［原著］A Prospective Trial of Oral Betamethason and Oral Lorazepam in the Management of Delayed Nausea and Vomiting Induced by Cisplatin-Based Chemotherapy

A Prospective Trial of Oral Betamethason and Oral Lorazepam in the Management of Delayed Nausea and Vomiting Induced by Cisplatin-Based Chemotherapy

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ABSTRACT

Purpose: The optimal treatment modality for delayed emesis occurring later than 24 hours after the administration of cisplatin-based chemotherapy has not yet been established. *Patients and Methods*: Twenty patients received 5-hydroxytryptamine 3 receptor antagonist intravenously for the treatment of acute emesis just before cisplatin infusion in the first cycle of treatment, and the thereafter they received oral administration of betamethason (2 mg × 3/day) plus oral lorazepam (0.5 mg × 3/day) for 5 days in trial I. In trial II, 14 patients who received the other anti-emetic regimen (methylprednisolone plus metoclopramide) for delayed emesis in the first cycle of chemotherapy were treated by this regimen for the second cycle of treatment. A complete response (CR) was defined as no emetic episodes and a partial response (PR) as no vomiting episodes but some nausea. The effects of anti-emetic treatments were evaluated for 5 days from the next day after cisplatin administration. *Results*: The mean control rate (percentage of CR+PR) and CR rate for delayed emesis for the 5-day period were 97% and 84%, respectively in trial I. The mean control rate in patients undergoing the other anti-emetic regimen in the first cycle of chemotherapy was 60% compared to 96% in the same patients undergoing this regimen in the second cycle of the same chemotherapy in trial II. *Conclusions*: Oral betamethason plus lorazepam demonstrated a high control rate for delayed nausea and vomiting induced by cisplatin-based chemotherapy. *Ryukyu Med. J., 25(1,2) 17～22, 2006*

Key words: Betamethason, Chemotherapy, Cisplatin, Delayed emesis, Lorazepam, Lung Cancer

INTRODUCTION

Chemotherapy-induced emesis is one of the troublesome adverse events that impair not only the quality of life in cancer patients but also reduces their desire to receive further chemotherapy. Cisplatin, which is one of the most effective anti-cancer drugs used in the treatment of various neoplasms[1], is well known to frequently induce nausea and vomiting[2,3]. Thanks to the development of 5-hydroxytryptamine 3 (5HT3)-receptor antagonist, the occurrence of acute emesis has decreased dramatically[4-8]. However, the optimal treatment modality for delayed emesis which occurs later than 24 hours after cisplatin administration has yet to be established[9]. Adrenal cortical hormone alone or a combination of adrenal cortical hormone and metoclopramide is generally used to control emesis, but the effectiveness of these agents remains both insufficient and controversial[10-18]. Lorazepam, which is a widely used anti-anxiety drug, has been reported to prevent the acute emesis induced by

Table 1 The Patient Characteristics

	Trial I (n=20)	Trial II (n=14)
Sex		
Male	17	12
Female	3	2
Age (years)		
Mean (range)	57 (46-77)	57 (46-73)
Performance status		
0	18	13
1	2	1
Stage		
IIIA	3	1
IIIB	5	1
IV	12	12
Histology		
Adenocarcinoma	18	13
Squamous cell carcinoma	1	0
Small cell carcinoma	1	1
Chemotherapy (with concurrent radiotherapy)		
Cisplatin+UFT	10 (9)	5(5)
Cisplatin+docetaxel	9 (2)	8(2)
Cisplatin+etoposide	1 (0)	1(0)

chemotherapy[19,20]. We therefore conducted a prospective trial to determine whether or not oral betamethason plus lorazepam effectively prevents the delayed nausea and vomiting frequently induced by cisplatin-based chemotherapy.

PATIENTS and METHODS

The eligible lung cancer patients for this study were those who received cisplatin (80 mg/m^2)-based chemotherapy with/without radiotherapy, had an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and experienced neither nausea nor vomiting before starting chemotherapy. All patients gave their written informed consent before treatment. The protocol was approved by the National Kyushu Cancer Center institutional review board.

The present prospective trial of an anti-emetic regimen for delayed emesis consisted of two trials. Trial I was administered for patients who received chemotherapy for the first time. Trial II was designed for those patients who had received one cycle of chemotherapy and then underwent the experimental anti-emetic regimen in the second cycle of the same chemotherapy.

All patients in both trials received anti-emetic therapy with 5HT3 receptor antagonist intravenously to prevent acute emesis just before cisplatin infusion. From the day after the intravenous administration of cisplatin was started, betamethason (2 mg × 3/day) plus lorazepam (0.5 mg × 3/day) was given orally for 5 days (Fig. 1). In trial II, the patients received methylprednisolone sodium succinate (125 mg/day) plus metoclopramide (10 mg/day) intravenously for 5 days starting from the day after the intravenous infusion of cisplatin was given in the first cycle of chemotherapy. In the second cycle of the same chemotherapy regimen, these patients were treated with oral administration of betamethason plus lorazepam.

