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Comparison of antiemetic effects of granisetron and palonosetron in patients receiving bendamustine-based chemotherapy

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The antiemetic effects and safety of granisetron and palonosetron against chemotherapy-induced nausea and vomiting (CINV) were retrospectively evaluated in patients with non-Hodgkin lymphoma receiving bendamustine-based chemotherapy. A total of 61 patients were eligible for this study. Before starting the bendamustine-based chemotherapy, granisetron or palonosetron were intravenously administered with or without aprepitant and/or dexamethasone. The proportions of patients with complete control (CC) during the overall (during the 6 days after the start of the chemotherapy), acute (up to 2 days), and delayed (3 to 6 days) phases were assessed. CC was defined as complete response with only grade 0–1 nausea, no vomiting, and no use of antiemetic rescue medication. Granisetron or palonosetron alone were administered to 9 and 19 patients, respectively. Aprepitant and/or dexamethasone were combined with granisetron and palonosetron in 28 and 5 patients, respectively. Acute CINV was completely controlled in all patients. Both granisetron monotherapy and palonosetron combination therapy could provide good control of delayed CINV, although the CC rates during the delayed and overall phases were not significantly different among mono- and combination therapy of the antiemetics. There was no significant difference in the frequencies of adverse drug events between the granisetron and palonosetron treatment groups. The present study showed that the antiemetic efficacy and safety of granisetron-based therapy were non-inferior to those of palonosetron-based therapy. Taken together with treatment costs, granisetron monotherapy would be adequate to prevent CINV in patients with non-Hodgkin lymphoma receiving bendamustine-based chemotherapy.

1. Introduction

Bendamustine is a unique cytotoxic agent containing a benzimidazole heterocyclic ring, which has multifaceted mechanisms of action. Several studies have demonstrated the efficacy of bendamustine-based chemotherapy in hematological cancers, including refractory and/or relapsed indolent non-Hodgkin lymphoma (NHL) (Czuczman et al. 2015b; Flinn et al. 2014; Kouroukis et al. 2015) and mantle cell lymphoma (MCL) (Czuczman et al. 2015a; Flinn et al. 2014; Rummel et al. 2013; Visco et al. 2017). In Japan, some phase II clinical trials of bendamustine as monotherapy or in combination with rituximab have been carried out in patients with refractory and/or relapsed indolent B cell NHL or MCL (Matsumoto et al. 2015; Ogura et al. 2017; Ohmachi et al. 2010), providing an overall response rate of more than 90%. Chemotherapy-induced nausea and vomiting (CINV) is a common and one of the most problematic adverse events for patients with cancer (Hesketh 2008). If left uncontrolled, it can lead to a physical disorder, including dehydration, electrolyte abnormality, and malnourishment, and consequently, to a poor quality of life (Lindley et al. 1992; Morita et al. 2003). To maintain quality of life and enable patients to complete therapy, it is very important to control CINV with the appropriate use of antiemetics. According to some antiemetic guidelines (Hesketh et al. 2017; NCCN 2017; Roila et al. 2017), bendamustine-based chemotherapy is classified as moderately emetogenic chemotherapy (MEC). The combination of a 5-HT_3 receptor antagonist with neurokinin-1 antagonist, such as aprepitant and/or dexamethasone, is recommended for antiemetic management of CINV with MECs, although dosages and timing of administration of these antiemetic agents are required to be adequately adjusted depending on clinical situations.The first-generation 5-HT_3 receptor antagonists, such as ondansetron and granisetron, have shown significant antiemetic effects since the 1990s, and have been used as a prophylactic agent for CINV (Jantunen et al. 1997). However, these agents are less effective for the treatment of delayed CINV (more than 24 h after the start of chemotherapy) than the acute one (up to 24 h) (Geling and Eichler 2005). Even when a 5-HT_3 receptor antagonist was administered both 2 and 3 days after the beginning of the chemotherapy, the antiemetic therapy did not entirely prevent CINV beyond 24 h after the chemotherapy (Geling and Eichler 2005). Palonosetron has been developed as a second-generation 5-HT_3 receptor antagonist with longer half-life and higher binding affinity to the 5-HT_3 receptor, compared to the first-generation one, resulting in persistent inhibition of the 5-HT_3 receptor function (Rojas et al. 2010b). It is therefore expected that palonosetron can prevent delayed CINV, as well. To date, it has been reported that palonosetron has superior antiemetic effects against delayed CINV, and equivalent effects compared with first-generation 5-HT_3 receptor antagonists in various types of cancers (Aapro et al. 2006; Eisenberg et al. 2003; Gralla et al. 2003; Saito et al. 2009). Most of these data have been

