Supportive Care in Cancer (2019) 27:1139–1147
https://doi.org/10.1007/s00520-018-4403-y

ORIGINAL ARTICLE

# Risk factors associated with chemotherapy-induced nausea and vomiting in the triplet antiemetic regimen including palonosetron or granisetron for cisplatin-based chemotherapy: analysis of a randomized, double-blind controlled trial

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Received: 7 March 2018 / Accepted: 3 August 2018 / Published online: 10 August 2018


## Abstract

**Purpose** The triplet antiemetic regimen is recommended for cisplatin-based highly emetogenic chemotherapy, in the current guidelines for antiemetic prophylaxis. Although risk factors related to chemotherapy-induced nausea and vomiting (CINV) have been identified by several prior studies, there are only few studies evaluating risk factors associated with the prophylactic triplet antiemetic therapy, particularly in palonosetron use. The present study aimed to reveal the risk factors related to CINV development in patients receiving cisplatin and to compare CINV risk factors between palonosetron and granisetron use.

**Methods** In total, 825 patients in a phase III trial receiving palonosetron with graniestron were evaluated. Multivariate logistic regression models were used to predict risk factors associated with CINV development. Additionally, risk factors associated with CINV development were separately evaluated in each treatment group.

**Results** Multivariate analysis of the entire study group revealed that sex, age, cisplatin dose, and granisetron use were significant and independent factors affecting CINV development in the overall phase. Similarly, sex and age were risk factors for CINV in both treatment groups. Kaplan–Meier curves classified by each treatment group showed no significant difference between the groups among patients without any risk factors for CINV ($P = 0.353$). Conversely, complete response rates for patients with at least one risk factor were higher in patients receiving palonosetron ($P = 0.049$).

**Conclusions** This analysis revealed the importance of previously reported CINV risk factors when using triplet antiemetics. Palonosetron might be preferred for patients with at least one risk factor.

**Keywords** Chemotherapy-induced nausea and vomiting (CINV) · Risk factors · Granisetron · Palonosetron · Aprepitant

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00520-018-4403-y) contains supplementary material, which is available to authorized users.

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## Introduction

Chemotherapy-induced nausea and vomiting (CINV) are two of the most undesirable adverse drug reactions related to cancer treatment, and they lead to poor quality of life (QOL) and reduced compliance to chemotherapy [1, 2]. The introduction of two antiemetics, palonosetron, which is a second-generation 5-hydroxytryptamine 3 (5-$HT_3$) receptor antagonist having long half-life, and aprepitant, which is a neurokinin-1 (NK-1) receptor antagonist, has greatly improved CINV management. The second-generation 5-$HT_3$ receptor antagonist, such as palonosetron, has almost 100-fold stronger binding affinity for 5-$HT_3$ receptor than the first-generation serotonin antagonist, such as granisetron; further, they show positive cooperativity and bind to the 5-$HT_3$ receptor. This binding leads to the inhibition of 5-$HT_3$-NK-1 receptor crosstalk [3–5].

The latest guidelines for antiemetic treatment recommend the use of triplet antiemetic combination (i.e., concomitant administration of 5-HT3 receptor antagonist, NK-1 receptor antagonist, and dexamethasone) for cancer patients receiving highly emetogenic chemotherapy (HEC), such as cisplatin regimen [6–8]. Although compliance to the antiemetic guidelines has led to the reduction in CINV incidence, improving the QOL in cancer patients, some patients are still bothered with CINV during chemotherapy, particularly at 24 h or later following cisplatin administration [9–11]. There is increasing evidence of the possible factors related to CINV development or response to antiemetic treatment among patients treated with cisplatin-containing regimen. The risk factors associated with CINV development can be categorized into patient-related and treatment-related factors [12, 13]. With regard to patient-related factors, it has long been well known that younger age and female sex are related to a high risk for CINV, whereas high alcohol intake is associated with low risk [14–18]. However, these previous investigations were mainly based on first-generation 5-HT3 antagonists, and without the use of NK-1 antagonists.

Identification of risk factors related to CINV and classification of high- or low-risk patients may lead to a reduction in CINV incidence through antiemetics use. Knowledge of the patient-related risk factors of CINV before cisplatin administration could help focus preventive effects improving patient QOL.

