Published in Supportive Care in Cancer 2014;22(8):2161-6.

Antiemetic efficacy and safety of a combination of palonosetron, aprepitant and dexamethasone in patients with testicular germ cell tumor receiving 5-day cisplatin-based combination chemotherapy

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Published in Supportive Care in Cancer 2014;22(8):2161-6.

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Abstract

Purpose

To determine the antiemetic efficacy and safety of a combination of palonosetron, aprepitant and dexamethasone in patients with testicular germ cell tumor (TGCT) receiving 5-day cisplatin-based combination chemotherapy.

Methods

An open-label, single-arm, multicenter study was performed in patients with TGCT who were scheduled to receive 5-day cisplatin-based combination chemotherapy. The antiemetic therapy consisted of palonosetron 0.75 mg on day 1, aprepitant 125 mg on day 1 and 80 mg on days 2 to 5, and dexamethasone 9.9 mg on day 1 and 6.6 mg on days 2 to 8. The primary endpoint was complete response (CR) rate, which was defined as no vomiting and no rescue medication, in the overall period (0 to 216 h) in the first chemotherapy course. Incidence and severity of nausea were assessed based on the CTCAE and a subjective rating scale completed by patients.

Results

Thirty patients were included in the analysis. CR was achieved in 90.0% of the patients in the first chemotherapy course, and high CR rates were also observed in the second and third courses (82.1% and 78.3%, respectively). The incidence of nausea peaked on days 4 to 6 in about 50% of the patients. The reported adverse drug reactions were hiccups (12.9%), anorexia (3.2%), and stomach pain (3.2%). None of these were unexpected and none were grade 3 or 4.

Conclusions

The combination antiemetic therapy examined in this study was highly effective and well-tolerated in patients with TGCT receiving 5-day cisplatin-based combination chemotherapy.

Keywords: chemotherapy-induced nausea and vomiting; emesis; multiple-day chemotherapy; multiple-cycle; antiemetic

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse event associated with cancer chemotherapy and impairs quality of life (QoL) and daily functioning [1,2]. Adequate control of CINV is important to complete all planned chemotherapy courses without a reduction of dose intensity, so that patients receive the maximum clinical benefit from treatment. CINV is generally classified as acute CINV that occurs within the first 24 h of chemotherapy, and delayed CINV that occurs more than 24 h after chemotherapy [3]. In the setting of multiple-day chemotherapy, CINV can develop through a more complex mechanism involving overlap of acute and delayed CINV. However, most clinical studies of antiemetic therapy have been conducted in patients receiving single-day chemotherapy, and thus there is limited evidence on antiemetic therapy for patients receiving multiple-day chemotherapy.

Cisplatin, a highly emetogenic agent, is the key drug in chemotherapy for testicular germ cell tumor (TGCT). Patients with TGCT are generally treated with 5-day cisplatin-based combination chemotherapy. A high cure rate has been achieved [4], and there is a growing emphasis on the QoL during treatment. Fractionated administration of cisplatin can reduce adverse drug reactions (ADRs) such as nephrotoxicity; however, CINV remains as a significant problem. The current standard prophylactic antiemetic therapy for patients with TGCT receiving 5-day cisplatin-based combination chemotherapy is a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone [5], but the complete response rate with this therapy is <60% [6]. Therefore, more effective antiemetic therapy is needed to achieve adequate control of CINV.

Palonosetron and aprepitant are newer antiemetic agents with demonstrated efficacy for both acute and delayed CINV [7]. Indeed, antiemetic guidelines recommend that aprepitant should be added to a 5-HT_3 receptor antagonist and dexamethasone in patients receiving highly emetogenic single-day chemotherapy [5]. Hence, these drugs are promising for improvement of control of CINV in 5-day cisplatin-based combination chemotherapy, as well as in single-day chemotherapy. However, only a few clinical studies have examined antiemetic therapy including these new drugs in 5-day cisplatin-based combination chemotherapy [8,9]. Therefore, we examined the antiemetic efficacy and safety of a combination of palonosetron, dexamethasone, and aprepitant in patients receiving such chemotherapy.

Patients and methods

Study design and patients

An open-label, single-arm study was conducted in 9 hospitals in Japan (Supplemental Table 1, online only). The inclusion criteria were aged ≥20 years old; a diagnosis of TGCT pathologically; an ECOG performance status of 0 to 2; and scheduled treatment with 5-day cisplatin-based combination chemotherapy (Table 1). A previous history of chemotherapy more than 1 year before the start of the current chemotherapy courses was allowed. The exclusion criteria were primary cancer or metastasis in the brain or intestine; vomiting and retching within 24 h before chemotherapy; use of drugs with antiemetic activity, including benzodiazepines, within 48 h before chemotherapy; and use of drugs (such as azole antifungal agents and barbiturates) with possible effects on metabolism of the study drugs within 2 weeks before chemotherapy.