A complete response (CR) and partial response (PR) were defined as when patients had no emetic episodes, and no vomiting episodes but some nausea, respectively. The control rate was defined as the percentage of CR plus PR. The effects of anti-emetic treatments on delayed emesis were evaluated for 5 days beginning from the day after the cisplatin administration was given. In addition, the anti-emetic effect of 5HT3 alone on the acute phase of emesis was also evaluated in trial I.

All patients were hospitalized for their treatments. The number of episodes of vomiting and presence of nausea were monitored and recorded

Trial I

			day 1	2	3	4	5	6
5-HT3 receptor antagonist	1	ampule, i.v.	○					
Betamethasone	2.0	mg × 3, p.o.		○	○	○	○	○
Lorazepam	0.5	mg × 3, p.o.		○	○	○	○	○

Trial II

First course

			day 1	2	3	4	5	6
5-HT3 receptor antagonist	1	ampule, i.v.	○					
Methylprednisolone	125	mg, i.v.		○	○	○	○	○
Metoclopramide	10	mg, i.v.		○	○	○	○	○

Second course

			day 1	2	3	4	5	6
5-HT3 receptor antagonist	1	ampule, i.v.	○					
Betamethasone	2.0	mg × 3, p.o.		○	○	○	○	○
Lorazepam	0.5	mg × 3, p.o.		○	○	○	○	○

5-HT3: 5-hydroxytryptamine3

Fig. 1 Treatment Schema.

for each patient. The other adverse effects of the treatment were also directly monitored and recorded.

A statistical analysis was performed using Fisher's exact probability test to compare the control rate between the two groups. The results were considered significant when p values were less than 0.05.

RESULTS

From September 1999 to January 2000, 20 and 14 patients were entered into trials I and II, respectively. The patient characteristics are shown in Table 1.

The control rate of this anti-emetic treatment from days 1 to 6 in trial I is shown in Fig. 2. The CR rate of acute emesis in the patients treated with 5HT3-receptor antagonist on day 1 was 35%. On the other hand, the CR rates for delayed emesis from days 2 through 6 were 75% or more. An especially notable finding was that the delayed vomiting was completely controlled from days 3 through 6. Fifteen (75%) patients achieved a CR for the entire duration from day 2 through day 6.

The mean CR rates and PR rates from days 2 through 6 according to the cancer treatment modalities are shown in Figure 3. The mean CR rates were 89% in the chemotherapy group and 80 % in the concurrent chemoradiotherapy group. There were no significant differences in the control rates

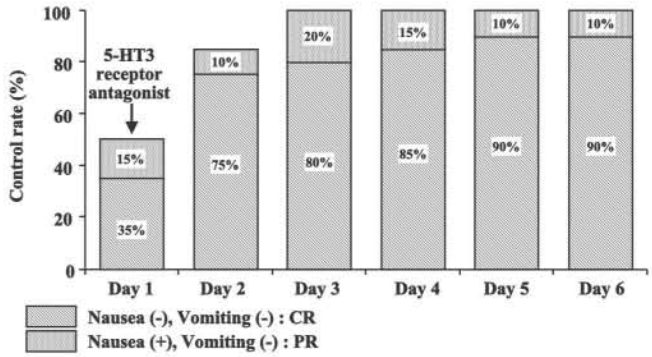

Fig. 2 The control rates of nausea and vomiting from days 1 to 6 in trial I. Twenty patients were entered into trial I.

between the two groups for nausea, and vomiting. The mean control rate for delayed emesis (CR+PR) was 97% for all patients. In addition, appetite loss, which is one of the most common side effects of anti-cancer drug therapy, was not observed in 90% of all the patients.

As shown in Fig. 4, the mean control rates of delayed emesis (CR+PR) according to the type of anti-emetic treatment in trial II was 96% for the treatment with betamethason plus lorazepam and 60% for the treatment with methylprednisolone plus metoclopramide ($P<0.001$). All patients reported the treatment with betamethason plus lorazepam in the second cycles of chemotherapy to be much better for the prevention of delayed nausea and vomiting than the treatment with methylprednisolone plus metoclopramide in the first cycle of chemotherapy.

Some mild toxicity was observed during the treatment. Hiccups occurred in 6 (30%), sleepiness in 2 (10%) and thirst in 1 (5%). However, all of these adverse events were manageable.

DISCUSSION

Cisplatin is one of the most effective anti-cancer drugs used in the treatment of various neoplasms[1]. Nausea and vomiting induced by cisplatin remains, however, a troublesome complication. The frequency of emesis in patients receiving cisplatin consisting of more than 50 mg/m^2 has been reported to be 90%, while in those receiving less than 50 mg/m^2 it has been reported to range from 60-90%[2,3].

