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Original Article

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Clinical Significance of Non-neutropenic Fever in the Management of Diffuse Large B-Cell Lymphoma Patients Treated with Rituximab-CHOP: Comparison with Febrile Neutropenia and Risk Factor Analysis

Silvia Park, MD[1]
Cheol-In Kang, MD, PhD[2]
Doo Ryeon Chung, MD, PhD[2]
Kyong Ran Peck, MD, PhD[2]
Won Seog Kim, MD, PhD[1]
Seok Jin Kim, MD, PhD[1]

Divisions of [1]Hematology-Oncology and [2]Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence: Seok Jin Kim MD, PhD
Division of Hematology-Oncology,
Department of Medicine,
Samsung Medical Center,
Sungkyunkwan University School of Medicine,
81 Irwon-ro, Gangnam-gu,
Seoul 135-710, Korea
Tel: 82-2-3410-1766
Fax: 82-2-3410-1754
E-mail: kstwoh@skku.edu

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Purpose

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard chemotherapy in diffuse large B-cell lymphoma (DLBCL) patients. Although febrile neutropenia (FN) is the major toxicity of this regimen, non-neutropenic fever (NNF) becomes an emerging issue.

Materials and Methods

We analyzed clinical features and outcomes of febrile complications from 397 patients with newly diagnosed DLBCL who were registered in the prospective cohort study. They had completed R-CHOP between September 2008 and January 2013.

Results

Thirty-nine patients (9.8%) had NNF whereas 160 patients (40.3%) had FN. Among them, 24 patients (6.0%) had both during their treatment. Compared to frequent occurrence of initial FN after the first cycle (> 50% of total events), more than 80% of NNF cases occurred after the third cycle. Interstitial pneumonitis comprised the highest proportion of NNF cases (54.8%), although the causative organism was not identified in the majority of cases. Thus, pathogen was identified in a limited number of patients (n=9), and *Pneumocystis jiroveci* pneumonia (PJP) was the most common. Considering that interstitial pneumonitis without documented pathogen could be clinically diagnosed with PJP, the overall rate of PJP including probable cases was 4.5% (18 cases from 397 patients). The NNF-related mortality rate was 10.3% (four deaths from 39 patients with NNF) while the FN-related mortality rate was only 1.3%.

Conclusion

NNF was observed with incidence of 10% during R-CHOP treatment, and showed different clinical manifestations with respect to the time of initial episode and causes.

Key words
Fever, Lymphoma, Rituximab

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma, and a curable disorder with systemic chemotherapy [1]. Since a phase III study demonstrated the superior efficacy of the addition of rituximab, an anti-CD20 monoclonal antibody to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen to CHOP alone in elderly patients with DLBCL [2], rituximab plus CHOP (R-CHOP) regimen has been the mainstay for treatment of DLBCL. However, treatment-related morbidity and mortality remain as an obstacle to overcome in DLBCL patients, particularly elderly patients because CHOP regimen induces myelosuppression with high probability of febrile neutropenia (FN) [3]. Thus, previous studies have shown that lymphoma was a tumor type at risk of FN [4-6], and the occurrence of FN significantly reduced the dose-intensity of R-CHOP [7]. A previous meta-analysis showed that the addition of rituximab to chemotherapy regimen did

not increase the overall risk of severe infection as well as treatment related mortality [8]; however, rituximab-induced B-cell depletion might induce additional risk of infection. In clinical practice, we often experienced febrile complications in the "absence" of neutropenia in patients who received R-CHOP. This non-neutropenic fever (NNF) might be related to various clinical situations, such as virus, drug hypersensitivity, or idiopathic cases. A recent retrospective study underscored the clinical significance of interstitial pneumonitis in hematologic malignancy including patients treated with R-CHOP [9]. Likewise, an increase in the occurrence of *Pneumocystis jiroveci* pneumonia (PJP) was also reported in patients treated with R-CHOP [10-12]. However, all of these studies were retrospective and the study population was relatively small. Therefore, we analyzed the frequency of NNF as well as its clinical and microbiological features in our patients registered in the prospective cohort study. In this study, we also compared clinical significance and risk factors of NNF with those of FN.

