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Original Article

Infections in patients with lymphoma: An analysis of incidence, relationship and risk factors

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Abstract

Introduction: Bacterial infections and febrile neutropenia (FN) are major causes of morbidity and mortality in patients with hematological malignancy. The aim of this study was to investigate the incidence and risk factors of infections in lymphoma patients.

Methodology: This retrospective study was conducted on 200 lymphoma patients diagnosed and treated between January 2009 and December 2017 in Diskapi Yildirim Beyazit Training and Research Hospital, a tertiary referral hospital in Ankara, Turkey.

Results: The mean follow-up period was 20.09 ± 19.81 months. The incidence of infection episode (IE) was 32.5% (65/200) and FN was 18.5% (37/200). Analysis of the data revealed that patients with IE had significantly higher rates of diagnosis of primary central nervous system lymphoma (PCNSL), lower baseline hemoglobin, lower baseline hematocrit, higher baseline lactate dehydrogenase levels, higher usage of central cathater, and a higher number of chemotherapy lines compared to patients with no IE. In logistic regression analysis, disease subtype of PCNSL, usage of central catheter and lactate deyhydrogenase (LDH) were found to increase the risk of infection. The odds ratio for PCNSL was 37.866 (p = 0.003), 2.679 for central catheter (p = 0.008) and 1.001 for LDH (p = 0.011).

Conclusions: The risk of infection in patients with lymphoma was associated with central catheter usage, higher LDH levels and a diagnosis of PCNSL. Baseline hematological parameters were not determined to have any impact on the occurrence of infection. Patients with these risk factors should be monitored more carefully and the maximum level of infection prevention should be taken.

Key words: lymphoma; infection; risk factors.

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Introduction

There is an increased risk of infection in patients with cancer that results in higher morbidity and mortality. Neutropenia has been reported as a major risk factor for the development of infections and febrile neutropenia (FN). It remains the most important dose limiting toxicity of anti-cancer treatment, and affects quality of life and clinical outcomes, with the potential to cause death in patients with cancer [1-4].

Therefore, the identification of risk factors associated with infection and FN is important for the development of effective strategies to prevent and manage infectious complications [1]. The identification of patients at high risk may help clinicians to consider detailed and careful management. Previous trials investigating risk factors for severe infections and febrile neutropenia in patients with Non-Hodgkin lymphoma (NHL) have usually had small sample sizes and unvalidated models for risk stratification.

The current study was undertaken to investigate the incidence of total infection episodes (IE) and FN and to identify the potential risk factors associated with infection episodes in a large population of patients with lymphoma who were receiving chemotherapy regimens. It was aimed for the results of the study to help clinicians in the development of effective strategies to improve outcomes.

Methodology

A retrospective analysis was made of patients admitted to the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital, a tertiary referral hospital in Ankara, Turkey, between January 2009 and December 2017. Patients who were diagnosed with any type of lymphoma and given chemotherapy were included in the study. During this study period, a total of 200 lymphoma patients were identified. Diffuse large B cell lymphoma (DLBCL), T

cell lymphoma, Mantle cell lymphoma, Burkitt lymphoma and Primary Central Nervous System Lymphoma (PCNSL) patients were inluded in the High Grade NHL (HG-NHL) group, and marginal zone lymphoma, follicular lymphoma, Lymphoplasmacytic lymphoma and Hairy cell leukemia patients were included in the Low Grade NHL (LG-NHL) group. The patient characteristics are summarized in Table 1. Investigation was made of the incidence of total IE, including FN, non-neutropenic clinically documented infection (CDI) and microbiologically documented infection (MDI) in the overall follow-up period. Neutropenia was defined as absolute neutrophil count (ANC) < 0.5 × 10^9/L. CDI was defined as body temperature > 38°C and the presence of symptoms or signs of inflammation at an anatomic site, irrespective of whether or not pathogens were recovered from the affected site. MDI was defined as the presence of symptoms or signs of inflammation at an anatomic site where pathogens were recovered from the affected site. FN was defined as fever with a single oral temperature of 38.3º C or a temperature of > 38.0º C sustained for more than 1 hour in a patient with neutropenia. The patients were divided into 2 groups: Group 1: Patients with at least one IE during the total follow-up period and Group 2: Patients with no IE during the total follow-up period.

