A Randomized Controlled Non-inferiority Study Comparing the Antiemetic Effect between Intravenous Granisetron and Oral Azasetron Based on Estimated 5-HT_3 Receptor Occupancy

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Abstract. *Background: The acute antiemetic effect was compared between oral azasetron and intravenous granisetron based on the 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor occupancy theory. Patients and Methods: Receptor occupancy was estimated from reported data on plasma concentrations and affinity constants to 5-HT$_3$ receptor. A randomized non-inferiority study comparing acute antiemetic effects between oral azasetron and intravenous granisetron was performed in 105 patients receiving the first course of carboplatin-based chemotherapy for lung cancer. Results: Azasetron exhibited the highest 5-HT$_3$ receptor occupancy among various first-generation 5-HT$_3$ antagonists. The complete response to oral azasetron was shown to be non-inferior to that of intravenous granisetron, in which the risk difference was 0.0004 (95% confidence interval: −0.0519-0.0527). The lower limit of the confidence intervals did not exceed the negative non-inferiority margin (−0.1). The complete response during the overall period was not different (68% versus 67%). Conclusion: Oral azasetron was found to be non-inferior to intravenous granisetron in the acute antiemetic effect against moderately emetogenic chemotherapy.*

Cancer chemotherapy is associated with a number of adverse events, among which, when surveyed in 1983, nausea and vomiting were the second and the first most distressing patient-reported adverse reactions, respectively (1). However, the development of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists and subsequent implementation of the clinical practice guidelines for prevention of chemotherapy-induced nausea and vomiting (CINV), including the American Society of Clinical Oncology (ASCO) guideline (2) and the American Society of Hospital Pharmacists (ASHP) guideline (3) for the use of antiemetics, have since greatly improved the control of CINV (4). More recently, the antiemetic guidelines have been upgraded by ASCO (5), the Multinational Association of Supportive Care in Cancer (MASCC) (6) and the National Comprehensive Cancer Network (NCCN) (7) after development of the neurokinin NK_1 receptor antagonist, which contributed to a marked improvement of the control of acute as well as delayed CINV (8, 9).

On the other hand, the dose of 5-HT$_3$ receptor antagonist is not always consistent among various antiemetic guidelines. Particularly, the oral dose of ondansetron varies from 16 mg to 24 mg. In addition, the oral dose of ondansetron approved in Japan is much lower (4 mg) than doses used in Western countries. Thus, little is known about the appropriate doses of 5-HT$_3$ receptor antagonists for preventing acute CINV.

It has been demonstrated that the potencies of pharmacological effects of several receptor antagonists, including those for dopamine D_2 receptor (10, 11), α_1 adrenergic receptor (12), 5-HT_{2A} receptor (13), muscarinic acetylcholine receptor (14), and histamine H_1 receptor (15), depend on the rate of occupancy of the target receptor. The receptor occupancy can be estimated from the unbound drug concentration in the plasma and the binding affinity of the drug for the receptor (12, 15) or from images of positron-emission tomography using radiolabeled receptor ligands (10, 11, 13, 14).

In the present study, the occupancy at the 5-HT$_3$ receptor of oral as well as intravenous formulations of various 5-HT$_3$ receptor antagonists at doses approved in Japan was compared, using published data on the receptor binding, protein binding, and plasma concentrations. Based on the estimated 5-HT$_3$ receptor occupancy, a randomized controlled non-inferiority study comparing the antiemetic

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effects of oral azasetron and granisetron injection was subsequently carried out in patients undergoing moderately emetogenic chemotherapy for lung cancer.

Patients and Methods

Estimation of 5-HT$_3$ receptor occupancy. The rate of 5-HT$_3$ receptor occupancy was estimated according to the method reported by Yamada *et al*. (16). Briefly, 5-HT$_3$ receptor exists in unbound (R_{free}), agonist (5-HT)-bound ($R_{agonist}$) and antagonist-bound ($R_{antagonist}$) states in a biological environment. Thus, the rate of 5-HT$_3$ receptor occupancy (ϕ) is shown by the equation 1:

$$\phi=100\times R_{antagonist}/(R_{free}+R_{agonist}+R_{antagonist}) \quad \text{Eq. 1}$$

