Support Care Cancer (2017) 25:3313–3320
DOI 10.1007/s00520-017-3747-z

ORIGINAL ARTICLE

Incidence and risk factors of febrile neutropenia in patients with non-Hodgkin B-cell lymphoma receiving R-CHOP in a single center in Japan

Masahiro Yokoyama[1] · Yoshiharu Kusano[1] · Anna Takahashi[1] · Norihito Inoue[1] · Kyoko Ueda[1] · Noriko Nishimura[1] · Yuko Mishima[1] · Yasuhito Terui[1] · Tomoyuki Nukada[2] · Takanobu Nomura[2] · Kiyohiko Hatake[1]

Received: 29 March 2017 / Accepted: 12 May 2017 / Published online: 27 May 2017

Abstract

Purpose The incidence of and risk factors for febrile neutropenia (FN) in Japanese non-Hodgkin B-cell lymphoma (B-NHL) patients receiving rituximab, cyclophosphamide, doxorubicin, vincristine, and predonisolone (R-CHOP) chemotherapy are unknown. We conducted this study to address this issue.

Methods In this single-center, retrospective, observational study, 466 patients with B-NHL who completed an R-CHOP regimen within a 7-year period and who planned to undergo at least three cycles of this regimen were analyzed. The following FN-related factors were assessed: fever, infection, disease state, neutrophil count, and prophylactic interventions such as use of antibiotics and/or granulocyte colony-stimulating factor (G-CSF). We simulated the FN incidence and 95% confidence interval (CI) of patients without prophylaxis with G-CSF (cycle 1) using bootstrap sampling.

Results The incidence of FN was 9.1% (42 of 462) in cycle 1 and 12.3% (57 of 462 patients) throughout all cycles, with 73.7% (42/57) developing FN during cycle 1. Risk factors for FN among patients with B-NHL treated with R-CHOP were albumin <35 g/L (p = 0.0047), relative dose intensity <85% (p = 0.0007), and lack of prophylaxis with G-CSF (p = 0.0006) in cycle 1. In the simulation analysis, the estimated FN incidence in cycle 1 was 16.2% (95% CI [10.9–22.2]).

Conclusions At 9.1% in cycle 1 and 12.3% throughout all cycles, the incidence of FN was lower than previously reported, possibly reflecting the appropriate use of G-CSF in this clinical setting. For patients with risk factors, the prophylaxis with G-CSF may decrease the occurrence of FN.

Keywords Febrile neutropenia · Incidence · Japan · Non-Hodgkin B-cell lymphoma · R-CHOP · Risk factor

✉ Masahiro Yokoyama
masahiro.yokoyama@jfcr.or.jp

[1] Division of Hematology Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan

[2] Medical Affairs, Kyowa Hakko Kirin Co. Ltd., Tokyo, Japan

Introduction

In patients who undergo chemotherapy, febrile neutropenia (FN) caused by myelosuppression contributes to increased mortality and prolonged hospitalization [1]. Current treatment guidelines stress the need for FN prevention [2–4].

Currently, granulocyte colony-stimulating factor (G-CSF) is used to prevent and treat FN induced by chemotherapy [2]. Japanese guidelines recommend prophylaxis with G-CSF for patients receiving a chemotherapy regimen with a known FN incidence of ≥20%, regardless of their risk of developing FN. Additionally, these guidelines recommend the prophylaxis with G-CSF even with regimens with an FN incidence of 10 to <20% if the patient presents risk factors for FN [5].

The chemotherapeutic regimen comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is the standard treatment for non-Hodgkin B-cell lymphoma (B-NHL). Data obtained from a Japanese cohort indicated that in patients with follicular lymphoma receiving R-CHOP-21 regimens without prophylaxis with G-CSF, the incidence of FN was 15% [6]. In other countries, the incidence of FN in patients receiving R-CHOP chemotherapy is <20% [7]. The incidence of FN in patients receiving R-CHOP regimens listed in the guidelines [2–4] ranges between 18 and

19%. Based on the results of a Japanese study that showed an FN incidence of 15% among patients receiving concurrent chemoradiotherapy [8], Japanese guidelines [5] recommend prophylaxis with G-CSF. However, as the number of cases in the Japanese study was small (10 cases), more reliable evidence is required.