Although several pharmacoepidemiology studies have already reported the risk factors associated with CINV development, these identified risk factors were not consistent among the studies and some studies have no distinctions between the acute, delayed, and overall phase. Moreover, only few studies have evaluated the triplet antiemetic combination, particularly with palonosetron. The objective of the current study was to reveal the risk factors related to CINV development in acute, delayed, and overall phase receiving cisplatin and to compare the risk factors for CINV development related to the use of palonosetron and granisetron.

## Methods

### Study design and treatment

Patients registered in our trial were chemo-naïve and had various types of solid tumor. Our clinical trial TRIPLE is a prospective randomized, double-blind, multicenter phase III trial comparing the use of palonosetron and granisetron under the concomitant administration of aprepitant and dexamethasone for the control of cisplatin-induced CINV in Japanese patients. All enrolled patients were scheduled to receive cisplatin administration ($\geq 50$ mg/m$^2$) as their first cycle of chemotherapy, at hospital admission. All patients were administered with 125 mg aprepitant on day 1, followed by 80 mg daily on days 2–3; 9.9 mg dexamethasone on day 1, followed by 6.6 mg daily on days 2–4; and intravenous dose of 1 mg granisetron or 0.75 mg palonosetron before cisplatin administration on day 1. For a detailed description of our phase III study, the study endpoints and the primary results have been provided previously [19]. The trial was registered with UMIN 000004863.

### Assessment and statistical analysis

All the evaluated patients were hospitalized and observed for a 5-day study period. Rescue antiemetic medications were permitted when investigators determined that medication was necessary for CINV or patients desired additional antimemetics for these symptoms. Usual antiemetic therapy, including domperidone, metoclopramide, or dexamethasone, was allowed, but additional administration of granisetron or palonosetron was prohibited during the study period. Episodes of CINV and any use of rescue antiemetic medication after cisplatin administration were recorded in each patient's diary during the first 24 h (acute) and during the following 4 days (delayed). In our phase III trial, except for the pharmacist who prepared the clinical trial medicine, all clinical staff (doctors, clinical pharmacists, and nurses) were blinded. Moreover, our clinical trial designated study pharmacists at each center who were blinded to antiemetic treatment allocation and who evaluated efficacy endpoints for each patient every day on the basis of diary data and interview. The assignment of study pharmacists together with hospitalization were for the purpose of the rigorous assessment of nausea and vomiting and rescue medication use.

The TRIPLE study included 827 patients. Patients who received the study medication and confirmed a nausea or vomiting episode or had rescue antiemetic use and those who could undergo evaluation of events within 120 h after

cisplatin administration were candidates for this analysis. Of these patients, 825 patients were assessed in this analysis of CINV risk factors. The efficacy endpoint of this analysis was complete response (CR, defined as no vomiting and no use of rescue antiematics) within 120 h after the start of cisplatin administration. The endpoint was also separately evaluated in the acute and delayed phases. Treatment failure for this risk factor analysis was defined as no CR.

Multivariate logistic regression analysis, with adjustments for potential clinical factors, including sex, age, cisplatin dose, performance status (PS), body mass index (BMI), and 5-$HT_3$ receptor antagonist, was conducted to identify significant risk factors associated with CINV, and odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

The risk factors associated with CINV incidence were also evaluated separately in each treatment group. The age cutoff of 60 years and cisplatin dose cutoff of 79.2 mg/$m^2$ were determined using receiver operating characteristic curve analysis. Patients with a BMI ≥ 25 kg/$m^2$ were considered overweight. This cutoff value of BMI was determined according to the universal criteria developed by World Health Organization [20]. The incidence trends of the relationship between treatment failure and the number of identified factors were evaluated using the Cochran–Armitage trend test. Furthermore, the treatment failure curves classified by the number of identified factors in each subgroup were evaluated using the Kaplan–Meier method, with comparison between the granisetron and palonosetron groups using the log-rank test.

## Results

### Patient characteristics

Eight hundred and twenty-five patients were evaluated in this post hoc analysis. The baseline patient characteristics (all patients and patients grouped according to treatment) are listed in Table S1. The median age of the evaluated patients was 64 years with a range of 25–83 years, and 74.5% of patients were men. Significantly, the percentage of patients who had well-known risk factors associated with CINV development was well balanced between the treatment groups.