Materials and Methods

1. Patients

The study population came from two prospective cohort studies of Samsung Medical Center: Samsung Medical Center Lymphoma Cohort Study (NCT#00822731, 2008-2011) and Samsung Medical Center Lymphoma Cohort Study-II (NCT#01877109, 2012-ongoing). These studies were approved by the Institutional Review Board of the Samsung Medical Center, and patients were registered prospectively and followed. Their comprehensive baseline characteristics, including disease-related factors, including stage, extranodal involvement, serum lactate dehydrogenase (LDH), and bone marrow involvement, and host-related factors, including age, sex, and performance status were recorded. Treatment-related data including treatment response and toxicity were recorded during and after treatment. From the patients enrolled in the cohort study, we selected patients newly diagnosed with DLBCL who were treated with R-CHOP as a primary treatment. Patients with HIV-associated DLBCL were not included in this study. R-CHOP chemotherapy was repeated every 21 days, and each cycle consisted of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose, 2.0 mg/dose) administered intravenously on day 1, and oral prednisone 100 mg on days 1 through 5. Prophylactic granulocyte–colony stimulating factor (G-CSF) or antibiotics was not routinely administered. Because of insurance issues in Korea, G-CSF could be administered when an absolute neutrophil count below 1,000/mm^3 was detected. Antibiotics were not initiated unless a patient experienced any febrile event. Patients were instructed to visit the emergency room if they felt febrile sense during the nadir period, and were started on initial empirical antibiotic therapy with cefepime or piperacillin/tazobactam according to institutional strategy for management of FN. All patients received intravenous administration of doxorubicin via central line: Hickman catheter in almost all cases, but peripherally inserted central catheter as acceptable if the technical approach for Hickman catheter insertion was difficult because of the tumor location.

Table 1. Baseline characteristics

Characteristic	No. (%)
Age (yr)	
≤ 60	255 (64.2)
> 60	142 (35.8)
Gender	
Male	228 (57.4)
Female	169 (42.6)
Ann Arbor stage	
I/II	208 (52.4)
III/IV	189 (47.6)
ECOG performance status	
0/1	344 (86.6)
≥ 2	53 (13.4)
Extranodal involvement	
0/1	267 (67.3)
≥ 2	130 (32.7)
Serum LDH	
Normal	221 (55.7)
Elevated	176 (44.3)
Bone marrow involvement	
Absence	361 (90.9)
Presence	36 (9.1)
B Symptoms	
Absence	296 (74.6)
Presence	101 (25.4)
IPI risk group	
Low/low-intermediate	273 (68.8)
High-intermediate/high	124 (31.2)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

2. Objectives and definition

The primary objective of this study was to determine the incidence of NNF in patients receiving R-CHOP, and the

Table 2. Causes of non-neutropenic fever (NNF)

Cause of NNF[a]	No. (%)
Clinical presentation	
Interstitial pneumonitis	23 (54.8)
Pneumonia other than interstitial pneumonitis	3 (6.8)
Catheter related infection	9 (20.5)
Intra-abdominal infection	2 (4.5)
Bacteremia of uncertain source	1 (2.3)
Infectious spondylitis	1 (2.3)
Other	5 (11.4)
Cytomegalovirus esophagitis	2
Clostridium difficile colitis	1
Fever with hemophagocytic lymphohistiocytosis (HLH)	1
Candidemia	1
Causative organism	
Interstitial pneumonitis	
Pathogen unidentified	14 (60.9)
Pathogen identified[b]	9 (26.1)
Pneumocystis jiroveci pneumonia	4
Adenovirus	2
Respiratory syncytial virus	2
Cytomegalovirus	1
Bacterial[c] (positive blood and/or tissue culture)	
Coagulase-negative *Staphylococcus*	3 (21.4)
Staphylococcus aureus	5 (35.7)
Pseudomonas spp.	1 (7.1)
Klebsiella pneumoniae	1 (7.1)
Acinetobacter spp.	2 (14.3)
Other	2 (14.3)

[a]Including the multiple episodes of infection in a single patient, 42 infections were identified in 39 patients, [b]In nine episodes of NNF with identifiable pathogen, 10 pathogens were identified, [c]In 13 episodes of NNF with identifiable bacterial pathogen, 14 pathogens were identified.

