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A Randomized Cross-over Study of High-dose Metoclopramide plus Dexamethasone versus Granisetron plus Dexamethasone in Patients Receiving Chemotherapy with High-dose Cisplatin

Hironobu Ohmatsu,[1,5] Kenji Eguchi,[1] Tetsu Shinkai,[1] Tomohide Tamura,[1] Yuichiro Ohe,[1] Masato Nisio,[1] Hiroshi Kunikane,[1] Hitoshi Arioka,[1] Atsuya Karato,[1] Hajime Nakashima,[1] Yasutsuna Sasaki,[3] Kinuko Tajima,[2] Noriko Tada[1] and Nagahiro Saijo[4]

[1]Department of Internal Medicine and Thoracic Oncology, [2]Division of Drug Therapy and Biostatistics, National Cancer Center Central Hospital, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104, [3]Division of Drug Therapy, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277 and [4]Division of Pharmacology, National Cancer Center Research Institute, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104

We carried out a randomized, single-blind, cross-over trial to compare the antiemetic effect, for both acute and delayed emesis, of granisetron plus dexamethasone (GRN+Dx) with that of high-dose metoclopramide plus dexamethasone (HDMP+Dx). Fifty-four patients with primary or metastatic lung cancer, given single-dose cisplatin (>80 mg/m^2) chemotherapy more than twice, were enrolled in this study. They were treated with both HDMP+Dx and GRN+Dx in two consecutive chemotherapy courses. On day 1, patients experienced a mean of 2.5 (SD=4.3) and 0.1 (SD=0.4) episodes of vomiting in the HDMP+Dx and the GRN+Dx groups, respectively ($P=0.0008$). Complete response rate on day 1 was 45 and 90% in the HDMP+Dx and the GRN+Dx groups, respectively ($P=0.0001$). Patients treated with GRN+Dx had a tendency to suffer more episodes of vomiting than the HDMP+Dx group on days 2–5, but it was not statistically significant. Twenty-four patients (57%) preferred the GRN+Dx treatment and 14 patients (33%), HDMP+Dx. In the HDMP+Dx group, nine patients (21%) had an extrapyramidal reaction, and 5 patients (12%) had constipation that lasted for at least two days. In contrast, no patients had extrapyramidal reactions, and 18 patients (43%) had constipation in the GRN+Dx group ($P<0.01$). GRN+Dx was more effective than HDMP+Dx only in preventing the acute emesis induced by cisplatin. An effective treatment for delayed emesis is still needed.

Key words: Granisetron — Dexamethasone — Antiemetic — Cisplatin — Chemotherapy

Chemotherapy-induced emesis remains a serious problem. The severity of chemotherapy-induced emesis depends on the intrinsic emetogenicity or drug dose of chemotherapeutic agents. Cisplatin, one of the most emetogenic agents, is included in the treatment of advanced lung cancer. However, because of severe nausea and vomiting, the quality of life of the patients often declines, and sometimes patients refuse to continue the chemotherapy.[1–3] Therefore optimal control of emesis in patients receiving highly emetogenic chemotherapy remains an important objective of supportive care in cancer chemotherapy.[4]

High-dose metoclopramide (HDMP), an antagonist acting on both dopamine and serotonin receptors, is effective in preventing chemotherapy-induced emesis. The antiemetic efficacy of HDMP was proved to be enhanced by the addition of dexamethasone (Dx) in patients receiving cisplatin-based chemotherapy.[4] Thus, HDMP+Dx is currently used in many hospitals as a standard antiemetic treatment. However, extrapyramidal symptoms are the major adverse effect of HDMP. Furthermore, delayed emesis after chemotherapy can hardly be prevented with the HDMP+Dx regimen.[4]

Recently, selective 5-HT$_3$ (5-hydroxytryptamine) receptor blocking agents have been developed as antiemetic drugs.[5] Although a direct effect of these agents on the central nervous system has not been excluded, 5-HT$_3$ receptor antagonists are thought to exert their effect mainly by acting in the gastrointestinal tract, where serotonin-containing enterochromaffin cells exist.[6–8] Ondansetron (OND), one of the 5-HT$_3$ receptor antagonists, has been evaluated for prophylaxis of chemotherapy-induced emesis.[9] It has been shown to be superior to metoclopramide (MP).[10–12] Granisetron (GRN), another 5-HT$_3$ receptor antagonist, was also effective for preventing chemotherapy-induced nausea and vomiting,[13–18] with fewer adverse events than MP+Dx.[13,19] Recently, a combination of OND and Dx was shown to be more effective than OND alone in patients with cisplatin-induced emesis.[12,20] In this study we tested the efficacy and safety of GRN+

[5] To whom correspondence should be addressed (present address: Department of Respiratory Medicine, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277).