### Risk factors for CINV

Univariate and multivariate logistic regression analyses of various baseline variables were performed to confirm the independent risk factors related to CINV development. The clinical factors considered in this risk factor analysis were sex, age, 5-$HT_3$ receptor antagonist (granisetron or palonosetron), BMI, PS, and cisplatin dose.

The results of logistic regression analyses are shown with ORs, 95% CIs, and $P$ values in Table 1. Female sex (OR 2.572, $P < 0.0001$), age < 60 years (OR 1.717, $P = 0.0008$), cisplatin dose (OR 1.017, $P = 0.0350$), and granisetron administration (OR 1.357, $P = 0.0409$) were revealed to be independent and significant CINV risk factors in the overall phase. Similarly, female sex (OR 2.626, $P < 0.0001$), age < 60 years (OR 1.666, $P = 0.0016$), cisplatin dose (OR 1.016, $P = 0.0488$), and granisetron administration (OR 1.454, $P = 0.0125$) were shown to be risk factors for CINV during delayed phase. In contrast, female sex (OR 3.068, $P < 0.0001$) and age < 60 years (OR 1.737, $P = 0.0384$) were identified to be CINV risk factors in acute phase.

Multivariate logistic regression revealed that female sex (OR 2.543, $P < 0.0001$) and age < 60 years (OR 1.841, $P = 0.0069$) were significant factors in the granisetron group (Table 2, multivariate analysis in the overall phase). Similarly, female sex (OR 2.597, $P < 0.0001$) and age < 60 years (OR 1.658, $P = 0.0306$) were identified as risk factors in the palonosetron group (Table 2, multivariate analysis in the overall phase).

### Relationship between CINV development and the number of identified risk factors

Based on the multivariate analysis results, two patient-related factors (sex and age) and two treatment-related factors (cisplatin dose and type of 5-$HT_3$ receptor antagonist) were identified to be significant independent risk factors associated with CINV development during the overall phase. The identified factors and their numbers were related to the proportion of treatment failure; these associations are reported in Table 3. Increased number of holding risk factors was related to the proportion of treatment failure during the overall phase ($P < 0.0001$). Antiemetic treatment failure was observed in 22.7% of patients without any risk factors, 32.0% of patients with one risk factor, 42.6% of patients with two risk factors, 63.3% of patients with three risk factors, and 66.7% of patients with four risk factors. The increased number of identified factors was strongly related to CINV development in a similar fashion in both phases (acute: $P < 0.0001$; delayed: $P < 0.0001$).

We performed a similar analysis in each treatment group. CR rate was significantly decreased in both the treatment groups in accordance with increased number of risk factors (Table 4).

### Relationship between time to antiemetic treatment failure and the number of identified factors

Figure 1 shows the Kaplan–Meier curves of the time to antiemetic treatment failure in accordance with the number of identified risk factors (sex, age, cisplatin dose, and the type of 5-$HT_3$ receptor antagonist) for CINV in overall patients. Time to treatment failure was significantly related to the increased number of identified factors ($P < 0.0001$). Similarly,

