Chemotherapy continuity and incidence of febrile neutropenia with CHOP therapy in an outpatient setting

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Abstract. The cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) regimen is considered to be a standard treatment for non-Hodgkin's lymphoma (NHL). Patients receiving CHOP chemotherapy often experience febrile neutropenia (FN) due to myelotoxicity. The proper management of FN is essential to guarantee a positive outcome of the NHL treatment. Therefore, the present study retrospectively examined chemotherapy continuity and the incidence of FN during CHOP therapy in an outpatient setting. The subjects were 136 patients who received CHOP chemotherapy between January 2012 and December 2014. A total of 31 patients unable to be treated in an outpatient setting were excluded from the study. Of the remaining 105 patients, 73 patients who did not require hospitalization during the chemotherapy treatment were included in the non-hospitalized group, and 32 patients who required hospitalization during chemotherapy treatment were included in the re-hospitalization group. The numbers of patients from these two groups who completed the planned treatment were 71 and 24, respectively (P<0.01). In addition, the duration of granulocyte-colony stimulating factor (G-CSF) treatment was 5.3±1.22 and 6.1±1.46 days, respectively (P<0.01). The numbers of patients experiencing FN in an outpatient setting were 14 and 19, respectively (P<0.01). During administration of primary prophylaxis with G-CSF, the incidence of FN was 21.0% (22/105) in cycle 1. In conclusion, the present study has revealed a requirement to educate patients about infection prevention prior to the first cycle of chemotherapy. Patients who require the administration of long- term G-CSF are at risk of unplanned re-hospitalization, and treating them with polyethylene glycol G-CSF to reduce the number of required injections should be considered as an option. Therefore, proper supportive therapy and management of infection are important to safely treat patients with CHOP in an outpatient setting.

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Introduction

Over time, the administration of chemotherapy has moved from an inpatient to an outpatient setting. Over 95% of patients with solid tumors, including those with breast or colorectal cancers, are treated in an outpatient setting. However, only 30% of the patients with hematological malignancies are treated in an outpatient setting, due to intensive myelotoxicity or daily administration regimens. A regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) is considered to be a standard treatment for non-Hodgkin's lymphoma (NHL). Although CHOP therapy leads to intensive myelosuppression, an increasing number of patients are being treated in an outpatient setting. It is important that NHL patients receive the full chemotherapy regimen, since the survival rate may be markedly decreased when CHOP chemotherapy is delivered at <90% of the planned relative dose intensity (RDI) (1,2). Therefore, prophylactic administration of granulocyte-colony stimulating factor (G-CSF) is recommended for NHL patients.

Patients receiving CHOP therapy often experience febrile neutropenia (FN) due to myelotoxicity. The presence of FN necessitates a reduction in the planned RDI, and also leads to hospitalization with the administration of antibiotics (3). The prompt administration of antibiotics is crucial, since infection can progress rapidly. Although varying degrees of FN have been reported, the general risk factors for FN are well known, and include an older age, advanced disease, poor performance status (PS), comorbidities, baseline hemoglobin and body surface area (4-7). The proper management of FN is essential to maintain the RDI and to guarantee a positive outcome of the NHL treatment. Therefore, the present study retrospectively examined chemotherapy continuity and incidence of FN with CHOP therapy in an outpatient setting.

Subjects and methods

Subjects. The subjects were 136 patients who received CHOP chemotherapy at Ogaki Municipal Hospital (Ogaki-shi, Japan) between January 2012 and December 2014. The first cycle of CHOP chemotherapy was administered in an inpatient setting for

all patients, and the treatment was moved to an outpatient setting based on a consideration of the patient's condition. A total of 31 patients were excluded since they were unable to be moved to an outpatient treatment setting. Of the remaining 105 patients,32 (30.5%) were assigned to the re-hospitalization group, who required hospitalization again during the chemotherapy treatment in an outpatient setting, and 73 (69.5%) were assigned to the non-hospitalization group, who did not require hospitalization until after the patients had finished their outpatient chemotherapy (Fig. 1). The CHOP regimen [750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin and 1.4 mg/m^2 vincristine, all on day 1; and 100 mg/body or 60 mg/m^2 (for patients >65 years) prednisolone daily for 5 days] was administered every 3 weeks. The present study was reviewed and approved by the Ethics Committee at Ogaki Municipal Hospital.