obtained from patients with solid tumors, whereas limited studies have been conducted in patients with hematological malignancies. More recently, we have evaluated the effects of palonosetron- and granisetron-based antiemetic therapy on CINV in patients with malignant lymphoma receiving first-line rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, suggesting that palonosetron was superior to granisetron for the prevention of delayed CINV (Uchida et al. 2017). However, there appears to be little information about antiemetic efficacy and safety of palonosetron mono- or combination therapy in patients with malignant lymphoma receiving bendamustine-based chemotherapy.In this retrospective study, we assessed the antiemetic efficacy and safety of palonosetron, comparing to those of granisetron, in patients with NHL receiving bendamustine-based chemotherapy.

2. Investigations and results

2.1. Patient baseline clinical characteristics

A total of 61 patients with NHL were eligible in this study. The patients' baseline clinical characteristics are shown in Table 1. There was no significant difference in the sex, age, ECOG-PS, types of lymphoma, and chemotherapy regimens. The proportion of number of the patients receiving granisetron alone or in combination with other antiemetics, where aprepitant was most frequently co-administered, was significantly different compared to that of those receiving palonosetron-based antiemetic therapy ($p < 0.001$).

Table 1: Patient characteristics

Variable	Granisetron	Palonosetron	p value[a]
Number of patients	37	24	
Sex			
Male	23	14	0.794
Female	14	10	
Age (years)			
Mean ± s.d.[b]	61.5 ± 10.3	61.8 ± 9.9	0.901
Age (years)			
less than 60	17	9	0.601
60 and above	20	15	
ECOG-PS[c] score			
0	16	13	0.509
1	19	11	
2	2	0	
Diagnosis			
Follicular lymphoma	25	16	0.840
Mantle cell lymphoma	2	1	
MALT[d] lymphoma	4	1	
Waldenstrom macroglobulinemia	3	2	
Other	3	4	
Regimen			
Bendamustine	7	1	0.132
Bendamustine + Rituximab	30	23	
Combined antiemetics			
None	9	19	*<0.001*
+ Aprepitant	27	2	
+ Dexamethasone	0	3	
+ Dexamethasone + aprepitant	1	0	

[a] A significant difference is in italics.
[b] s.d., standard deviation.
[c] ECOG-PS, Eastern Cooperative Oncology Group performance status.
[d] MALT, mucosa-associated lymphoid tissue

2.2. Antiemetic effects

In all patients receiving bendamustine-based chemotherapy, acute CINV was completely controlled by treatment with granisetron- or palonosetron-containing antiemetics. This indicated that the overall CINV was reflected by the delayed one. Both granisetron monotherapy and palonosetron combination therapy could completely control CINV during the delayed and overall phases (Table 2). The CC rate in the patients whom overall CINV were well-controlled after granisetron monotherapy was higher compared to the CC rate obtained after palonosetron monotherapy, although statistical significance was not observed (100% and 63%, respectively; $p = 0.062$) (Table 2). Univariate analyses were performed to detect factors influencing CINV control; specifically, age was detected to influence the CC rate throughout the study period (Table 3). Multivariate logistic regression analysis showed that sex and age of more than 65 years were identified as significant influencing factors on the CC rates during delayed and overall phases (odds ratios were 4.8 [95% confidence interval (CI) 1.1–20.4] and 10.6 [95% CI 1.9–59.2], respectively) (Table 3).

