Oral Granisetron with or without Methylprednisolone versus Metoclopramide plus Methylprednisolone in the Management of Delayed Nausea and Vomiting Induced by Cisplatin-Based Chemotherapy

A Prospective Randomized Trial

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Background. A single-institution, randomized open trial was prospectively performed to compare orally administered granisetron with or without intramuscularly administered methylprednisolone to metoclopramide plus methylprednisolone in the prevention of delayed nausea and vomiting induced by cisplatin-based chemotherapy. The effects of antiemetic treatments were evaluated from days 2 to 5 of the first cycle after cisplatin administration among patients who had never before received chemotherapy.

Methods. All patients were treated with chemotherapeutic regimens containing cisplatin greater than or equal to 80 mg/m^2 and received antiemetic therapy with granisetron 3 mg intravenously for the control of acute emesis. Patients who responded to treatment during the first 24 hours were randomized to receive (1) metoclopramide (0.5 mg/kg) intramuscularly three times daily plus methylprednisolone (125 mg) intramuscularly once a day or (2) granisetron (1 mg) orally twice daily or (3) oral granisetron (1 mg) orally plus methylprednisolone (125 mg) intramuscularly from days 2 to 5.

Results. Of the patients treated with metoclopramide plus methylprednisolone (n = 92), 53% had complete protection from delayed emesis, 16% a major response, 15% a minor response, and 15% no response. Of the patients treated with granisetron alone (n = 84), 33% had a complete response, 21% a major response, 23% a minor response, and 21% no response. In the patients treated with orally administered granisetron plus intramuscularly administered methylprednisolone (n = 86), 47% had a complete response, 17% a major response, 23% a minor response, and 13% no response. These differences reached statistical significance only when the complete response rate achieved in the metoclopramide plus methylprednisolone group was compared with that recorded in the oral granisetron group ($P = 0.012$). Moreover, the metoclopramide plus methylprednisolone and the orally administered granisetron plus corticosteroid arms were superior to the orally administered granisetron alone arm in preventing nausea ($P < 0.038$ and $P < 0.002$, respectively). No extrapyramidal side effects were noted for the granisetron alone and the granisetron plus methylprednisolone arms, whereas 6% of patients treated with metoclopramide had extrapyramidal adverse effects. Headache was recorded in 8% of patients treated with granisetron alone, in 9% treated with granisetron plus methylprednisolone, and in 3% treated with metoclopramide plus methylprednisolone.

Conclusions. These data suggest that orally administered granisetron with or without methylprednisolone may be given safely to patients with cancer as prophylactic therapy against delayed emesis after high dose cisplatin therapy. Orally administered granisetron alone was less active than a standard combination of metoclopramide plus methylprednisolone. However, the addition of corticosteroid to orally administered granisetron improved the control of delayed emesis. The efficacy of the combination of metoclopramide plus methylprednisolone and oral granisetron with or without methylprednisolone against delayed emesis still is not entirely satisfactory. *Cancer* 1995;76:1821–8.

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Received March 6, 1995; revisions received May 15, 1995, and July 21, 1995; accepted July 21, 1995.

Key words: delayed vomiting, delayed nausea, cisplatin, chemotherapy, granisetron, metoclopramide, methylprednisolone.

Although there is a certain degree of variation in the pattern of emetic response among different individuals, most patients with neoplasms receiving high dose cisplatin without pharmacologic antiemetic protection experience moderate to very severe nausea and vomiting.[1] For this reason, cisplatin as well as other chemotherapeutic agents is considered to be a highly emetogenic drug whose administration must be preceded by intensive antiemetic treatment to avoid vomiting-related clinical complications and to improve the patient's quality of life and compliance to further treatments.[1,2]