$R_{agonist}$ and $R_{antagonist}$ can be calculated by equations 2 and 3, respectively, where [agonist] and [antagonist] are the concentrations of 5-HT and 5-HT$_3$ receptor antagonist, respectively, in the extracellular fluid, and *K*a and *K*i represent the affinity constant of the agonist and the inhibition constant of the antagonist, respectively:

$$R_{agonist}=[agonist]\times R_{free}/Ka \quad \text{Eq. 2}$$

$$R_{antagonist}=[antagonist]\times R_{free}/Ki \quad \text{Eq. 3}$$

Using equations 2 and 3, equation 1 becomes:

$$\phi=100\times[antagonist]/[Ki\times(1+[agonist]/Ka)+[antagonist]] \quad \text{Eq. 4}$$

Based on the assumption that [agonist]/*K*a is nearly 0, since [5-HT] is much lower than *K*a (150 nM) and [antagonist] is approximated by the plasma concentration of the unbound antagonist (Cplasma-free), the 5-HT$_3$ receptor occupancy can be estimated from equation 5:

$$\phi=100\times C_{plasma\text{-}free}/(Ki+C_{plasma\text{-}free}) \quad \text{Eq. 5}$$

$C_{plasma\text{-}free}$ can be calculated from the total plasma concentration of the antagonist and the percentage of protein binding, both of which are referred to in the clinical pharmacokinetic data shown in the Ethical Drug Package Inserts and in manufacturer's product summaries of injectable formulations such as granisetron, azasetron, ondansetron and ramosetron, and oral preparations of these and indisetron and tropisetron. The clinical effects, named control of acute emesis, of these oral and injectable 5-HT$_3$ receptor antagonists were referred from data of clinical phase II and III studies in patients receiving cisplatin-based chemotherapy that are shown in the Ethical Drug Package Insert of each 5-HT$_3$ receptor antagonist.

Patients. One-hundred and five chemonaive patients undergoing carboplatin-based moderately emetogenic chemotherapy for lung cancer, who were hospitalized in Gifu University hospital during November 2010 and March 2012, were enrolled in the study. Patients were randomly assigned to receive oral azasetron (N=53) or intravenous granisetron (N=52). Randomization was carried out by using the random number table. Azasetron (10 mg) or granisetron (3 mg) was administered 30 min before the start of the chemotherapy. The rate of complete response to intravenous granisetron for CINV in patients with moderately emetogenic chemotherapy was reported to be 81% (17). Thus, the sample size for non-inferiority test was estimated to be 50 per group, when the efficacy rates of granisetron and azasetron are set to 0.8 and 0.9, respectively, with the non-inferiority margin of 0.1, α 0.05, and power of 0.8. The exclusion criteria were age under 18 years, use of emetogenic drugs such as opioid analgesics, experience of previous chemotherapy, and patients with organic disorders accompanied by nausea and vomiting. Patients' characteristics are shown in Table I.

The present clinical 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.

Chemotherapy. Patients were treated with carboplatin (area under the concentration *versus* time curve of 5-6) in combination with paclitaxel (200 mg/m^2), etoposide (100 mg/m^2), gemcitabine (1,000 mg/m^2) or pemetrexed (500 mg/m^2).

Antiemetic medication. For prevention of CINV, a combination of oral azasetron or intravenous granisetron with intravenous dexamethasone (12 mg) was administered on day 1, followed by the treatment with oral dexamethasone (8 mg/day) on days 2 and 3.

Endpoints. The primary endpoint was the complete response (*i.e*. no vomiting, no rescue treatment) during the acute period (0-24 h after chemotherapy). Secondary endpoints were complete response during delayed (24-120 h) and overall (0-120 h) periods, and complete protection from nausea and vomiting on each day up to 5 days after chemotherapy. Patients received a daily check sheet on which the incidence and grade of nausea (slight, moderate, severe) and vomiting (number of vomiting episodes in a day) and the absence or presence of additional intake of antiemetic drug for the breakthrough treatment were self-checked every day starting from day 1 to day 5 after chemotherapy. The incidence of other adverse reactions, such as constipation and hematological toxicities, including leucopenia, thrombocytopenia and anemia, was checked from the medical record. Constipation was regarded as a stool-free interval of 72 h or the use of laxative during the first week after chemotherapy (18). The severity of hematological toxicities was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (19).