Table 2: Efficacy of granisetron- and palonosetron-contained antiemetics during delayed and overall phases

Variable	CC[a]	Non-CC[a]	p value
Number of patients	48	13	
Antiemetic regimen			
Granisetron	9	0	0.416
+ Aprepitant	21	6	
+ Dexamethasone + aprepitant	1	0	
Palonosetron	12	7	0.406
+ Aprepitant	2	0	
+ Dexamethasone	3	0	

[a] CC, complete control.

Table 3: Factors influencing chemotherapy-induced nausea and vomiting control during delayed and overall phases

	Univariate			Multivariate	
Variables	CC[a]	non- CC[a]	p value[c]	OR[b]	p value[c]
Sex					
Male	32	5	0.108	1	
Female	16	8		4.8 (1.1–20.4)	*0.032*
Age (years)					
65 and above	28	2	*0.011*	1	
less than 65	20	11		10.6 (1.9–59.2)	*0.007*
ECOG-PS[d] score					
0	21	8	0.606	–	–
1	25	5		–	
2	2	0		–	
Type of lymphoma					
Follicular lymphoma	33	8	0.466	–	–
Mantle cell lymphoma	2	1		–	
MALT[e] lymphoma	5	0		–	
Waldenstrom macroglobulinemia	3	2		–	
Other	5	2		–	
Regimen					
Bendamustine	6	2	1.000	–	–
Bendamustine + Rituximab	42	11		–	

	Univariate			Multivariate	
Variables	CC[a]	non- CC[a]	p value[c]	OR[b]	p value[c]
5-HT_3 receptor antagonist					
Granisetron	31	6	0.338	–	–
Palonosetron	17	7		–	

[a] CC, complete control.
[b] OR, odds ratio with 95% confidence interval in parenthesis.
[c] A significant difference is in italics.
[d] ECOG-PS, Eastern Cooperative Oncology Group performance status.
[e] MALT, mucosa-associated lymphoid tissue

2.3. Adverse drug events

The number of patients experiencing ADEs after treatment with granisetron- or palonosetron-based antiemetics is shown in Table 4. The most frequent ADE was anorexia in both groups (62.2% and 70.8%, respectively). Leucopenia, malaise, constipation, gastric distress, neutropenia, fever, and renal dysfunction were also observed with frequencies of more than 5% in either group, with no significant difference between the two groups.

Table 4: Number of patients experiencing ADEs[a]

ADE	Granisetron-based antiemetics (n = 37)	Palonosetron-based antiemetics (n = 24)	p value
Anorexia	23 (62.2%)	17 (70.8%)	0.586
Leucopenia	13 (35.1%)	11 (45.8%)	0.433
Malaise	12 (32.4%)	5 (20.8%)	0.391
Constipation	12 (32.4%)	9 (37.5%)	0.785
Gastric distress	10 (27.0%)	6 (25.0%)	1.000
Neutropenia	8 (21.6%)	7 (29.2%)	0.553
Fever	2 (5.4%)	3 (12.5%)	0.373
Renal dysfunction	2 (5.4%)	0 (0%)	0.515

[a] ADEs, adverse drug events with frequencies of more than 5% (shown in parentheses) in either group are listed.