Intensive antineoplastic chemotherapy may result in two different patterns of nausea and vomiting: (1) an acute emetic response that arbitrarily includes all of the vomiting episodes and nausea occurring within the first 24 hours since chemotherapy administration and a (2) second emetic response (i.e., delayed emesis) that may occur 24–120 hours after chemotherapy.[1-3] The incidence of delayed nausea and vomiting varies, ranging in medical literature from 20–90% of cases, depending largely on patient selection and the intensity of chemotherapy.[3-6] However, the majority of patients treated with high dose cisplatin experience delayed emesis, which generally reaches maximal intensity between days 2 and 3 after chemotherapy administration, and may persist up to day 6.[3-6]

Despite significant recent advances in the management of acute emesis after cisplatin administration because of the commercial availability of the new antagonists of the serotonin receptors (5-HT3),[7-9] delayed nausea and vomiting remain a largely unsolved problem. About half of patients treated with high dose cisplatin and a standard combination of antiemetic drugs report delayed nausea and vomiting, which thus remains an important cause of physical and psychological stress for these patients and a leading cause of refusal of otherwise successful chemotherapeutic treatments.[10] The substituted benzamide metoclopramide, a dopamine receptor blocking agent, has been shown to provide relatively effective acute antiemetic control when given intravenously at the dose of 2–3 mg/kg along with intravenously administered corticosteroids, such as dexamethasone[11-13] or methylprednisolone.[14,15] The same combination has also been reported to protect against delayed emesis in up to 60% of patients treated with high dose cisplatin.[10]

Several Phase III trials have demonstrated that intravenously administered granisetron is more effective against acute emesis, at least in reducing failure rates, than commonly used antiemetic combinations, such as high dose metoclopramide plus dexamethasone,[16,17] alizapride plus dexamethasone,[18] and chlorpromazine plus dexamethasone.[19] Experimental preclinical investigations of the antiemetic activity of granisetron against total body irradiation and cisplatin have demonstrated that granisetron is more potent than other 5-HT3 antagonists and has a more prolonged activity and a linear dose–response profile.[20,21] Despite the above-mentioned pharmacologic and pharmacokinetic data,[20,21] dose-finding studies of granisetron given intravenously to patients with neoplasms treated with cisplatin failed to detect any significant advantage in increasing the intravenously administered granisetron dosage above 3 mg/day.[22] In fact, 3 mg/day has been considered to be the standard dose in most studies on antiemetic therapy using granisetron.

Recently, granisetron has been developed as an oral formulation that, when tested among patients receiving moderately emetogenic chemotherapy, has been successful.[23,24] A large multicenter, dose-finding clinical study has shown that optimal protection against emesis was achieved with an orally administered granisetron dose of 1 mg twice daily, with an incidence of headache and constipation similar to previous studies with the intravenous formulation.[23]

Relatively few trials that have focused on the prevention of acute emesis have compared the antiemetic activity against delayed emesis of granisetron with other 5-HT3 receptor antagonists or other standard antiemetic protocols.[17,18,25,26] Particularly, to the best of our knowledge, no randomized trial has directly addressed whether granisetron is superior to standard antiemetic protocols in the prevention of chemotherapy-related delayed emesis consequent to high dose cisplatin administration.

In the current paper, we reported the results of a Phase III prospective, randomized, open study in which orally administered granisetron with or without concomitant corticosteroids was compared to intramuscularly administered metoclopramide plus methylprednisolone in the protection of delayed nausea and vomiting induced by cisplatin-based polychemotherapeutic regimens in a series of outpatients all treated with intravenously administered granisetron alone for acute emesis.

Materials and Methods

Study Design

After obtaining written informed consent from eligible patients and approval from the Ethical Committee, we entered patients with various types of cancer into a sin-

gle-center randomized, prospective, open study comparing orally administered granisetron with or without methylprednisolone to intramuscularly administered metoclopramide plus methylprednisolone in the prevention of delayed nausea and vomiting caused by chemotherapy.