To determine the risk factors for infection, these two groups were compared in respect of hematological and biochemical parameters at the time of diagnosis including Hemoglobin (Hb) levels, Hematocrit (Hct) levels, Platelet (Plt) count, Lymphocyte count, monocyte count, Neutrophil count, plateletcrit (Pct), platelet distribution width (Pdw), lactate dehydrogenase (LDH) levels, Platelet/lymphocyte ratio (PLR), Neutrophil/lymphocyte ratio (NLR), Lymphocyte/monocyte ratio (LMR), vitamin B12 levels, ferritin levels and beta-2 microglobulin levels (B2M).

Statistical Analysis

SPSS Statistics 20 software (IBM, Armonk, NY, USA) was used for statistical analysis. In the comparison of variables distributed homogeneously, the Independent Samples-t test was used for parametric variables and data were expressed as mean ± standard deviation. The Chi-Square test was used for non-parametric variables. For variables not showing

Table 1. Baseline characteristics of the patients and disease subtypes.

	All (N = 200)	HG-NHL (n = 129)	LG-NHL (n = 36)	HL (n = 35)
Age (years)	56.52 ± 18.33	60.93 ± 15.45	60.36 ± 15.78	36.31 ± 17.38
Gender				
Male	101	64	22	15
Female	99	65	14	20
Stage				
1	-	14	2	2
2	-	25	5	14
3	-	44	7	11
4	-	56	10	8
IPI				
0-1	-	34	23	-
2-3	-	70	10	-
4 and above	-	25	3	-
Number of chemotherapy lines	1.0 [1.0-5.0]	1.0 [1.0-5.0]	1.0 [1.0-4.0]	1.0 [1.0-2.0]
First line chemotherapy				
RCHOP-CHOP	117	97	20	-
RCVP-CVP	18	10	8	-
ABVD	35	-	-	35
Others	34	26	8	-
Number of cycles (first line)	6.0 [1.0-8.0]	6.0 [1.0-8.0]	6.0 [1.0-8.0]	6.0 [2.0-8.0]
Follow-up (months)	20.09 ± 19.81	18.38 ± 19.66	22.10 ± 20.29	24.34 ± 19.68
Final status				
Exitus	61	50	7	4
Survivor	139	79	29	31

HG-NHL: High grade- non-Hodgkin lymphoma, LG-NHL: Low grade- non Hodgkin lymphoma; HL: Hodgkin lymphoma, IPI: International prognostic index, RCHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCVP: Rituximab, cyclophosphamide, vincristine, prednisone, ABVD: Adriamycine, bleomycin, vincristine, dacarbazine; mean: average ± standard deviation, median: [Min-Max].

homogeneous distribution, the Mann Whitney U test was applied. Data were expressed as median [Min-Max] values. When the relationships of two qualitative variables were examined, "χ^2-cross tables" were used according to the expected value levels. Relative risk (RR = Relative risk) was calculated according to this table. Multiple logistic regression analyses were used to determine the risk factors for IE. A value of $p < 0.05$ was accepted as statistically significant.

Ethical approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As a standard of care/action of the Ankara Diskapi Yildirim Beyazit Research and Training Hospital, it was confirmed based on patient records that all of the study patients gave informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

Results

The total of 200 lymphoma patients comprised 101 males (50.5%) and 99 females (49.5%) with a mean age of 56.52 ± 18.33 years. A total of 61 (30.5%) patients died during the follow-up period. HG-NHL was diagnosed in 129 (64.5%) patients, Hodgkin's Lymphoma (HL) in 35 (17.5%) patients and LG-NHL in 36 (18%) patients. The mean follow-up period was 20.09 ± 19.81 months. The most common chemotherapy regimen given was RCHOP or CHOP (Rituximab ± Cyclophosphamide, Adriamycin, Prednisolone) which was administered to half the patients. The baseline characteristics of the patients and disease subtypes are presented in Table 1.