3. Discussion

Uncontrolled emesis associated with chemotherapy sometimes provides a negative experience, which could lead to refusal by the patient to undergo potentially life-saving treatments for their malignancy (Hesketh 2008). The present study showed that granisetron mono- and palonosetron combination antiemetic therapies were effective and well-tolerated in the patients with malignant lymphoma receiving bendamustine-based chemotherapy. According to recent guidelines (Hesketh et al. 2017; NCCN 2017; Roila et al. 2017), bendamustine is classified as an MEC, and some antiemetic regimens have been applied in patients receiving bendamustine-based chemotherapy. Ohmachi et al. (2010) reported that nausea of any grade occurred in 86% of patients with relapse of refractory indolent B-cell NHL or MCL, where a particular protocol for emesis was not provided, although prophylactic antiemetics were used. When the intravenous and oral administration of dexamethasone together with granisetron were used as antiemetic prophylaxis, nausea occurred in 34% patients with relapsed or refractory diffuse large B-cell lymphoma during the observation period; however, nausea grades 3 and 4 were not observed (Ohmachi et al. 2013). In the present study, the overall CINV in the patients receiving the combination antiemetic therapy of dexamethasone with the 5-HT_3 receptor antagonist was successfully suppressed (Table 2). These findings suggested that a combined administration of dexamethasone can be a useful option for CINV control, which is in line with the guidelines.Clinicians, however, have some concerns about the use of dexamethasone in clinical practice because of its potential side effects; the patients are often excessively immunosuppressed and thereby, they are at a greatly increased risk of infection. In the present study, regardless of whether dexamethasone and/or aprepitant were combined, the antiemetic therapy containing granisetron or palonosetron achieved CC for the acute CINV in the patients with NHL receiving bendamustine-based chemotherapy. All patients receiving granisetron alone had no significant symptoms associated with CINV throughout the observation period, although the combination therapy of aprepitant and/or dexamethasone with granisetron did not entirely improve the CINV control in the delayed phase (Table 2). Although the present study was limited by small sample size, CINV in patients receiving bendamustine-based chemotherapy could be controlled by granisetron monotherapy even without dexamethasone administration.For MEC regimens, in a prospective cohort study in Japanese patients, the CC rate in the acute phases was 93.3% and the value was higher than that in the delayed phase (58.3%) (Tamura et al. 2015). The delayed CINV is more common and less responsive to antiemetic therapy (Tamura et al. 2015), and its control is still suboptimal. Palonosetron, a second-generation 5-HT_3 receptor antagonist, has higher $5HT_3$ receptor binding affinity, leading to longer activity, compared to first-generation agents such as granisetron (Rojas et al. 2010a). Furthermore, it has been observed that its effectiveness for CINV is more remarked in the delayed phase than in the acute phase (Aapro et al. 2006; Eisenberg et al. 2003; Gralla et al. 2003; Saito et al. 2009). In current antiemetic guidelines for MECs, the use of a 5-HT_3 receptor antagonist and dexamethasone is recommended (Hesketh et al. 2017; NCCN 2017; Roila et al. 2017), and the addition of aprepitant is also considered to prevent CINV (Hesketh et al. 2017; NCCN 2017; Roila et al. 2017). In the present study, a monotherapy of either granisetron or palonosetron could exert antiemetic effects against CINV during the acute phase, resulting in a CC rate of 100%. During the delayed phase, on the other hand, a CC rate of 100% was also achieved following the administration of granisetron alone, but the value was 63.2% after palonosetron administration alone (Table 2). In bendamustine-based chemotherapy, bendamustine was administered on days 1 and 2 of each cycle of the chemotherapy. In the present study, granisetron and palonosetron were administered on day 1. Granisetron was administered repeatedly on day 2, whereas palonosetron was not because its administration is limited to once a week. Therefore, the difference in the antiemetic efficacy of monotherapy between granisetron and palonosetron against the CINV might be attributed to the difference in their administration schedules. Although the palonosetron monotherapy could not well-control the delayed CINV for the bendamustine-based chemotherapy, the combination antiemetic therapy with either aprepitant or dexamethasone could improve the disease control, successfully achieving a CC rate of 100%, (Table 2). In case of using palonosetron, the combination therapy of other antiemetics might be more effective compared to the monotherapy.Previously, we compared the effects of granisetron and palonosetron in patients with malignant lymphoma receiving highly emetogenic chemotherapy, in which the multivariate logistic regression analysis showed that palonosetron use and younger age were independent significant factors improving the complete response rate during the delayed phase, compared to granisetron use (Uchida et al. 2017). In the present study, female sex and age less than 65 years were significant factors associated with CINV during the delayed phase (Table 3), which was almost consistent with the results of previous reports (Hesketh et al. 2010; Roila et al. 1987; Tonato et al. 1991; Uchida et al. 2017; Warr et al. 2011). There was no significant difference in the CC rate between granisetron- and palonosetron-based antiemetic therapies, suggesting that these therapies could provide equivalent antiemetic efficacy during the delayed phase in patients receiving bendamustine-based chemotherapy. Some adverse events, including anorexia, leucopenia, malaise, and constipation were observed at a frequency of more than 30%, although the frequency of each adverse event related to the treatment was not significantly different between

the granisetron- and palonosetron-containing antiemetic treatment groups. Besides, granisetron would have an advantage of reduced costs compared to palonosetron (Hesketh et al. 2017).In summary, our present study demonstrated that the antiemetic efficacy and safety of granisetron-based therapy seemed to be non-inferior to those of palonosetron-based therapy. Taken together with treatment costs, granisetron monotherapy would be adequate to prevent CINV in patients with NHL receiving bendamustine-based chemotherapy, even if the administration of granisetron is required for two consecutive days.

