Original Article

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Quick Response Code:

Website: www.ijhonline.org

DOI: 10.4103/ijh.ijh_37_21

Febrile neutropenia risk factors in actively treated diffuse large B-cell lymphoma patients

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Abstract:

BACKGROUND: Febrile neutropenia (FN) is a serious problem, especially in hematologic malignancies, and can cause high mortality rates and it occurs in 10%–20% of patients with lymphoma. The aim of this research is to assess the risk factors for FN, and the impact of FN on overall survival (OS) in patients with diffuse large B-cell lymphoma (DLBCL).

MATERIALS AND METHODS: The study included 263 patients who were diagnosed with DLBCL and treated with mostly R-CHOP-based chemotherapy. Data including gender, age, Ann Arbor stage, International Prognostic Index (IPI) score, immunohistologic subtype, treatment regimens, response to treatment, and any FN episode were recorded. The factors predicting FN were analyzed.

RESULTS: Significant predictors of FN were the number of chemotherapy lines received and IPI score. The median OS was significantly different between DLBCL patients who had at least one FN episode during the first-line chemotherapy and those who did not ($P < 0,001$). Significant predictors of OS in the multivariate analysis were the number of chemotherapy lines received, stage, Eastern Cooperative Oncology Group, and disease status.

CONCLUSION: Our study reveals that OS is significantly shorter in patients who had an FN episode than those who did not. Therefore, it is crucial to demonstrate all factors related to FN to prevent FN episodes. In our study, the number of chemotherapy lines received and IPI score was found to be significant predictors of FN. Close follow-up should be done in these patients as the risk of FN is higher.

Keywords:

Diffuse large B-cell lymphoma, febrile neutropenia, neutropenic fever, R-CHOP

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Submission: 10-10-2021
Accepted: 27-11-2021
Published: 09-06-2022

Introduction

The most common histologic subtype of non-Hodgkin lymphoma (NHL) is diffuse large B-cell lymphoma (DLBCL), and it accounts for almost 25% of all NHL cases.[1-3] At presentation, the median age is 64 years and there is a male predominance.[1,4]

The initial standard treatment for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy and 3-year overall survival (OS) is between %50 and %95.[5] Age, serum lactate dehydrogenase (LDH) concentration, Eastern Cooperative Oncology Group (ECOG) performance status, clinical stage, and the existence of extranodal disease sites are found to be related to the prognosis of DLBCL. Infection is also associated with reduced OS.

Infections are unfortunately widespread among patients with DLBCL who are receiving R-CHOP and R-CHOP-like chemotherapy; they are a cause of increased morbidity and mortality. In general, the incidence of febrile neutropenia (FN) was

How to cite this article: Bakirtas M, Yiğenoğlu TN, Başci S, Ulu BU, Yaman S, Çakar MK, *et al*. Febrile neutropenia risk factors in actively treated diffuse large B-cell lymphoma patients. Iraqi J Hematol 2022;11:7-12.

reported to be approximately 17% among cancer patients receiving chemotherapy.[6,7]

FN is a serious problem, especially in hematologic malignancies, and can cause high mortality rates and it occurs in 10%–20% of patients with lymphoma.[7-9] As neutropenia is a strong predictor of FN, granulocyte colony-stimulating factors (G-CSF) are widely used to reduce neutropenia duration. International guidelines recommend primary prophylaxis with G-CSF when FN incidence is >20% for the chemotherapy regimen used in that treatment.

Lymphoma patients of geriatric age, especially with comorbidities, are recommended for primary prophylaxis with G-CSF after chemotherapy.[7] Although previous studies have reported a reduced risk of neutropenia and FN with G-CSF, no significant effect on mortality was observed.[10] DLBCL patients with comorbidities, low-performance status, and a high National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) score are at higher risk of infection.

The previous studies that evaluated the factors related to FN are inconsistent. Therefore, predicting the risk of infection in these patients is a challenge prior to the introduction of rituximab; a study conducted by Lyman and Delgado showed that age, LDH, albumin, neutropenia, and bone marrow involvement may predict hospitalization for FN.[11] Pettengell *et al*. revealed that older age, low albumin, previous chemotherapy, and recent infection were predictive of FN in cycle one.[12]

There is a lack of data on FN risk factors and the influence of FN on survival in DLBCL patients. The aim of this research is to assess risk factors for FN and the impact of FN on OS in patients with DLBCL.