Risk factors for FN are related to treatment and depend on the chemotherapy drug used and its dosage. Risk factors are also related to the patient's characteristics and include advanced age (≥65 years) and poor performance status (PS) [9]. The definition of the risk factors varies among international guidelines, and their impact varies according to the disease and the type of chemotherapy used. For instance, in breast cancer patients, low absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were found to be risk factors for FN [10].

Few studies have investigated the incidence of FN in patients with B-NHL receiving the R-CHOP regimen in Japan. The potential risk factors for the development of FN in association with R-CHOP chemotherapy for B-NHL have not been studied either. To address these gaps, we performed a retrospective study to analyze the incidence of FN in patients with B-NHL receiving R-CHOP chemotherapy at our institution. We also examined risk factors associated with the development of FN in this population.

Material and methods

Study design

In this single-center, retrospective, observational study, data from patients who underwent R-CHOP therapy within a 7-year period between January 2006 and December 2013 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan, were retrospectively analyzed. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Studies. Based on those guidelines, and because this study was based only on existing data from medical records, informed consent from subjects was not required. The Ethical Review Board of our institute approved the study protocol.

Patients

Patients diagnosed with B-NHL who started and completed an R-CHOP regimen and who planned to undergo at least three cycles of this regimen were included in this study. Patients with HIV-related B-NHL were excluded from this study.

Assessments

The following pretreatment patient demographic characteristics were collected: age, sex, PS, body mass index (BMI), disease (pathological diagnosis, Ann Arbor stage, bone marrow infiltration), complications (diabetes mellitus; hepatic, renal, or cardiac diseases; others), previous illness (surgery, infections, and FN within 1 month before initiation of the most recent R-CHOP regimen), and blood parameters (albumin, total bilirubin, hemoglobin, ANC, ALC). Data on R-CHOP regimen, including the dose of each drug and the number of days to the next cycle, were collected. The following data on the development of FN after R-CHOP regimen were collected: conditions of fever (highest body temperature, the onset date reckoned from the initiation of chemotherapy), neutrophil count, and prophylactic interventions (antibiotics, G-CSF, treatment date reckoned from the initiation of chemotherapy). The collected data were used to create a database, which was managed by our institution. The relative dose intensity (RDI) was calculated as the mean RDI for cyclophosphamide and doxorubicin: RDI = [(actual dose) / (planned dose)] / [(actual duration of treatment) / (planned duration of treatment)].

Study endpoints

The primary endpoint was the incidence of FN in cycle 1 of chemotherapy, which was calculated as the proportion of patients who developed FN in all patients receiving R-CHOP regimen. FN was defined as having an axillary temperature ≥37.5 °C within 48 h and a neutrophil count $<0.5 \times 10^9$/L. The secondary endpoints were as follows: incidence of FN throughout all chemotherapy cycles, incidence of FN in cycle 1 of chemotherapy by patient demographic characteristics, risk factors involved in the onset of FN in cycle 1, and the relationship between the incidence of FN in cycle 1 and ANC or ALC.

Sample size

The sample size was defined as the number of subjects to be accumulated during the study period to guarantee precision (point estimates and variance) in the estimation of FN incidence and to enable the exploration of factors involved in FN development through secondary endpoints. Assuming an FN incidence of 20%, approximately 400 patients were required for enrolment.

Statistical analyses

The Institute of Japanese Union of Scientists and Engineers carried out the statistical analysis of this study, using the database created by the research institution. In principle, continuous variables were summarized using basic statistics

(number of patients, mean [standard deviation (SD)], minimum, median, and maximum), and categorical variables were summarized in frequency tables. All statistical analyses were performed using SAS Versions 9.2 and 9.3 (SAS Institute, Inc., Cary, NC, USA). The significance of the relationship between the incidence of FN and patient demographic characteristics was tested using a chi-squared test. Odds ratios were estimated using a logistic regression model. Based on the univariate logistic regression model (univariate model) for the analysis of factors involved in the development of FN in cycle 1, a multivariate model was constructed by combining the statistically relevant indicators (with $p < 0.10$ in the univariate model) and factors considered necessary from a medical viewpoint. Multivariate re-analysis was performed by a stepwise variable selection procedure with an entry and removal probability of 0.20 to avoid overlooking factors affecting FN onset [11]. Although this was not a hypothesis-testing study, all tests were two-sided, and a p value <0.05 was considered significant.