4. Experimental

4.1. Patients

The patient's age were between 39 and 79 years, who received bendamustine with or without rituximab as a treatment for NHL in the Department of Hematology, Kyushu University Hospital (April 2007 to December 2015). Patients were excluded as follows: (a) if they had hyponatremia, hypercalcemia, adrenal metastasis, or an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of more than 3; (b) if they had nausea and/or vomiting in the last 24 h prior to treatment initiation; or (c) if they were taking laxative agents and antiemetic drugs, including olanzapine and lorazepam.

4.2. Dosage and administration of therapy

The regimens of bendamustine-based chemotherapy are shown in Table 5. Bendamustine was administered alone at a dose of 120 mg/m^2 on days 1 and 2 in regimen A, or at a dose of 90 mg/m^2 in combination with rituximab (375 mg/m^2) in regimen B; patients were received either chemotherapy regimen. Granisetron (3.0 mg/body) or palonosetron (0.75 mg/body) were intravenously administered 30 min before the initiation of the bendamustine-based chemotherapy. Granisetron was administered on days 1 and 2, whereas palonosetron on day 1. Aprepitant was orally administered at a dose of 125 mg once daily, 1 h before start of chemotherapy on day 1, and at a dose of 80 mg once daily on days 2 and 3 in the morning for each cycle. Dexamethasone (6.6 mg/body) was intravenously administered 30 min prior to chemotherapy once daily on days 1 and 2. Metoclopramide, prochlorperazine, haloperidol, and/or hydroxyzine were used as rescue medications.

Table 5: Regimens of bendamustine-based chemotherapy

Regimen	Drugs[a,b]	Daily dosage	Timing of administration
A	Bendamustine	120 mg/m^2	once daily on days 1 and 2
B	Bendamustine	90 mg/m^2	once daily on days 1 and 2
	Rituximab	375 mg/m^2	once daily on day 1

[a] Granisetron (3 mg/body) was intravenously administered on days 1 and 2.
[b] Palonosetron (0.75 mg/body) was intravenously administered on day 1.

4.3. Data collection and assessment

All data were retrospectively collected from the electronic medical record system. Occurrences of nausea, vomiting, or use of rescue medication during overall (during the 6 days after the start of the chemotherapy), acute (up to 2 days), and delayed (3 to 6 days) phases were assessed. Adverse drug events (ADEs), including nausea and vomiting, were monitored during the overall study period and described in the electronic medical record system twice a day (morning and evening) by doctors, nurses, and pharmacists, according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. This study was conducted in accordance with the Declaration of Helsinki and its amendments and with the approval of Kyushu University Graduate School and Faculty of Medicine (approval Nos. 24-12 and 24-359 of the institutional review board).The endpoint of this study was the proportion of patients with complete control (CC) during the overall, acute, and delayed phases. CC was defined as complete response and no more than mild nausea (grade 0 or 1).

4.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics package, version 24, software (IBM Corp, Armonk, NY). Fisher's exact test was used to examine differences in frequencies of categorical data between the granisetron- and palonosetron-based antiemetic treatments. The statistical significance of the difference between the mean values of age was calculated using the unpaired *t*-test. In the univariate analysis, sex, age, ECOG-PS, types of lymphoma, chemotherapy regimens, and use of granisetron or palonosetron were chosen as variables. The factors with p values < 0.25 in univariate analyses were included in a stepwise multivariate logistic regression analysis with backward selection. Two-tailed p values of less than 0.05 were considered to indicate a statistically significant difference.

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