Materials and Methods

Patients

Two hundred sixty-three DLBCL patients who were diagnosed and treated accordingly at our center between 2012 and 2021 were included. Patients at the age of 18 and older diagnosed with DLBCL by examining tissue biopsy with immunohistochemical analysis were included in the study. Hypertension, diabetes mellitus, ischemic heart disease, chronic renal failure, chronic respiratory disorder, and chronic liver disease were assessed as comorbidities.

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (No: 2021-01/964).

Data

Data including gender, age, Ann Arbor stage, international prognostic score (IPI) score, immunohistologic subtype, treatment regimens, and response to treatment of any FN episode were recorded and analyzed. Patients were staged according to the Ann Arbor Staging.[13] The staging was made according to computed tomography scans and/or positron-emission tomography.

Febrile neutropenia

Neutropenia is defined by absolute neutrophil count (ANC) <500 cells/μL or ANC <1000 cells/μL and predict to decrease until <500 cells/μL within 48 h later. FN is defined according to the definition of Infectious Diseases Society of America as a single oral body temperature more than 38.3°C or more than 38.0°C and continues 1 h with neutropenia.[14]

Statistics

IBM SPSS Statistics for Windows (Version 26.0. Armonk, NY, USA) was employed for analyses. Categorical data were presented as percentages and the numerical data were presented as median (minimum–maximum). The disease stages were categorized as early for Ann Arbor I-II and late for Ann Arbor III-IV, IPI score was categorized as IPI ≤ 3 and IPI >3, and the treatment response was categorized as remission and nonremission. Logistic regression analysis was done to evaluate the predictors of FN. Cox regression analysis was performed to analyze factors influencing survival. Variables with $P \leq 0.05$ were included for the multivariate analysis. $P \leq 0.05$ was considered statistically significant.

Results

There were 263 patients with DLBCL who received R-CHOP or R-CHOP-like chemotherapy. The median follow-up was 18 months. There were 137 (52.1%) males and the median age at diagnosis was 61 (17–87) years. Ninety-nine (37.6%) patients experienced at least one FN episode. The characteristics of the patients are given in Table 1. A significant relation was found in univariate analysis between FN and age, number of chemotherapy line, stage, IPI score, ECOG, and disease status. The FN incidence was significantly higher in patients – refractory to first-line chemotherapy – than patients who achieved remission after first-line chemotherapy ($P < 0.001$).

On the other hand, we could not demonstrate any relation between FN and gender, the number of comorbidities, histological subtype (germinal center B-cell like and activated B-cell like), body mass index (BMI), and radiotherapy history. Significant predictors of FN in the multivariate analysis were the number of chemotherapy lines received and IPI score. The predictors of FN in univariate and multivariate analysis are given in Table 2.

Table 1: The characteristics of the patients

Characteristics	*n* (%)
Sex	
Male	137 (52.1)
Female	126 (47.9)
ECOG	
0-1	178 (67.7)
2-4	85 (32.3)
Stage	
Early stage (I-II)	87 (33.1)
Late stage (III-IV)	176 (66.9)
DLBCL IHC subtype	
GCB/ABC/NA	63/163/37
IPI	
<4	218 (82.9)
≥P	45 (17.1)
R-CHOP exposure	
R-CHOP	238 (90.5)
Number of chemotherapy line	
1	220 (83.7)
2	34 (12.9)
≥4	9 (3.4)
RT	68 (25.9)
Comorbidities	
0	152 (57.8)
1	63 (24)
≥3	48 (18.3)
FN episode	
FEN	99 (37.6)
Chemotherapy regimen before FEN	
R-CHOP	63 (63.6)
Non-R-CHOP*	36 (36.4)

*Non-R-CHOP regimens include R-GDP, R-DHAP, R-EPOCH, R-CVP and the others. ABC: Activated B-cell-like subtype, ECOG: Eastern Cooperative Oncology Group, DLBCL: Diffuse large B-cell lymphoma, FN: Febrile neutropenia, GCB: Germinal center B-cell-like subtype, IPI: International Prognostic Index, IHC: Immunohistological subtype, NA: Not available, RT: Radiotherapy, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, FN: Febrile neutropenia, R-GDP: Rituximab, gemcitabine, dexamethasone and cisplatin. R-DHAP: Rituximab, dexamethasone, cytarabine and cisplatin. R-EPOCH: Rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin. R-CVP: Rituximab, cyclophosphamide, vincristine and prednisone

There was a significant difference in FN incidence when patients were grouped as patients who were aged 65 years and older and under 65 years (P = 0.02). The median OS in patients with at least one FN episode during the first-line chemotherapy was 43 months.