In calculating sample size, we considered that most patients treated with high dose cisplatin without any antiemetic therapy experience delayed emesis,[3] whereas about 60% of patients treated with cisplatin who are given the combination of metoclopramide and corticosteroids experience complete protection from delayed emesis.[10] Granisetron has been reported to offer complete protection for 7 days after cisplatin administration in about 33% of cases.[16,19] Thus, a total of 85 patients per arm had to be enrolled to demonstrate a 25% advantage for metoclopramide plus methylprednisolone over orally administered granisetron at the significance level of $\alpha = 0.05$ with a power of $\beta = 0.8$.

Eligible patients had to fulfill the following entry criteria: no previous chemotherapy; age 18–70 years; a performance status according to Eastern Cooperative Oncology Group scale of below 2; absence of clinically detectable brain metastases; adequate renal function (blood urea nitrogen $\leq$ 50 mg/dl, serum creatinine $\leq$ 1.2 mg/dl, creatinine clearance $>$ 60 ml/minute); serum bilirubin less than or equal to 1.2 mg/dl and serum transaminase less than 2 times the normal value; no history of nonneoplastic severe gastrointestinal disease; absence of massive neoplastic infiltration of the stomach and the bowel that could cause obstruction; no drug abuse or use of psychotropic drugs; and no concomitant severe neurologic, hepatic, or renal disease. The occurrence of anticipatory emesis or uncontrolled assumption of any drug without previous contact and approval by investigators caused patient withdrawal from the study. All enrolled patients were required to receive a single-day chemotherapeutic regimen of cisplatin ($\geq$80 mg/m^2) combined with vinorelbine, epirubicin, methotrexate, and cyclophosphamide.

Antiemetic Schedule

All patients enrolled in the study had received prophylactics against acute emesis with granisetron (3 mg) diluted in 100 ml normal saline given intravenously for 15 minutes before chemotherapy. During the first 24 hours after cisplatin administration, we observed the patients to evaluate protection from acute nausea and vomiting and then randomized according to acute response. Patients who did not respond during the first 24 hours were not included in the study. All remaining patients were randomly allocated to receive: (1) metoclopramide (0.5 mg/kg) intramuscularly three times per day plus methylprednisolone (125 mg) intramuscularly once a day from days 2 to 5; (2) granisetron (1 mg) orally twice daily from days 2 to 5; or (3) granisetron (1 mg) orally plus methylprednisolone (125 mg) intramuscularly once daily from days 2 to 5. Patients in the granisetron groups who did not respond to treatment were given metoclopramide (0.5 mg/kg) three times a day plus methylprednisolone (125 mg) once daily.

Response Assessment

Patients were initially observed for protection against acute emesis (i.e., vomiting within 24 hours after chemotherapy). After randomization, patients were evaluated for delayed emesis on a 4-day study period (days 2–5) starting 24 hours after cisplatin completion. Antiemetic efficacy was evaluated during the first cycle. Any episode of vomiting or dry retching was considered an emetic episode. The number of emetic episodes, the intensity of nausea, and the occurrence of adverse events were recorded by direct interview of enrolled patients and by the use of a dietary card.

The antiemetic activity of treatments was defined as follows: complete response (no emetic episodes), major response (1–2 vomiting episodes and/or dry retching), minor response (3–5 vomiting episodes and/or dry retching), and failure or withdrawal (>5 emetic episodes). Nausea was recorded according to the degree of interference with normal daily life, as follows: (1) no nausea; (2) mild nausea (present but with no interference with normal daily life); (3) moderate nausea (interference with normal daily life); and (4) severe nausea (bedridden because of nausea).

Statistics

Data were reported as relative incidence expressed in percentage approximated to the nearest unit. Statistical analysis was performed with use of the Mantel–Haenszel chi-square test.