secondary objective was to determine causes and identify clinical features of NNF. We also compared NNF with FN in terms of incidence, causes and clinical features, and risk factors. Fever was defined as a single oral temperature measurement of ≥ 38.3°C, or a temperature of ≥ 38°C sustained over a 1-hour period. Fever without evidence of grade 3 or 4 neutropenia was referred to as NNF whereas FN was defined as the occurrence of fever in a state of grade 3 or 4 neutropenia. Life threatening febrile event was reported as a grade IV adverse event. Fever associated with R-CHOP chemotherapy was defined as any febrile event occurring during repeated cycles of R-CHOP or up to 3 months after completion of R-CHOP chemotherapy. If anti-cancer treatment other than R-CHOP chemotherapy, such as radiotherapy or salvage chemotherapy was administered for progressive disease, any febrile episode after these other anti-cancer treatments was excluded from the R-CHOP chemotherapy-associated NNF or FN.

The incidence and onset of NNF and FN were calculated according to the first episode of NNF and FN in each patient. However, given that occurrence of multiple episodes of fever was possible in a single patient, all febrile events were considered when describing the causes of NNF and FN. According to the identification of a causative microorganism, the terms "microbiologically defined infection" (MDI), "clinically-defined infection" (CDI), and "unexplained fever" (UF) were used. Infections were defined as MDI when a clinically significant pathogen was identified from a culture or a biopsy of an affected site. The definition of CDI was used if fever was accompanied by appropriate clinical findings (for example, pulmonary infiltrates and respiratory symptom associated with fever). Finally, fever without definite evidence of infection was defined as UF.

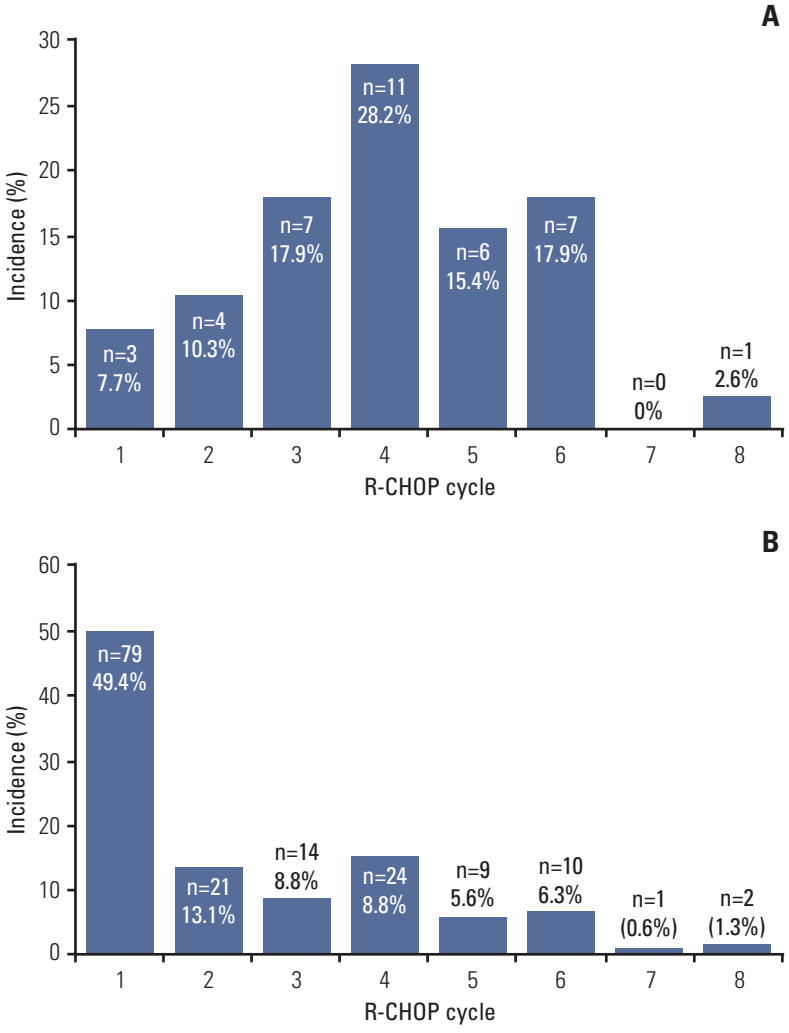

Fig. 1. Incidence of non-neutropenic fever (A) and febrile neutropenia (B) according to R-CHOP cycle. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