Characteristics of the subjects. The characteristics of the subjects treated with CHOP therapy in an outpatient setting were investigated. Gender, age, histology, clinical stage, PS [Eastern Cooperative Oncology Group (ECOG) (8)], B symptoms, chemotherapy treatment times, doses and RDI, the total cycles, planned treatment completion, duration of treatment with G-CSF, nadir [day, white blood cell (WBC) and neutrophil count] and the presence of FN were compared between the re-hospitalization and non-hospitalization groups.

Incidence of FN in an outpatient setting. Incidences of FN were compared between the re-hospitalization and non-hospitalization groups in an outpatient setting.

Timing of FN occurrence. The timing of FN during the CHOP treatment cycle was examined.

Investigation of the factors affecting re-hospitalization. The factors affecting re-hospitalization during treatment in an outpatient setting were examined.

Causes of re-hospitalization. The factors affecting re-hospitalization during outpatient treatment were investigated.

Statistical analysis. The data were analyzed using JMP software (version 5.0.1J; SAS Institute Japan Ltd., Tokyo, Japan). The Mann-Whitney U test was used for comparison of the backgrounds of the subjects between the groups. The recorded P-values were two-sided, and P<0.05 was considered to indicate a statistically significant difference. The areas under the receiver-operator characteristic (ROC) curves were calculated to estimate the accuracy and cut-off values for the continuous variables obtained by univariate logistic regression analysis. Subsequently, the data were analyzed using multivariate logistic regression analysis.

Results

Characteristics of the subjects. Table I summarizes the background characteristics of the subjects. The numbers of patients in the non-hospitalization and re-hospitalization groups were 73 and 32, respectively, of which 71 and 24 completed the planned treatment, respectively (therefore, 2 and 8, respectively, did not complete the treatment). In addition, the duration of the

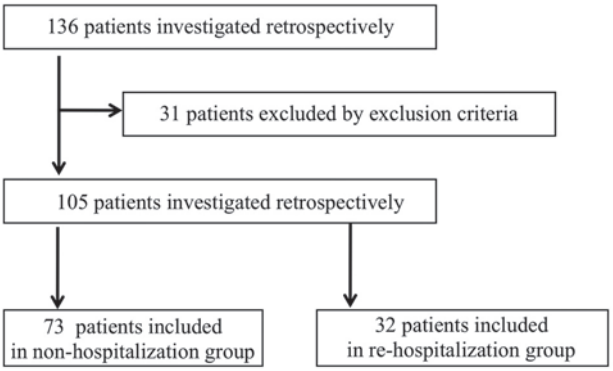

Figure 1. Subject selection and number of subjects analyzed.

G-CSF treatment was 5.3±1.22 and 6.1±1.46 days, respectively. The numbers of patients who experienced FN were 14 and 19, respectively.

Incidence of FN in an outpatient setting. Overall, 31.4% (33/105) of patients receiving CHOP therapy experienced FN at a certain point during the present study. Among these, a total of 18.1% (19/105) of the patients experienced FN in an outpatient setting, and 9.5% (10/105) experienced it for the first time in an outpatient setting. Additionally, 8.6% (9/105) of the patients experienced more than two episodes of FN during all the chemotherapy cycles.

Timing of FN occurrence. FN occurred in 21.0% (22/105) of the patients during cycle 1, 2.9% (3/105) in cycle 2, 4.8% (5/104) in cycle 3, 5.6% (5/89) in cycle 4, 6.9% (6/87) in cycle 5, 2.4% (2/83) in cycle 6 and 0% (0/46) of the patients in cycles 7 and 8.

