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ORIGINAL ARTICLE

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# A comparative study of administration methods of granisetron injection used to treat nausea/vomiting induced by cancer chemotherapy without cisplatin in tumors of hematopoietic organs

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**Abstract** *Purpose*: The antiemetic effect of granisetron injection at a dose of 40 μg/kg used in the treatment of nausea/vomiting induced by multidrug combined cancer chemotherapy excluding cisplatin in patients with tumors of hematopoietic organs was evaluated by comparing a 30-min infusion and a slow intravenous injection given over 30 s. *Methods*: A two-group random-allocation comparative study was performed with the cooperation of multiple institutions using a central registration system. *Results*: In the treatment of acute clinical symptoms, appetite was described as "similar to that during good health" by 61.1% of patients (55/93) in the instillation group and by 47.3% (44/93) in the slow injection group, a significant advantage in the infusion group. However, no significant differences in the number of episodes of vomiting, the severity of nausea or clinical efficacy were found. In the final clinical evaluation and assessment of usefulness based on the subjective judgement of physicians throughout the entire therapeutic period, no differences were discernible. No side effects were reported for either method and there was no indication of a sex difference concerning efficacy. However, the efficacy in patients with an anemic tendency was slightly inferior. *Conclusions*: The maintenance of appetite during the administration of anticancer drugs is very important to maintain patients' daily activities and quality of life. The present results support the usefulness of infusion of granisetron as an administration method during chemotherapy for malignant hemopathy.

**Key words** Granisetron · Hematopoietic malignancies · Nausea · Vomiting

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## Introduction

Granisetron injection is a 5HT3 receptor antagonist developed by SmithKline Beecham in the UK, which quickly suppresses nausea/vomiting induced by cancer chemotherapy [1]. In general use, a dose of 40 μg/kg is given by infusion, the same dose that by slow intravenous injection is known to be effective. In clinical studies of the treatment of gynecological tumors to date, the intravenous injection method has been found to be slightly inferior to the infusion method in terms of antiemetic effect [10, 11]. Although combined chemotherapy excluding cisplatin is a rather common therapeutic method for tumors of hematopoietic organs, long-term continuous administration of antiemetic drugs during combined chemotherapy appears to be preferable because of the occurrence of chronic nausea caused by continued long-term administration of antibiotics and blood preparations, as well as antitumor drugs, adequate drug serum levels of which need to be maintained for several hours. However, no effective administration method for antiemetics has been established yet.

Therefore, by using granisetron injection, a representative antiemetic, the effects on nausea/vomiting induced by basic chemotherapy regimens (CHOP, DCMP, etc.) used in the treatment of tumors of hematopoietic organs were examined in two groups, namely an infusion group and a slow intravenous injection group. This investigation was performed as a wide area group study using a random allocation comparative method.

## Material and methods

### Subjects

All subjects were patients with tumors of the hematopoietic organs who were examined at 18 institutions in the Osaka area from July 1995 to March 1997, and who received multidrug combined chemotherapy mainly comprising cyclophosphamide (cisplatin was excluded). A total of 190 patients (119 men and 71 women) who had had nausea/vomiting during previous chemotherapy or who were going to receive chemotherapy which was known to be emetogenic were included [5]. The following patients were excluded from the study: (1) patients under 16 years of age, (2) patients having complications such as severe cardiopathy, nephropathy and hepatopathy, (3) patients who were pregnant or possibly pregnant, (4) patients with gastrointestinal obstruction, (5) patients with brain tumors, epilepsy, or who were receiving psychotropic drugs, and (6) patients who were judged inappropriate by the physician-in-charge.

### Registration procedure

The physicians-in-charge provided sufficient information, including an explanation of the experimental methods, to all patients in accordance with the Declaration of Helsinki prior to enrolment. After consent had been obtained, each patient was registered with the registration center by fax. The center judged the eligibility of each patient, and then randomly allocated the patient to an administration group. Each patient was registered once only.

### Drugs and administration procedures

In group A, 30 min before the administration of anticancer drugs, 40 μg/kg of granisetron injection mixed with 100 ml physiological saline was infused over 30 min. In group B, shortly before the administration of anticancer drugs, 40 μg/kg of granisetron injection mixed with 10–20 ml physiological saline was injected intravenously over more than 30 s. During the experimental period, use of other antiemetic drugs that have a similar pharmacological activity was prohibited. Use of corticosteroids for antiemetic purposes was also prohibited.