3. Statistics

Statistical analysis was performed using the SPSS ver. 19.0 (SPSS Inc., Chicago, IL). The incidence of febrile episode during courses of R-CHOP chemotherapy and the incidence of given type of infection and microbiologic etiology were described using frequency analysis. The cumulative probability of febrile events by cycle and overall survival (OS) were calculated using the Kaplan-Meier method. The time to the first NNF or FN was defined as the time between the first day of R-CHOP and the date of the first NNF or FN. OS was defined as the duration from the date of the first day of R-CHOP to the date of last follow-up or the date of death from any cause. Univariate and multivariate logistic regression models were used for risk factor analysis. Two-sided p-values less than 0.05 were considered statistically significant.

Results

1. Characteristics of patients

Between September 2008 and January 2013, a total of 1,142 lymphoma patients were registered in the two prospective cohort studies. Among them, 435 patients were newly diag-

Table 3. Causes of febrile neutropenia (FN)

Characteristic of FN	No. (%)
Type of infection[a]	
CDI	74 (26.8)
MDI	70 (25.4)
UF	132 (47.8)
Clinical sites of infection[a]	
Upper respiratory tract infection[b]	24 (8.5)
Lower respiratory tract infection[c]	28 (10.0)
Gastroenteritis[d]	30 (10.7)
Catheter-related infection	40 (14.2)
Urinary tract infection	18 (6.4)
Skin and soft tissue infection	2 (0.7)
Other[e]	7 (2.5)
UF	132 (47.0)
Causative organism	
Positive blood cultures[f]	
Staphylococcus aureus	8 (17.0)
Coagulase-negative *Staphylococcus*	13 (27.7)
Escherichia coli	5 (10.6)
Pseudomonas aeruginosa	4 (8.5)
Klebsiella pneumoniae	4 (8.5)
Enterococcus spp.	5 (10.6)
Acinetobacter spp.	1 (2.1)
Bacillus spp.	2 (4.3)
Others	5 (10.6)
Positive tissue cultures other than bacterial blood[g]	
Escherichia coli	11 (18.0)
Staphylococcus aureus	12 (19.7)
Klebsiella pneumoniae	6 (9.8)
Clostridium difficile	5 (8.2)
Enterococcus spp.	4 (6.6)
Acinetobacter spp.	3 (4.9)
Pseudomonas spp.	5 (8.2)
Others	9 (14.8)
Nonbacterial	
Pneumocystis jiroveci pneumonia	2 (3.3)
Mucor	1 (1.6)
H1N1	1 (1.6)
Cytomegalovirus	1 (1.6)
Respiratory syncytial virus A	1 (1.6)

CDI, clinically defined infection; MDI, microbiologically defined infection; UF, unexplained fever. [a]Including the multiple sites of infections in a single FN event, 281 infections were present in 276 FN cases, [b]Includes rhinitis, pharyngitis, otitis media, and sinusitis, [c]Includes pneumonia and pneumonitis, [d]Includes mucositis, typhlitis, anal, and/or hemorrhoidal complication, [e]Includes dental infection, biliary tract infection, and infective endocarditis, [f]In 46 episodes of FN, 47 bacterial pathogens were identified from blood culture, [g]In 42 episodes of FN, 61 pathogens were identified from tissue cultures other than blood as follows: urine (n=15, 34.1%), sputum and/or bronchial aspiration (n=10, 22.7%), catheter tip (n=6, 13.6%), others (n=13, 29.5%).