Statistical analyses. Data were analyzed using Statistics Program for Social Science (SPSS X, version 11) for Windows (SPSS Inc., Chicago, IL, USA). The relationship between the 5-HT$_3$ receptor occupancy and the control of emesis was evaluated by linear regression using Pearson's correlation coefficient. Non-inferiority analysis was carried out according to the method reported by da Silva *et al*. (20). Briefly, null hypothesis (H0) and alternative hypothesis (HA) are postulated as follows: H_0: $P_{azasetron} - P_{granisetron} \leq -\delta$, HA: $P_{azasetron} - P_{granisetron} > -\delta$, where $P_{azasetron}$ and $P_{granisetron}$ are the rates of complete response to azasetron and granisetron, respectively, in the general population, and δ is an inferiority margin that was set at 0.1. Noninferiority is evident when H_0 is rejected and H_A is statistically proven. The inferiority *p*-value was calculated from the z-value, as shown by equation 6:

$$z = \frac{(p_{azasetron}-p_{granisetron}+\delta)}{\sqrt{\frac{(p_{azasetron}\times(1-p_{azasetron})}{n_{azasetron}}+\frac{p_{granisetron}\times(1-p_{granisetron})}{n_{granisetron}}}} \quad \text{Eq. 6}$$

where $p_{azasetron}$ and $p_{granisetron}$ are the proportion of the rates of complete response of lung cancer patients receiving oral azasetron and intravenous granisetron, respectively, and $n_{azasetron}$ and $n_{granisetron}$ represent the number of patients receiving oral azasetron and intravenous granisetron, respectively.

Patients' characteristics and the incidence of constipation and hematological side-effects were statistically compared between the

Table I. *Patient characteristics*.

	Therapy group		*p*-Value
	Azasetron (N=53)	Granisetron (N=52)	
Age	67.8 (41-85)	68.0 (44-83)	0.715[a]
Gender (male/female)	39/14	41/11	0.686[b]
Height (cm)	160.1±8.1	161.0±7.5	0.557[c]
Body weight (kg)	54.8±10.8	58.0±10.1	0.130[c]
Alanin-aminotransferase (IU/L)	22.2±9.4	20.1±9.3	0.258[c]
Aspartate-aminotransferase (IU/L)	21.5±12.1	17.8±13.4	0.141[c]
Serum creatinine (mg/dL)	0.74±0.20	0.71±0.18	0.338[c]
White blood cells (/mm^3)	6821±2624	6689±2814	0.805[c]
Hemoglobin (g/L)	12.5±2.3	12.5±1.6	0.911[c]
Platelet (10^4/mm^3)	24.8±10.1	26.6±10.1	0.355[c]
Cancer type			1.000[d]
Non-small cell lung cancer	44 (83.0%)	41 (78.8%)	
Small cell lung cancer	9 (17.1%)	9 (17.3%)	
Malignant mesothelioma	0 (0%)	2 (3.8%)	
Carboplatin dose (mg/body)	456.1±112.4	466.5±112.4	0.667[c]
Additional anticancer drugs			0.969[d]
Vinorelbine	6 (11.3%)	4 (7.7%)	
Etoposide	11 (20.8%)	9 (17.3%)	
Paclitaxel	20 (37.7%)	21 (40.4%)	
Pemetrexed	15 (28.3%)	17 (32.7%)	
Gemcitabine	0 (0%)	1 (1.9%)	
TS-1	1 (1.9%)	0 (0%)	

Data are expressed as the mean±SD. Figures in parentheses represent the range. [a]Mann-Whitney *U*-test, [b]Chi-square test, [c]*t*-test, [d]Kolmogorov-Smirnov test.

two groups by the Mann-Whitney *U*-test or χ^2-test for non-parametric data or by *t*-test for parametric data. *p*-Values of less than 0.05 were regarded as statistically significant.

Results

5-HT_3 receptor occupancy. Figure 1 shows the time course of 5-HT_3 receptor occupancy by injections and oral administration of various 5-HT_3 antagonists. In both cases, azasetron (10 mg for intravenous as well as oral treatment) exhibited the highest 5-HT_3 receptor occupancy among the 5-HT_3 antagonists determined, for which the occupancy was nearly 100% during a few hours after treatment, and remained high (85% for injection and 80% for oral formulation) at 24 h after administration. Granisetron (2 mg for oral treatment, 3 mg for injection) revealed moderate receptor occupancy, for which the occupancy rate was approximately 70% for injection and 65% for oral administration at 24 h after administration. In contrast, ondansetron (4 mg for intravenous and oral administrations) had the least 5-HT_3 receptor occupancy among the 5-HT_3 receptor antagonists tested, for which the receptor occupancy at 24 h was only 18.5% for injection and 7.5% for the oral formulation.