**Table 1** Univariate and multivariate analyses of association of complete response with clinical variables

| Factors | *N* | Overall (0–120 h) | | | | Acute (0–24 h) | | | | Delayed (24–120 h) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Sex | | | | | | | | | | | | | |
| Male | 615 | 1 | < 0.0001 | 1 | < 0.0001 | 1 | < 0.0001 | 1 | < 0.0001 | 1 | < 0.0001 | 1 | < 0.0001 |
| Female | 210 | 2.607 (1.892–3.592) | | 2.572 (1.855–3.566) | | 3.186 (1.918–5.294) | | 3.068 (1.832–5.138) | | 2.656 (1.927–3.661) | | 2.626 (1.894–3.647) | |
| Age | | | | | | | | | | | | | |
| ≥ 60 | 580 | 1 | 0.0006 | 1 | 0.0008 | 1 | 0.0254 | 1 | 0.0384 | 1 | 0.0011 | 1 | 0.0016 |
| < 60 | 245 | 1.705 (1.258–2.311) | | 1.717 (1.258–2.311) | | 1.790 (1.074–2.982) | | 1.737 (1.030–2.929) | | 1.661 (1.224–2.254) | | 1.666 (1.213–2.288) | |
| 5-$HT_3$RA | | | | | | | | | | | | | |
| Palonosetron | 412 | 1 | 0.0473 | 1 | 0.0409 | 1 | 0.9068 | 1 | 0.9377 | 1 | 0.0154 | 1 | 0.0125 |
| Granisetron | 413 | 1.331 (1.003–1.766) | | 1.357 (1.013–1.817) | | 1.030 (0.625–1.698) | | 1.021 (0.613–1.698) | | 1.421 (1.070–1.888) | | 1.454 (1.084–1.952) | |
| BMI | | | | | | | | | | | | | |
| ≥ 25.0 | 148 | 1 | 0.0726 | 1 | 0.1080 | 1 | 0.1861 | 1 | 0.2846 | 1 | 0.0738 | 1 | 0.1182 |
| < 25.0 | 677 | 1.417 (0.968–2.074) | | 1.380 (0.932–2.044) | | 1.671 (0.781–3.576) | | 1.525 (0.740–3.303) | | 1.418 (0.967–2.080) | | 1.370 (0.923–2.035) | |
| PS | | | | | | | | | | | | | |
| 0 | 556 | 1 | 0.8688 | 1 | 0.7678 | 1 | 0.616 | 1 | 0.5149 | 1 | 0.863 | 1 | 0.7643 |
| 1–2 | 269 | 0.975 (0.722–1.317) | | 0.954 (0.698–1.304) | | 0.870 (0.504–1.500) | | 0.831 (0.477–1.450) | | 0.974 (0.720–1.317) | | 0.953 (0.696–1.305) | |
| CDDP dose | 825 | 1.011 (0.996–1.027) | 0.1419 | 1.017 (1.001–1.033) | 0.0350 | 1.012 (0.985–1.039) | 0.3933 | 1.018 (0.990–1.047) | 0.2059 | 1.010 (0.995–1.026) | 0.1806 | 1.016 (1.000–1.032) | 0.0488 |

*OR* odds ratio, *CI* confidence interval, *5-$HT_3$RA* 5-$HT_3$ receptor antagonist, *BMI* body mass index, *PS* performance status, *CDDP* cisplatin

**Table 2** Risk factors for CINV in overall phase according to treatment group

| | | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| Factors | *N* | Treatment failure, *n* (%) | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Granisetron (*n* = 413) | | | | | | |
| Sex | | | | | | |
| Male | 309 | 108 (35.0) | 1 | < 0.0001 | 1 | < 0.0001 |
| Female | 104 | 61 (58.5) | 2.640 (1.675–4.161) | | 2.543 (1.600–4.043) | |
| Age | | | | | | |
| ≥ 60 | 290 | 105 (36.2) | 1 | 0.0030 | 1 | 0.0069 |
| < 60 | 123 | 64 (52.0) | 1.911 (1.247–2.930) | | 1.841 (1.182–2.867) | |
| BMI | | | | | | |
| ≥ 25.0 | 70 | 27 (38.6) | 1 | 0.6611 | 1 | 0.7325 |
| < 25.0 | 343 | 142 (41.4) | 1.125 (0.664–1.906) | | 1.099 (0.638–1.894) | |
| PS | | | | | | |
| 0 | 282 | 119 (42.2) | 1 | 0.4384 | 1 | 0.2591 |
| 1–2 | 131 | 50 (38.2) | 0.846 (0.553–1.293) | | 0.774 (0.496–1.208) | |
| CDDP dose | 413 | 310 | 1.009 (0.988–1.031) | 0.3975 | 1.013 (0.991–1.035) | 0.2585 |
| Palonosetron (*n* = 412) | | | | | | |
| Gender | | | | | | |
| Male | 306 | 87 (28.4) | 1 | < 0.0001 | 1 | < 0.0001 |
| Female | 106 | 54 (50.9) | 2.614 (1.659–4.118) | | 2.597 (1.632–4.132) | |
| Age | | | | | | |
| ≥ 60 | 290 | 91 (31.4) | 1 | 0.0614 | 1 | 0.0306 |
| < 60 | 122 | 50 (41.0) | 1.519 (0.980–2.353) | | 1.658 (1.049–2.621) | |
| BMI | | | | | | |
| ≥ 25.0 | 91 | 19 (24.4) | 1 | 0.0433 | 1 | 0.0670 |
| < 25.0 | 50 | 122 (36.5) | 1.787 (1.018–3.138) | | 1.716 (0.963–3.059) | |
| PS | | | | | | |
| 0 | 274 | 91 (33.2) | 1 | 0.5421 | 1 | 0.5512 |
| 1–2 | 138 | 50 (36.2 | 1.143 (0.744–1.754) | | 1.145 (0.733–1.787) | |
| CDDP dose | 412 | 141 | 1.014 (0.9927–1.037) | 0.2040 | 1.020 (0.997–1.044) | 0.0853 |

the two risk factors (i.e., sex and age) had cumulative effects in both groups (granisetron group: $P < 0.0001$; palonosetron group: $P < 0.0001$).