Dx against acute and delayed emesis for 6 consecutive days, as compared to the standard HDMP+Dx, when used in conjunction with cisplatin chemotherapy in patients with advanced pulmonary tumors.

MATERIALS AND METHODS

Patient eligibility Patients with histologically or cytologically proven primary or metastatic lung cancer, aged less than 80 years old and with a performance status of 0–3 (ECOG) were eligible for this study. Patients with carcinomatous meningitis, uncontrolled brain metastasis, life-threatening infection, evidence of uncontrollable cardiovascular disease, or uncontrollable diabetes were ineligible. Written informed consent was obtained from all patients. The registration office was at the Statistical Center of the Japanese Clinical Oncology Group (JCOG) in the National Cancer Center Central Hospital, Tokyo. The enrolled patients were scheduled to receive chemotherapy with cisplatin more than twice, with a single dose of at least 80 mg/m^2. All patients were admitted to the hospital during their treatment.

Chemotherapy regimens Patients received a single dose of cisplatin-based chemotherapy. The dose of cisplatin was $\geq$80 mg/m^2. The combinations of chemotherapeutic agents were as follows: cisplatin (80–100 mg/m^2 day 1) + vindesine (VDS: 3 mg/m^2 days 1, 8); cisplatin (80 mg/m^2 day 1) + mitomycin (MMC: 8 mg/m^2 day 1) + VDS (3 mg/m^2 days 1, 8); cisplatin (80 mg/m^2 day 1) + etoposide (100 mg/m^2 days 1–3); cisplatin (80 mg/m^2 day 1) + VDS (3 mg/m^2 days 1, 8) + CPT-11 (60 mg/m^2 days 1, 8); cisplatin (80 mg/m^2 day 1) + 5-fluorouracil (50 mg/m^2 days 1–7). After prehydration of 1,000 ml over 2 h, cisplatin was administered i.v. over the course of 1 h followed by hydration and mannitol diuresis.

Antiemetic treatment This study was a randomized, single-blind, crossover trial. There were two antiemetic regimens: HDMP+Dx and GRN+Dx. After the stratification of patients with or without prior chemotherapy, patients were randomly assigned to two arms, Arm A: HDMP+Dx in the first cycle and GRN+Dx in the second cycle of the same chemotherapy, Arm B: GRN+Dx in the first cycle and HDMP+Dx in the second cycle. When a third cycle of the same chemotherapy was planned, the patients were requested to indicate their preferred antiemetic regimen.

On the first day of chemotherapy with the HDMP+Dx, MP (2 mg/kg), Dx (8 mg/body) and promethazine