Investigation of the factors affecting re-hospitalization. A total of 14 factors affecting re-hospitalization from an outpatient setting were analyzed using univariate logistic regression analysis. The independent variables of the dosage data were analyzed as continuous variables, and the results are shown in Table II. The average duration of G-CSF treatment [odds ratio (OR), 25.73; 95% confidence interval (CI), 2.68-308.29; P<0.01], incidence of FN (OR, 4.77; 95% CI, 1.95-12.08; P<0.01), and patients who could not complete the planned treatment (OR, 11.83; 95% CI, 2.74-82.09; P<0.01) demonstrated significant differences between the non-hospitalization and re-hospitalization groups. The area under the ROC curve of the average duration of G-CSF treatment was 0.67, and the cut-off value was 5.5 days. Table III shows the results of the multivariate analysis based on the factors affecting re-hospitalization, with P<0.25 by univariate logistic regression analysis. This analysis revealed that the incidence of FN (OR, 4.61; 95% CI, 1.68-13.19; P<0.01) and unreached planned treatment (OR, 11.81; 95% CI, 2.07-99.74; P<0.01) were independent factors that significantly contributed to re-hospitalization.

Causes of re-hospitalization. The cause of hospitalization with respect to the 32 re-hospitalization patients was FN in 59.4% (19/32) of the patients, delayed WBC recovery in 12.5% (4/32), *Pneumocystis carinii* pneumonia in 9.4% (3/32), pneumonia in 9.4% (3/32), a decline in PS in 6.3% (2/32), and heart failure in 3.1% (1/32) of the patients.

Table I. Baseline characteristics of the patients.

	Non-hospitalization	Re-hospitalization	P-value
No. of patients	73	32	
Gender			0.11
Male	31	19	
Female	42	13	
Age, median (years)	66.0	73.0	0.17
Range	(37-93)	(18-87)	
Histology			
Diffuse large B-cell lymphoma	38	17	
Follicular lymphoma	12	6	
T-cell lymphoma	3	1	
Mucosa-associated lymphoid tissue lymphoma	10	3	
Mantle cell lymphoma	4	2	
Others	6	3	
Clinical stage (Ann Arbor staging)[a]			0.41
I	16	3	
II	13	6	
III	13	8	
IV	31	15	
Performance status (ECOG)			0.11
0	62	22	
1	5	6	
2	6	3	
3	0	1	
4	0	0	
B symptoms			0.32
Present	9	2	
Absent	64	30	
Chemotherapy			
Treatment times, media (range)	6 (3-8)	6 (2-8)	0.49
Treatment dose (%), median (range)	100 (70-100)	100 (80-100)	0.71
RDI, median (range)	0.93 (0.62-1.00)	0.9 (0.61-1.00)	0.22
Total cycles of CHOP			0.49
2	0	1	
3	14	1	
4	1	1	
5	0	4	
6	27	10	
7	0	1	
8	31	14	
Planned treatment			<0.01
Completion	71	24	
Unreached	2	8	
G-CSF			
Duration of treatment (days), mean ± SD	5.3±1.22	6.1±1.46	<0.01
Duration of treatment (days), median (range)	5 (3-8)	5 (4-14)	0.01
Nadir			
Day, median (range)	11 (6-16)	11 (7-16)	0.07
WBC (per μl), median (range)	1230 (260-8180)	1395 (50-6080)	0.86
Neutrophil (per μl), median (range)	357 (15-7443)	378 (6-4013)	0.44

Table I. Continued.

	Non-hospitalization	Re-hospitalization	P-value
FN			<0.01
Present	14	19	
Absent	59	13	

[a]For further details on Ann Harbor staging, see Ref (9). Data are presented as n or the median (range) or the mean ± SD (n=105). RDI, relative dose intensity; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; G-CSF, granulocyte colony-stimulating factor; WBC, white blood cell; FN, febrile neutropenia, S.D., standard deviation. A B symptom is any systemic finding associated with lymphomas which is a clinical systemic condition.