Kaplan–Meier curves of time to vomiting event according to each antiemetic treatment group confirmed that there were no significant associations in both groups among patients without any risk factors (Fig. 2a, $P = 0.353$). In contrast, for the patients possessing at least one risk factor, the CR rates were lower in patients received granisetron than in those received palonosetron and a statistically significant difference was observed (Fig. 2b, $P = 0.049$).

## Discussion

Multivariate logistic regression analysis of entire study group revealed that female sex, age of < 60 years, cisplatin dose, and granisetron use were significant and independent CINV risk factors in the overall phase. Additionally, sex and age were confirmed as risk factors associated with acute and delayed phases. A similar tendency was found in the analysis of granisetron and palonosetron group.

Several previous reports have mainly performed investigations on the risk factors associated with CINV development

**Table 3** Relationship between CINV development and the number of risk factors

| Number of risk factors | N | Treatment failure | | |
|---|---|---|---|---|
| | | Overall (0–120 h), *n* (%) | Acute (0–24 h), *n* (%) | Delayed (24–120 h), *n* (%) |
| 0 | 132 | 30 (22.7) | 6 (4.6) | 28 (21.2) |
| 1 | 334 | 107 (32.0) | 20 (6.0) | 104 (31.1) |
| 2 | 265 | 113 (42.6) | 23 (8.7) | 113 (42.6) |
| 3 | 79 | 50 (63.3) | 16 (20.4) | 49 (62.0) |
| 4 | 15 | 10 (66.7) | 2 (13.3) | 10 (66.7) |
| Cochran–Armitage trend test | | $P < 0.0001$ | $P < 0.0001$ | $P < 0.0001$ |

*N* number of patients

Risk factors: female, age < 60, cisplatin dose ≥ 79.2 mg/m$^2$, and granisetron use

using the first-generation 5-$HT_3$ receptor antagonists without NK-1 receptor antagonists and have already revealed that younger age and female are two of important risk factors.

Although it has long been recognized that female sex is an important and well-known risk factor for cisplatin-induced CINV, a previously published integrated analysis that investigated two large clinical trials using the first-generation 5-$HT_3$ receptor antagonists and dexamethasone with or without aprepitant for cisplatin-based chemotherapy demonstrated that sex was no longer a major CINV risk factor in the aprepitant-containing group [21]. However, the current study confirmed some CINV risk factors that were previously reported, including female sex, among patients treated with the triplet antiemetic regimen. This difference might be explained by the percentage of patients with CR, particularly female patients in both studies. The CR proportion in the overall phase was 68% (male/female = 66.2%/68.9%) in the previously published analysis, whereas the CR proportion was 62% (male/female = 68.3%/45.2%) in this analysis in spite of palonosetron use. Although the reason for the difference between both studies is unclear, there could have been ethnic differences in aprepitant response in female patients.

This analysis also revealed the relationship between the proportion of antiemetic treatment failure, time to treatment failure, and an increased number of CINV risk factors in all patients, including granisetron-treated patients and palonosetron-treated patients. With the increase in the number of identified factors, an increase in the proportion of the patients with antiemetic treatment failure was observed (CINV within 120 h after chemotherapy was noted in 66.7% of patients with four risk factors and 22.7% of patients without risk factors). Recently, Navari and colleagues demonstrated that adding olanzapine, a multi-acting receptor targeted antipsychotic, to standard antiemetic triplet regimen greatly improves nausea as well as the proportion of CR among cancer patients who received HEC regimen [22]. Therefore, it might be worth considering additional antiemetics, such as olanzapine, in high-risk patients who have some risk factors for CINV.