### Clinical evaluation

The following were evaluated for 24 h after administration of the anticancer drugs: (1) nausea graded as 'no symptoms', 'mild' or 'severe', (2) the number of vomiting episodes was recorded (including episodes of retching), (3) appetite was graded as 'similar to that during good health', 'about three-quarters that during good health', 'about half that during good health', 'about one-quarter that during good health', or 'no appetite at all'. Clinical efficacy was graded as 'remarkably effective', 'effective', 'slightly effective' or 'ineffective'.

The severity of adverse reactions was evaluated as mild, moderate or severe, and the causal relationship with the test drug was estimated according to five grades ('definitely related', 'probably related', 'possibly related', 'not related', 'unknown')

An Overall evaluation was carried out on the basis of clinical symptoms and adverse reactions observed on all the days of granisetron administration during the administration period of the anticancer drugs. The clinical efficacy of granisetron on the day of administration was graded as 'remarkably effective', 'effective', 'slightly effective' or 'ineffective'. On the basis of adverse reactions and the results of the clinical examination, safety was graded as 'safe', 'not completely safe', 'some safety problems' or 'unsafe'. On the basis of the final clinical evaluation and overall clinical safety, the usefulness was graded as 'remarkably useful', 'fairly useful', 'slightly useful' or 'not useful'.

### Statistical analysis

The chi-squared test the $t$-test and the Mann-Whitney $U$-test were used to compare the two groups. Findings of $P < 0.05$ in two-tailed tests were considered to be statistically significant. Version 6.11 of SAS was used for all the analyses.

## Results

### Patients' background

Among the 190 patients (Table 1), one patient in group A with gastrointestinal obstruction occurring before the start of the experiment and three patients in group B who did not receive the assigned treatment were included only in the safety evaluation. The other 186 evaluable patients were compared by sex, age, etc., and no significant differences were found between the two groups.

### Comparison of physical reactions and clinical efficacy during the 24 h after the administration of anticancer drugs

A comparison of clinical symptoms and clinical efficacy between the two groups in the acute stage was

**Table 1** Patient demographics

| | Group A (30 min) | Group B (30 s) |
|---|---|---|
| No. of patients | 93 | 93 |
| Females | 38 | 31 |
| Males | 55 | 62 |
| Mean age (years) | 50.0 | 49.3 |
| Diagnosis | | |
| Malignant lymphoma | 53 | 55 |
| Acute myelogenous leukemia | 23 | 27 |
| Acute lymphocytic leukemia | 8 | 5 |
| Myelodysplastic syndromes | 4 | 1 |
| Adult T-cell leukemia (lymphoma) | 2 | 1 |
| Adult T-cell leukemia | 0 | 2 |
| Multiple myeloma | 2 | 0 |
| Chronic myelomonocytic leukemia | 1 | 1 |
| Hybrid leukemia | 0 | 1 |
| Chemotherapy regimens | | |
| Cyclophosphamide combinations | 46 | 46 |
| Cytarabine combinations | 15 | 14 |
| Other combinations | 32 | 33 |

**Table 2** Antiemetic effect of granisetron on acute stage nausea/vomiting induced by cancer chemotherapy excluding cisplatin. The chi-squared test for each item was performed by making a comparison with 'no nausea', 'no vomiting', 'similar to that during good health' or complete responder, respectively

| | Group A (30 min) | Group B (30 s) | |
|---|---|---|---|
| Nausea | | | |
| No nausea | 72 (77.4%) | 64 (68.8%) | NS (Chi-squared test) |
| Mild | 20 (21.5%) | 25 (26.9%) | NS (*U*-test) |
| Severe | 1 (1.1%) | 4 (4.3%) | |
| No. of vomiting/retching episodes | | | |
| 0 | 90 (96.8%) | 91 (97.8%) | NS (Chi-squared test) |
| 1–2 | 3 (3.2%) | 2 (2.2%) | NS (*U*-test) |
| >3 | 0 | 0 | |
| Appetite | | | |
| Similar to that during good health | 55 (61.1%) | 44 (47.3%) | |
| 75% | 21 (23.3%) | 21 (22.6%) | |
| 50% | 10 (11.1%) | 21 (22.6%) | NS (Chi-squared test) |
| 25% | 4 (4.4%) | 4 (4.3%) | $P = 0.0263$ (*U*-test) |
| No appetite at all | 0 | 3 (3.2%) | |
| Obscure due to IVH control, etc. | 3 | 0 | |
| Clinical efficacy | | | |
| Remarkably effective | 88 (94.6%) | 89 (95.7%) | |
| Effective | 4 (4.3%) | 2 (2.2%) | NS (Chi-squared test) |
| Slightly effective | 0 | 2 (2.2%) | NS (*U*-test) |
| Ineffective | 1 (1.1%) | 0 | |

