Comparison of Antiemetic Efficacy between Single and Repeated Treatments with a 5-HT_3 Receptor Antagonist in Breast Cancer Patients with High-risk Emetogenic Chemotherapy

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Abstract. *Background: The significance of repeated treatment with the 5-HT_3 receptor antagonist for prophylaxis of chemotherapy-induced emesis remains to be clarified. Patients and Methods: A retrospective analysis was performed to compare the effects of single and repeated treatment with granisetron on anorexia, nausea and vomiting in patients with breast cancer who undertook anthracycline and cyclophosphamide-based cancer chemotherapy. Results: The control of anorexia was significantly better in the single treatment group than in the repeated treatment group (54% versus 73%; odds ratio (OR), 0.433; 95% confidence intervals (CI), 0.226-0.828; p=0.016), although the rate of complete response to any signs of the gastrointestinal side-effects was not different between the two groups (37% versus 39%; OR, 0.911; CI, 0.489-1.700; p=0.874). However, the incidence of constipation was more frequent in the repeated treatment group (60% versus 37%; OR, 2.586; CI, 1.388-4.818; p=0.003). Conclusion: Repeated treatment with 5-HT_3 receptor antagonist is not likely to be beneficial to breast cancer patients who undertook anthracycline/cyclophosphamide combination chemotherapy.*

Several clinical practice guidelines have suggested that anthracycline/cyclophosphamide-based chemotherapy (AC chemotherapy) is currently the standard regimen for adjuvant and neoadjuvant chemotherapy of breast cancer, as well as for the therapy of metastatic or recurrent breast cancer (1-5). However, AC chemotherapy causes a number of adverse drug reactions (ADRs) such as myelosuppression, congestive heart disease and emesis. Nausea and vomiting associated with cancer chemotherapy include acute and delayed events (6-8). Acute emesis occurs within a day of chemotherapy, while delayed event appears after 24 h and persists for several days. Moreover, anticipatory emesis develops before chemotherapy, particularly in patients who experienced emesis in the previous chemotherapy (9-11). According to the guidelines for prevention of cancer chemotherapy-induced emesis documented by the Multinational Association of Supportive Care in Cancer (MASCC) (12), the American Society of Clinical Oncology (ASCO) (13, 14), and the National Comprehensive Cancer Network (NCCN) (15), anticancer agents are classified into four risk categories (high, moderate, low and minimal risks) based on the frequency of emesis. Anthracyclines or cyclophosphamide are on their own categorized as moderate risk anticancer agents, but they are regarded as high-risk regimen when used in combination (12, 14). For high-risk anticancer agents, the combination of three classes of agents such as 5-HT_3 receptor antagonists, dexamethasone and the neurokinin NK_1 receptor antagonist aprepitant is prescribed before chemotherapy for prevention of acute emesis, while the combination of dexamethasone and aprepitant is recommended for the prophylaxis of delayed emesis (12, 14-17). However, in Japan, the combination of 5-HT_3 receptor antagonist and dexamethasone is used before chemotherapy, and dexamethasone alone or in combination with dopamine D_2 receptor antagonists or anti-anxiety drugs is prescribed after chemotherapy, since none of the NK_1 receptor antagonists are currently available.

The 5-HT_3 receptor antagonist is highly effective in suppressing acute emesis since 5-HT liberated from enterochromaffin cells largely contributes to the early phase of chemotherapy-induced emesis (18-20). However, it remains uncertain whether the repeated administration of

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Table I. *Patients' demographics.*

	Single treatment	Repeated treatment
Number of patients	29	30
Average of age (years, range)	49.2 (30-68)	53.3 (26-69)
Body surface area (m^2)	1.50±0.02	1.53±0.02
Number of courses	79	90
Aspartic aminotransferase (U/L)	24.3±1.5	24.6±1.3
Alanine aminotransferase (U/L)	25.5±2.8	25.3±1.9
Serum creatinine (mg/dL)	0.61±0.01	0.65±0.03
Chemotherapy regimens		
EC	70 courses	62 courses
FEC	9 courses	28 courses
Doses		
Epirubicin (mg)	124±19	113±22
Cyclophosphamide (mg)	783±118	694±132
Delayed treatment		
Dexamethasone	47 courses	85 courses

EC: Epirubicin + cyclophosphamide; FEC: fluorouracil + epirubicin+ cyclophosphamide.