During the total follow-up period, the incidence of total IE was 32.5%. There were 65 lymphoma patients with 93 IE. The incidence of FN was 18.5%. There were 51 FN episodes in 37 lymphoma patients. There were 42 non-neutropenic CDI episodes in 34 patients. The IE characteristics are shown in Table 2. Of all the infection episodes, 78 (83.8%) IE in 65 (100%) patients, and 43 (84.3%) FN episodes in 36 (97.2%) patients occurred in the first 6 months. MDI were 13 (20%) in total with Gram-negative infections accounting for 12 (92.3%) and *Escherichia coli (E. coli)* was the most common isolate, which was isolated in 6 cases. Half of the *E. coli* cases were multi-drug-resistant (MDR) strains.

Patients with at least one IE (n: 65) were compared with patients with no IE (n: 135) to analyse the risk factors for infection. A significant difference was seen between the disease subtypes in favor of PCNSL ($p = 0.004$), which was diagnosed in 7 patients (10.8%) in the infection group and in 1 patient (0.7%) in the non-infectious group. The number of chemotherapy lines was higher in the infectious group than in the non-infectious group (2.0 [1.0-5.0] vs 1.0 [1.0-4.0], $p = 0.001$). A significant difference was determined between the two groups in respect to the usage of central catheter ($p = 0.00$). Mortality rates showed a significant difference as 29 patients (21.5%) in the non-infectious group and 32 patients (49.2%) in the infectious group were non-survivors at the end of the follow-up period ($p = 0.00$). The comparisons of patients with and without infection are shown in Table 3.

According to the Cox-regression analysis of overall survival, among all the parameters including gender, age, disease subgroups, number of comorbidity, first line chemotherapy regimen, number of chemotherapy lines and presence of any IE, only the IE was found to have a significant effect on overall survival (OS) ($\chi^2 = 16.207$; $p = 0.003$). The odds ratio for having at least one IE was found to be 2.457. Initial complete blood count parameters, vitamin B12 and ferritin levels were not found to have any effect on OS ($p > 0.05$).

The relationships of baseline hematological and biochemical parameters with IE were analyzed. There was a significant difference only in the Hb, Hct and LDH levels. The Hb and Hct levels were significantly lower in the infectious group than in the non-infectious group ($p = 0.020$, $p = 0.034$).

Table 2. Characteristics of infection episodes.

		All (N:200)	NHL (n:165)	HL (n:35)
IE	n of patients	65	54	11
	n of episode	93	81	12
FN	n of patients	37	34	3
	n of episodes	51	48	3
Non-neutropenic CDI	n of patients	34	26	8
	n of episodes	42	31	11

IE: Infection episode, FN: Febrile neutropenia, NHL: Non-Hodgkin lymphoma, HL: Hodgkin lymphoma, CDI: Clinically documented infection.

Table 3. Comparison of patients with infection and patients without infection.

	Infection episode (no. of patients) (N = 200)		
	Yes (n = 65)	**No (n = 135)**	**p**
Age (years)	60.0 [18.0-85.0]	57.0 [18.0-86.0]	0.995
Diagnosis subtypes			
DLBCL	32 (49.2%)	58 (43.0%)	
MCL	6 (9.2%)	13 (9.6%)	
HL	11(16.9%)	24 (17.8%)	
TCL	4 (6.2%)	8 (5.9%)	
PCNSL	7 (10.8%)*	1 (0.7%)	**0.004**
LG-NHL	5 (7.7%)	31 (23.0%)	
Gender			
Male	31 (47.7%)	70 (51.9%)	0.582
Female	34 (52.3%)	65 (48.1%)	
Number of comorbidities	0.0 [0.0-4.0]	0.0 [0.0-3.0]	0.843
Number of chemotherapy lines	2.0 [1.0-5.0]	1.0 [1.0-4.0]	**0.001**
First line chemotherapy			
RCHOP-CHOP	29 (44.6%)	71 (52.6%)	0.228
MRCHOP	6 (9.2%)	13 (9.6%)	
ABVD	11 (16.9%)	24 (17.7%)	
RCVP-CVP	4 (6.2%)	14 (10.4%)	
Others	15 (23.1%)	13 (9.6%)	
Number of cycles (first line)	6.0 [1.0-8.0]	6.0 [1.0-8.0]	0.411
Central catheter			
Yes	34 (52.3%)	31 (23.0%)	**0.000**
No	31 (47.7%)	104 (77.0%)	
Follow-up (months)	10.2 [0.3-77.4]	14.4 [0.5-92.4]	0.180
Final status			
Exitus	32 (49.2%)	29 (21.5%)	**0.000**
Survivors	33 (50.8%)	106 (78.5%)	