Estimation of the incidence of FN in cycle 1 without prophylaxis with G-CSF: simulation analysis

We also simulated the point estimate and 95% confidence interval (CI) for the incidence of FN in cycle 1 without prophylaxis with G-CSF before the occurrence of FN for all the patients ($N = 462$) included in the incidence calculation of FN in cycle 1. First, 1000 bootstrap samples were built by resampling from the population ($N = 462$) analyzed for the incidence of FN in cycle 1. Then, for each bootstrap sample, the incidence of FN in cycle 1 without prophylaxis with G-CSF was estimated for all patients included in the bootstrap samples, according to the following procedures: (1) Only the data from patients who were not receiving G-CSF before the occurrence of FN were analyzed by a multivariate model using the occurrence of FN in cycle 1 as a response variable. Explanatory analysis of the multivariate model was performed by a stepwise variable selection procedure where the criterion for entry and removal of variables for the population analyzed for the incidence of FN in cycle 1 was set at $p = 0.20$ (however, excluding "prophylaxis with G-CSF in cycle 1"). (2) Using the variables selected by the multivariate model, the incidence of FN in cycle 1 was estimated for each patient receiving prophylactic G-CSF. Then, a value of 0 or 1 was assigned using a Bernoulli random variable where the estimated FN incidence in cycle 1 was the occurrence probability. This was used as the estimate for the occurrence of FN in cycle 1 without prophylaxis with G-CSF for each patient receiving prophylactic G-CSF. (3) For patients without prophylaxis with G-CSF, an FN episode observed in cycle 1 was defined as the occurrence of FN in cycle 1 without prophylaxis with G-CSF. (4) Using the estimate obtained above for the occurrence of FN in cycle 1 without prophylaxis with G-CSF, the incidence of FN in cycle 1 without prophylaxis with G-CSF was estimated for all patients included in the bootstrap samples.

Finally, from the 1000 estimates of the incidence of FN in cycle 1 without prophylaxis with G-CSF obtained from the bootstrap samples, the mean was calculated and used as the point estimate of the incidence of FN in cycle 1 without prophylaxis with G-CSF for all patients included in the population analyzed for the incidence of FN in cycle 1. A confidence interval was constructed based on the 2.5th and 97.5th percentiles of the estimated incident of FN over 1000 bootstrapped samples. All analyses were performed without applying any imputation approach to deal with the missing data.

Results

Of the 466 patients analyzed, 4 received cycle 1 at another hospital; therefore, 462 patients were included in the analyses of cycle 1. The demographic and clinical characteristics of patients included in the analysis are shown in Table 1. Of the 466 patients, 263 were men (56.4%). Patients had a mean (SD) age of 63.3 (12.89) years. Most patients (439; 94.2%) had an Eastern Cooperative Oncology Group (ECOG) PS of 0–1. Most patients (378; 81.1%) had a diagnosis of diffuse large B-cell lymphoma (DLBCL). Slightly over half of the patients had limited disease (Ann Arbor stage I–II; 262; 56.2%), and 204 (43.8%) had advanced disease. Less than 10% of patients had bone marrow infiltration. The most common complication was diabetes (9.9%). Patients were receiving R-CHOP at a mean RDI (SD) of 89.0% (12.41).

The demographic and clinical characteristics of patients with and without FN included in the analysis of cycle 1 are shown in Table 2. At cycle 1, of 462 patients, 42 had developed FN. Most of the patients (31; 73.8%) with FN were 65 years or older, were female (25; 59.5%), had a PS of 0–1 (37; 88.1%), were diagnosed with DLBCL (34; 81.0), had advanced disease (24; 57.1), were receiving R-CHOP at a RDI <85% (23; 57.5%), and had not received G-CSF prophylaxis (29; 69.0%). In contrast, the 420 patients without FN were almost equally distributed in both age groups (<65 and ≥65 years of age), most were male (243; 57.9%), had limited disease (243; 57.9%), had higher albumin and hemoglobin levels, and had received G-CSF prophylaxis (234; 55.7%). When comparing patients with and without FN, there were significant differences in age ($p = 0.0056$), sex ($p = 0.03$), albumin levels ($p = 0.004$), hemoglobin levels ($p = 0.014$), RDI ($p = 0.001$), and prophylaxis with G-CSF ($p = 0.002$).

