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Evaluation of the compliance with antiemetic guidelines for prevention of chemotherapy-induced nausea and vomiting in patients with hematologic malignancy

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To assess compliance with the Japanese antiemetic guidelines for chemotherapy-induced nausea and vomiting (CINV), the frequencies of CINV occurrence and use of antiemetic rescue medications were examined in patients with hematological malignancy. A total of 40 patients with hematologic malignancy were eligible in this study. This study was performed in the Department of Hematology, Kyushu University Hospital, as a subgroup analysis from a nationwide, multicenter prospective cohort study conducted by the CINV Study Group of Japan. In the patients with hematological malignancy, the guideline compliance rate was 45 %. Five patients (22.7 %) experienced vomiting during the observation period after receiving non-guideline-consistent antiemetic prophylaxis, whereas no patient experienced vomiting after receiving guideline-consistent antiemetic prophylaxis. The study was not sufficiently powered to reach a statistical significance in its frequency of occurrence between the compliance and non-compliance groups. In the entire study period, 8 out of 40 patients required rescue medication, but there was no association between the status of compliance and the antiemetic guidelines. A total of 22 (55.0 %) patients achieved complete response, which was defined as no vomiting and no use of antiemetic rescue medication, during the study period. The rate of compliance with the prophylactic antiemetic treatment guidelines seemed to be low in patients with hematological malignancy, although the status of the guideline compliance did not always influence the antiemetic effects.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a serious adverse event that affects cancer patients (Hesketh 2008). Proper management of CINV can prevent physical disorders, including dehydration, electrolyte abnormality, and malnutrition, and consequently improve patients' quality of life (Lindley et al. 1992; Morita et al. 2003). International guidelines for antiemetic therapy were published and have been updated by several cancer societies such as the American Society of Clinical Oncology (Hesketh et al. 2017), the Multinational Association of Supportive Care in Cancer/ European Society of Medical Oncology (Roila et al. 2017), and the National Comprehensive Cancer Network (Berger et al. 2017). In Japan, in reference to these guidelines, the antiemetic guidelines were published by the Japan Society of Clinical Oncology (JSCO) (Japan Society of Clinical Oncology 2010) and was summarized by Takeuchi et al. (2016) Here, the chemotherapy agents that cause severe nausea and vomiting are classified into two groups: highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). Current antiemetic guidelines recommend a combination of two prophylactic antiemetics (5-hydroxytryptamine-3 (5-HT_3) receptor antagonist and corticosteroids) for MEC, and three-drug combination of neurokinin 1 (NK_1) antagonist, 5-HT_3 receptor antagonist, and corticosteroids for HEC and certain MEC regimens. The use of antiemetic prophylaxis has greatly improved the control of CINV in recent years, which helped patients to complete their chemotherapy and maintain quality of life.

Tamura et al. (2015) conducted a nationwide survey of various cancer chemotherapy regimens to assess compliance with the Japanese antiemetic guidelines for CINV. This study demonstrated that approximately 74 % and 95 % of patients receiving HEC and MEC, respectively, received prophylactic antiemetics in compliance with the guidelines, which resulted in good control of vomiting. However, the status of compliance with the antiemetic guidelines is different among chemotherapy regimens for different cancer types, presumably because there are some background factors. As an example, hematological malignancy, unlike solid tumors, is caused by the tumorigenesis of neutrophils and lymphocytes which play pivotal roles in the immune system. The patients with hematological malignancy are often brought into a state of immunosuppression (Lopez-Jimenez et al. 2006; Mattiuzzi et al. 2010), resulting in increased susceptibility to opportunistic infections. It has been so far reported that the incidence of bloodstream infections in the patients with hematologic malignancies receiving chemotherapy ranged from 11 to 38 % (Gaytan-Martinez et al. 2000; Madani 2000). A retrospective analysis also demonstrated that the patients undergoing intensive chemotherapy for acute myeloid leukemia have experienced febrile neutropenia (80.2 %), bacteremia/fungemia (8.3 %), and pulmonary infection (10.3 %) (Kato et al. 2018). Though infectious diseases are the most serious complications during the chemotherapy of hematological malignancies, glucocorticoids such as dexamethasone and prednisolone are administered to these patients for prevention of CINV despite leading to immunosuppression. In such cases, the physician may avoid using corticosteroids even when the patients are treated with HEC regimen, although it remains obscure to what extent CINV

can be controlled. It is very important to prevent CINV to enable patients to complete chemotherapy and maintain quality of life, but there is little information about the association between the CINV management and the guideline-consistent antiemetic prophylaxis in patients with hematological malignancies.
In the present study, a compliance survey was performed in patients with hematological malignancy to examine the effect of compliance to antiemetic guidelines on the frequency of CINV occurrence and use of antiemetic rescue medications.