Palonosetron is widely used as a prophylactic antiemetic drug for CINV in clinical practice. Indeed, palonosetron is generally recognized to be the most effective 5-$HT_3$ receptor antagonist to prevent CINV incidence according to the results of previous meta-analyses [23, 24]. In this study, it was shown that sex and age were two common CINV risk factors in both the granisetron and palonosetron groups. However, for patients with at least one risk factor, the CR rates in palonosetron-treated patients were significantly higher than in granisetron-treated patients, whereas these were not significantly different between the subgroups among patients without any risk factor. Thus, palonosetron can be preferred over granisetron for patients who have at least one risk factor. On the other hand, palonosetron is expensive and has widespread use; thus, its use may lead to an increase in healthcare costs. The already high and continuously rising medical costs are a serious concern,

**Table 4** Relationship between CINV development and the number of risk factors according to treatment group in overall phase

| Granisetron (*n* = 413) Number of risk factor | N | Treatment failure Overall (0–120 h), *n* (%) | Palonosetron (*n* = 413) Number of risk factor | N | Treatment failure Overall (0–120 h), *n* (%) |
|---|---|---|---|---|---|
| 0 | 227 | 71 (31.3) | 0 | 216 | 58 (26.9) |
| 1 | 145 | 71 (49.0) | 1 | 164 | 62 (37.8) |
| 2 | 41 | 27 (65.9) | 2 | 32 | 21 (65.6) |
| Cochran–Armitage trend test | | $P < 0.0001$ | Cochran–Armitage trend test | | $P < 0.0001$ |