Written informed consent was obtained from all patients. The protocol of the study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee and the ethical review board at each hospital. The study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research in Japan. This study was registered with the UMIN-Clinical Trials Registry in Japan (UMIN000005506).

Antiemetic therapy

The antiemetic therapy examined in this study consisted of intravenous palonosetron 0.75 mg on day 1, oral aprepitant 125 mg on day 1 and 80 mg on days 2 to 5, and intravenous dexamethasone 9.9 mg (12 mg as dexamethasone

sodium phosphate) on day 1 and 6.6 mg (9 mg) on days 2 to 8. All antiemetics were administered approximately 1 h before administration of cisplatin on the chemotherapy days (days 1 to 5) or at the same time of day on days 6 to 8.

The dosing schedule of the antiemetics was determined based on the characteristics and availability of these drugs. The recommended dose of palonosetron is 0.75 mg in Japan and the antiemetic efficacy of this dose is estimated to persist over about 5 days [10]. Aprepitant has been used up to 5 days with high tolerability and the antiemetic efficacy persists for about 2 days after the last dose [11]. An available intravenous formulation of dexamethasone was used with the dose adjustment required when used with aprepitant. Judgments of the need for and selection of antiemetics as rescue medication were at the discretion of the physicians in charge when nausea or vomiting occurred.

Assessment

Data were collected using a case report form and a patient diary in the overall period, from 0 to 216 h after the start of chemotherapy, for a maximum of 3 consecutive chemotherapy courses. The acute and delayed phases were defined as 0 to 120 h and 121 to 216 h, respectively. The case report form included recording of a daily assessment of the severities of nausea and vomiting based on CTCAE v4.0 [12], antiemetics added to the test antiemetic therapy, and ADRs considered to have a causal relationship with the study drugs. Patients were asked to record the severity of nausea (based on a 10-point scale: 0, none; 10, worst nausea imaginable) and the number of vomiting episodes in the patient diary.

The primary endpoint was a complete response (CR), which was defined as no vomiting and no rescue medication, in the overall period in the first chemotherapy course. The secondary endpoints were CRs in the acute and

delayed phases each in the first chemotherapy course, CRs in the second and third chemotherapy courses, frequency of rescue medication, incidence and severity of nausea based on CTCAE and the subjective rating scale completed by the patients, and safety based on the types, incidences and severities of ADRs. Severity of nausea based on the subjective rating scale was classified into 3 groups: mild (1–3 points), moderate (4–6 points), and severe (7–10 points). As an ad hoc analysis, complete control (CC, defined as CR plus no more than mild nausea) rates were calculated.

Statistical analysis

Descriptive statistics such as mean, standard deviation, and percentage were calculated to summarize and evaluate the data. Microsoft Office Excel 2010 was used for all analyses.

Results

Patient demographics and chemotherapy

Thirty-two patients were registered in the study between May 2011 and January 2013. However, two patients were subsequently excluded from analysis: one because data could not be obtained for evaluation due to marked deterioration of his systemic condition after registration, and another because it was discovered after registration that the patient received previous chemotherapy within 1 month of the start of the study. The characteristics of the patients and chemotherapy are shown in Table 2. All patients were males who had been diagnosed with TGCT and were chemotherapy-naïve. The dosage of cisplatin was 20 mg/m^2/day for all the chemotherapy courses investigated and no patients needed dose reduction of cisplatin. No patient discontinued chemotherapy due to development of CINV.

Efficacy

CR in the overall period was achieved in 27 of 30 patients (90.0%) in the first chemotherapy course, and high CR rates were also observed in the second and third courses (82.1% and 78.3%, respectively) (Table 3 and Fig. 1). No vomiting occurred during the first chemotherapy course, but there were 6 episodes in 3 patients in the delayed phase in the second course, and 2 episodes in one patient in the acute phase and 3 episodes in another patient in the delayed phase in the third course. Patients with vomiting in a given course did not have vomiting in other chemotherapy courses. A total of 26 rescue medications were provided in 6 patients (median, 3; range, 1 to 12 times per patient). The antiemetics used for rescue medication included the first-generation 5-HT$_3$ receptor antagonists but not

palonosetron (13 times), dopamine D2 receptor antagonists (12 times), and metoclopramide (once). The patients without the risk factors for CINV including younger age, pretreatment anxiety about CINV, low alcohol consumption, and motion sickness tended to achieve higher CR rates compared to the patients with the risk factors, despite the small sample size of this study.