**Table 3** Overall evaluation of antiemetic effect of granisetron on nausea/vomiting induced by cancer chemotherapy excluding cisplatin. The chi-squared test for each item was performed by making a comparison with 'remarkably effective' or 'remarkably useful', respectively

| | Group A (30 min) | Group B (30 s) | |
|---|---|---|---|
| Final clinical evaluation | | | |
| Remarkably effective | 73 (78.5%) | 75 (80.6%) | |
| Effective | 17 (18.3%) | 13 (14.0%) | NS (Chi-squared test) |
| Slightly effective | 3 (3.2%) | 3 (3.2%) | NS (*U*-test) |
| Ineffective | 0 | 2 (2.2%) | |
| Usefulness | | | |
| Remarkably useful | 73 (78.5%) | 70 (75.3%) | |
| Fairly useful | 17 (18.3%) | 18 (19.4%) | NS (Chi-squared test) |
| Slightly useful | 3 (3.2%) | 3 (3.2%) | NS (*U*-test) |
| Not useful | 0 | 2 (2.2%) | |

performed on the first day of administration of anticancer drugs (Table 2). No significant differences in the severity of nausea, the number of vomiting episodes or clinical efficacy were found between the two groups. Regarding the degree of appetite, 'similar to that during good health' was reported by 61.1% of patients in group A and by 47.3% in group B. Significant differences were found between the groups using the *U*-test.

## Overall evaluation

The mean number of days of granisetron administration was 3.3 in group A and 3.4 in group B. No significant differences in the overall evaluation or the assessment of usefulness were found between the two groups (Table 3). No granisetron-related adverse reactions were found in any patient, and granisetron was evaluated as being 'safe'.

## Efficacy evaluation

No significant differences were found between men and women in terms of the effect on nausea/vomiting in the acute stage either in the final clinical evaluation or in the assessment of usefulness (Table 4).

In patients with malignant lymphoma and acute myelocytic leukemia, that is the majority of patients, an efficacy ('remarkably effective' or better) of more than 90% was found in the acute stage. In the final clinical evaluation, an efficacy in patients with malignant lymphoma and acute myelocytic leukemia of 88% and 72% was found, respectively. In the grading for usefulness, 'fairly useful' or better was recorded for more than 90% of patients (Table 5).

Patients with low blood hemoglobin concentrations (less than 13.0 g/dl for men and less than 11.5 g/dl for women) before the start of this study were grouped together as patients with an anemic tendency, and the antiemetic efficacy was compared between the patients with an anemic tendency and those without. No significant difference in the clinical efficacy in the acute stage was found between these two groups. However, the efficacy in those patients with an anemic tendency was found to be significantly inferior to that in the non-anemic patients in the final evaluation and the grading for usefulness (Table 6).

**Table 4** Comparison of the effect of granisetron injection between the sexes. The chi-squared test for each item was performed by making a comparison with 'remarkably effective' or 'remarkably useful', respectively

| | Males | Females | |
|---|---|---|---|
| Clinical efficacy (acute stage) | | | |
| Remarkably effective | 113 (96.6%) | 64 (92.8%) | |
| Effective | 2 (1.7%) | 4 (5.8%) | NS (Chi-squared test) |
| Slightly effective | 1 (0.9%) | 1 (1.4%) | NS (*U*-test) |
| Ineffective | 1 (0.9%) | 0 | |
| Final clinical evaluation (overall evaluation) | | | |
| Remarkably effective | 97 (82.9%) | 51 (73.9%) | |
| Effective | 17 (14.5%) | 13 (18.8%) | NS (Chi-squared test) |
| Slightly effective | 2 (1.7%) | 4 (5.8%) | NS (*U*-test) |
| Ineffective | 1 (0.9%) | 1 (1.4%) | |
| Usefulness (overall evaluation) | | | |
| Remarkably useful | 92 (78.6%) | 51 (73.9%) | |
| Fairly useful | 22 (18.8%) | 13 (18.8%) | NS (Chi-squared test) |
| Slightly useful | 2 (1.7%) | 4 (5.8%) | NS (*U*-test) |
| Not useful | 1 (0.9%) | 1 (1.4%) | |