Table 4. Risk factors for febrile neutropenia (FN) and non-neutropenic fever (NNF)

Characteristic	FN				NNF			
	Univariate		Multivariate[a]		Univariate		Multivariate[a]	
	p-value	p-value	HR	95% CI for SHR	p-value	p-value	HR	95% CI for SHR
Age	> 60 yr	< 0.001	< 0.001	2.757	1.766-4.302	0.006	0.012	2.406	1.211-4.778
Gender	Female	0.066	0.118	1.413	0.916-2.180	0.585	0.430	0.755	0.376-1.517
ECOG PS	≥ 2	0.002	0.377	1.350	0.694-2.624	0.694	0.676	0.808	0.296-2.202
Serum LDH	Elevated	< 0.001	0.085	1.563	0.941-2.597	0.056	0.195	1.710	0.760-3.847
Extranodal involvement	≥ 2	< 0.001	0.171	1.482	0.844-2.603	0.063	0.178	1.824	0.761-4.371
Ann Arbor stage	III/IV	< 0.001	0.271	1.380	0.778-2.448	0.249	0.865	0.923	0.366-2.329
BM involvement	Presence	0.054	0.632	1.209	0.556-2.631	0.375	0.171	0.344	0.074-1.588
B Symptom	Presence	0.313	0.727	0.912	0.545-1.527	0.976	0.842	0.922	0.412-2.060

HR, hazard ratio; CI, confidence interval; SHR, subhazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; BM, bone marrow.

nosed with DLBCL and received at least one cycle of R-CHOP chemotherapy as a first-line treatment. We excluded 38 patients who were transferred to other hospitals during courses of treatment. Finally, 397 patients with DLBCL were analyzed in this study, and their clinical characteristics at diagnosis are summarized (Table 1). The median age was 55 years (range, 16 to 86 years), and elderly patients aged 60 years or older accounted for approximately 36% of patients. Male and female patients comprised 57.4% and 46.2%, respectively. Approximately one half of patients (n=189, 47.6%) presented as Ann Arbor stage III or IV; however, the International Prognostic Index (IPI) showed that 69% of patients belonged to low (n=194, 49%) and low-intermediate risk groups (n=79, 20%), while 31% of patients belonged to high-intermediate (n=60, 15%) and high (n=64, 16%) risk groups. The median number of R-CHOP cycles was 6 (range, 1 to 8).

2. Incidence and the first onset of NNF and FN

Among 397 patients, 39 (9.8%) and 160 patients (40.3%) experienced NNF and FN, respectively. Of those, 24 patients (6.0%) experienced both febrile complications. The initial episode of NNF was most frequently observed around the fourth cycle of R-CHOP. Thus, approximately 28% of the first visit for NNF occurred following the fourth cycle (Fig. 1A). By contrast, the initial FN event was commonly observed in earlier courses of cycle, and approximately 50% of the first hospital visits for FN occurred after the first chemotherapy cycle (Fig. 1B). The cumulative incidence of NNF after R-CHOP chemotherapy increased from 0.8% following the first cycle to 12.9% following the eighth cycle, whereas the cumulative incidence of FN increased from 20% following the first cycle to 47% following the eighth cycle.

3. Clinical features and microorganisms of NNF

Forty two episodes of NNF occurred in 39 patients with NNF; three of these patients experienced multiple episodes of NNF. Interstitial pneumonitis was the predominant clinical feature of NNF (23 out of 42 episodes, 54.8%) (Table 2). In all cases of atypical pneumonia, infectious broncho-alveolar lavage (BAL) was performed for identification of causative pathogens; 10 organisms were detected in nine patients. Out of identified organisms causing interstitial pneumonitis, PJP was the most common pathogen (n=4). Other pathogens included adenovirus (n=2), respiratory syncytial virus (RSV) (n=2), and cytomegalovirus (CMV) (n=1). For 14 patients in whom no pathogen was identified, trimethoprim-sulfamethoxazole was administered empirically under the impression of PJP. Beside interstitial pneumonitis, catheter-related infection was the second most