2. Investigations and results

2.1. Background characteristics

A total of 40 patients with hematologic malignancy were eligible in this study. As shown in Table 1, the patients' baseline clinical characteristics were not influenced by the status of compliance with the antiemetic guideline. The chemotherapy regimens are shown in Table 2. thirty-five patients received HEC, whereas 5 patients received MEC. A significant difference was observed in the combinations of selected antiemetics in patients receiving HEC regimens between the compliance and non-compliance groups, whereas no significant difference was observed in the combinations in those receiving MEC regimens (Table 2).

Table 1: Patient characteristics

Variable	Prophylactic antiemetics		*p* value
	Compliance with guidelines	Non-compliance with guidelines	
Number of patients	18	22	
Sex			
Male	8	10	1.000
Female	10	12	
Age	54 (22-69)	52 (22-71)	
Median, year (range)			0.815
ECOG-PS[a] score			
0	16	17	0.197
1	1	5	
2	1	0	
Diagnosis			
Leukemia	7	9	0.087
Non-Hodgkin lymphoma	7	11	
Hodgkin lymphoma	0	2	
Multiple myeloma	4	0	
Primary stage			
None	7	9	0.367
Stage I	0	1	
Stage II	2	5	
Stage III	7	3	
Stage IV	2	4	
Motion sickness			
Yes	5	3	0.430
No	13	19	
Alcohol intake			
Habitual	2	2	1.000
Non-habitual	16	20	

[a]ECOG-PS, Eastern Cooperative Oncology Group performance status

2.2. Use of prophylactic antiemetics

Of the patients receiving HEC or MEC, 14 (40.0 %) and 4 (80.0 %) patients were treated with guideline-based prophylactic antiemetics, respectively (Table 3). Twenty-eight out of 40 patients were given granisetron, a 5-HT_3 receptor antagonist, while the others were given palonosetron. All prophylactic antiemetic regimens including palonosetron were found to be inconsistent with the antiemetic guidelines.

The proportions of patients who did not experience nausea and vomiting in the entire study period were 55.0 % and 87.5 %, respectively (Table 4). The proportions of patients in the "compliance" group who did not experience nausea and vomiting during the entire study period were 55.6 % and 100 %, respectively, whereas their values in the "non-compliance" group were 54.5 % and 77.3 %, respectively (Table 4). None of the patients experienced vomiting during the observation period after receiving guideline-consistent antiemetic prophylaxis, although the study was not sufficiently powered to reach a statistical significance in its frequency of occurrence between the compliance and non-compliance groups. In the entire study period, 8 out of 40 patients required metoclopramide as a rescue medication, but there was no association between the status of compliance and the antiemetic guidelines (Table 5). A total of 22 (55.0 %) patients achieved complete response, which was defined as no vomiting and no use of antiemetic rescue medications, during the study period. Seven of these patients received palonosetron-based antiemetic treatment, whereas the other 15 patients did granisetron-based treatment.

3. Discussion

Recently, some cancer societies have published guidelines that recommend the use of antiemetics for CINV, and increase in guideline compliance rate was associated with improvement in CINV control. Previous studies reported that increased compliance with antiemetic guidelines for CINV control resulted in a decreased incidence of CINV in patients receiving HEC or MEC (Aapro et al. 2012; Gilmore et al. 2014). In Japan, the compliance rates of hepatobiliary and pancreatic cancer patients with HEC and MEC were 40 % and 82 % (Nitta et al. 2016), those of gynecologic cancer patients were 71 % and 96 % (Mizuno et al. 2016), and those of esophageal cancer patients were 82 % and 81 % (Baba et al. 2017), respectively. The compliance rate of colorectal cancer patients receiving MEC was 99 % (Tsuji et al. 2017). As for the patients with hematological malignancy, the guideline compliance rates for HEC and MEC were 40 % and 80 %, respectively (Table 2). These results suggested that the compliance rate of patients receiving MEC tended to be higher than that in those receiving HEC, although our present pilot study was limited by a small sample size. It was also considered that the type of cancer might influence the status of compliance with the antiemetic guidelines.
To our knowledge, the present study is the first report concerning the association between the CINV management and the guideline-consistent antiemetic prophylaxis in patients with hematological malignancies. According to the Japanese and international guidelines, three-drug combination of NK_1 antagonist, 5-HT_3 receptor antagonist, and corticosteroids is recommended for patients receiving HEC or certain MEC regimens. Patients with hematological malignancy receiving chemotherapy agents, such as cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), which are included in the HEC regimen, are often in a state of immunosuppression (Lopez-Jimenez et al. 2006; Mattiuzzi et al. 2010). Hence, glucocorticoids may not be administered in these patients to avoid severe immunosuppression. In addition, aprepitant, a potential inhibitor of cytochrome P450 (CYP) 3A4, may not be administered to avoid drug-drug interactions, because CHOP drugs, including cyclophosphamide and prednisolone, are metabolized by CYP3A4 (Aapro et al. 2010; Georgy et al. 2007; Majumdar et al. 2003). In the present study, 19 patients received CHOP therapy. Eight patients were given a combination of aprepitant, granisetron, and prednisolone in compliance with the guideline, whereas the other 11 patients were treated with a combination of palonosetron and prednisolone. There was no significant difference in the antiemetic effects between these treatment groups, which suggested that the use of palonosetron alone could provide prophylatic antiemetic effects comparable to the combination treatment of aprepitant and granisetron in patients receiving CHOP therapy. This might be due to the difference in the efficacy of 5-HT_3 receptor antagonists. Previously, we compared the efficacy of granisetron and palonosetron in patients with non-Hodgkin lymphoma receiving CHOP plus rituximab therapy.