In cycle 1, the incidence of FN was 9.1% (42 of 462). The incidence of FN was 12.3% (57 of 462) throughout all cycles. The majority (73.7%; 42 of 57) of FN cases occurred during cycle 1.

Table 1 Demographic and clinical characteristics of patients

	Patients $N = 466$
Age (years), mean (SD)	63.3 (12.89)
Sex, male, *n* (%)	263 (56.4)
ECOG performance status, *n* (%)	
0–1	439 (94.2)
2–4	27 (5.8)
Body mass index (kg/m^2), mean (SD)	22.5 (3.52)
Pathological diagnosis	
Diffuse large B-cell lymphoma	378 (81.1)
Follicular lymphoma	36 (7.7)
Transformed diffuse large B-cell lymphoma	15 (3.2)
Other B-cell lymphoma	37 (7.9)
Ann Arbor stage, *n* (%)	
Limited (I–II)	262 (56.2)
Advanced (III–IV)	204 (43.8)
Bone marrow infiltration, *n* (%)	44 (9.4)
Complications, *n* (%)	
Diabetes	46 (9.9)
Hepatic, renal, or heart disease	30 (6.4)
History of surgery 1 month earlier R-CHOP[a]	3 (0.6)
Active infection	15 (3.2)
Albumin (g/L), mean (SD)	38.2 (5.49)
Total bilirubin (μmol/L), mean (SD)	10.3 (5.87)
Hemoglobin (g/L), mean (SD)	124.1 (18.72)
Absolute neutrophil count (×10^9/L), mean (SD)	4.6 (2.54)
Absolute lymphocyte count (×10^9/L), mean (SD)	1.5 (1.82)
Relative dose intensity (%), mean (SD)	89.0 (12.41)

ECOG Eastern Cooperative Oncology Group, *FN* febrile neutropenia, *N* number of patients analyzed

[a] Chemotherapeutic regimen comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

In the univariate analysis, the risk factors that were statistically relevant factors ($p < 0.05$) which associated with the development of FN in cycle 1 were age (odds ratio [OR] 95% CI, 2.66 [1.30–5.44]; $p = 0.0072$), sex (2.02 [1.06–3.85]; $p = 0.0330$), albumin (2.58 [1.32–5.03]; $p = 0.0055$), hemoglobin (2.20 [1.16–4.17]; $p = 0.0155$), RDI (2.88 [1.48–5.57]; $p = 0.0017$), and use of prophylactic G-CSF (0.36 [0.18–0.71]; $p = 0.0030$), and clinically relevant factors were PS (2.57 [0.92–7.21]; $p = 0.0731$) and disease stage (1.83 [0.96–3.48]; $p = 0.0645$) (Table 3). The statistically and clinically relevant factors identified for cycle 1 were then entered into a multivariate stepwise analysis. As a result, albumin <35 g/L (OR [95% CI], 2.86 [1.38–5.93]; $p = 0.0047$), RDI <85% (3.31 [1.66–6.60]; $p = 0.0007$), and lack of prophylaxis with G-CSF (0.27 [0.13–0.57]; $p = 0.0006$) were found to be significant risk factors for FN among these patients.

We also performed a re-analysis of data to identify risk factors of FN by multivariate analysis. As a result, six factors were extracted (Table 4). Additionally, in order to estimate the incidence of FN in patients without prophylactic administration of G-CSF, we performed a simulation analysis by multivariate logistic regression model using five factors except prophylactic administration of G-CSF. We found that the estimated FN incidence [95% CI] was 16.2% [10.9–22.2] (Table 4). Based on a previous report of markedly higher incidence of FN in breast cancer patients showing the lowest ANC and ALC values [10], we examined the relationship between the incidence of FN in cycle 1 and ANC or ALC. However, no significant relationship was found (Table 5).

Discussion

We examined the incidence of FN among Japanese patients with B-NHL after receiving one cycle and all cycles of R-CHOP. We also identified risk factors of FN among our patients.