DLBCL: Diffuse large B cell lymphoma, MCL: Mantle cell lymphoma, TCL: T cell lymphoma, PCNSL: Primary central nervous system lymphoma, LG-NHL: Low grade- non-Hodgkin lymphoma, HL: Hodgkin lymphoma, IPI: International prognostic index; RCHOP: Rituximab, cyclophosphamide, doxorubicin, vincristin, prednisone, RCVP: Rituximab, cyclophosphamide, vincristine, prednisone; ABVD: Adriamycin, bleomycin, vincristine, dacarbazine; mean: average ± standard deviation, median: [Min-Max].

Table 4. Relationship of baseline hematological and biochemical parameters with infection episodes.

	Infection episode (no. of patients) (N = 200)'		
	Yes (n = 65)	**No (n = 135)**	**p**
Hemoglobin (gr/dl)	11.57 ± 2.48	12.44 ± 2.46	**0.020**
Hematocrit (%)	34.93 ± 7.09	37.34 ± 7.63	**0.034**
Platelet ($\times 10^6$/L)	248000.0 [23000.0-551000.0]	253000.0 [330000.0-1058000.0]	0.885
White blood cell ($\times 10^6$/L)	8600.0 [1900.0-186900.0]	8100.0 [1740.0-44600.0]	0.256
Lymphocyte ($\times 10^6$/L)	1700.0 [500.0-157400.0]	1600.0 [400.0-35900.0]	0.941
Monocyte ($\times 10^6$/L)	600.0 [100.0-14100.0]	600.0 [10.0-11900.0]	0.497
Neutrophil ($\times 10^6$/L)	5300.0 [900.0-19400.0]	5000.0 [300.0-33300.0]	0.710
MPV (fL)	8.1 [6.1-9.9]	8.1 [5.5-12.2]	0.552
PCT	0.20 [0.02-0.41]	0.20 [0.02-0.74]	0.779
PDW	16.9 [15.4-65.7]	16.9 [10.6-71.6]	0.791
LDH (/l)	265.0 [113.0-1933.0]	215.0 [118.0-2314.0]	**0.001**
PLR	167.1 [1.1-756.7]	152.8 [4.4-1142.6]	0.622
NLR	3.3 [0.1-17.6]	2.8 [0.1-27.8]	0.589
LMR	2.5 [0.5-25.3]	2.7 [0.4-50.0]	0.336
Vitamin B12 (pmol/L)	233.0 [12.0-970.0]	264.5 [31.0-2000.0]	0.222
Ferritin (ng/mL)	146.5 [9.0-1616.0]	83.0 [2.0-1500.0]	0.064
B2M	2.9 [1.1-208.0]	2.9 [1.3-209.0]	0.674

MPV: mean platelet volume, PCT: plateletcrit, PDW: platelet distribution width, LDH: Lactate dehydrogenase, PLR: Platelet/lymphocyte ratio, B2M: Beta-2 microglobulin, NLR: Neutrophil/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio; mean: average ± standard deviation, median: [Min-Max].

LDH levels were higher in patients with infection than in those without infection (p = 0.001). The relationships of baseline hematological and biochemical parameters with IE are shown in Table 4. In the logistic regression analysis, disease subtype of PCNSL, usage of central catheter line and LDH were found to increase the risk of infection. The odds ratio for PCNSL was 37.866 (p = 0.003), for central catheter 2.679 (p = 0.008) and for LDH 1.001 (p = 0.011).