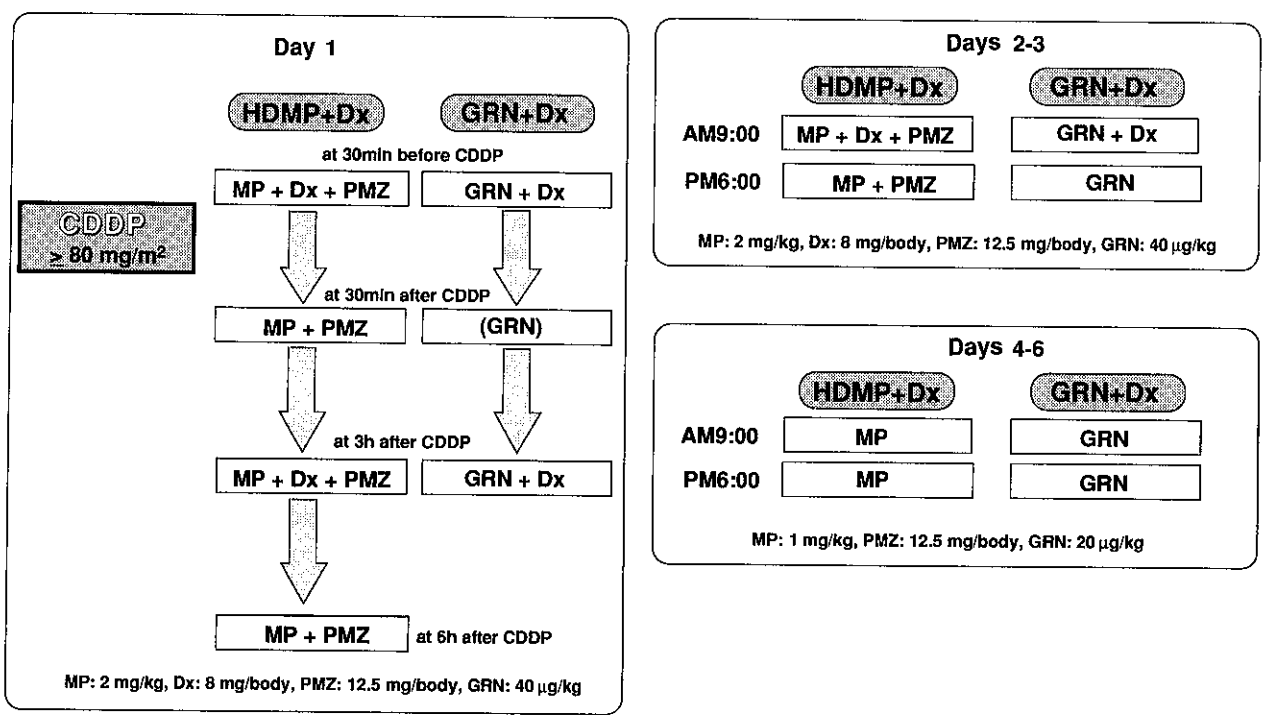

Fig. 1. Schema of antiemetic treatment. There were two antiemetic treatment regimens: HDMP+Dx and GRN+Dx. Patients received these treatments from the first to the sixth day to control not only early emesis but also delayed emesis. An additional dose of GRN was given in the event of nausea and vomiting 30 min after infusion of cisplatin (CDDP) in the GRN+Dx group. PMZ, promethazine.

(12.5 mg/body, for protection from extrapyramidal symptoms) with 100 ml of normal saline were administered intravenously over 30 min, both 30 min before and 3 h after the infusion of cisplatin (Fig. 1). MP (2 mg/kg) and promethazine (12.5 mg/body) with 100 ml of normal saline were administered intravenously both 30 min and 6 h after the infusion of cisplatin. MP (2 mg/kg), Dx (8 mg/body) and promethazine (12.5 mg/body) with 100 ml of normal saline were administered intravenously over 30 min at 9 am, and MP (2 mg/kg) and promethazine (12.5 mg/body) with 100 ml of normal saline were administered intravenously at 6 pm on days 2 and 3 of chemotherapy. MP (1 mg/kg) with 100 ml of normal saline was administered intravenously at 9 am and 6 pm on days 4–6 after chemotherapy.

On the first day of chemotherapy with GRN+Dx, GRN (40 μg/kg) and Dx (8 mg/body) with 100 ml of normal saline were administered intravenously over 30 min, both 30 min before and 3 h after the cisplatin infusion. If patients still experienced nausea and vomiting 30 min after the infusion of cisplatin, an additional dose of GRN (40 μg/kg) with 100 ml of normal saline was administered. GRN (40 μg/kg) and Dx (8 mg/body) with 100 ml of normal saline were administered intravenously over 30 min at 9 am, and GRN (40 μg/kg) with 100 ml of normal saline was administered intravenously at 6 pm on days 2 and 3 of chemotherapy. GRN (20 μg/kg) with 100 ml of normal saline was administered intravenously at 9 am and 6 pm on days 4–6 after chemotherapy.

Additional medication If a patient experienced nausea or vomiting after the prophylactic antiemetic regimens, an additional dose, such as MP (2 mg/kg) + promethazine (12.5 mg/body) with 100 ml of normal saline in the cycle of HDMP+Dx treatment, or GRN (40 μg/kg) with 100 ml of normal saline in the cycle of GRN+Dx treatment, was allowed. These additional dose was given at least 2 h after the prophylactic dose. If patients experienced uncomfortable extrapyramidal symptoms, the antiemetic drug dose was reduced by 50%. Further administration of the antiemetic drug was discontinued when the extrapyramidal symptoms persisted even after the dose reduction. The administration of the antiemetic drug used in the other arm of the study during the single treatment period was prohibited. When a patient had uncontrollable nausea or vomiting, the use of a domperidone (60 mg) suppository was permitted as a salvage treatment.