The present results are very reliable because this was a large retrospective study conducted in a single institution. Another strength is that patients in Japan are administered the treatment for cycle 1 in an inpatient setting, which allows proper follow-up of patients, leading to accurate identification of the incidence of FN in cycle 1.

The incidence of FN in this study was 9.1% in cycle 1 and 12.3% throughout all cycles. In contrast, the incidence of FN was 15% in patients with follicular lymphoma receiving R-CHOP-21 regimens that were not undergoing prophylaxis with G-CSF [6]. A previous study on Japanese cancer patients at high risk of FN [12] reported an overall incidence of FN of approximately 20% among patients undergoing chemotherapy with R-CHOP. However, specific data on the incidence of FN among patients with B-NHL are scarce, which stresses the importance of our study.

According to the Guidelines for the Appropriate Use of G-CSF [2], the incidence of FN in patients receiving myelosuppressive chemotherapy is 13–21%. Interestingly, the incidence of FN in this study was lower than that reported previously. Possible reasons for this lower incidence may be that cycle 1 of R-CHOP chemotherapy in Japan is administered in an inpatient setting for most patients, allowing timely detection of a decrease in neutrophil count. It is also possible that the lower FN incidence in the present study is a reflection of the actual clinical practice in Japan in which G-CSF is used early on according to the patient's risk profile as stated in the recent Japanese guidelines [5]. Therefore, the high frequency of patients receiving prophylactic G-CSF may be the reason for the lower incidence of FN in the present study compared with that reported previously [6, 12]. However, it is impossible to exclude the influence of other factors (e.g., the influence of race and differences in clinical practices across different medical settings in Japan). To clarify this point, we performed a

Table 2 Demographic and clinical characteristics of patients in cycle 1

	Patients with FN $N = 42$, n (%)	Patients without FN $N = 420$, n (%)	p value
Age (years)			
<65	11 (26.2)	204 (48.6)	0.0056
≥65	31 (73.8)	216 (51.4)	
Sex			
Male	17 (40.5)	243 (57.9)	0.0304
Female	25 (59.5)	177 (42.1)	
ECOG performance status			
0–1	37 (88.1)	399 (95.0)	0.0758
2–4	5 (11.9)	21 (5.0)	
Body mass index			
<23 kg/m^2	29 (69.0)	239 (56.9)	0.1284
≥23 kg/m^2	13 (31.0)	181 (43.1)	
Pathological diagnosis			
Diffuse large B-cell lymphoma	34 (81.0)	340 (81.0)	0.7302
Follicular lymphoma	2 (4.8)	34 (8.1)	
Transformed diffuse large B-cell lymphoma	2 (4.8)	13 (3.1)	
Other B-cell lymphoma	4 (9.5)	33 (7.9)	
Ann Arbor stage			
Limited (I–II)	18 (42.9)	243 (57.9)	0.0615
Advanced (III–IV)	24 (57.1)	177 (42.1)	
Bone marrow infiltration			
Yes	4 (9.5)	39 (9.3)	1.0000
No	38 (90.5)	381 (90.7)	
Complications			
Diabetes			
Yes	6 (14.3)	39 (9.3)	0.2790
No	36 (85.7)	381 (90.7)	
Hepatic, renal, or heart disease			
Yes	4 (9.5)	26 (6.2)	0.3378
No	38 (90.5)	394 (93.8)	
History of surgery 1 month earlier R-CHOP[a]			
Yes	0 (0.0)	3 (0.7)	1.0000
No	42 (100.0)	417 (99.3)	
Active infection			
Yes	2 (4.8)	13 (3.1)	0.6371
No	40 (95.2)	407 (96.9)	
Albumin			
<35 g/L	16 (38.1)	81 (19.3)	0.0043
≥35 g/L	26 (61.9)	339 (80.7)	
Total bilirubin			
<17.1 μmol/L	39 (92.9)	379 (90.2)	0.7847
≥17.1 μmol/L	3 (7.1)	41 (9.8)	
Hemoglobin			
<120 g/L	22 (52.4)	140 (33.3)	0.0136
≥120 g/L	20 (47.6)	280 (66.7)	
Absolute neutrophil count			
<3.1 × 10^9/L	11 (26.2)	118 (28.1)	0.7930
≥3.1 × 10^9/L	31 (73.8)	302 (71.9)	
Absolute lymphocyte count			
<1.5 × 10^9/L	27 (64.3)	263 (62.6)	0.8313
≥1.5 × 10^9/L	15 (35.7)	157 (37.4)	
Relative dose intensity			
<85%	23 (57.5)	128 (32.0)	0.0012
≥85%	17 (42.5)	272 (68.0)	
Prophylaxis wtih G-CSF			
Yes	13 (31.0)	234 (55.7)	0.0022
No	29 (69.0)	186 (44.3)	