Results

Patient Population

Three hundred patients treated with high dose cisplatin-based regimens for various types of cancer received granisetron (3 mg) intravenously before cisplatin administration on day 1 as protection against acute emesis. Among these patients, 54% experienced complete protection against acute vomiting, 21% had a partial response, 16% a minor response, and 9% no response. Because patients who did not respond during the first 24 hours were not considered eligible for the

Table 1. Clinical Characteristics of Patients

Patients characteristic	Antiemetic treatment		
	Meto + MP	*Granisetron*	*Granisetron + MP*
No. of enrolled patients	92 (100%)	84 (100%)	86 (100%)
Age (yr)			
Mean	58.8	61.2	60.0
Range	36–74	38–75	40–76
Sex			
Male	66 (70%)	69 (71%)	58 (68%)
Female	28 (30%)	25 (29%)	28 (32%)
Performance Status			
Median	1	1	1
Range	0–2	0–2	0–2
Primary tumor			
Head/neck	25	28	26
Lung	23	25	24
Ovary	11	08	07
Endometrium	05	05	06
Cervix	02	03	0
Breast	07	06	08
Kidney	03	03	02
Stomach	06	03	04
Sarcoma	03	01	01
Urinary bladder	07	04	05
Mean cisplatin dose (mg/m^2)	89	88	90

Meto: metoclopramide; MP: methylprednisolone.

delayed emesis study (n = 27), 273 patients (91%) treated with intravenously administered granisetron for acute emesis were randomized for the 4-day study on delayed emesis. Eleven patients were unevaluable because of protocol violation or assumption of other drugs such as other antiemetics or psycothropic drugs.

Table 1 shows the main demographic and clinical characteristics of evaluable patients. All groups of patients (metoclopramide plus methylprednisolone versus granisetron versus granisetron plus methylprednisolone) were comparable for sex, median performance status, mean age, and type of primary neoplasm. Patients with ovarian carcinoma were treated with a combination of cisplatin (100 mg/m^2) and cyclophosphamide (750 mg/m^2) on day 1; patients with squamous cell head/neck carcinoma, oat cell carcinoma of the lung, carcinoma of the endometrium, or carcinoma of the cervix received cisplatin (80–120 mg/m^2) plus vinorelbine (25 mg/m^2) on days 1 and 8. Vinorelbine administered on day 8 did not affect the aim of the study. Other patients with nonsmall cell lung cancer or with breast carcinoma were given cisplatin (80–100 mg/m^2) plus epirubicin (100–120 mg/m^2) or vinorelbine (25 mg/m^2). Patients with urinary bladder carcinoma were given cisplatin plus methotrexate (50 mg/m^2), and other patients with head/neck carcinoma received cisplatin plus methotrexate (50 mg/m^2) plus bleomycin (10 mg/m^2).

Effects on Delayed Emesis

Figure 1 shows the effects of the antiemetic treatments on the incidence of vomiting episodes and/or dry retching in terms of response rates during the whole study period (days 2–5) according to the type of antiemetic treatment used. Evaluation of protection of emesis was performed at cycle 1.

In the metoclopramide plus methylprednisolone group, 49 of 92 patients (53%) experienced complete protection, 15 (16%) a major response, 14 (15%) a minor response, and 28 (15%) no response. In the group receiving oral granisetron alone, 28 of 84 evaluable patients (33%) had a complete response, 18 (21%) a major response, 19 (23%) a minor response, and 18 (21%) no response. In the oral granisetron plus intramuscularly administered methylprednisolone group, 40 patients (47%) had complete protection from delayed emesis, 15 (17%) a major response, 19 (23%) a minor response, and 12 (13%) no response. These differences reached statistical significance only when complete response rate achieved in the metoclopramide plus methylprednisolone arm was compared to that in the group treated