Table II. *Comparative effects of single and repeated treatment with 5-HT_3 receptor antagonist on the incidence of anorexia, nausea, vomiting and other adverse reactions such as constipation and hematological toxicities in patients with breast cancer who underwent chemotherapy containing anthracycline and cyclophosphamide.*

Adverse events	Single treatment (79 courses)	Repeated treatment (90 courses)	*p*-Value[a]
Anorexia			
Grade 1	15 (19%)	29 (32%)	0.055
Grade 2	6 (8%)	10 (11%)	0.600
Grade 3	0 (0%)	2 (2%)	0.499
Any grade	21 (27%)	41 (45%)	0.016
Nausea			
Grade 1	45 (57%)	35 (39%)	0.021
Grade 2	5 (6%)	9 (10%)	0.419
Grade 3	0 (0%)	2 (2%)	0.500
Any grade	50 (63%)	46 (51%)	0.122
Vomiting			
Grade 1	8 (10%)	5 (6%)	0.387
Grade 2	4 (5%)	5 (6%)	1.000
Grade 3	0 (0%)	0 (0%)	1.000
Any grade	12 (15%)	10 (12%)	0.496
Other ADRs			
Constipation			
Grade 1	25 (32%)	35 (39%)	0.339
Grade 2	4 (5%)	19 (21%)	0.003
Grade 3	0 (0%)	0 (0%)	1.000
Leukopenia			
Grade 1	11 (14%)	9 (10%)	0.480
Grade 2	17 (22%)	11 (12%)	0.146
Grade 3	14 (18%)	9 (10%)	0.179
Anemia			
Grade 1	21 (27%)	20 (22%)	0.590
Grade 2	8 (10%)	10 (11%)	1.000
Grade 3	1 (1%)	1 (1%)	1.000
Thrombocytopenia			
Grade 1	3 (4%)	9 (10%)	0.142
Grade 2	0 (0%)	0 (0%)	0.600
Grade 3	0 (0%)	0 (0%)	1.000

[a]Fisher's exact probability test. ADRs, adverse drug reactions.

5-HT_3 receptor antagonist is effective for prevention of delayed emesis. A meta-analysis of 5 randomized control trials has shown that the effect of 5-HT_3 receptor antagonist on delayed emesis is slightly but significantly higher than that of placebo but is not different from that of dexamethasone (21). On the other hand, 5-HT_3 receptor antagonist causes constipation by reducing gastrointestinal motility (22, 23), which may hinder the antiemetic action. Nevertheless, repeated administration of 5-HT_3 receptor antagonist is an alternative for prevention of chemotherapy-induced delayed emesis in the NCCN guideline for antiemesis (14-17). In the present study, the effect of single *versus* repeated treatment with the 5-HT_3 receptor antagonist granisetron was retrospectively studied in patients with breast cancer who underwent anthracycline/cyclophosphamide combination chemotherapy from the view point of the therapeutic effect as well as the cost effectiveness.

Patients and Methods

Subjects. Fifty-nine patients with breast cancer who underwent AC chemotherapy at Gifu University Hospital and Gifu Prefectural General Medical Center during January 2007 and December 2007 were included in the study. Patients' demographics are shown in Table I. Patients were all treated with intravenous granisetron (3 mg) and dexamethasone (16-24 mg) before chemotherapy. After chemotherapy, granisetron was administered orally for 3 days in a total of 90 cases (repeated treatment group) but not in a total of 79 patients (single treatment group).

Chemotherapy. The combination chemotherapy containing epirubicin (75-100 mg/m^2) and cyclophosphamide (500-600 mg/m^2) alone (EC) or with 5-fluorouracil (500 mg/m^2) (FEC) was performed every 21 days for up to 6 courses. Fifty-nine patients received a total of 169 courses of the chemotherapy.