Data collection and evaluation of response The incidence of vomiting and the amount of food intake were monitored and recorded for each patient over the 6 days. Monitoring was accomplished by bedside observation and by interviewing patients.

The response was defined as follows: complete response (CR), no vomiting in 24 h; major response (MAJ), vomiting once or twice in 24 h; minor response, vomiting 3–5 times in 24 h; failure, vomiting more than five times in 24 h. This accords with the response criteria of previous studies.[12, 20–23]

In addition to the vomiting, a visual analog scale (VAS) was used for the evaluation of nausea. The VAS consisted of a 100 mm line, as previously described, where 0 = no nausea and 100 = nausea as severe as it could be.[24] Each patient completed VAS recording every morning for 6 consecutive days following cisplatin chemotherapy, and the length from the left end to the recorded point was measured.

Clinical and laboratory monitoring Blood pressure, pulse rate, temperature, urinary output and the number of evacuations were recorded every day. Hematological and chemical data were taken before the treatment and at least once a week during the chemotherapy cycles. Assessment of toxicity was based on the Eastern Cooperative Oncology Group (ECOG) Common Toxicity Criteria established by the Division of Cancer Treatment, National Cancer Institute.

Statistical analysis Overall response rate including delayed emesis was around 50% with the HDMP+Dx regimen, and that of the GRN+Dx regimen was estimated to increase by about another 30%. The patient accrual would be 30–40 if the evaluation were done with a 5% significance level and 80% power.

Difference in the distribution of patients between the two groups was examined using the chi-square test. The Wilcoxon rank-sum test was used for comparison between the treatments concerning the number of vomiting episodes and the response rate. The VAS was evaluated using the SAS program (SAS Institute Inc., Cary, NC, USA).

RESULTS

Fifty-four patients (41 males and 13 females) with the median age of 57 years (range 34–79) were randomly assigned to the two arms from August 1991 to June 1992. There was no significant difference in patients' characteristics between the two groups (Table I).

Twelve patients, six in each group, did not receive the second cycle of the same chemotherapy and were not evaluable. The reasons for exclusion were as follows: 5 patients had progressive disease after the first chemotherapy; 3 had dose reduction of cisplatin in the second cycle due to hematological or renal toxicity; 3 exhibited worsening of the performance status after the first chemotherapy; 1 misused the antiemetic drug. The mean interval between the first and second cycles of chemotherapy was 28 days.

No patient received an additional dose of GRN at 30 min after cisplatin administration.

Table I. Patients' Characteristics

	Total	Arm A	Arm B
Gender (male/female)	41/13[a)]	21/6	20/7
PS 0	7	5	2
1	41	19	22
2	6	3	3
Prior chemotherapy (−)	32	16	16
(+)	22	11	11
Primary lung cancer	50	26	24
Metastatic lung cancer	4	1	3
Chemotherapy regimen			
CDDP+VDS	23	12	11
MVP	14	7	7
PVP	13	7	6
CDDP+VDS+CPT-11	3	1	2
CDDP+5FU	1	0	1
Dose of CDDP 80 mg/m^2	46	21	25
100 mg/m^2	8	6	2

a) Number of patients.
PS, performance status; CDDP, cisplatin; VDS, vindesine; MVP, mitomycin C+vindesine+cisplatin; PVP, cisplatin+etoposide; CTP-11, irinotecan; 5FU, 5-fluorouracil.

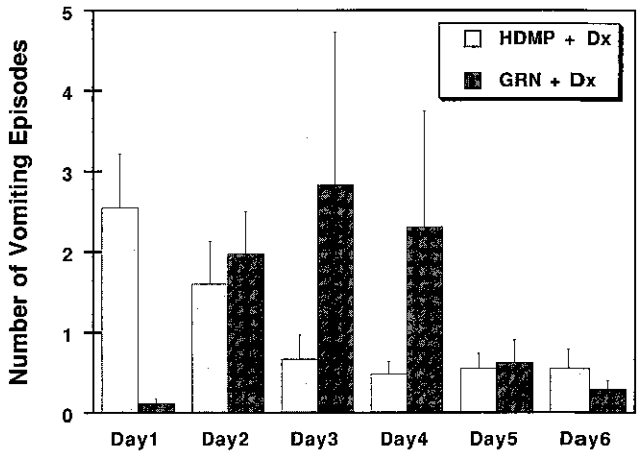

Fig. 2. Comparison of incidence of vomiting between the two groups. The HDMP+Dx and the GRN+Dx group patients suffered a mean of 2.5 and 0.1 episodes of vomiting ($P=0.0008$) on day 1. The GRN+Dx group patients had more episodes of vomiting than the HDMP+Dx group patients on days 2–5, although the difference was not statistically significant (mean value and standard error).