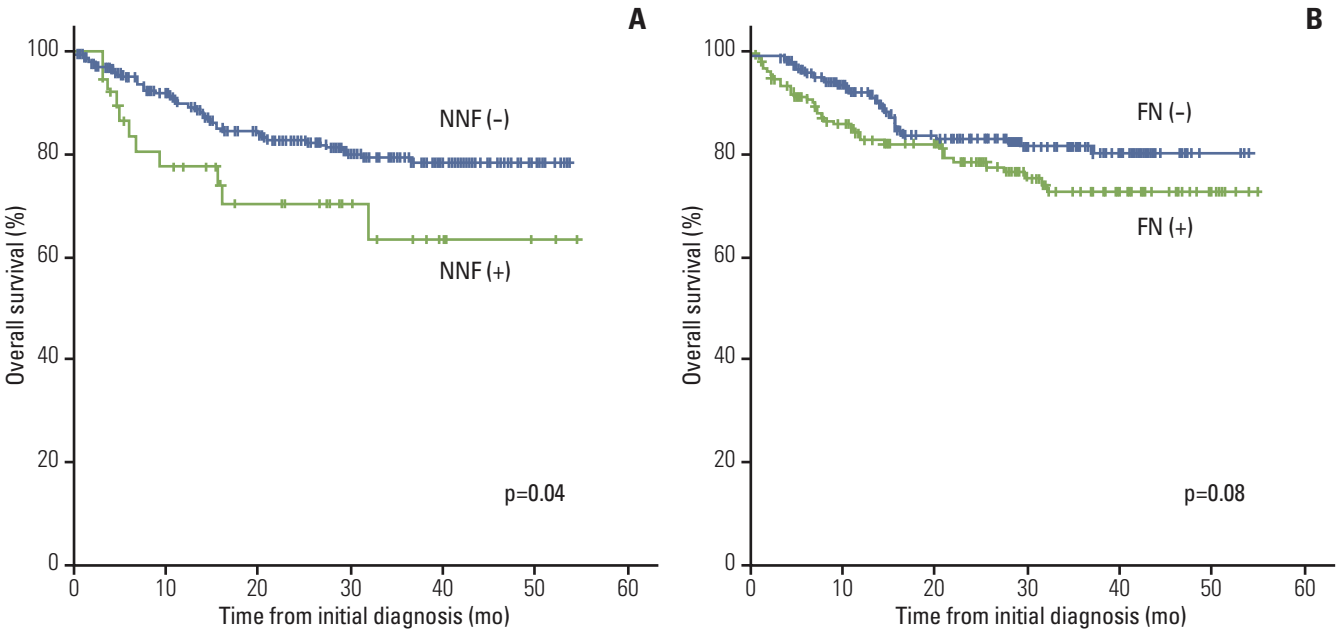

Fig. 2. Comparison of overall survival curves between patients with non-neutropenic fever (NNF) (A) or febrile neutropenia (FN) (B) and patients without any febrile event.

common form of NNF (n=9, 20.5%). Among the identified pathogens causing bacterial infection, gram-positive organisms, including coagulase-negative *Staphylococcus* and *Staphylococcus aureus* were the most common (8/14, 57.1%). Grade IV febrile events were reported in four patients (4/39, 10.3%), including three cases of interstitial pneumonitis, all of which were associated with mortality cases. Two patients died due to adenoviral pneumonia and one due to interstitial pneumonitis of unknown pathogen. Therefore, the mortality rate of interstitial pneumonitis was 13.0% (3/23). The remaining patient developed severe sepsis with candidemia even in the normal range of neutrophil count, and died despite receiving antifungal treatment with active supportive care. Among other cases of NNF, two patients developed CMV esophagitis, which occurred after completion of the sixth cycle of R-CHOP, and was proven by endoscopic biopsy; both patients recovered with antiviral treatment.

4. Clinical features and microorganisms of FN

Among the 160 patients with FN, 65 patients (40.9%) experienced at least two episodes of FN during their treatment period. Of these 65 patients, 39 patients experienced two episodes of FN, whereas 26 patients experienced three or more: three episodes (n=11), four episodes (n=8), five episodes (n=4), and six episodes (n=3) of FN during R-CHOP cycles. As a result, a total of 276 FN events were observed in 160 patients. There were 74 cases of CDI (26.8%), 70 cases of MDI (25.4%), and 132 cases of UF (47.8%). Among the 144 cases with CDI and MDI, catheter-related infection (14.2%), gastroenteritis (10.7%), and lower respiratory tract infection (10.0%) accounted for more than 35% of febrile events (Table 3). Bacteremia was detected in 46 cases, and coagulase-negative *Staphylococcus* was the most common microorganism responsible for bacteremia (27.7%); *Staphylococcus aureus* (17.0%), *Enterococcus* spp. (10.6%), and *Escherichia coli* (10.6%) were the next most prevalent organisms identified in blood (Table 3). Nine patients (9/160, 5.6%) experienced grade IV FN, two were mortality cases associated with FN, including septic shock with *Klebsiella* bacteremia and fungal sinusitis with mucormycosis.