Surveillance for adverse drug reactions (ADRs). The incidence of anorexia, nausea, vomiting and other ADRs that occurred during 4 days after AC chemotherapy were retrospectively analyzed from the electronic medical records and nursing records. The rate of complete absence of anorexia, nausea and vomiting was also calculated. The severity of the adverse events was graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Statistical analysis. Data were analyzed using Statistics Program for Social Science (SPSS X, version 11) for Windows (SPSS Inc., Chicago, IL, USA). The incidence of ADRs or the rate of complete absence of anorexia, nausea and vomiting was compared between

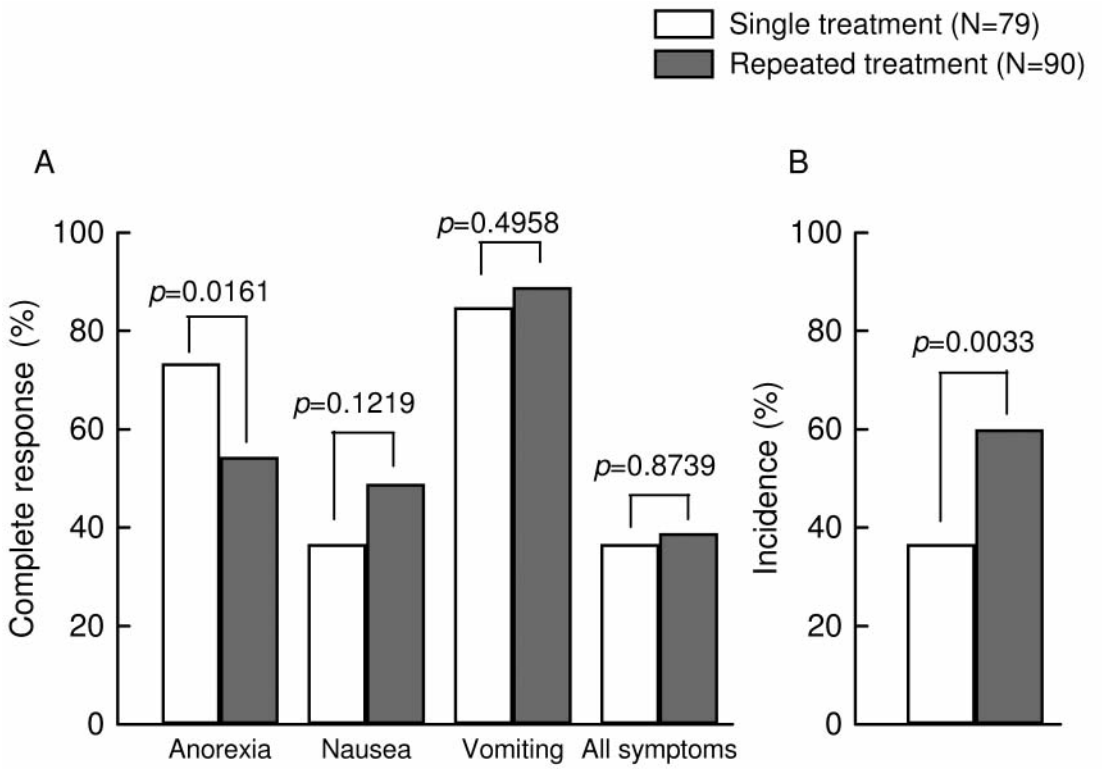

Figure 1. *Comparison of the antiemetic response (A) and the incidence of constipation (B) between single and repeated treatment with granisetron in patients with breast cancer who underwent combination chemotherapy with anthracycline and cyclophosphamide. Granisetron was administered intravenously on day 1 in all patients, while the agent was administered orally on days 2-4 in the repeated treatment group. The antiemetic effects were shown as the rate of complete absence of anorexia, nausea, vomiting or all symptoms. Data were statistically compared by Fisher's exact probability test.*

single treatment group and repeated treatment group and the statistical significance was analyzed by Fisher's exact probability test. The *p*-values of less than 0.05 were regarded as statistically significant.

Results

Comparison of chemotherapy regimens and medications for the prophylaxis of emesis. There were no significant differences in patient characteristics between the two groups, except for the frequency in the use of dexamethasone after chemotherapy, in which dexamethasone was used on days 2-4 in 47 courses of single treatment group and in 85 courses of repeated treatment group ($p<0.001$ by Fisher's exact probability test).