Table 2: Classification of the emetogenicity risks associated with HEC or MEC

Regimen	Prophylactic antiemetics		*p* value[d]
	Compliance with guideline (N=18)	Non-compliance with guideline (N=22)	
HEC regimen[a]			
Cyclophosphamide + doxorubicin + prednisolone + vincristine	8	11	*0.008*
Cyclophosphamide + daunorubicin + prednisolone + vincristine ± Imatinib	4	0	
Cyclophosphamide + dexamethasone + doxorubicin + vincristine	1	0	
Idarubicin + cytarabine ± ATRA[c]	1	8	
Adriamycin + bleomycin + dacarbazine + vinblastine	0	2	
MEC regimen[b]			
Bortezomib + cyclophosphamide + dexamethasone	4	0	0.200
ATRA[c] + Idarubicin	0	1	

[a]HEC: Highly emetogenic chemotherapy
[b]MEC: Moderately emetogenic chemotherapy
[c]ATRA: All-trans retinoic acid
[d]A significant difference is in italics.

Table 3: Prophylactic antiemetics used for HEC or MEC

Prophylactic antiemetics	Compliance with guideline (N=18)	Non-compliance with guideline (N=22)
For HEC regimens[a]		
Granisetron + aprepitant + prednisolone	12	0
Granisetron + aprepitant + dexamethasone	2	0
Granisetron + aprepitant	0	9
Palonosetron + prednisolone	0	11
Palonosetron	0	1
For MEC regimens[b]		
Granisetron + aprepitant + dexamethasone	3	0
Granisetron + dexamethasone	1	0
Granisetron + aprepitant	0	1

[a]HEC: Highly emetogenic chemotherapy
[b]MEC: Moderately emetogenic chemotherapy

Table 4: Number of patients experiencing CINV

Phase	Variable	Prophylactic antiemetics		*p* value
		Compliance with guidelines (N=18)	Non-compliance with guidelines (N=22)	
Overall	Nausea			
	Yes	8	10	1.000
	No	10	12	
	Vomiting			
	Yes	0	5	0.053
	No	18	17	
Acute	Nausea			
	Yes	5	6	1.000
	No	13	16	
	Vomiting			
	Yes	0	4	0.114
	No	18	18	
Delayed	Nausea			
	Yes	6	8	1.000
	No	12	14	
	Vomiting			
	Yes	0	1	1.000
	No	18	21	

Table 5: Number of patients requiring rescue medication

Variable	Prophylactic antiemetics		*p* value
	Compliance with guidelines (N=18)	Non-compliance with guidelines (N=22)	
Metoclopramide use			
Yes	3	5	0.472
No	15	17	

Results showed that palonosetron was superior to granisetron in the prevention of delayed CINV, even without co-administration of dexamethasone and aprepitant (Uchida et al. 2017). In the present study, 58.3 % of patients had complete CINV suppression after receiving palonosetron-based antiemetic treatment. The use of palonosetron might be associated with improved CINV control in patients receiving guideline-inconsistent antiemetic prophylaxis.