Subsequently, the relationship between the 5-HT_3 receptor occupancy (at 12 h and 24 h) and the control of emesis during the acute period (0-24 h) after chemotherapy was examined. As shown in Figure 2, there was a significant correlation between the antiemetic effect and the receptor occupancy estimated at 12 h (R=0.978, p=0.02 for injection, R=0.832, p=0.04 for oral treatment) but not at 24 h (R=0.925, p=0.075 for injection, R=0.798, p=0.057 for oral treatment).

Antiemetic effect. There were no significant differences in patients' characteristics between the azasetron-treated group and the granisetron-treated group (Table I). As shown in Table II, the complete response rate during the acute period (0-24 h) was 98.11% (52/53) for oral azasetron and 98.08 % (51/52) for intravenous granisetron. The risk difference (RD) was 0.0004 (95% confidence interval, CI −0.0519–0.0527). The lower limit of the 95% CI of RD did not exceed the negative inferiority margin (−δ=−0.1). The z-value calculated from the proportion of the complete antiemetic control and δ of 0.1 was 3.761, indicating that the non-inferiority *p*-value was 0.0002. Therefore, it was shown that the antiemetic effect of oral azasetron was non-inferior to that of intravenous granisetron.

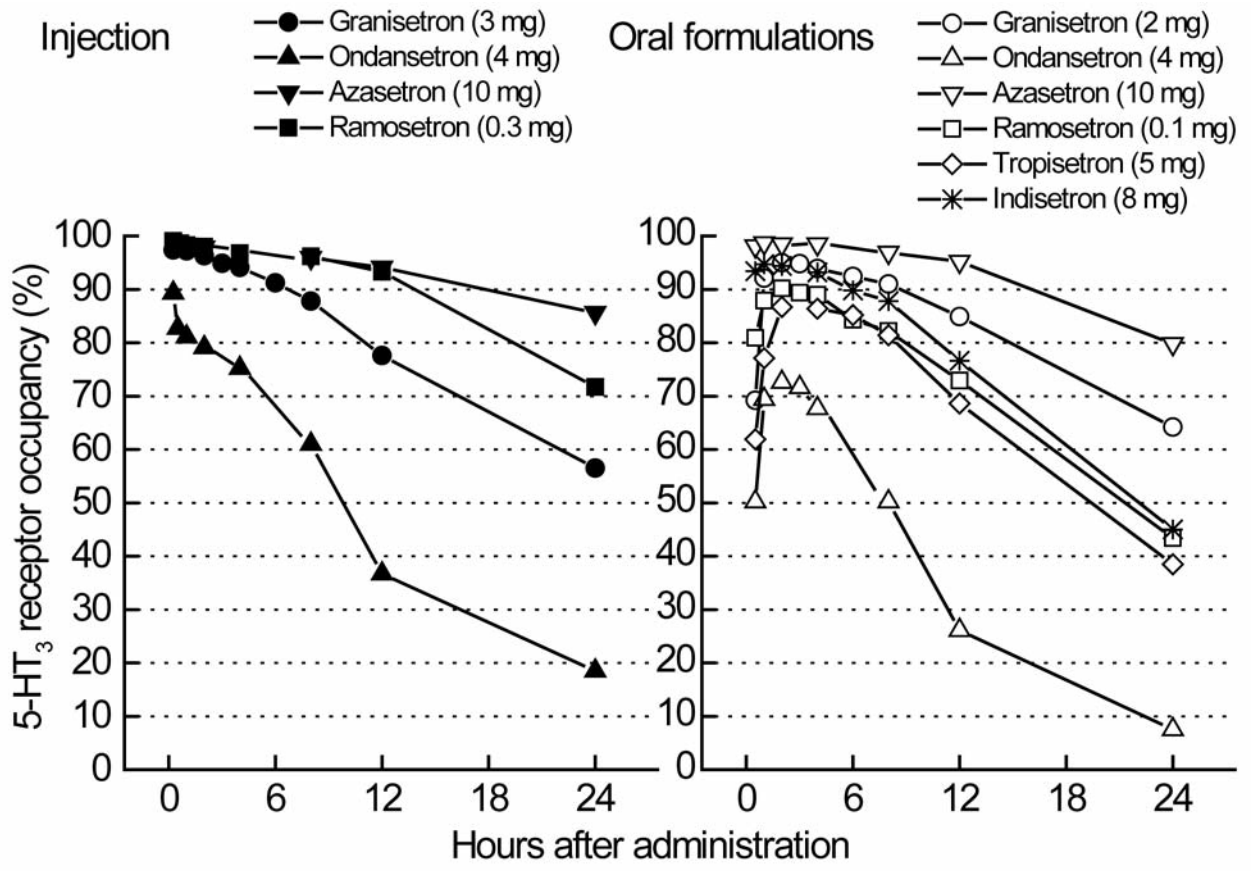

Figure 1. *Time course of 5-hydroxytryptamine 3 (5-HT$_3$) receptor occupancy after administration of various injectable (A) and oral (B) 5-HT$_3$ receptor antagonists. 5-HT$_3$ receptor occupancy was calculated as $100\times C_{plasma\text{-}free}/(Ki+C_{plasma\text{-}free})$, where Ki is the inhibition constant of each antagonist for 5-HT$_3$ receptor binding and $C_{plasma\text{-}free}$ is plasma concentration of unbound 5-HT$_3$ receptor antagonist.*