5. Risk factors and survival outcome

Univariate and multivariate analyses were performed to determine the risk factors associated with development of NNF as well as FN (Table 4). The results of univariate analysis for risk factors of NNF showed that age older than 60 years increased the risk of NNF. Other parameters were not related with the occurrence of NNF. As a result, in multivariate analysis, age was also demonstrated to be an independent risk factor for NNF. In univariate analysis, compared to NNF, the occurrence of FN showed significant association with all parameters of the IPI. However, multi-

variate analysis showed the same result as that of NNF, thus, advanced age was the only significant factor affecting development of FN ($p < 0.001$; hazard ratio, 2.757). Over the median follow-up period of 34.4 months (range, 3.7 to 63.0 months), 326 patients were alive, while 71 patients died. The NNF-related mortality rate was 10.3% (four deaths from 39 patients with NNF) while the FN-related mortality rate was 1.3% (two deaths from 160 patients with FN). At the time of analysis, the 4-year OS was 77.3%. In comparison of OS according to the presence of FN and/or NNF, patients who had experienced any febrile events showed worse survival compared to patients who did not have FN or NNF (p=0.004). Separately, patients who experienced NNF showed significantly worse OS (p=0.04) (Fig. 2A), whereas OS was not significantly different between patients with and without FN (p=0.08) (Fig. 2B).

Discussion

This study was a large-scale analysis focusing on the occurrence of NNF in DLBCL patients who were uniformly treated with R-CHOP and enrolled in prospective observation cohort studies. We found that approximately 10% of DLBCL patients experienced NNF whereas 40% of patients experienced at least one episode of FN during R-CHOP chemotherapy. Besides the incidence, clinical features and causative microorganisms of NNF differed significantly from those of FN. Thus, half of patients experienced FN after the first cycle of R-CHOP, consistent with previous studies reporting that hospital visits for FN were most likely to occur in early courses of treatment [7,13,14]. However, the occurrence of NNF tended to increase with continuation of treatment and was most commonly observed around the fourth cycle. In addition, FN showed strong association with bacterial infection in which gram-positive organisms predominated, with a high incidence of catheter-related infection, and was usually controlled well with broad-spectrum antibiotics. In contrast, many cases of NNF showed interstitial pneumonitis without definite evidence of blood stream infection.

We found that interstitial pneumonitis comprised approximately 55% of NNF cases (n=23, 54.8%). However, causative organisms were identified in only nine patients (39.1%) in spite of active evaluation including BAL, and PJP was the most common pathogen (n=4). Although the rate of microbiologically proven PJP was extremely low, most cases with interstitial pneumonitis were treated with trimethoprim-sulfamethoxazole because they were diagnosed with probable PJP. Given that most patients with probable PJP showed a response and recovered, the majority of our interstitial pneumonitis could be PJP, except for a few cases found to have adenovirus, RSV, and CMV. Thus, in this study, the overall rate of PJP including definite and probable cases was 4.5% (18 cases from 397 patients). Likewise, a recent survey regarding the prevalence of PJP in 713 patients receiving R-CHOP reported diagnosis of 14 and 18 patients with definite and probable PJP, respectively [15]. Thus, PJP incidence of 4.5% (32/713), including definite and probable cases was reported, and the majority cases of PJP (22/32, 68.7%) developed after administration of the fourth R-CHOP cycle, similar to our results.