Vomiting episodes and response Fig. 2 compares the mean occurrence of vomiting between the HDMP+Dx and the GRN+Dx groups. There was a significant difference in the mean number of vomiting episodes between the two groups on day 1 ($P=0.0008$). The mean number of vomiting episodes of the GRN+Dx group was higher than that of the HDMP+Dx group on days 2–6, but there was no statistically significant difference in delayed emesis.

There was a significant difference in the CR rates of the two groups on day 1: 45% with HDMP+Dx, and 90% with GRN+Dx ($P=0.0001$). Overall response rates (CR+MAJ) on day 1 were 67 and 98%, respectively ($P=0.0001$). CR rates on days 2–6 were 69, 79, 74 ,76 and 81%, respectively, in the HDMP+Dx group and 60, 62, 71, 81 and 83% in the GRN+Dx group. Response rates (CR+MAJ) on days 2–6 were 76, 93, 93, 90 and 93%, respectively, in the HDMP+Dx group and 74, 79, 83, 93 and 98% in the GRN+Dx group. The CR and overall response rates of the HDMP+Dx group were higher than those of the GRN+Dx group. The rates of failure and minor response of the GRN+Dx group tended to be higher on days 2–4 than those of the HDMP+Dx group, although there was no statistically significant difference (Fig. 3).

Nausea and food intake Fig. 4 shows a comparison of the mean lengths of the VAS between the two groups. In comparison with the HDMP+Dx group, patients in the GRN+Dx group were almost free from nausea on day 1 ($P=0.0001$). However, there was no significant differ-

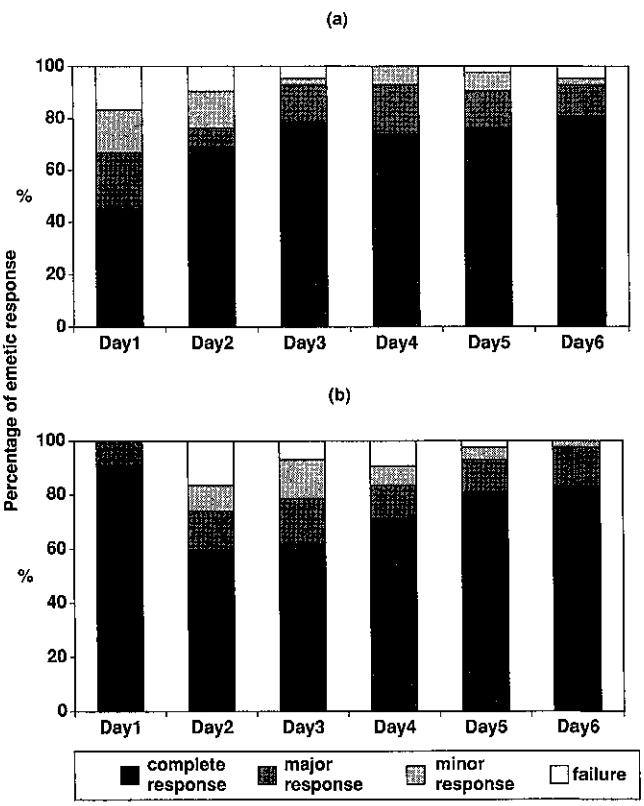

Fig. 3. Comparison of response rates: (a) HDMP+Dx, (b) GRN+Dx. Overall response rates (CR+MAJ) on day 1 were 67 and 98%, respectively ($P=0.0001$). But there was no significant difference in the response rates of the two groups on days 2–6.

