatin ≥50 mg/m^2. *Significantly different at p<0.01 versus no risk (Kruskal–Wallis test followed by Scheffe's test).*

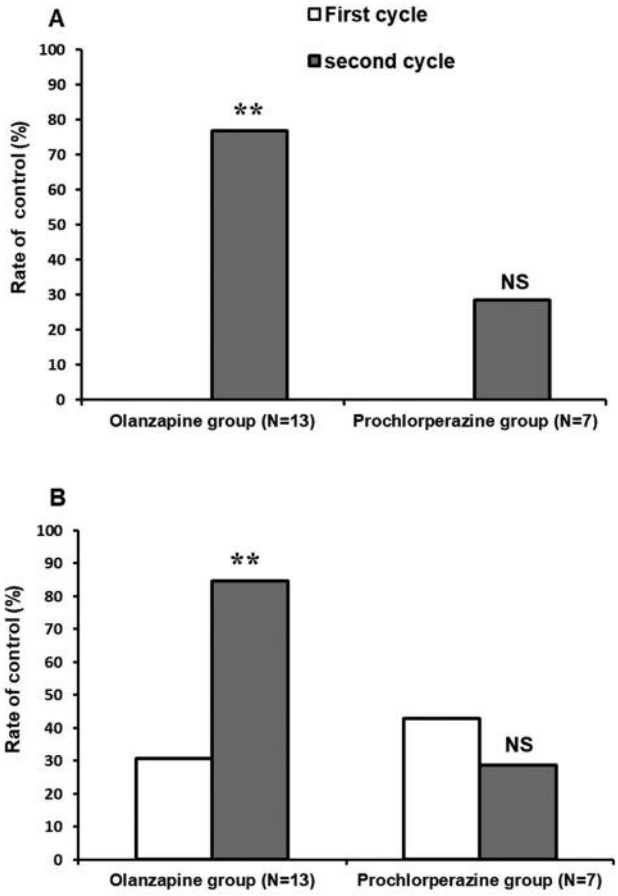

Figure 3. *Comparison of the effects of olanzapine and prochlorperazine on the rate of no significant nausea (A) and complete response (B) for the overall treatment period in patients who showed nausea in the first cycle of chemotherapy. Olanzapine (5 mg/day once a day for 5 days) or prochlorperazine (15 mg/day 3 times a day for 5 days) was added to the standard three-drug antiemetic medication. Control of nausea and vomiting was assessed in the second cycle of chemotherapy. **Significantly different at p<0.01 versus the first cycle (McNemar's test).*

Olanzapine is classified as an atypical antipsychotic drug (27). Unlike typical antipsychotic drugs such as haloperidol and prochlorperazine, olanzapine has a weaker dopamine D_2 receptor blocking activity than typical antipsychotic drugs, although it acts on various receptors, including 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, histamine H1, muscarinic m_1, m_2, m_3, m_4, and adrenergic α_1 receptors (28-30). Interestingly, increase in appetite or overeating is a well-known side-effect associated with olanzapine (31, 32). In the present study, we examined the effect of olanzapine in patients in whom nausea control failed during the first cycle of chemotherapy, and compared it with that of prochlorperazine. It was notable that olanzapine dramatically increased the rate of no significant nausea (from 0% to 76.9%, $p<0.01$), whereas prochlorperazine had no significant effect. These findings suggest that olanzapine is useful for improving the control of nausea in high-risk patients who had nausea in the previous chemotherapy cycle or in those who have either or both female and cisplatin at ≥50 mg/m^2 as risks for nausea. Our data were generally consistent with the data reported by Navari *et al*., in a phase 3 study compared the antiemetic effect between olanzapine and aprepitant in combination with palonosetron and dexamethasone in patients receiving cisplatin (≥70 mg/m^2) or cyclophosphamide and doxorubicin combination chemotherapy. They found that olanzapine was significantly more effective than aprepitant in the control of delayed nausea (69% *versus* 38%, $p<0.01$), although there were no significant differences in the control of acute nausea or vomiting (33). Based on the data reported by Navari *et al*. (33), the NCCN guideline recommends a combination regimen of olanzapine (10 mg *per os*, days 1-4), palonosetron (0.25 mg *i.v.*, day 1), and dexamethasone (20 mg *i.v.*, day 1) as an alternative antiemetic regimen for HEC and MEC in 2014.

On the other hand, it is still uncertain why olanzapine is superior to prochlorperazine in the control of nausea. It has been demonstrated in rats that cisplatin reduces the plasma concentration of ghrelin, an appetite-stimulating hormone (34), and food intake, both of which are reversed by 5-HT_{2B} or 5-HT_{2C} receptor antagonist but are mimicked by 5-HT_{2B} or 5-HT_{2C} receptor agonist (35). Therefore, it is considered that cisplatin reduces appetite and food intake by inhibiting the release of ghrelin *via* release of serotonin from enterochromaffin-like cells and subsequent stimulation of 5-HT_{2B} and 5-HT_{2C} receptors (35). Olanzapine but not

prochlorperazine has high affinity for both 5-HT_{2B} and 5-HT_{2C} receptors (30). Indeed, the plasma ghrelin level is reported to be elevated acutely but decreases during chronic treatment with olanzapine (36). It has also shown in rats that olanzapine leads to hyperphagia and weight gain by up-regulating ghrelin signaling pathway (37). Taken together, it is suggested that the blockade of 5-HT_{2B} and 5-HT_{2C} receptors followed by stimulation of ghrelin release may contribute at least in part to the olanzapine-induced improvement of the control of nausea in patients receiving cisplatin-based chemotherapy.

Therefore, it is suggested that olanzapine is useful for improving the control of nausea in high-risk patients who have nausea in their previous chemotherapy cycle or in those who have either or both female gender and cisplatin at ≥50 mg/m^2 as risks for nausea.

There are several limitations to the present study: Firstly, this was a retrospective study performed at a single center. Secondly, the sample size of the study comparing the antiemetic effect between olanzapine and prochlorperazine was too small to obtain highly reliable data. Thirdly, the influence of confounding factors was not excluded.

In conclusion, cisplatin-induced delayed nausea was still insufficiently controlled even after implementation of the guideline-consistent three-drug antiemetic medication. The dose of cisplatin (≥50 mg/m^2) and female gender were significant risks for nausea. The addition of olanzapine to the standard antiemetic medication was effective for prevention of delayed nausea in patients who experienced nausea in the previous chemotherapy cycle.

Conflicts of Interest

All Authors have no conflict of interest in regard to this study.

Source of Funding

None declared.

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Received September 7, 2017
Revised October 2, 2017
Accepted October 9, 2017