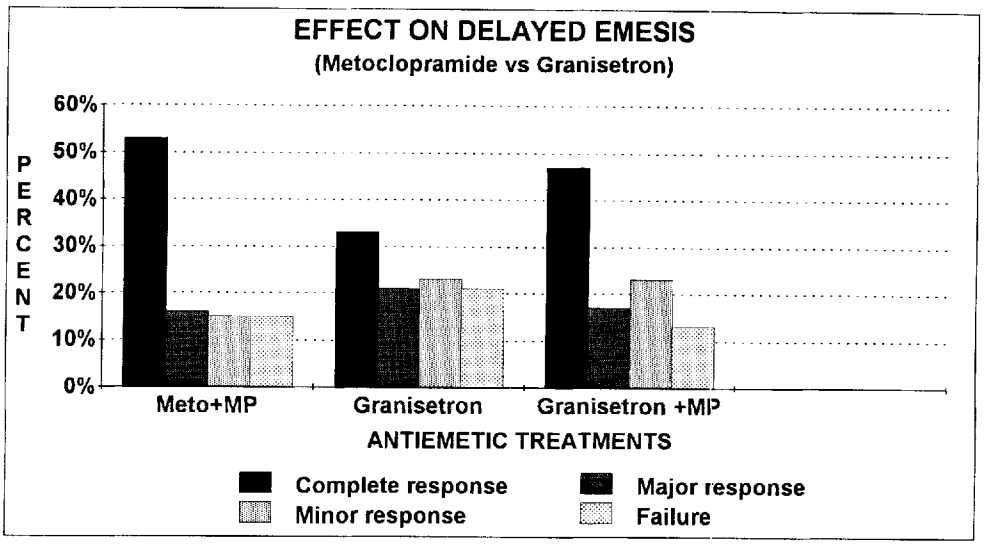

Figure 1. The effects of metoclopramide and methylprednisolone vs. granisetron with or without methylprednisolone on cisplatin-correlated delayed emesis.

with oral granisetron only (53% versus 33%; $P = 0.012$). No other statistically significant difference was found among all the comparable groups.

The onset of delayed emesis was recorded for 159 patients who had had an antiemetic response other than complete. Overall, delayed emesis began on day 2 for 42 patients (26%), on day 3 for 55 patients (35%), on day 4 for 38 patients (24%), and on day 4 for 24 patients (15%). No significant differences in time course analysis of delayed emesis were found among the three study arms. No correlation was found between the type of antiemetic response and the onset of delayed emesis.

The effects of antiemetic treatments on the incidence and severity of delayed nausea are shown in Figure 2. No or mild nausea was observed in 61% of patients treated with metoclopramide plus methylprednisolone, in 45% of patients treated with oral granisetron alone, and in 66% of patients treated with oral granisetron plus methylprednisolone. The difference between the first two arms reached statistical significance ($P < 0.038$) as did that between oral granisetron alone and granisetron plus methylprednisolone ($P < 0.002$). Complete protection from nausea was experienced by 17 patients (18%) in the metoclopramide plus methylprednisolone arm, by 18 patients (21%) in the oral granisetron alone arm, and by 25 patients (26%) in the granisetron plus methylprednisolone arm. Major protection was recorded for 40 (43%), 20 (24%), and 34 (40%) patients for the three arms, respectively. Moderate nausea was recorded for 33 (36%), 44 (45%), and 25 (34%) of patients for the three arms, respectively. Severe nausea was observed only sporadically: 2% in the