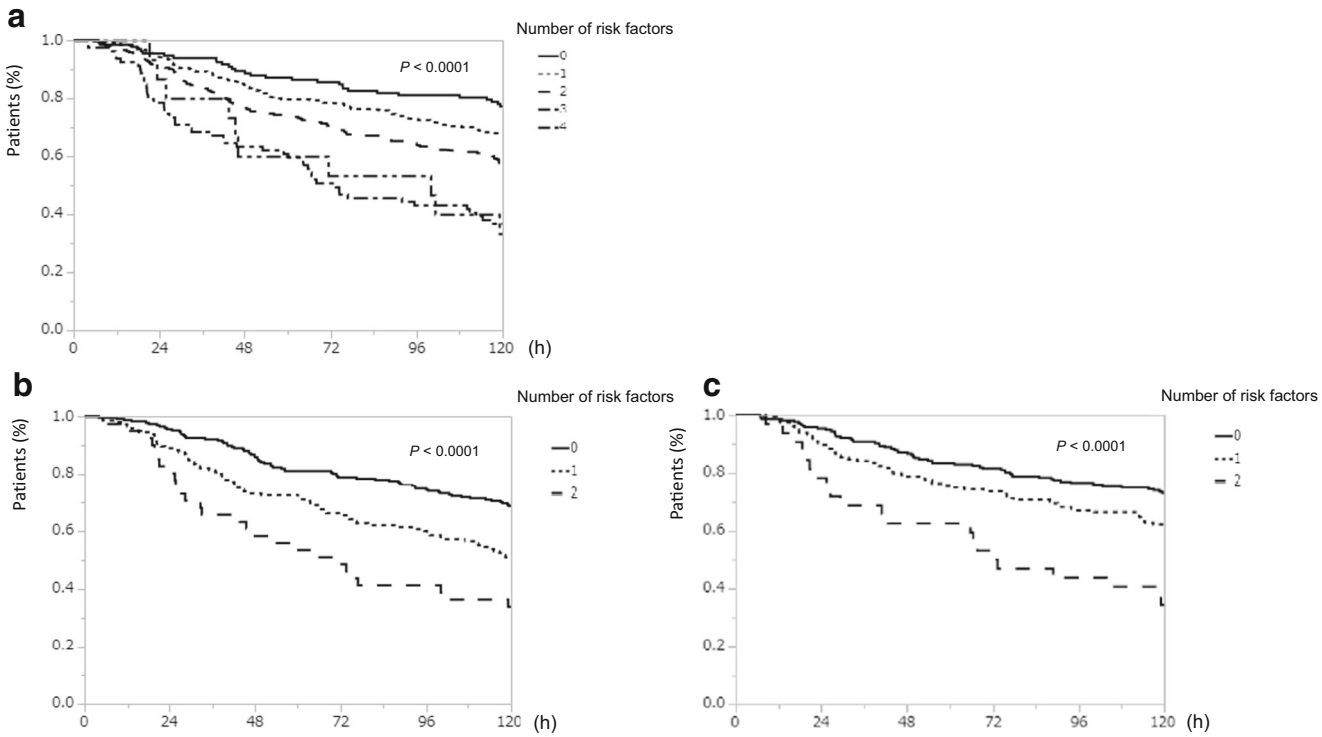


**Fig. 1** Kaplan–Meier curve of time to antiemetic treatment failure classified in accordance with the number of identified risk factors in the overall phase. **a** Kaplan–Meier plot of time to treatment failure classified according to the number of risk factors in all patients. Solid line, dotted line, dashed line, dashed dotted line, and dashed double-dotted line correspond to zero ($n = 132$), one ($n = 334$), two ($n = 265$), three ($n = 79$), and four ($n = 15$) risk factors, respectively. Risk factors: female sex, age < 60 years, cisplatin dose ≥ 79.2 mg/m$^2$, and granisetron use. **b** Kaplan–Meier plot of time to treatment failure classified according to the number of risk factors in granisetron-treated patients. Solid line, dotted line, and dashed line correspond to zero ($n = 227$), one ($n = 145$), and two ($n = 41$) risk factors, respectively. Risk factors: female sex and age < 60 years. **c** Kaplan–Meier plot of time to treatment failure classified according to the number of risk factors in palonosetron-treated patients. Solid line, dotted line, and dashed line correspond to zero ($n = 216$), one ($n = 164$), and two ($n = 32$) risk factors, respectively. Risk factors: female sex and age < 60 years

and pharmacoeconomic evaluation is important. Du and colleagues have reported the results of a cost-effectiveness analysis comparing palonosetron and conventional 5-HT$_3$ antagonists under the concomitant administration of dexamethasone, and concluded that palonosetron is not cost-effective in cancer patients treated with HEC regimen [25]. Therefore, it is considered that patients who have no risk factors should not be treated with palonosetron.

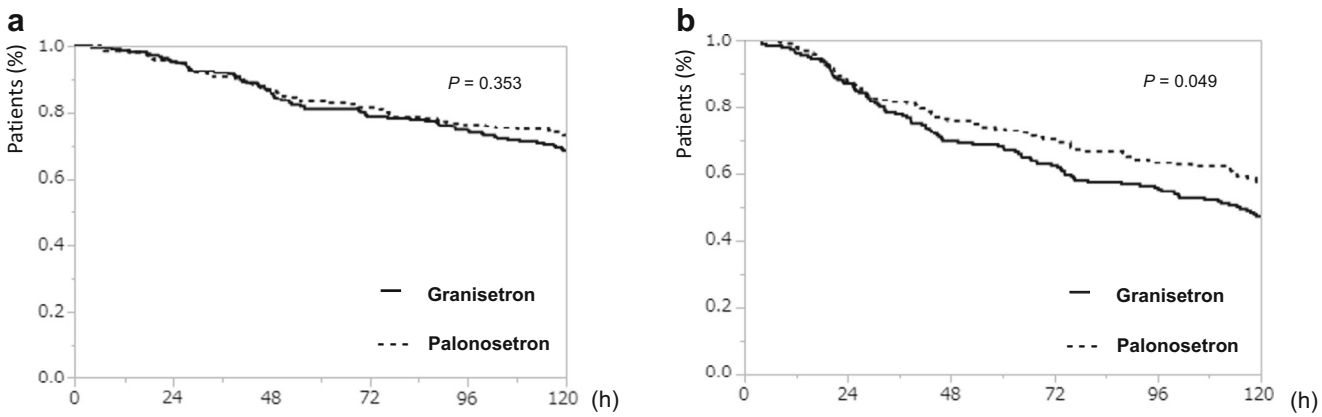


**Fig. 2** Comparison of Kaplan–Meier curves in each treatment group classified in accordance with the number of identified risk factors. **a** Kaplan–Meier plot of time to treatment failure classified according to the treatment group in patients without any risk factors. Solid and dotted lines correspond to the granisetron group and palonosetron group, respectively. **b** Kaplan–Meier plot of time to treatment failure classified according to the treatment group in patients with one or more risk factors. Solid and dotted lines correspond to the granisetron group and palonosetron group, respectively

The emetogenicity of anticancer agents and its dose are well recognized as treatment-related risk factors. Although evidence-based and consensus antiemetic guidelines have been useful in establishing the emetogenicity of chemotherapeutic agents, these guidelines have recommended antiemetic treatment only on the basis of the emetogenicity levels of chemotherapeutic agents without taking into account the individual patient's condition. Individualized antiemetic prophylaxis considering not only treatment-related risk factors but also patient-related risk factors is required. Indeed, more recently, the prediction models of CINV risk have been developed to identify each patient's CINV risk and it may help incorporate these factors into the choice of appropriate antiemetics [26, 27]. Thus, it may be possible to optimize prophylacitc antiemetic therapy using the identified risk factors in the clinical setting in the near future.