**Table 5** Antiemetic effect of granisetron injection on nausea/vomiting by disease type

| | Malignant lymphoma | Acute myelogenous leukemia | Others |
|---|---|---|---|
| Clinical efficacy (acute stage) | | | |
| Remarkably effective | 105 (97.2%) | 49 (98.0%) | 23 (85.2%) |
| Effective | 2 (1.9%) | 1 (2.0%) | 2 (7.4%) |
| Slightly effective | 1 (0.9%) | 0 | 1 (3.7%) |
| Ineffective | 0 | 0 | 1 (3.7%) |
| Final clinical evaluation (overall evaluation) | | | |
| Remarkably effective | 95 (88.0%) | 36 (72.0%) | 18 (66.7%) |
| Effective | 12 (11.1%) | 11 (22.0%) | 7 (25.9%) |
| Slightly effective | 1 (0.9%) | 2 (4.0%) | 2 (7.4%) |
| Ineffective | 0 | 1 (2.0%) | 0 |
| Usefulness (overall evaluation) | | | |
| Remarkably useful | 90 (83.3%) | 36 (72.0%) | 17 (62.9%) |
| Fairly useful | 17 (15.7%) | 11 (22.0%) | 7 (25.9%) |
| Slightly useful | 1 (0.9%) | 2 (4.0%) | 3 (11.1%) |
| Not useful | 0 | 1 (2.0%) | 1 (3.7%) |

**Table 6** Comparison of the effect of granisetron injection by anemic tendency. The chi-squared test was performed by making a comparison with complete responders or 'remarkably useful', respectively

| | Tendency toward anemia absent | Tendency toward anemia present[a] | |
|---|---|---|---|
| Clinical efficacy (acute stage) | | | |
| Remarkably effective | 67 (95.7%) | 110 (94.8%) | |
| Effective | 2 (2.9%) | 4 (3.4%) | NS (Chi-squared test) |
| Slightly effective | 1 (1.4%) | 1 (0.9%) | NS (*U*-test) |
| Ineffective | 0 | 1 (0.9%) | |
| Final clinical evaluation (overall evaluation) | | | |
| Remarkably effective | 63 (90.0%) | 85 (73.3%) | |
| Effective | 2 (2.9%) | 28 (24.1%) | $P = 0.006$ (Chi-squared test)<br>$P = 0.0147$ (*U*-test) |
| Slightly effective | 3 (4.3%) | 3 (2.6%) | |
| Ineffective | 2 (2.9%) | 0 | |
| Usefulness (overall evaluation) | | | |
| Remarkably useful | 62 (88.6%) | 81 (69.8%) | |
| Fairly useful | 3 (4.3%) | 32 (27.6%) | NS (Chi-squared test) |
| Slightly useful | 3 (4.3%) | 3 (2.6%) | NS (*U*-test) |
| Not useful | 2 (2.9%) | 0 | |

[a] When the blood hemoglobin concentration was less than 13.0 g/dl for men and 11.5 g/dl for women before the start of the study, the subject was classified as being 'anemic tendency positive'

## Discussion

Recently in cancer chemotherapy, much importance has been attached to patient quality of life. Among the various types of cancer chemotherapy, treatment of malignant hemopathy can be used for establishing a cancer treatment model because a high rate of complete remission can be expected. For malignant hemopathy, multidrug combination therapy with priority given to cyclophosphamide has been widely employed with the objectives of enhancing the main effect and of reducing the incidence of adverse reactions. Severe nausea/vomiting, which occurs during and after the administration of anticancer drugs, is one of the main factors that prevents the achievement of these treatment aims and threatens patient quality of life. Moreover, a high remission rate can be expected through the skilful control of these symptoms. In contrast to tumors originating in other organs, in malignant hemopathy, fever due to leukopenia, hemorrhage due to thrombocytopenia, and a decreased gas exchange capacity due to anemia frequently develop. When these symptoms are present in the context of malignant hemopathy, adverse reactions to anticancer drugs are amplified, and systemic conditions are further aggravated. Nausea, vomiting and symptoms in digestive organs are frequently observed with chemotherapy for almost all types of malignant hemopathy, and the success of chemotherapy is dependent on the reduction of these adverse reactions [7]. Therefore, in order to establish a safe and optimally effective method for the administration of antiemetics, we planned to compare administration methods of granisetron injection.