The complete response during delayed (24-120 h) and overall (0-120 h) periods were 67.9% for oral azasetron and 67.3% for intravenous GRN (p=1.000 by χ^2-test), in which the relative risk was 1.009 (95% CI 0.774-1.315). The time course of the complete protection from nausea (Figure 3A) and vomiting (Figure 3B) was also similar for oral azasetron and intravenous granisetron during 5 days after chemotherapy.

Constipation and hematological toxicities. As shown in Table III, the incidence of constipation was 17.0% (9/53) for oral azasetron and 11.5% (6/52) for intravenous granisetron, indicating no significant difference (p=0.605). The incidence of chemotherapy-induced hematological toxicities was also similar between the two groups, in which the incidence rates of leucopenia (grade≥3), anemia (grade≥2) and thrombocyto-penia (grade≥3) were 24.5%, 28.3% and 3.8%, respectively, for oral azasetron and 28.8%, 13.5%, and 5.8%, respectively, for intravenous GRN. There were no significant differences in the incidence of leucopenia (p=0.780), anemia (p=0.103) and thrombocytopenia (p=0.983) between the two groups.

Discussion

In the present study, the 5-HT$_3$ receptor occupancy, following administration of injectable and oral formulations of 5-HT$_3$ antagonists at the dose approved in Japan, was estimated from plasma concentrations of unbound drugs and the Ki value for the 5-HT$_3$ receptor binding. Unexpectedly, the extent of the 5-HT$_3$ receptor occupancy varied remarkably among the four injectable and six oral formulations. By either route of administration, azasetron was found to show the highest receptor occupancy, in which the occupancy was still 85% (injection) or 80% (oral administration) even at 24 h after treatment. The high occupancy of 5-HT$_3$ receptor by azasetron may be due to it having the lowest protein binding (31%) among the 5-HT$_3$