In recent years, it has been reported that palonosetron-based antiemetic prophylaxis had the advantage of reducing the total dose of corticosteroids in patients with solid tumors receiving MEC regimens (Aapro et al. 2010; Celio et al. 2011; Furukawa et al. 2015; Komatsu et al. 2015). This would help to reduce side-effects of

corticosteroid such as anorexia, gastrointestinal disorders, depression, hyperglycemia, and fatigue, as well as severe immunosuppression. Similarly, in patients receiving HEC, the noninferiority of single-day dexamethasone regimen to the multiple-day regimen has been demonstrated when a combination antiemetic therapy of palonosetrone and aprepitant was used (Ito et al. 2018; Kosaka et al. 2016). There was a possibility that 1-day dexamethasone can be administered as an alternative to 3-day dexamethasone in the prophylaxis of CINV (Chow et al. 2018). However, it remains unclear to what degree palonosetron-based antiemetic regimens contribute to the reduction in the dose of corticosteroids in patients with hematological malignancy, and therefore further large studies for various chemotherapy regimens are required to address this issue.

In the present study, the patients treated with guideline-consistent prophylactic antiemetics did not experience vomiting during the observation period (Table 4). Recently, some efforts have been made to increase patients' awareness on antiemetic guidelines and observe them from the viewpoint of oncology specialists (Clark-Snow et al. 2018; Mellin et al. 2018). Meanwhile, there have been some cases that the management of CINV in patients receiving guideline-consistent antiemetic prophylaxis was insufficient, and the development of new drugs with different mechanisms is expected (Tamura et al. 2017; Hesketh et al. 2015). Prevention of CINV can lead to completion of chemotherapy, thereby improving cure rates of cancers, survival rate, and quality of life. In the patients with hematological malignancy receiving HEC, it appeared that a rate of compliance with the prophylactic antiemetic treatment guidelines was lower than that in those receiving MEC. It remains obscure whether the status of the guideline compliance between HEC and MEC influences the antiemetic effects and also whether the difference between the first- and second-generation 5-HT_3 receptor antagonists influences the prophylactic antiemetic effects. Therefore, further studies in a large population are warranted to appropriately investigate these possibilities. The rate of compliance with the prophylactic antiemetic treatment guidelines tended to be lower in patients with hematological malignancy, although the status of the guideline compliance did not always influence the antiemetic effects.

4. Experimental

4.1. Study design

This study was performed at the Department of Hematology, Kyushu University Hospital, as a subgroup analysis from a nationwide, multicenter prospective cohort study conducted by the CINV Study Group of Japan (Tamura et al. 2015). The study was conducted in accordance with the Declaration of Helsinki and its amendments. A written informed consent was obtained from all patients. In the present study, eligible participants were patients 20 years of age and older who received chemotherapy as the first treatment for malignant lymphoma, multiple myeloma and leukemia in the Department of Hematology, Kyushu University Hospital (February 2012 to November 2012). This protocol was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval no. 23-93 of the institutional review board).

4.2. Enrollment of patients

In the present study, we enrolled patients who were scheduled to receive either HEC or MEC for the first time (Table 1). Classification of the emetogenicity risks associated with HEC or MEC was based on the antiemetic guidelines for CINV released Version 1" published by the JSCO prepared according to some antiemetic guidelines (Berger et al. 2017; Hesketh et al. 2017; Roila et al. 2017) (Table 2). Prophylactic antiemetics used in the HEC or MEC regimen are shown in Table 3. In the present study, the three-drug combination of a 5-HT_3 receptor antagonist, a corticosteroid and aprepitant for HEC and the two-drug combination of a 5-HT_3 receptor antagonist and a corticosteroid for MEC were classified as "compliance" with the antiemetic guidelines, and "non-compliance" otherwise. When nausea and vomiting occurred after chemotherapy, metoclopramide (10 mg) was intravenously administered as a rescue medication. The patients' data were collected from the electronic medical record system. Acute and delayed CINV were defined as nausea and vomiting that developed within or after 24 hours after the start of chemotherapy, respectively.

4.3. Collection of patient diaries

Patients were provided with 7-day diaries for recording CINV before commencement of cancer chemotherapy. They were asked to record their digestive symptoms, i.e., development and severity of nausea, frequency of vomiting, amount of food intake, number of salvage treatments, and confirmation of hospitalization or an outpatient visit. Patients were required to fill in the diary every day for 7 days from commencement of anticancer HEC or MEC.

4.4. Exclusion criteria

We excluded patients with hyponatremia, hypercalcemia, adrenal metastasis and organic obstacles such as constipation and fecal impaction at the start of chemotherapy. And, the patients did not take laxative gents and antiemetic drugs including olanzapine and lorazepam at the start of chemotherapy.

4.5. Statistical analysis

Fisher's exact test was used to examine the differences in frequencies of categorical data between the compliance and non-compliance group. The statistical significance of the difference between the median values of age was calculated using the Mann-Whitney U-test. Data were analyzed using SPSS Statistics 25 (IBM Corp., Tokyo, Japan), and a p value of <0.05 was considered significant.

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