In cycle 1, the incidence of FN was 9.1% (42 of 462). The incidence of FN was 12.3% (57 of 462) throughout all cycles. The majority (73.7%; 42 of 57) of FN cases occurred during cycle 1

ECOG Eastern Cooperative Oncology Group, *FN* febrile neutropenia, *N* number of patients analyzed

[a] Chemotherapeutic regimen comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

simulation analysis using the bootstrap method, including all patients who were not receiving prophylactic G-CSF administration. This simulation yielded an incidence of FN of 16.2%, which was indeed similar to that previously reported [6, 10]. Further, other studies [7, 13, 14] have reported risk factors other than the three identified in our main analysis. To extract a wider range of candidate risk factors from this simulation analysis, we performed a re-analysis of the raw data using multivariate analysis (stepwise method). This re-analysis yielded RDI <85% throughout all cycles and lack of prophylaxis with G-CSF as candidate FN risk factors. These factors differed from those reported by Lyman et al. for patients on chemotherapy, which included poor PS, BMI <23 kg/m^2, and disease stage III–IV [7]. However, in patients with intermediate-grade non-Hodgkin lymphoma receiving CHOP, Lyman et al. [13] reported that age >65 years, renal and cardiovascular diseases, and baseline hemoglobin were associated with high risk of FN in addition to RDI >80% and no G-CSF prophylaxis. Because RDI and lack of prophylaxis with G-CSF were identified as risk factors in both the main analysis and the simulation, as well as in previous studies on similar populations, we consider that these risk factors for FN will remain consistent. These simulation findings suggest that the lack of prophylaxis with G-CSF may contribute to the development of FN among Japanese patients with B-NHL.

Japanese guidelines recommend the use of G-CSF in lymphoma patients based on a report by Smith et al. [15]. However, the number of patients included in Smith et al.'s analysis was relatively small. In comparison, a larger number of patients were enrolled in our study, and our findings strongly support the current guideline recommendations. Furthermore, the single-center design ensured that the diagnostic criteria remained constant. The present study supports the recommendation of proper prophylactic administration of G-CSF in patients with high risk of developing FN.

In this study, FN occurred during cycle 1 in most patients (73.7%), which is concordant with previous findings [16]. This indicates that prophylaxis with G-CSF should be actively considered from cycle 1 for patients at risk of developing FN. This finding is also supported by the findings of a systematic review of 17 studies aimed at evaluating the impact of primary prophylaxis with G-CSF on FN and mortality in adult cancer patients receiving chemotherapy. In that study, it was concluded that prophylactic G-CSF reduced the risk of FN and early deaths, including infection-related mortality, while increasing the RDI [17]. With the launch of G-CSF >20 years ago, appropriate management methods for patients receiving G-CSF have been established to avoid risks associated with G-CSF treatment.

A decrease in serum albumin levels is considered a marker of acute inflammatory response (called "B symptom" in lymphoma). Therefore, a decrease in serum albumin levels