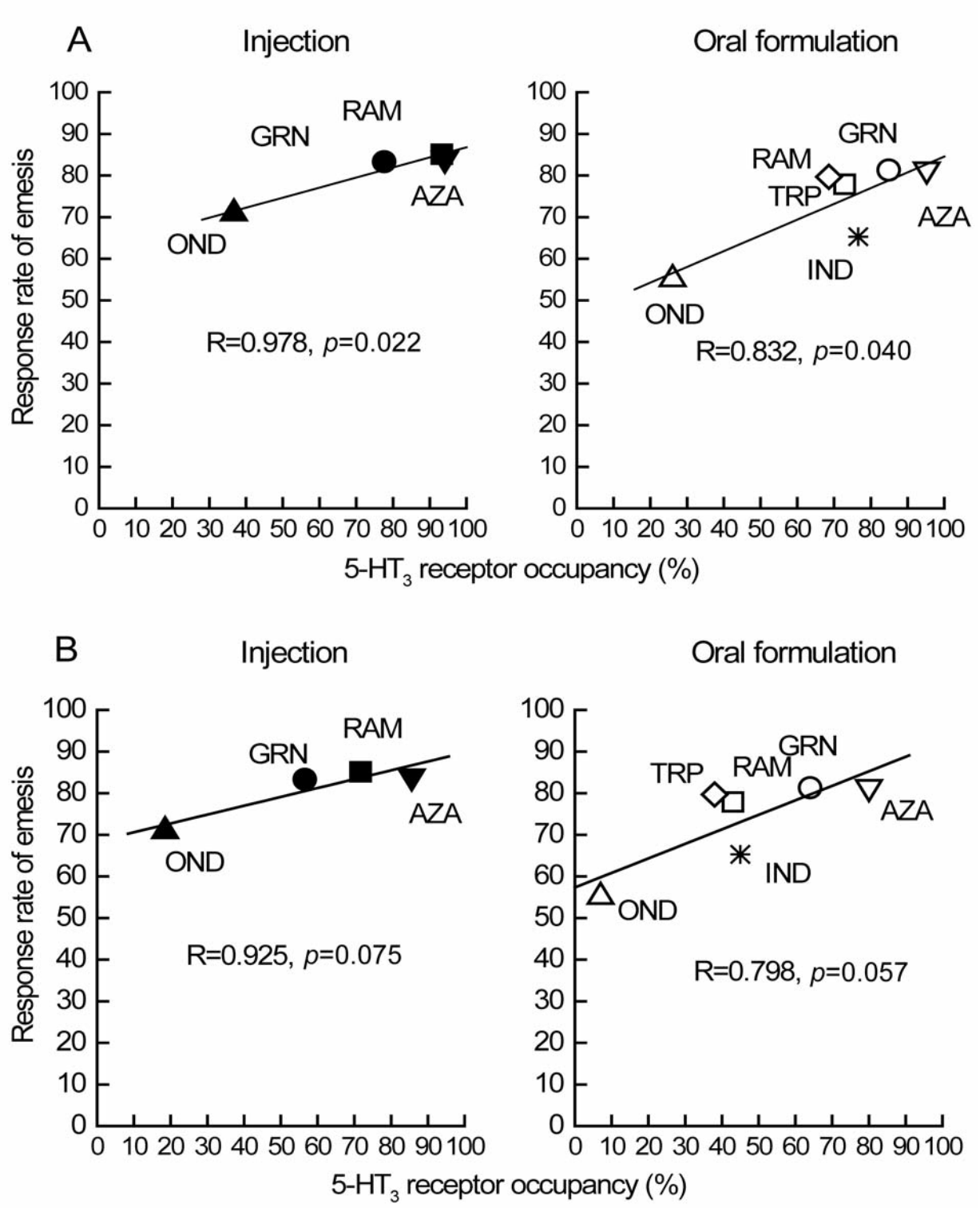

Figure 2. *Correlation between 5-hydroxytryptamine 3 (5-HT$_3$) receptor occupancy estimated at 12 h (A) and 24 h (B) after treatment and the control of emesis after treatment with injectable and oral formulations of 5-HT$_3$ antagonists in patients undergoing cisplatin-containing cancer chemotherapy. Pharmacokinetic, physicochemical and clinical data were obtained from the Ethical Drug Package Insert of each 5-HT$_3$ receptor antagonist. The 5-HT$_3$ receptor occupancy was calculated from the Ki (inhibition constant) and plasma concentration of each unbound 5-HT$_3$ antagonist. Control of emesis represents no emesis and no rescue treatment during the first 24 h after chemotherapy. GRN, Granisetron; AZA, azasetron; OND, ondansetrron; RAM, ramosetron; TRP, tropisetron; IND, indisetrron.*