Given that opportunistic infection caused by virus or fungus is affected by impaired immunity, NNF might be associated with rituximab-induced impaired immunity. Depletion of B cells after repeated doses of rituximab may have direct effects on antibody production [16]. Indeed, previous studies demonstrated impaired humoral immune response after rituximab treatment, which might be related to the risk of infection [17,18]. However, altered T-cell–mediated immunity following rituximab has also been suggested [16,19], and CD4+ T-cell activation in response to pathogen was substantially impaired by B-cell depletion in an animal study [20]. Of note, the majority of interstitial pneumonitis (20/23, 87%) occurred after the third or fourth cycle of R-CHOP. We do not know exactly why this phenomenon appears to be more common at this period of time; however, delayed recovery of CD4+ T cells after rituximab might be an explanation in part. In a Japanese study, the number of CD4+ T cells in B-cell lymphoma patients showed a different time trend after R-CHOP–based chemoimmunotherapy when compared to the number of CD3+, CD8+, and CD56+ cells [21]. In this study, six cycles of R-CHOP like regimen followed by additional weekly rituximab two times was administered to the patients, and absolute numbers of peripheral blood T- and B-cells were determined. Of the T cell subsets, the number of CD3+, CD8+, and CD56+ cells showed the lowest level after three cycles of treatment, and continued to increase until one year after therapy. Regarding CD4+ T cells, the number of cells showed a constant decrease during treatment and the level was lowest after six courses of R-CHOP–based chemotherapy. Thereafter it increased again; however, the recovery was much slower and lasted for 2 years. And, importantly, the level of CD4+ count at 2 years after treatment was still lower compared to baseline level, whereas CD3+, CD8+, and CD56+ T cells showed slightly higher levels than observed at diagnosis. Regarding the impact of rituximab on impaired CD4+ response, a previous randomized phase III trial of CHOP with or without rituximab in patients with human immunodeficiency virus–associated non-Hodgkin lymphoma reported a significant increase in infection-related mortality in patients with lowered CD4+ T-cell numbers [22].

Although many cases of infection-related mortality in these patients were directly related to uncontrolled bacterial infection, opportunistic infection was also more frequently observed in individuals randomized to rituximab. Thus, opportunistic infections due to *Candida*, PJP, CMV, and *Mycobacterium avium* occurred in six of 99 R-CHOP–treated patients, whereas no opportunistic infections were observed in the 51 patients of the CHOP group.

Taken together, these results suggest that febrile events occurring in a non-neutropenic state, mainly interstitial pneumonitis might be related to rituximab-induced impaired cellular immunity. However, as quantitative assessment of lymphocyte subsets was not performed during treatment, it was impossible to determine the association of the occurrence of opportunistic infection with serial changes of the CD4+ T count. In addition, the probability of rituximab-induced interstitial pneumonitis also existed because several reports suggested the presentation of rituximab-induced lung injury as interstitial pneumonitis [23,24]. However, rituximab-induced interstitial pneumonitis usually occurred after the first or second cycle of R-CHOP. Thus, in our study, the majority of cases of interstitial pneumonitis might not be associated with rituximab-induced reactions.

Univariate risk factor analyses for NNF and FN showed different patterns of association. Parameters reflecting advanced disease, such as elevated serum LDH, advanced stage, and extranodal involvement ≥ 2 were more likely to be associated with FN rather than NNF. This finding might be related to the fact that FN occurred mainly after the first or second cycle of R-CHOP because patients with higher tumor burden might be more susceptible to development of febrile complications owing to their poor performance status in relation to high tumor burden. On the other hand, the occurrence of NNF was mainly associated with old age, rather than tumor burden, which may be due to its relatively late occurrence compared to that of FN. The results of multivariate analysis showed that only age was an independent risk factor for FN as well as NNF. The incidence of both FN and NNF was significantly higher in elderly patients (31.0% in ≤ 60 years vs. 57.0% in > 60 years for FN, $p < 0.001$; 6.7% in ≤ 60 years vs. 15.5% in > 60 years for NNF, $p=0.005$). This finding implies that much more attention is required and more effective infection prophylaxis is warranted in elderly patients. The inferior survival outcome of patients who had ever experienced FN or NNF implied a negative impact of febrile complications on survival outcomes. Although the number of events was not large, relatively higher mortality rate in patients with NNF (10.3%, 4/39) compared with FN-related mortality (1.3%, 2/160) underscored the clinical significance of NNF, particularly interstitial pneumonitis.

Conclusion

In conclusion, considering the negative impact of NNF on survival outcome and the higher vulnerability of elderly patients, effective preventive measures as well as close monitoring are warranted.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

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