The incidences and severities of nausea are shown in Fig. 2. The incidence of nausea peaked on days 4 to 6 in about 50% of the patients, consistent with the period of highest systemic exposure to cisplatin due to accumulation of this drug. The assessment of nausea was generally consistent between the CTCAE results and the records on the patient diaries. Approximately 70% of patients experienced at least one episode of nausea cumulatively from days 1 to 10, but the severity was mild in most of these episodes. Relatively high CC rates indicated that both nausea and vomiting were well-controlled (Fig. 1).

Safety

ADRs included hiccups in 4 patients (13.3%) and anorexia or stomach pain in one patient each (3.3%). None of these were unexpected and none were grade 3 or 4.

Discussion

There is a substantial need for development of more effective and safe antiemetic therapy for patients receiving 5-day cisplatin-based chemotherapy. In this study, we found that tested antiemetic therapy with palonosetron, aprepitant and dexamethasone achieved high CR rates over 3 consecutive chemotherapy courses. To assist with further improvement of this therapy and for the purpose of precautions when using this antiemetic therapy outside Japan, we discuss the use of each antiemetic agent in the following paragraphs.

We used palonosetron at a dose of 0.75 mg, which is the recommended dose in Japan based on the results of domestic clinical trials [13]; however, the recommended dose of this drug is 0.25 mg in other countries. Intravenous palonosetron at 0.25 mg on days 1, 3 and 5 has been shown to be effective and well-tolerated [8], and thus, this dosing schedule may be another option.

The optimal dosage and duration of dexamethasone is uncertain. Use of dexamethasone as an antiemetic causes ADRs such as insomnia, indigestion or epigastric discomfort, and agitation [14]. An association between corticosteroids used as antiemetics and avascular necrosis has been also reported [15,16]. Since there are some safety concerns for dexamethasone, the dosing schedule of dexamethasone should be further studied.

A recent randomized crossover study demonstrated that addition of aprepitant on days 3 to 7 to a first-generation 5-HT_3 receptor antagonist and dexamethasone improved the CR rate significantly [17], although the CR rate achieved was similar to that in studies without aprepitant [6]. The 2013 update of the antiemetic guideline recommends use of a 5-HT_3 receptor antagonist and dexamethasone for patients receiving multiple-day cisplatin, as in earlier

guidelines, but provides the option of addition of aprepitant for patients receiving 5-day cisplatin [18]. This guideline indicates that dosing of aprepitant should start no later than day 3, but the optimal dosing schedule has not been defined. Based on the results of the present study, dosing of aprepitant on days 1 to 5 may be an attractive option. Use of aprepitant on days 1 to 7 has been examined [9,19], and further studies are needed to determine the optimal dosing schedule.

There were two major limitations in this study. First, regarding the study design, establishment of a control group was difficult because of the low incidence of testicular cancer in Japan [20]. Thus, comparative studies are needed to verify the favorable results found in the study. Second, only ADRs with a suspected association with the study drugs were recorded. This may have led to underreporting of ADRs because those induced by chemotherapy masked those induced by the study drugs. Therefore, we may have overestimated the safety of the antiemetic therapy. Actually, in this study, common ADRs, including headache, constipation and diarrhea were not recorded [9,10], but we believe that the absence of unexpected or severe ADRs indicates that the combination antiemetic therapy was well-tolerated. Within these limitations, we conclude that tested antiemetic therapy with palonosetron, dexamethasone and aprepitant is highly effective and well-tolerated in patients with TGCT receiving 5-day cisplatin-based combination chemotherapy.

Acknowledgments

None.

Conflict of Interest

Shota Hamada was an employee of MSD K.K., a subsidiary of Merck & Co., Inc. Whitehouse Station, N.J., U.S.A., when the study was conducted. Hiroyuki Nishiyama received honoraria, grants or other funding from Taiho Pharmaceutical Co., Ltd. and received grants or other funding from Ono Pharmaceutical Co., Ltd. Tomonori Habuchi, Osamu Ogawa and Koji Kawakami received grants and other funding from Taiho Pharmaceutical Co., Ltd. The other authors declare that they have no conflicts of interest.