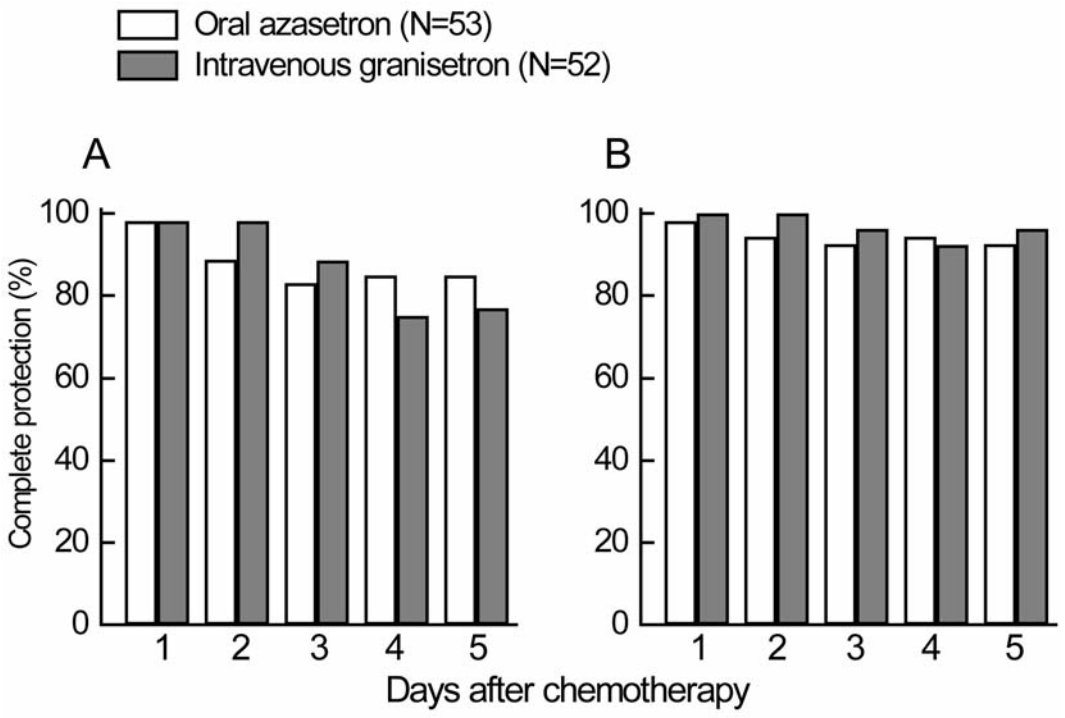

Figure 3. *Comparison of the time course in the complete protection from nausea (A) and vomiting (B) by oral azasetron and intravenous granisetron in patients with lung cancer undergoing the first course of moderately emetogenic cancer chemotherapy.*

antagonists, since only the unbound form is able to occupy the 5-HT_3 receptor. In contrast, ondansetron had the lowest receptor occupancy at any time point after administration, in which the occupancy at 24 h was below 20% (intravenous injection) or less than 10% (oral administration). This may be explained by the fact that the dose of ondansetron approved in Japan (4 mg) is much lower than those (16-24 mg as oral dose and 8-12 mg or 0.15 mg/kg as the intravenous dose) recommended by several clinical practice guidelines (5-7). It was notable that the rate of 5-HT_3 receptor occupancy at 12 h correlated well with the clinical antiemetic effect for oral as well as intravenous formulations.

Uchida *et al*. (11) summarized the data from 12 studies on the relationship between the clinical antipsychotic effect and the occupancy at dopamine D_2 receptor estimated by positron emission tomography of antipsychotic agents in patients with schizophrenia. They showed that 72% receptor occupancy is required to reduce the psychological symptoms by ≥50%, and that 77-78% occupancy leads to the incidence of extrapyramidal side-effects. Rasmussen *et al*. (13) also reported the relationship between the occupancy of 5-HT_{2A} receptor and the clinical outcomes of patients receiving the atypical antipsychotic drug quetiapine, and showed that 60-70% receptor occupancy is required to improve the positive symptoms in patients with schizophrenia.

However, little is known about the threshold of the rate of 5-HT_3 receptor occupancy that prevents acute CINV. In the present study, the 5-HT_3 receptor occupancy estimated at 12 h was more closely related to the clinical outcomes than that estimated at 24 h after administration. The 5-HT_3 receptor antagonists except for ondansetron had 70% and higher receptor occupancy at 12 h and the antiemetic response of those 5-HT_3 antagonists, excluding indisetron, was approximately 80%. Therefore, it is assumed that the rate of 5-HT_3 receptor occupancy required to produce a sufficient antiemetic effect is ≥70% at 12 h after administration.

Acute CINV is considered to result mostly but not exclusively from an excessive release of 5-HT from enterochromaffin-like cells in gastrointestinal tracts (21). Thus, the 5-HT_3 receptor antagonists are highly effective in suppressing acute but not delayed CINV (22-27). Indeed, it has been shown that the concentration of 5-hydroxyindole acetic acid, a predominant metabolite of 5-HT, was elevated in the urine of patients undergoing cancer chemotherapy, in which the peak appeared within 24 h after injection and had disappeared by the second day (28).