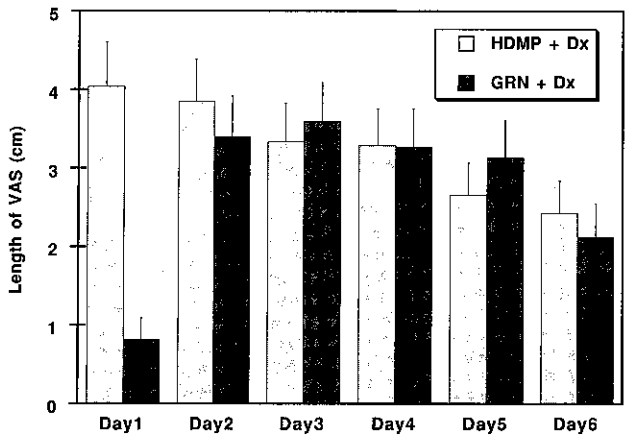

Fig. 4. Comparison of length of the visual analog scale (VAS) between the two groups. The GRN+Dx group patients were almost free from nausea on day 1 as compared with the HDMP+Dx group patients ($P=0.0001$), and both groups suffered almost equally from moderate nausea thereafter.

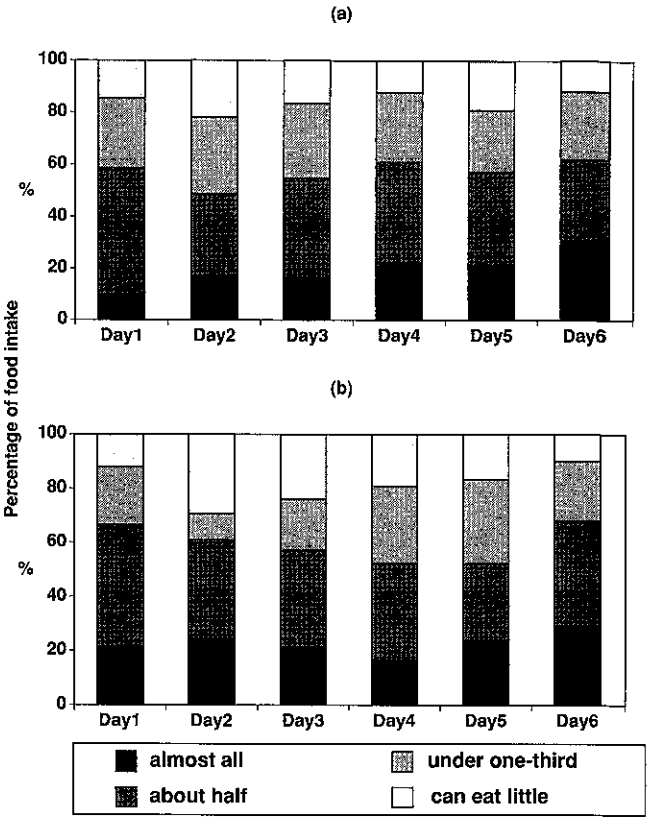

Fig. 5. Comparison of food intake: (a) HDMP+Dx, (b) GRN+Dx. Food intake was classified into four categories, (1) almost all; (2) about half; (3) under one-third; (4) almost none. There was no statistically significant difference in the amount of food intake between the two groups.

ence in the mean lengths of the VAS of the two groups on days 2–6.

We classified the food intake into four categories: (1) almost enough; (2) about half; (3) under one-third; (4) almost nothing. As shown in Fig. 5, there was no statistically significant difference in the amount of food intake between the two groups.

Patients' preferences Twenty-four patients (57%) preferred GRN+Dx, and 14 patients (33%), HDMP+Dx. Four patients (10%) did not express a treatment preference for the third cycle of chemotherapy. There was no statistically significant difference between the two treatments in terms of patients' preferences.

Carry-over effect Fig. 6 shows the mean numbers of vomiting episodes in each cycle for the 42 evaluable patients who received both treatment regimens sequentially. There was no significant difference in the mean number of vomiting episodes in the same regimen between the first and the second cycles, and we could not find evidence of a time effect or carry-over effect between the first and the second treatments. Although we found a time effect on days 1 and 4 ($P=0.02$) and a carry-over effect on day 4 ($P=0.02$) in the VAS, there was a significant difference between the HDMP+Dx and the GRN+Dx treatment only during the first cycle of chemotherapy ($P<0.05$).

Multivariate analysis of antiemetic response We examined the influence of some independent characteristics of patients on the response to the antiemetic regimens using Cox's logistic regression model. In this multivariate analysis there was no significant factor, as related to the acute emesis response, which influenced the antiemetic response in either HDMP+Dx and GRN+Dx treatments.