Comparison of the incidence of nausea, vomiting and other ADRs between the two groups. As shown in Table II, the incidence of anorexia, nausea and vomiting of any grade was 27% , 63% and 15% , respectively, in the single treatment group, and 46% , 51% and 12% , respectively, in the repeated treatment group, in which the rate of anorexia was significantly higher (odds ratio [OR], 2.311; 95% confidence interval [CI], 1.208-4.423; $p=0.0161$). Figure 1 shows the comparison of antiemetic response and the incidence of constipation of any grade between the two groups. The control of anorexia was better in the single treatment group than in the repeated treatment group (54% *versus* 73% , OR, 0.433; 95% CI, 0.226-0.828; $p=0.016$), although the rate of complete response to any signs of the gastrointestinal side-effects was not different between the two groups (37% *versus* 39% ; OR, 0.911; 95% CI, 0.489-1.700; $p=0.874$).

On the other hand, constipation occurred more frequently in the repeated treatment group (Table II, Figure 1): 21% *versus* 5% for grade 2 symptoms (OR, 5.018; 95% CI, 1.627-15.471; $p=0.0029$), 60% *versus* 37% for symptoms of any grade (OR, 2.586; 95% CI, 1.388-4.818; $p=0.0033$). The incidence of hematological ADRs was not different between the two groups.

Discussion

In the present study, the effects of single and repeated administration of 5-HT_3 receptor antagonist on the incidence of anorexia, nausea and vomiting were compared in out-patients with breast cancer who underwent AC chemotherapy, and no significant difference in the rate of complete response to nausea and vomiting was found between the two groups, whereas the rate of complete

response to anorexia was rather better in the single treatment group. The rate of complete response to any of these emetic symptoms was almost comparable between the two groups. On the other hand, dexamethasone was administered on days 2-4 in 85 cases (94%) in the repeated treatment group, while the same treatment was performed only in 47 cases (59%) in the single treatment group. The definite inhibitory effect of dexamethasone on the delayed emesis has been demonstrated (12, 14-17, 24-26). Even under such conditions, complete response to anorexia was superior in the single treatment group. Moreover, constipation occurred more frequently in the repeated treatment group than in the single treatment group (60% *versus* 37%, p=0.003). In particular, moderate constipation (grade ≥2) was observed in 21% of the repeated treatment group but appeared only in 5% of single treatment group (p=0.003). The OR was 2.586 (95% CI: 1.388-4.818) for constipation of all grades and 5.018 (CI: 1.627-15.471) for moderate constipation (grade ≥2). Therefore, it is likely that the incidence of constipation associated with repeated administration of granisetron may hinder its antiemetic effect.

It has been demonstrated that 5-HT_3 receptor antagonist possesses only a marginal effect on delayed emesis, while showing a marked prophylactic effect on acute emesis induced by high to moderate emetogenic chemotherapy. It has been demonstrated that the antiemetic effect of delayed treatment of 5-HT_3 receptor antagonist is significantly better than placebo (absolute risk reduction: 2.6%, 95% CI: –0.6-5.8%) but is almost comparable to dexamethasone on delayed emesis (21). The Italian Group for Antiemetic Research (27) has also shown, in 618 patients who undertook moderate risk of chemotherapy that, there is no additional effect of repeated ondansetron treatment to the antiemetic effect of dexamethasone. On the other hand, acute emesis is considered to result from the excessive release of 5-HT from enterochromaffin-like cells in gastrointestinal tracts evoked by emetogenic anticancer agents (22). Indeed, it has been shown that the concentration of 5-hydroxyindole acetic acid (5-HIAA), a predominant metabolite of 5-HT, is elevated in urine of patients who received cancer chemotharapy (28), in which the peak appears within 24 h after injection and disappeared after the second day.

On the other hand, chemotherapy-induced release of substance P and subsequent activation of neurokinin NK_1 receptors in the central nervous system may also contribute to some extent to the acute as well as delayed emesis (29-32). Thus, the 3-drug regimen including the 5-HT_3 receptor antagonist, dexamethasone and the NK_1 receptor antagonist, and 2-drug regimens such as dexamethasone and the NK_1 receptor antagonist, are recommended for the prevention of acute and delayed emesis, respectively (12, 14-17, 31, 33), although no NK_1 receptor antagonist is available in Japan.

In conclusion, repeated administration of 5-HT_3 receptor antagonist after chemotherapy increased the risk of constipation and decreased the inhibitory response to anorexia in breast cancer patients who underwent AC chemotherapy. Therefore, the use of 5-HT_3 receptor antagonist after chemotherapy is of limited value from the viewpoints of efficacy, adverse events and cost effectiveness.

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