Table 3 Factors associated with the risk of febrile neutropenia in cycle 1

		Univariate analysis		Multivariate analysis	
	N	Odds ratio [95% CI]	*p* value	Odds ratio [95% CI]	*p* value
Age (years) (<65, ≥65)	462	2.66 [1.30–5.44]	0.0072	–	–
Sex (male, female)	462	2.02 [1.06–3.85]	0.0330	–	–
Performance status (0–1, 2–4)	462	2.57 [0.92–7.21]	0.0731	–	–
Body mass index (kg/m^2) (<23, ≥23)	462	0.59 [0.30–1.17]	0.1319	–	–
Pathological diagnosis (DLBCL, FL)	410	0.59 [0.14–2.56]	0.4790	–	–
Pathological diagnosis (DLBCL, transformed DLBCL)	389	1.54 [0.33–7.10]	0.5810	–	–
Pathological diagnosis (DLBCL, others B-cell lymphoma)	411	1.21 [0.41–3.63]	0.7307	–	–
Disease stage (I–II, III–IV)	462	1.83 [0.96–3.48]	0.0645	–	–
Bone marrow infiltration (no, yes)	462	1.03 [0.35–3.03]	0.9592	–	–
Diabetes (no, yes)	462	1.63 [0.65–4.11]	0.3016	–	–
Hepatic, renal, or heart disease (no, yes)	462	1.60 [0.53–4.81]	0.4071	–	–
Surgery within 1 month before initiation of R-CHOP[a] regimen (no, yes)	462	<0.001 [<0.001–>999.999]	0.9920	–	–
Active infection (no, yes)	462	1.57 [0.34–7.18]	0.5643	–	–
Albumin (g/L) (≥35, <35)	462	2.58 [1.32–5.03]	0.0055	2.86 [1.38–5.93]	0.0047
Total bilirubin (μmol/L) (<17.1, ≥17.1)	462	0.71 [0.21–2.40]	0.5837	–	–
Hemoglobin (g/L) (≥120, <120)	462	2.20 [1.16–4.17]	0.0155	–	–
ANC (≥3.1 × 10^9/L, <3.1 × 10^9/L)	462	0.91 [0.44–1.87]	0.7931	–	–
ALC (≥1.5 × 10^9/L, <1.5 × 10^9/L)	462	1.08 [0.56–2.08]	0.8313	–	–
Relative dose intensity (≥85, <85%)	440	2.88 [1.48–5.57]	0.0017	3.31 [1.66–6.60]	0.0007
Prophylaxis with G-CSF (no, yes)	462	0.36 [0.18–0.71]	0.0030	0.27 [0.13–0.57]	0.0006

ALC absolute lymphocyte count, *ANC* absolute neutrophil count, *CI* confidence interval, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *N* number of patients analyzed

[a] Chemotherapeutic regimen comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

indicates worsening of the patient's general condition. This finding suggests that worsening of the patient's general conditions is associated with an increase in the incidence of FN.

For RDI, there are two possibilities. One is that the development of FN leads to a reduction in RDI. The other is that FN is more likely to occur in patients in whom the RDI is set low owing to poor PS and worsened general condition, among other factors.

According to the American Society of Clinical Oncology (ASCO) guidelines as well as the review by Lyman et al. [3, 7], risk factors for the development of FN include sepsis syndrome, advanced age (≥65 years), poor PS, severe neutropenia, neutropenia persisting for 10 days or longer, low BMI, pneumonia, invasive fungal infections, other infection-related diagnoses, previous hospitalizations for febrile complications, treatment with myelosuppressive chemotherapies, and a history

Table 4 Candidate risk factors for febrile neutropenia in cycle 1 (data re-analysis by multivariate analysis)

	Parameter estimate (standard error)	Odds ratio [95% CI]	*p* value
Age (years) (<65, ≥65)	0.72 (0.41)	2.06 [0.928–4.549]	0.0756
Sex (male, female)	0.50 (0.36)	1.65 [0.821–3.318]	0.1599
Disease stage (I–II, III–IV)	0.60 (0.38)	1.82 [0.864–3.835]	0.1154
Albumin (g/L) (≥35, <35)	0.66 (0.41)	1.93 [0.867–4.275]	0.1076
Relative dose intensity (≥85, <85%)	1.02 (0.38)	2.78 [1.332–5.805]	0.0064
Prophylaxis with G-CSF (no, yes)	−1.40 (0.38)	0.25 [0.117–0.524]	0.0003
Estimated FN incidence in cycle 1 without prophylaxis with G-CSF: simulation analysis			
%		95% CI	
16.2		10.9–22.2	

CI confidence interval, *G-CSF* granulocyte colony-stimulating factor, *N* number of patients analyzed, *FN* febrile neutropenia

Table 5 Incidence of febrile neutropenia by ANC and ALC levels (cycle 1)