On the other hand, median OS was not reached in patients who did not have any FN episode during the first-line chemotherapy. The median OS was significantly different between DLBCL patients who had at least one FN episode during the first-line chemotherapy and those did not (P < 0.001). A significant relation was found in univariate analysis between FN and age, the number of chemotherapy lines, stage, IPI score, ECOG, and disease status. On the other hand, no relation was found between OS and gender and histological subtype (germinal center B-cell like and activated B-cell like). Significant predictors of OS in the multivariate analysis were the number of chemotherapy lines received, stage, ECOG, and disease status. The predictors of OS in univariate and multivariate analysis are given in Table 3.

Discussion

FN is a common cause of comorbidity in patients with hematologic cancers, especially in those receiving intense chemotherapies. According to the guidelines for the appropriate use of G-CSF, the incidence of FN in patients receiving myelosuppressive chemotherapy is 13%–21%.[15] FN occurs in 10%–20% of patients treated for lymphoma.[7-9] DLBCL is an aggressive lymphoma and FN commonly occurs after chemotherapy. It is crucial to determine all the factors related to FN to reduce the risk of FN. Therefore, in this study, we aimed to find out the incidence of FN during the first-line chemotherapy in patients with DLBCL and factors related to the risk of FN and its association with OS. In the study

Table 2: The predictors of febrile neutropenia in patients with diffuse large B-cell lymphoma

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.025 (1.008-1.042)	0.003	1.004 (0.984-1.024)	0.73
Gender (female based)	0.854 (0.518-1.408)	0.536		
Chemotherapy line (based one line)	0.111 (0.050-0.245)	<0.001	0.192 (0.73-0.501)	0.001
Stage (based early stage)	0.400 (0.225-0.710)	0.002	0.896 (0.456-1.762)	0.75
IPI score (based ≤3)	0.158 (0.077-0.325)	<0.001	0.304 (0.128-0.723)	0.007
Number of comorbidities	1.308 (0.952-1.798)	0.098		
RT (based not received)	1.002 (0.569-1.767)	0.994		
ECOG score (based 0-1)	0.246 (0.143-0.425)	<0.001	0.620 (0.3-1.28)	0.2
IHC subtype (based GCB)	0.913 (0.500-1.666)	0.77		
Treatment (based R-CHOP)	1.915 (0.837-4.382)	0.124		
Disease status (based remission)	0.203 (0.111-0.369)	<0.001	0.698 (0.312-1.561)	0.382
BMI	0.974 (0.924-1.026)	0.325		
Constant			9.827	0.11

Estimated by logistic regression, variables with P<0.05 after univariate analysis included for multivariate analysis, Nagelkerke R^2=0.283 for multivariate analysis. ECOG: Eastern Cooperative Oncology Group, IHC: Immunohistological subtype, IPI: International Prognostic Index, BMI: Body mass index, GBC: Germinal center B-cell like, OR: Odds ratio, CI: Confidence interval, GCB: Germinal center B-cell-like subtype, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, RT: Radiotherapy

Table 3: The predictors of survival in patients with diffuse large B-cell lymphoma

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.037 (1.017-1.057)	<0.001	0.994 (0.971-1.018)	0.639
Gender (female based)	0.757 (0.449-1.278)	0.297		
Chemotherapy line (based one line)	0.188 (0.111-0.317)	<0.001	2.481 (1.17-5.258)	0.018
Stage (based early stage)	0.226 (0.103-0.499)	<0.001	0.393 (0.159-0.969)	0.043
IPI score (based ≤3)	0.174 (0.102-0.297)	<0.001	0.649 (0.335-1.258)	0.201
Number of comorbidities	1.604 (1.171-2.197)	0.003	0.924 (0.601-1.421)	0.720
RT (based not received)	2.630 (1.289-5.367)	0.008	1.744 (0.777-3.914)	0.178
ECOG score (based 0-1)	0.162 (0.93-0.281)	<0.001	0.412 (0.192-0.883)	0.023
IHC (based GCB)	0.763 (0.401-1.451)	0.4		
Treatment (based R-CHOP)	5.102 (2.730-9.537)	<0.001	1.741 (0.765-3.963)	0.187
Disease status (based remission)	0.009 (0.003-0.030)	<0.001	0.007 (0.002-0.028)	<0.001
FN	0.225 (0.130-0.392)	<0.001	0.909 (0.474-1.742)	0.774