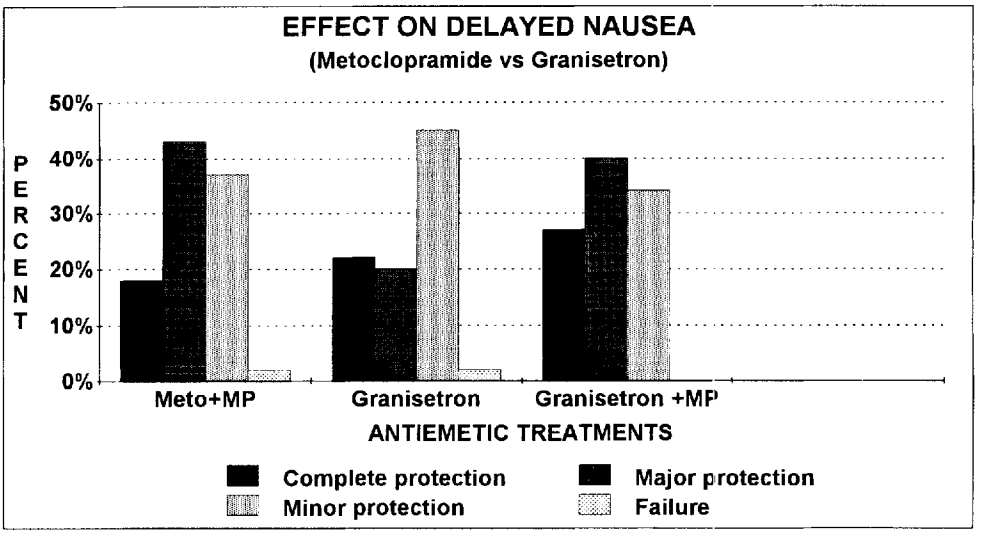

Figure 2. The effects of metoclopramide and methylprednisolone vs. granisetron with or without methylprednisolone on cisplatin-correlated delayed nausea.

metoclopramide plus methylprednisolone and the granisetron arms and none in the granisetron plus methylprednisolone arm. The differences among comparable groups were not statistically significant.

Safety

Oral granisetron with or without intramuscularly administered methylprednisolone and the combination of metoclopramide and methylprednisolone were well tolerated by most patients without severe adverse events. The most frequently reported side effects were headache, constipation, diarrhea, extrapyramidal effects, and somnolence. The figures reported below refer to toxicity recorded during the first cycle. In the metoclopramide plus methylprednisolone group, 6 patients (6%) experienced extrapyramidal side effects, whereas no patients in the granisetron alone and granisetron plus methylprednisolone arms experienced such effects. Diarrhea was recorded for 8 patients in the metoclopramide arm (9%), but for only 2 (2%) and 3 (3%) patients in the granisetron and the granisetron plus methylprednisolone arms, respectively. Headache was recorded for 7 patients (8%) treated with granisetron alone, for 8 patients (9%) treated with granisetron plus methylprednisolone, and for 3 patients (3%) treated with metoclopramide plus methylprednisolone. Constipation was not considered in the analysis because a large percentage of patients were receiving vinca alkaloids.

Discussion

The clinical availability of the new 5-HT3 antagonists, such as granisetron, ondansetron, and tropisetron, has protected patients with cancer against the nausea and vomiting induced by cisplatin-based chemotherapy.[6–9] However, despite the significant progress achieved in the prophylaxis of acute nausea and vomiting, the control of delayed emesis remains largely unsatisfactory, at least with the use of conventional combinations of antiemetic drugs.[1,3,10] In fact, delayed emesis, although less intense than acute nausea and vomiting, is still found to produce severe problems that impair patients' nutrition, hydration, and compliance with chemoradiotherapeutic treatments.[1–3]

Data from the medical literature are scanty regarding the comparative evaluation of anti-HT3 drugs with other conventional antiemetic drugs against delayed emesis.[1,21,25,26] In the study reported by Chevallier et al.,[16] granisetron was very effective in protecting patients from high dose cisplatin-related acute emesis but protected only 33% of patients from delayed vomiting, whereas metoclopramide plus dexamethasone protected 51% of patients against delayed vomiting. Different results were obtained by Marty,[19] who reported a 56% protection rate against delayed emesis in the granisetron group versus 48% achieved in the comparative group treated with chlorpromazine plus dexamethasone. These studies, however, focused on the evaluation of the effects of granisetron on acute emesis rather than on delayed vomiting.

In the current study we reported the results of a Phase III prospective, open trial comparing the effects on delayed emesis of an antiemetic regimen consisting of intramuscularly administered metoclopramide plus methylprednisolone to oral granisetron alone or in combination with intramuscularly administered methylprednisolone among patients receiving highly emetogenic chemotherapy. Pharmacokinetic and clinical studies have supported the use of granisetron (3 mg/day) intravenously as the standard antiemetic treatment for acute nausea and vomiting,[20–22] although a large multicenter study has tested the efficacy and toxicity of an oral formulation of granisetron and demonstrated that 1 mg taken orally twice daily is yields the best antiemetic response with minimal side effects.[23] Data on orally administered granisetron, however, are limited to emesis due to moderately emetogenic chemotherapy and have not been directly compared with standard antiemetic drugs.