Based on the present data on 5-HT_3 receptor occupancy, a randomized controlled non-inferiority study was carried out to compare the antiemetic effect of oral azasetron (10 mg) with that of intravenous granisetron (3 mg), the most frequently used antiemetic agent in Japan, in lung cancer

Table II. *Comparison of the complete response to antiemetic oral azasetron and intravenous granisetron during acute, delayed and overall periods in patients with lung cancer who underwent the first course of moderately emetogenic cancer chemotherapy. Azasetron was administered orally at a dose of 10 mg, while granisetron was injected intravenously at 3 mg, 30 min before chemotherapy. All patients were pre-treated intravenously with dexamethasone 12 mg, followed by oral administration at 8 mg on days 2 and 3.*

Periods	No. complete response (%)		Relative risk (95% CI)	Risk difference (95% CI)	Non-inferiority *p*-value
	Azasetron (N=53)	Granisetron (N=52)			
Acute (0-24 h)	52 (98%)	51 (98%)	1.000 (0.948-1.055)	0.0004 (–0.052-0.053)	0.0002
Delayed (24-120 h)	36 (68%)	35 (67%)	1.009 (0.774-1.315)		
Overall (0-120 h)	36 (68%)	35 (67%)	1.009 (0.774-1.315)		

CI: Confidence interval.

patients undergoing moderately emetogenic chemotherapy. Oral azasetron was found to be non-inferior to intravenous granisetron in preventing acute CINV (p=0.0002), provided that δ was set at 0.1. Moreover, complete antiemetic response during delayed and overall periods were similar for the two formulations. The daily complete protection from nausea or vomiting was also comparable between the two formulations.

It has been demonstrated by a randomized controlled study in patients receiving high doses of cisplatin, that the control of acute CINV is not different between ondansetron and tropisetron (29) or granisetron (30). Moreover, several studies in patients receiving highly emetogenic chemotherapy (31-33) or moderately emetogenic chemotherapy (34, 35) have shown that the antiemetic effects of intravenous injection of 5-HT_3 receptor antagonists are almost similar to those of oral administration, although a few studies have shown the non-inferiority or equivalence of the antiemetic response to different formulations of 5-HT_3 antagonists.

Constipation is a common non-hematological adverse reaction associated with 5-HT_3 receptor antagonist use. In the present study, the incidence of constipation was not different between oral azasetron and intravenous granisetron (17.0% *versus* 11.5%, p=0.605). The incidence rates of hematological toxicities were not different either between oral azasetron and intravenous granisetron.

In conclusion, azasetron had the highest 5-HT_3 receptor occupancy among different first-generation 5-HT_3 receptor antagonists. A randomized controlled non-inferiority study in lung cancer patients undergoing moderately emetogenic chemotherapy, demonstrated that oral azasetron (10 mg) was non-inferior to intravenous granisetron (3 mg) in preventing acute CINV, provided that δ was set at 0.1. Moreover, the safety profile was not significantly different between oral azasetron (10 mg) and intravenous granisetron (3 mg). Therefore, it is suggested that the use of oral azasetron is not only cost-effective in respect of the efficacy and safety but also time-consuming in comparison with the use of intravenous granisetron.

Table III. *Comparison of the incidence of constipation and hematological adverse events in patients with non-small cell lung cancer who underwent moderately emetogenic cancer chemotherapy and were treated with oral azasetron or intravenous granisetron.*

	Azasetron (N=53)		Granisetron (N=52)		*p*-Value
	N	%	N	%	
Constipation	9	17.0	6	11.5	0.605
Leukopenia					0.780
G1	6	11.3	4	7.7	
G2	15	28.3	15	28.8	
G3	10	18.9	11	21.2	
G4	3	5.7	4	7.7	
G≥3	13	24.5	15	28.8	
Anemia					0.103
G1	26	49.1	33	63.5	
G2	15	28.3	7	13.5	
G3	0	0.0	0	0	
G4	0	0.0	0	0	
G≥2	15	28.3	7	13.5	
Thrombocytopenia					0.983
G1	24	45.3	16	30.8	
G2	7	13.2	5	9.6	
G3	1	1.9	2	3.8	
G4	1	1.9	1	1.9	
G≥3	2	3.8	3	5.8	

Data were statistically compared by the Chi-square test.

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