Table II. Univariate analysis of factors affecting re-hospitalization from an outpatient setting (n=103)

Factor	OR	95% CI	P value	AUC	Cut-off
Duration of G-CSF treatment (days)	25.73	2.68-308.29	<0.01	0.67	5.5
Gender (female)	0.51	0.21-1.16	0.11		
Age	7.21	0.47-144.71	0.17		
PS≥2	0.62	0.16-2.61	0.49		
Chemotherapy treatment time	1.63	0.41-7.34	0.51		
Chemotherapy RDI	0.36	0.06-1.89	0.22		
Chemotherapy treatment dose (%)	1.43	0.26-11.26	0.71		
Day of nadir (days)	0.13	0.01-1.19	0.08		
White blood cell count of nadir (per μl)	0.79	0.03-10.97	0.86		
Neutrophil count of nadir (per μl)	0.32	0.01-4.75	0.47		
Incidence of FN	4.77	1.95-12.08	<0.01		
Clinical stage ≥3 (Ann Arbor)	0.59	0.23-1.43	0.25		
B symptoms present	2.11	0.51-14.39	0.35		
Unreached planned treatment	11.83	2.74-82.09	<0.01		

OR, odds ratio; CI, confidence interval; AUC, area under the curve; G-CSF, granulocyte colony-stimulating factor; PS, performance status; RDI, relative dose intensity; FN, febrile neutropenia.

Table III. Multivariate analysis of factors affecting re-hospitalization from an outpatient setting (n=103).

Factor	OR	95% CI	P-value
Duration of G-CSF treatment (≥5.5 days)	0.21	0.17-1.42	0.20
Female	0.43	0.15-1.17	0.11
Age	0.48	0.01-17.76	0.67
Chemotherapy RDI	0.51	0.06-4.01	0.51
Day of nadir (days)	0.33	0.02-4.97	0.43
Incidence of FN	4.61	1.68-13.19	<0.01
Unreached planned treatment	11.81	2.07-99.74	<0.01

OR, odds ratio; CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; RDI, relative dose intensity; FN, febrile neutropenia.

Discussion

The chemotherapy regimens used for patients with NHL are often dose-intensive, with high rates of associated neutropenic-related morbidity and occasional mortality (3). In the present study, grade 4 neutropenia occurred in 70.5% (74/105) of the patients, with grade 3 occurring in 20.0% (21/105) of the patients. Over 90% of the patients experienced serious hematological toxicity. The myelotoxic regimen often results in FN, which is the most serious

hematological toxicity (10,11). Hospitalization and prompt administration of antibiotics are necessary for patients with FN, since the infection can progress rapidly. Additionally, FN increases medical costs and may lead to delays in the treatment schedule and reductions in chemotherapy delivery. In the present study, 43.4% (59/136) of all patients receiving CHOP therapy experienced FN at a certain point during the study. The FN occurrence rate of the patients who could be treated in an outpatient setting was 31.4% (33/105), which is notably high. Furthermore, 22.8% (31/136) of the patients could not be treated in an outpatient setting, and 83.9% (26/31) of these experienced FN. Almost all these patients experienced long- term hospitalization and unreached treatment. The CHOP regimen is regarded as an intermediate risk for FN, with an occurrence rate of 10-20% recorded in the National Comprehensive Cancer Network and the European Organization for Research and Treatment of Cancer guidelines (4). However, several studies have previously reported an FN occurrence rate of 28-58% among NHL patients (5,12-14), suggesting that the CHOP regimen itself poses a high risk for FN in a real clinical situation.