Among the factors of age, sex, chemotherapy regimen (combination with two vs. three agents) and prior therapy, only chemotherapy regimen showed a significant influence on the response to antiemetic agents (in the HDMP+Dx group) for delayed emesis using both univariate and stepwise multivariate analyses ($P=0.045$). Patients who received three-drug regimens experienced a poorer response to antiemetic treatments when compared to patients who received two-drug regimens. Sex was important for the response in the GRN+Dx group and for the response to antiemetic agents as regards delayed emesis ($P=0.017$). Men responded less to antiemetic treatment than women did.

Adverse effects Nine patients (21%) experienced adverse reactions during HDMP+Dx treatment, and eight of them could not receive the complete antiemetic treat-

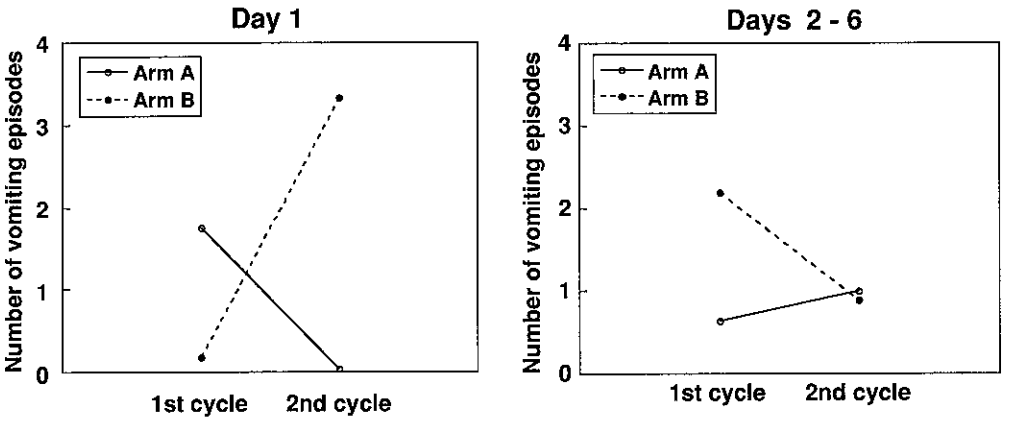

Fig. 6. Relative efficacy of both treatments in each cycle. The number of episodes of vomiting in patients receiving HDMP+Dx treatment was 1.76 in cycle 1 and 3.33 in cycle 2. That in patients receiving GRN+Dx treatment was 0.19 in cycle 1 and 0.05 in cycle 2.

Table II. Adverse Effects

Adverse effect	Treatment	
	HDMP+Dx	GRN+Dx
Extrapyramidal reactions[b]	9 (21)[a]	0
Constipation (≧2 days)[b]	5 (12)	18 (43)
Diarrhea	2 (5)	0
Abdominal pain	0	1 (2)
Headache	0	1 (2)

a) Number of patients (%).
b) $P<0.01$.
HDMP, high-dose metoclopramide; Dx, dexamethasone; GRN, granisetron.

ment. We stopped the administration of MP in two patients on day 1; one patient on each of days 3 and 4; two patients on each of days 5 and 6. None of the patients treated with GRN+Dx had extrapyramidal symptoms ($P<0.01$). Eighteen patients (43%) in the GRN+Dx group complained of constipation which lasted at least two days, compared to only 5 patients (12%) in the HDMP+Dx group ($P<0.01$). There were two patients in the HDMP+Dx group who suffered from grade 1 diarrhea, and in the GRN+Dx group one patient complained of a grade 1 headache and one of abdominal colicky pain. There was no fatal adverse effect in either regimen (Table II).

Cost effectiveness We calculated the actual cost of both treatments, using the exchange rate of one US dollar equal to 110 yen. The cost of the drugs was as follows: MP (Primperan) 10 mg/ample, 61 yen (US \$0.55); Dx (Decadron) 8 mg/vial, 495 yen (US \$4.50); promethazine (Pyretia) 25 mg/ample, 57 yen (US \$0.52); GRN (Kytril) 3 mg/ample, 10,020 yen (US \$90.09). The GRN+Dx and HDMP+Dx regimen cost 121,047±2,249 yen (US \$1,100.43±107.84) and 10,923±2,249 yen (US \$99.30±20.45), respectively, so that the former regimen costs more than 10 times as much as the latter.