	$N = 462$ n/N (%)	95% CI (%)	p value
All patients	42/462 (9.1)	[6.6–12.1]	
ANC <0.5 × 10^9/L, ALC <1.0 × 10^9/L	0/0 (–)	–	
ANC <0.5 × 10^9/L, ALC 1.0–2.0 × 10^9/L	0/0 (–)	–	
ANC <0.5 × 10^9/L, ALC ≥2.0 × 10^9/L	0/0 (–)	–	
ANC 0.5–1.0 × 10^9/L, ALC <1.0 × 10^9/L	0/2 (0.0)	[0.0–84.2]	0.4756[a]
ANC 0.5–1.0 × 10^9/L, ALC 1.0–2.0 × 10^9/L	0/1 (0.0)	[0.0–97.5]	
ANC 0.5–1.0 × 10^9/L, ALC ≥2.0 × 10^9/L	0/0 (–)	–	
ANC ≥1.0 × 10^9/L, ALC <1.0 × 10^9/L	17/138 (12.3)	[7.3–19.0]	
ANC ≥1.0 × 10^9/L, ALC 1.0–2.0 × 10^9/L	20/254 (7.9)	[4.9–11.9]	
ANC ≥1.0 × 10^9/L, ALC ≥2.0 × 10^9/L	5/67 (7.5)	[2.5–16.6]	

ALC absolute lymphocyte count, *ANC* absolute neutrophil count, *CI* confidence interval, *n/N* number of patients analyzed

[a] Fisher's exact test

of FN. In this study, FN development was only correlated with some of these factors. However, this study specifically evaluated the risk factors for FN of patients with B-NHL undergoing R-CHOP chemotherapy. In contrast, the ASCO guidelines as well as previous studies [3, 7, 12] on risk factor assessment cover all areas of chemotherapy practice. Thus, these comparisons must be interpreted carefully.

In breast cancer, it has been reported that the incidence of FN was markedly higher in patients showing the lowest ANC and ALC values [10]. We considered that a similar trend would be observed in B-NHL patients receiving R-CHOP chemotherapy. Therefore, we examined the relationship between the incidence of FN in cycle 1 and ANC or ALC. However, no significant relationship was found.

Taken together, the relatively lower incidence of FN in this study reflects that, in an actual clinical setting, G-CSF is used according to the patient's risk factors and changes in neutrophil count over time. This may contribute to the prevention of serious neutropenia and therefore to the prevention of FN.

Upon implementation of R-CHOP chemotherapy for patients with B-NHL, it may be advisable to actively consider prophylaxis with G-CSF early on, that is, from cycle 1. Additionally, patients with albumin <35 g/L or RDI <85%, which were other risk factors for FN identified in this study, should also be carefully considered when contemplating chemotherapy with R-CHOP.

This study has some limitations. In cycle 1, because the chemotherapy was administered in an inpatient setting, it was possible to accurately detect FN. However, in cycle 2 and subsequent cycles, treatment was given in an outpatient setting, which did not allow the accurate detection of FN. While the single-center design could be considered a strength because it guaranteed the consistency of the diagnostic criteria, it could also be considered a limitation from the viewpoint that the study subjects are not representative of the entire Japanese population.

In conclusion, the results of this single-center, retrospective study of R-CHOP chemotherapy in an actual clinical setting showed that the incidence of FN was 9.1% in cycle 1 and 12.3% throughout all cycles. The risk factors identified included albumin <35 g/L, RDI <85%, and lack of prophylaxis with G-CSF. Therefore, for patients with these risk factors, it may be advisable to actively consider the prophylaxis with G-CSF starting with cycle 1 for optimum management to reduce the occurrence of FN.

Acknowledgments The authors wish to thank Keyra Martinez Dunn, MD, of Edanz Group Japan K.K., for providing medical writing assistance. Funding for this research was provided by Kyowa Hakko Kirin Co., Ltd. T.N. and T.N. are current employees of Kyowa Hakko Kirin, Co., Ltd.

Compliance with ethical standards

Conflict of interest This study funded by Kyowa Hakko Kirin Co., Ltd.

Research involving human participants and/or animals

Informed consent For this type of study, formal consent is not required.

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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