Estimated by cox regression, variables with *P*<0.05 after univariate analysis included for multivariate analysis. ECOG: Eastern Cooperative Oncology Group, IHC: Immunohistochemical, IPI: International Prognostic Index, BMI: Body mass index, GBC: Germinal center B-cell like, FN: Febrile neutropenia, OR: Odds ratio, CI: Confidence interval, GCB: Germinal center B-cell-like subtype, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, RT: Radiotherapy

conducted by Dendle *et al*., among 325 patients with DLBCL, 206 (63.4%) patients experienced more than one infection.[16] Previous randomized controlled trials reported rates of infectious episodes ranging from 10% to 42%.[6,17,18] In our study, 37.6% of patients experienced at least one FN episode. In our center, we routinely administer primary prophylaxis with G-CSF in patients at the age of 65 years and older, and this may limit the number of FN episodes.

In several studies on NHL patients, being older than 60 or 65 years was related to FN.[19,20] However, in other studies, age was not related to FN in NHL patients treated with CHOP.[21,22] In one study, patients older than 70 years were classified into three age groups (70–74 years, 75–79 years, and >80 years of age) and researchers could not find a relation between age and FN. Instead, some studies have suggested that physiological age, as demonstrated by performance status, could be a better predictor of risk than chronological age itself.[23] In our study, there was a significant difference in FN incidence when patients were grouped as patients who were aged 65 years and older and under 65 years ($P = 0.02$).

In the studies with NHL, the female gender was shown to be related to FN. Drugs are more slowly cleared in females. Therefore, myelosuppression in female patients treated with an R-CHOP regimen may be higher.[11,22,24] However, in our study, we did not find any relation between FN and gender.

Although different cut points were analyzed, several studies have shown that low BMI or low body surface area is a risk factor for FN.[11,22,25] However, in our study, we did not find any relation between FN and BMI ($P = 0.325$).

In previous studies, low-performance status and comorbidities were found to be related to FN. Salar *et al*. reported that old age and lower performance status were independent risk factors for FN in NHL patients treated with R-CHOP regimen.[20] Dendle *et al*. reported that Charlson comorbidity score 3 or greater (reference category score of 2 or less), ECOG status of 1, 2, 3, or 4 (with zero the reference category) are related to an infectious episode.[16] Lyman and Delgado reported that renal and cardiovascular diseases were associated with a higher FN risk.[11] In our study, there was no relation between the number of comorbidities and FN. In univariate analysis, there was a significant difference regarding the rate of FN when patients with ECOG score 0–1 compared to patients with ECOG score 2, 3, and 4 ($P < 0.001$); however, no relation was found between FN and ECOG status in multivariate analysis (P: 0.2).

Advanced disease status was shown as a significant predictor of FN in studies with various cancers including NHL, breast, ovarian, lung, colorectal, and prostate cancer.[25,26] Dendle *et al*. reported that low/intermediate or greater NCCN-IPI is associated with an infectious episode compared to low NCCN-IPI.[16] Lyman and Delgado found that disease stage III–IV is related to FN.[11] In our study, in multivariate analysis, no relation was found between FN and stage. However, a significant relation was found between FN and IPI score ($P = 0.007$).

In the study conducted by Dendle *et al*., infection was an independent predictor of survival.[16] On the other hand, OS between patients never experienced FN and patients experienced at least more than one FN episode was not different statistically in the study conducted by Choi *et al*.[24] The median OS in patients who had at least one FN episode during the first-line chemotherapy was 43 months. On the other hand, median OS was not

reached in patients who did not have any FN episode during the first-line chemotherapy. The median OS was significantly different between DLBCL patients who had at least one FN episode during the first-line chemotherapy and those who did not ($P < 0.001$).

This study is limited due to its retrospective design and lack of data about the results of the cultures obtained during the fever. On the other hand, to the best of our knowledge, this is the first study that compared the rate of FN in patients with germinal center B-cell-like DLBCL to patients with activated B-cell-like DLBCL. No relation was found between FN and histological subtype (germinal center B-cell like and activated B-cell like) ($P = 0.77$).

Conclusion

Our study reveals that OS is significantly shorter in patients who had an FN than those who did not. Therefore, it is crucial to find out all factors related to FN to prevent FN episodes. In our study, the number of chemotherapy lines received and IPI score were significant predictors of FN. Close follow-up should be done and precautions such as antimicrobial prophylaxis and G-CSF prophylaxis may be considered in these patients as the risk of FN is higher.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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