DISCUSSION

Phase III studies showed regimens containing 5-HT_3 receptor antagonists to be superior to HDMP+Dx treatments for inducing antiemetic effects.[13,14] Hainsworth *et al.*[11] showed the superiority of OND as compared to MP in cisplatin (≥ 100 mg/m^2) chemotherapy; response rates were 65% versus 51%, respectively ($P=0.016$). Chevallier[13] evaluated the antiemetic effect of GRN in comparison with that of HDMP+Dx in patients receiving cisplatin (>49 mg/m^2) chemotherapy. The CR/response rate was 70/85% in the GRN group and 69/77% in the HDMP+Dx group. He observed that GRN and HDMP+Dx had similar effects. Roila *et al.*[12] showed that adding Dx to OND was more effective than using OND alone in chemotherapy with cisplatin. Complete protection from emesis/nausea was obtained in 91.0/88.8% using OND+Dx versus 64.0/66.3% using OND alone ($P=0.0005/0.0021$). We planned GRN+Dx as a new regimen because it was suggested that the combination of a 5-HT_3 receptor antagonist and Dx was most effective with highly emetogenic chemotherapy, at least during the first 24 h following cisplatin administration. In this study also, the suppression of vomiting on day 1 was significantly better with the GRN+Dx treatment than with the HDMP+Dx treatment. Acute emesis accompanying chemotherapy with cisplatin seemed to be almost completely controlled by using GRN+Dx.

Although delayed emesis is not always as severe as acute emesis, it has recently been recognized as the major problem in cisplatin chemotherapy. The pathogenesis of delayed emesis remains unclear. There have been some studies on chemotherapy-induced delayed emesis. Bonneterre *et al.*[10] showed that OND was more effective in controlling delayed emesis than MP; the response rate was 81 versus 65%, respectively ($P=0.033$). However, the chemotherapy regimen did not include cisplatin. Jones *et al.*[21] observed that Dx was more effective than OND in the control of delayed nausea induced by non-platinum-containing chemotherapy, 87 versus 72% ($P=0.003$). Moreno *et al.*[22] showed that MP+Dx was more effective than Dx alone for delayed emesis occurring with cisplatin chemotherapy, 70 versus 44% ($P=0.02$). Not every treatment had an adequate effect on delayed emesis after emetogenic chemotherapy. We tried to evaluate the efficacy of the combination of a 5-HT_3 receptor antagonist and Dx in delayed emesis. In this study, the mean number of vomiting episodes for HDMP+Dx tended to be lower than that for GRN+Dx on days 2–4, but this was not statistically significant. Over 20% of patients had more than three episodes of vomiting per day on days 2–4. Both treatments failed to show effectiveness against delayed emesis at the doses and schedules tested.

Although the difference was not statistically significant, the mean number of vomiting episodes of the GRN+Dx group was higher than that of the HDMP+Dx group on days 3–4 especially. In contrast, the length of VAS was similar on day 2–6 between two treatments.

The numbers of patients completely free from vomiting in the HDMP+Dx group and GRN+Dx group were 33 versus 26 on day 3 and 31 versus 30 on day 4. There was a larger individual variation for delayed vomiting in the GRN+Dx group. The patients who were not completely free from emesis during days 2–6 suffered from severe emesis. Additionally the VAS might have been influenced by discomfort caused by the extrapyramidal reaction, because 21% of the HDMP+Dx group patients experienced extrapyramidal reaction.

There were no severe side effects in either treatment, but extrapyramidal reaction was more frequent in the HDMP+Dx group and constipation was higher in the GRN+Dx group ($P<0.01$). The uncomfortable adverse effects of the antiemetics may have influenced the patients' preference of regimen.

Optimal dose of GRN is reported as 40 μg/kg/day intravenously over 5 min.[25] We administered GRN at a dose of 80 μg/kg/day on days 1–3 and at 40 μg/kg/day on days 4–6. However, we think a higher dose would not improve the antiemetic efficacy against delayed emesis because there was no evidence of superior efficacy of GRN+Dx during days 2–3 versus days 4–6.

In conclusion, the HDMP+Dx regimen may substitute for GRN+Dx as the first-line antiemetic therapy for acute emesis induced by cisplatin chemotherapy. Both treatments failed to prevent delayed emesis at the doses and schedules tested. Using GRN+Dx, at the same dosage and schedule as tested in this study, to control delayed emesis cannot be justified on the basis of cost-effectiveness.

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