Initially, CHOP chemotherapy was administered in an inpatient setting to gauge the possible adverse events. The FN occurrence rate for patients who received the CHOP regimen with primary prophylaxis of G-CSF was 17-22% (13,15,16). G-CSF primary prophylaxis was administered in 90.6% of the patients in the present study. The FN occurrence rate of patients in cycle 1 was 21.0% (22/105). In agreement with a report by Mayordomo *et al* (17), 53.7% of all FN events (22/41) occurred during cycle 1. Lyman *et al* (18) reported that a lack of primary prophylaxis with G-CSF in cycle 1 was associated with an increased risk of FN (18). However, although primary prophylaxis of G-CSF for almost all patients was administered in the present study, the FN occurrence rate in cycle 1 was the highest of all the treatment cycles. This result suggests that it is necessary to educate patients about FN prior to the first chemotherapy cycle.

Pegfilgrastim (Peg-G) comprises the protein filgrastim, to which a polyethylene glycol (Peg) molecule is bound covalently to the N-terminal methionine residue (19,20). It was first approved in the United States in 2002, and approved for use in Japan in November 2014. The addition of the Peg molecule increases the serum half-life of Peg-G, thus requiring fewer injections compared with unmodified G-CSF. In the present study, the duration of G-CSF treatment was longer in the re-hospitalization group compared with the non-hospitalization group (P<0.01). Since Peg-G was not used in the present study, a daily administration of G-CSF was required, in spite of severe neutropenia and the risk of infection in the outpatient setting. Requiring only one subcutaneous injection per cycle, Peg-G may be more convenient, and pose less of a risk, for the patient. It may become the standard of care to maintain the patients' quality of life, and to reduce the occurrence of FN.

Unplanned re-hospitalizations occurred in 30.5% (32/105) of the patients, which was due to FN or pneumonia in ~80% of the patients. Pettengell *et al* (15) reported a similar rate of re-hospitalization. The incidence of FN is an independent factor significantly contributing to the re-hospitalizations (OR, 4.61; 95% CI, 1.68-13.19; P<0.01). The FN rate in an outpatient setting was 18.1% (19/105). In this outpatient setting, 9.5% (10/105) of the patients experienced FN for the first time. Therefore, there is a continual requirement to educate patients on infection prevention.

In the present study, 9.5% (10/105) of the patients were not able to complete their planned treatment. The numbers of patients unable to complete the treatment were significantly different between the re-hospitalization and non-hospitalization groups (OR, 11.81; 95% CI, 2.07-99.74; P<0.01). The reasons why patients were unable to complete treatment were severe infection (5/10), a poor PS (4/10) and heart failure (1/10). Infection has been identified as an important risk factor for the completion of planned treatment. The mean age of the patients who were unable to complete their planned treatment was 80 years (range 63-93 years), which was significantly older compared with the age of the patients who were able to complete their planned treatment (P<0.01). In the present study, 20.6% (28/136) of all the patients who received CHOP chemotherapy were >80 years, and only ~50% of them (13/28) could be treated in an outpatient setting. From the first cycle, 76.9% (10/13) of the patients were treated with chemotherapy at an 80% reduced dose, and 38.5% (5/13) of patients were not able to complete their planned treatment. Age was not identified as an independent risk factor for re-hospitalization and the incidence of FN in the present study. However, Lymam *et al* (5) and Salar *et al* (16) reported that an older age was an independent risk factor for the occurrence of FN. Therefore, elderly patients may require special attention concerning infection prevention.

In conclusion, ~90% of the patients treated with CHOP chemotherapy experienced a greater- than- grade-3 neutrophil count decrease, and 31.4% (33/105) of the patients who were able to be treated in an outpatient setting experienced FN in the present study. Although primary prophylaxis with G-CSF was administered in this study, the incidence of FN was still as high as 21.0% (22/105) in cycle 1, which accounted for 53.7% of all FN events (22/41). These results suggested that the education of patients is required to prevent infections prior to the first chemotherapy cycle. In addition, for patients who require long-term G-CSF and are at risk of unplanned re-hospitalization, Peg-G treatment strategies should be taken into consideration. Therefore, proper supportive therapy and the management of infection are important to safely treat patients undergoing the CHOP regimen in an outpatient setting.

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