In a previous double-blind comparative study, granisetron instilled over 30 min immediately prior to the administration of cisplatin gave an efficacy rate of 85.5% [6]. In contrast, granisetron given intravenously by slow injection (over 30 s) to patients with gynecological malignancy gave efficacy rates of 72.6% [10] and 72.7% [11]. These differences in efficacy rate could be attributed to sex differences since, in a previous study [9] a weaker antiemetic effect of 5HT3 receptor antagonists has been shown in women. Nevertheless, a possible difference in antiemetic effect in the case of slow intravenous injection cannot be excluded. Hence, the present study was performed for the purpose of examining whether any differences exist in antiemetic efficacy between the two methods of administration, and whether such a difference if present would cause any clinical problem. In this study comparing infusion and intravenous injection of granisetron, it was shown that (1) there was no difference between the two methods in terms of clinical efficacy or clinical evaluation, (2) anorexia that develops shortly after administration of anticancer drugs was alleviated by intravenous injection, (3) there were no differences in relation to sex, but in relation to disease type, an efficacy rate of more than 90% was found during the acute stage in patients with malignant lymphoma and acute myelocytic leukemia and (4) in patients with an anemic tendency with low blood hemoglobin concentrations, although no differences were observed in the acute stage, the antiemetic effect of granisetron on nausea/vomiting during the delayed and acute stages in combination was not greater than that in the acute stage. No significant differences in the frequency of use of corticosteroids was found between group A and group B (46.2% vs 46.2%, $P = 1.000$, chi-squared test). Although the frequency of use of corticosteroids was different between patients with malignant lymphoma (63.9%) and those with acute myelocytic leukemia (16.0%), no significant difference in efficacy during the acute stage or in the final clinical evaluation was found between those receiving steroid and those not receiving steroids in both diseases. This suggests that administration of steroids does not affect clinical efficacy.

Nausea/vomiting induced by anticancer drugs is classified into acute stage symptoms which develop in a relatively short period of time after administration of the drugs [2] and delayed symptoms that occur the day after administration and last for several days thereafter [4]. For comparison of antiemetic effects against nausea/vomiting in the acute stage, in the present study the results from the first day of the administration period of anticancer drugs were analyzed in order to avoid the effects on delayed nausea/vomiting. The 30-min infusion method was slightly superior in the prevention anorexia, and showed a high clinical efficacy of 90% or more. For the use of granisetron in actual clinical practice, when an infusion line is secured, a high degree of efficacy and safety can be expected by infusion, and the dose can be controlled in response to the changes in symptoms, and planned concomitant administration with anticancer drugs can be achieved. In addition, taking emergency measures against anaphylactic shock is uncomplicated. Therefore, the infusion method seems to be the recommended method of administration.

Regarding differences according to sex, in particular, Roila et al. have reported that nausea/vomiting develops more readily in women [9]. In contrast, no significant sex differences were found in the present study. This discrepancy may be attributed to the use of cisplatin in the study by Roila et al., i.e. to the differences in the anticancer drugs used in these studies, or to background factors other than sex (e.g. alcohol consumption) that may have had a direct influence. On the other hand, patients with an anemic tendency are considered to lose their resistance to the development of nausea/vomiting with increasing days of administration of anticancer tumor drugs. Cancer chemotherapy is changing, with more powerful treatments being given. When chemotherapy is performed on patients with an anemic tendency, strict antiemetic measures such as changing the dose and frequency of granisetron infusion should be taken bearing in mind the easy development of stomatitis, rather than using oral antiemetic drugs [3, 8].

In the present study, a high degree of efficacy and usefulness of granisetron was demonstrated in the treatment of nausea/vomiting which had developed in the many patients with malignant lymphoma and acute myelocytic leukemia. Further examination involving more subjects should be performed in the future.

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