The present analysis had at least two limitations. First, the clinical efficacy of antiemetics is affected by numerous factors. It has been reported that alcohol consumption, morning sickness, and motion sickness may contribute to antiemetic effects [16–18]. Such factors that could be influenced for CINV development were not assessed in this analysis because we could not obtain the relevant data. However, all evaluated patients were hospitalized at least within 5 days after cisplatin administration. Accordingly, this minimized the effect of external factors on the onset of nausea and vomiting. The second limitation of the present study was that the study population comprised only Japanese patients. Therefore, these findings may not be generalizable to other populations.

In this study, analysis was conducted according to the primary endpoint (CR) of our phase III trial [19]. CR has long been used as a major efficacy endpoint in CINV studies and it has been adopted in a previously reported CINV risk factor analysis [21]. However, CR does not accurately include nausea evaluation and may not reflect the patient's actual experience with CINV. Some patients did not receive rescue medications in spite of experiencing nausea. Presently, nausea remains a major problem for many patients. In our phase III trial, the proportion of CR in overall phase was 63.1%, whereas the proportion of total control (TC), defined as no vomiting, no use of rescue antiemetics, and no nausea, was 44.1% in actuality. Therefore, it would become increasingly important to analyze CINV risk factors on the basis of TC.

In conclusion, this analysis of a large phase III trial revealed the importance of several CINV risk factors, including age, sex, cisplatin dose, and type of $5HT_3$ antagonist, for predicting the CINV development in patients treated with a standard antiemetic triplet regimen in cisplatin-based chemotherapy. We confirmed a significant association of an increased number of risk factors with CINV development. These findings might contribute to future clinical practice.

**Acknowledgements** We wish to thank all the patients and staff at all study institutions who participated in this study.

## Compliance with ethical standards

**Conflict of interest** DT reports grants from Yakult and personal fees from Chugai, Kyowa Hakko Kirin, Sawai, Taiho, and Nippon Kayaku outside the submitted work. KS reports personal fees from Taiho, Eli Lilly, Bristol-Myers Squibb, Astra Zeneca, Ono, and MSD outside the submitted work. KG reports grants and personal fees from Chugai, Taiho, and Ono; grants from Takeda, during the conduct of the study; grants and personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, MSD, Novartis, Pfizer, Kyowa Hakko Kirin, Merck Serono, RIKEN GENESIS, and GlaxoSmithKline; grants from Eisai, Sumitomo Dainippon Pharma, Oxonc, Astellas Pharma, AbbVie Stemcentrx, and Ignyta; personal fees from Nippon Kayaku, ABBOTT, Quintiles, Life Technologies Japan, and SRL, outside the submitted work. RM reports personal fees from Chugai, Taiho, Yakult, Novartis, Boehringer Ingelheim, Meiji Seika Pharma, Janssen, and Sawai outside the submitted work. NS reports grants and personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, Astra Zeneca, Daiichi Sankyo, MSD, Chugai, Taiho, Ono, and Bristol-Myers Squibb outside the submitted work. HH reports personal fees from Taiho, Ono, and Eli LIlly outside the submitted work. TH reports grants from Yakult, and Sawai, personal fees from Meiji Seika Pharma, and Towa outside the submitted work. TY reports grants and personal fees from Taiho, and Takeda, personal fees from Chugai, and Boehringer Ingelheim outside the submitted work. NY reports grants and personal fees from KYORIN, Ono, Taiho, Pfizer, Chugai, MSD, Daiich Sankyo, and Astra Zeneca, personal fees from M3., Otsuka Pharmaceutical, JASMIN, Bristol-Myers Squibb, Eli Lilly, Novartis Pharma, and FUJIFIRM, grant from Maruho, Shionogi, Meiji Seika Pharma, Quintiles, PAREXEL International, and ACMEDICAL outside the submitted work. All remaining authors have declared no conflicts of interest.

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