The most common treatments for acute or delayed nausea and vomiting induced by cisplatin

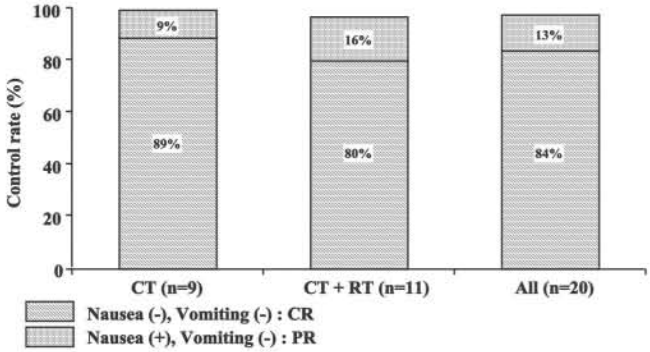

Fig. 3 The mean control rates of delayed nausea and vomiting from days 2 to 6 according to the treatment regimen used in trial I. CT: chemotherapy, RT: radiotherapy.

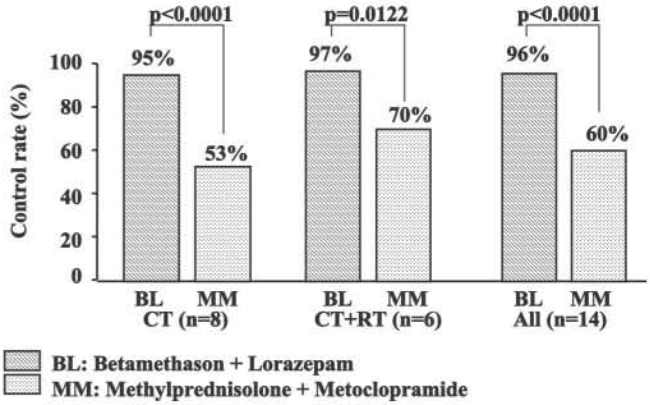

Fig. 4 The effects of betamethason and lorazepam (BL) vs. methylprednisolone and metoclopramide (MM) on cisplatin induced delayed nausea and vomiting in trial II. CT: chemotherapy, RT: radiotherapy.

are generally reported to be such drugs as adrenal cortical hormone, metoclopramide and serotonin antagonist[4-8,10-16]. Especially, the development of 5HT3-receptor antagonist has greatly helped to reduce the incidence of acute nausea and vomiting which occurs within 24 hours after the administration of anti-cancer drugs[4-7]. On the other hand, no effective treatment for delayed nausea and vomiting, occurring more than 24 hours after anti-cancer drug administration has yet been developed[9]. Either adrenal cortical hormone alone or a combination of adrenal cortical hormone and metoclopramide is generally used in order to control delayed nausea and vomiting, but the effectiveness of these agents is still not satisfactory. The control rate of delayed emesis has been reported to range from 40 to 70%[10-18]. In 1999, the American Society of Clinical Oncology (ASCO) proposed a clinical guideline for the management of delayed nausea and vomiting induced by cisplatin-based chemotherapy[19]. ASCO guidelines recommend corticosteroid plus metoclopramide (or plus a 5-HT3 antagonist) for the prevention of delayed emesis in all patients receiving cisplatin. However, the control rate of delayed emesis by using the above agents has been reported to range from 50 to 70%[15,17]. In fact, the mean control rate of delayed emesis by the combined usage of methylprednisolone and metoclopramide was also 60 % in the present study. On the other hand, in patients who received oral administration of betamethason plus lorazepam, the mean control rate of delayed emesis was 95% or more. In addition, 15 (75%) of all 20 patients in trial I experienced no delayed emesis at all from days 2 through 6.

Several trials have shown that benzodiazepins including an intravenous injection of lorazepam has an efficacy for acute emesis induced by cisplatin[20-22]. Therefore, these agents are listed as useful adjunctive agents in ASCO guidelines for the management of acute emesis[19]. In the present study, oral lorazepam with betamethason was used for the purpose of treatment for cisplatin-induced delayed emesis and an effect of these combination on the delayed emesis was observed. In addition, lorazepam may have a preventive effect on anticipatory emesis of patients who had poor control of emesis with prior chemotherapy[19], as shown in Trial II.

A result of recent randomized trials comparing neurokin-1 receptor antagonist plus standard antiemetics with standard antiemetics alone has been reported. The control rate of delayed emesis by the new combination ranged from 50% to 70% while the standard antiemetics had the control rate of approximately 50%[23-28]. These observations indicate that the combination of lorazepam plus betamethason in the present study may be worthy of further investigation.

The side effects of these oral drugs were mild and manageable. All patients (14 patients) in trial II who received the two different treatments (methylprednisolone plus metoclopramide vs oral betamethason plus lorazepam) reported the latter treatment would be better than the former, based on self evaluations. Regarding cost, the latter costs US$ 2.2 per day, while the former costs US$ 13.0.

Oral betamethason plus oral lorazepam demonstrated a good control of the delayed nausea and vomiting induced by cisplatin-based chemotherapy.

We are now planning a phase III trial study comparing this antiemetic regimen with a practice regimen in ASCO guidelines.

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