The data reported in the current study showed that the standard combination of metoclopramide plus corticosteroids given parenterally protected patients against delayed emesis in 53% of cases during cycle 1 of chemotherapy, whereas oral granisetron alone was successful only in 33% of patients. This difference reached statistical significance at the 0.05 level, but it was annulled when intramuscularly administered methylprednisolone was added to oral granisetron. These data are consistent with the preliminary data reported by other authors[27,28] who have shown that the addition of steroids contributes significantly to improving the antiemetic effect of granisetron.

The data reported in the current study also demonstrated that orally administered granisetron with or without intramuscularly administered methylprednisolone may be safely given to patients with cancer treated with high dose cisplatin without causing severe adverse events. Tolerability of granisetron was better than that observed in the group of patients treated with the combination of metoclopramide plus methylprednisolone. In fact, no extrapyramidal adverse effects were recorded in both groups of patients treated with granisetron, whereas 6% of patients who received metoclopramide plus methylprednisolone had extrapyramidal side effects. The incidence of headache, however, was higher in both groups treated with granisetron alone

(8%) or with granisetron plus methylprednisolone (9%) than in the group of patients treated with metoclopramide plus methylprednisolone (3%). The incidence of constipation was not considered, because many patients enrolled in the study were also receiving vinca alkaloids as a part of combination chemotherapy regimen, and these agents are associated with neurologic side effects.

A time-course analysis of the onset of delayed vomiting showed that delayed emesis started on day 2 or 3 after cisplatin administration in 61% of all patients included in the three arms of the study and on day 3 or 4 in 39% of patients. The highest incidence was observed on day 3 (35%) and the lowest on day 4 (15%). No differences in time-course analysis of delayed emesis were found among the three arms of the study, thereby suggesting that the addition of methylprednisolone does not modify the time course of delayed emesis after administration of oral granisetron despite improvement in antiemetic response.

The mechanisms underlying delayed emesis remain unclear, due perhaps to the lack of an established preclinical model for delayed emesis and to the relative rarity of clinical studies of the natural history and the pathophysiology of delayed emesis.[29] The data presented in the current study suggest that 5-HT3 receptor antagonists (in this case, granisetron) have only a limited effect on delayed emesis despite remarkable activity in the acute phase, thus supporting the experimental and clinical findings that the two phases of emetic response involve different mechanisms that may overlap partially.[29] As shown above, the addition of corticosteroids to orally administered granisetron is comparable in its control of delayed emesis to metoclopramide plus methylprednisolone, thus supporting the presence of a corticosteroid-sensitive mechanism underlying delayed emesis. Preclinical data with use of a dog model have revealed that cisplatin as well as cyclophosphamide may disrupt the blood–brain barrier and induce cerebral edema, which is not clinically apparent, but may potentiate antiemetic input.[30,31] These data are consistent with the antiemetic activity of corticosteroids, which may help reduce cerebral edema.[31]

In conclusion, our data suggest that orally administered granisetron with or without intramuscularly administered methylprednisolone may be safely given to patients with cancer as prophylactic therapy against delayed emesis caused by treatment with high dose cisplatin. Orally administered granisetron given with or without corticosteroids is moderately active against delayed emesis. Although orally administered granisetron alone is less active than a standard combination of metoclopramide plus methylprednisolone, when given with corticosteroids, it improves the control of delayed emesis. The efficacy of oral granisetron with or without methylprednisolone against delayed emesis remains unsatisfactory, however, and further studies are needed to elucidate the pathophysiologic characteristics of delayed emesis and to explore the possible combinations of different antiemetic drugs.

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