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Table 1 Chemotherapy regimens included in the study

Regimen	Dosing schedule
BEP	Bleomycin 30 U on days 1, 8, and 15, etoposide 100 mg/m^2 on days 1–5, and cisplatin 20 mg/m^2 on days 1–5; every 3 weeks
EP	Etoposide 100 mg/m^2 on days 1–5, and cisplatin 20 mg/m^2 on days 1–5; every 3 weeks
VIP	Etoposide 75 mg/m^2 on days 1–5, ifosfamide 1,200 mg/m^2 on days 1–5, and cisplatin 20 mg/m^2 on days 1–5; every 3 weeks

Table 2 Baseline characteristics of patients and chemotherapy

Characteristics		n (%)
Number of patients		30
Age	years, mean±SD	33.9±8.3
Presence of metastasis		25 (83.3)
Pretreatment anxiety about CINV	none or slight	17 (58.1)
	moderate or severe	13 (41.9)
Alcohol consumption	0–4 days/week	23 (76.7)
	5–7 days/week	7 (23.3)
Susceptive to motion sickness		6 (20.0)
Chemotherapy regimen	BEP	28 (93.3) [a]
	VIP	2 (6.7)
Number of chemotherapy courses investigated	1	2 (6.7)
	2	5 (16.7)
	3	23 (76.7) [a]

a: One patient was examined during 1 course of BEP and 2 subsequent courses of EP.

Table 3 Complete response to antiemetic therapy

Course	#1 (N=30) n (%)	#2 (N=28) n (%)	#3 (N=23) n (%)
Acute phase (0–120 h)	27 (90.0)	25 (89.3)	20 (87.0)
Delayed phase (121–216 h)	28 (93.3)	24 (85.7)	20 (87.0)
Overall period	27 (90.0)	23 (82.1)	18 (78.3)

Complete response was defined as no vomiting and no rescue medication.

Fig. 1 Daily rates of CR (left) and CC (right) shown as percentages of all patients included in each course: course 1, N=30; course 2, N=28; and course 3, N=23.

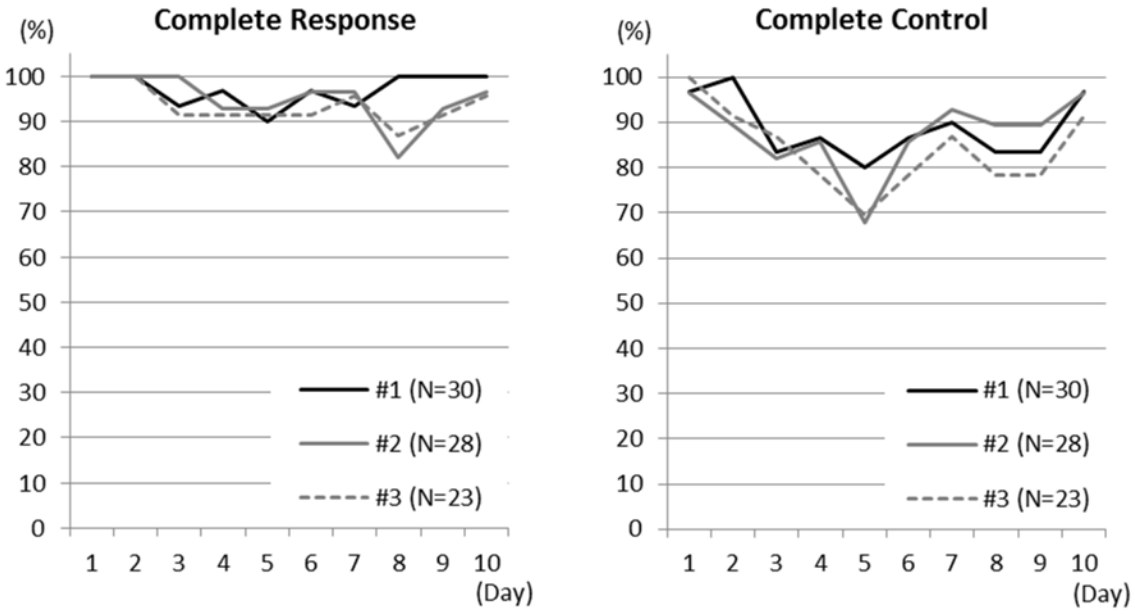

Fig. 2 Incidences and severities of nausea over time based on CTCAE (upper) and on a subjective rating scale completed by patients (lower). Cumulative incidences and severities for days 1–5, 6–10, and 1–10 are also shown. Each incidence is shown as percentages of all patients included in each course: course 1 (left), N=30; course 2 (middle), N=28; and course 3 (right), N=23.