Discussion

Patients with lymphoma are vulnerable to infections resulting mainly from neutropenia induced by chemotherapy and the disease itself. In the current study, all infection episodes were analysed, mainly based on the occurrence of fever (body temperature > 38°C) in neutropenic patients. Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because signs and symptoms of inflammation typically are attenuated [4]. In non-neutropenic patients, in addition to fever, the analysis of infection episodes was based on the clinical documentation of the infection site. On these bases, the incidence of total IE was 32.5% and FN was 18.5%. Almost all IE occurred in the first 6 months as expected, as first-line chemotherapy lasts about 6 months. This finding was similar to recent reports in literature [5,6]. It is important because IE and FN during the first cycles may cause premature termination of chemotherapy [6].

In the current study, total MDI in IE were 13 (20%) and FN were 4 (10.8%). This rate was slightly lower than in previous studies that have reported microbiological confirmation of BSI in only 15% to 43 % of cases of FN [7-10]. Bacteriological data revealed that Gram-negative infections accounted for 92.3% and E. coli was the most common isolate. This finding was consistent with many other trials which have reported that *E. coli* is still the most frequently isolated Gram-negative organism in hematological malignancies [7-11]. The antibiotic treatment prior to taking blood cultures may be considered a reason for the lower rates of isolation of bacteria, since half of the *E. coli* cases among MDI were MDR strains. Although it is routine protocol in our institution that culture samples are taken from every patient before starting antibiotherapy in the hospitalization period, in the out-patient setting, some patients might have been given antibiotherapy without a culture having been taken. In cases of febrile neutropenia, antibiotics are always started after taking cultures. Therefore, this may effect only episodes rather than febrile neutropenia cases.

In many studies, infections, especially febrile neutropenia, have been found to be associated with mortality in lymphoma patients [2,3,6]. According to the current study results, mortality rates were significantly higher in the infectious group. Infections, especially FN may have reduced the overall survival of the patients but this cannot be speculated on the basis of the current data, as all causes of mortality were not analysed. However, according to the current data, in the Cox regression analysis of overall survival, only the presence of at least one IE was found to affect survival independently rather than all the other parameters related with patients and disease characteristics (OR: 2.457, p = 0.003). Otherwise, there was no effect of hematological and biochemical parameters on survival.

In the comparison of patients with at least one infection episode and those without any, no significant difference was determined in respect of age, gender, comorbidity, first-line chemotherapy, number of cycles of first-line chemotherapy and follow-up period. As expected, there was a significant difference between the disease subtypes in favor of PCNSL and the number of chemotherapy lines received. Similar to the current study, a recent analysis confirmed a significant negative association between febrile neutropenia and the number of treatment cycles received [6]. No association was found with the number of cycles of first-line chemotherapy but an association with chemotherapy lines was seen. It is obvious that as the received chemotherapy lines increase, the number of chemotherapy cycles increases. Therefore this supports the current finding from a different aspect. In a study of NHL patients related to hospitalization for FN but not the incidence of infections, it was demonstrated that the risk of initial hospitalization for FN occurred early in the course of CHOP-like chemotherapy and was significantly associated with age of 65 years or older [12]. In the current study, there was no relationship between having any infection episode and chemotherapy regimen and age. Another important risk factor was found to be central catheter usage, which has been shown to be a risk factor for infection in many recent studies [13,14].

In addition, the relationship of hematological and biochemical parameters with infection episodes was analysed in the current study. With the exception of Hb, Hct and LDH levels, no significant relationship was determined. The patients with infection had lower Hb and Hct levels than patients without infection. Other recent studies have reported similar results of low hemoglobin levels associated with IE, FN and poorer outcomes [5,10,15,16]. This may be due to poor

performance status as a result of anemia or aggressive disease infiltrating bone marrow leading to higher infection rates. It has been previously shown that anemia can adversely affect the quality of life of patients and may even alter their response to cancer treatment. Moreover, anemia is often associated with the presence of several adverse prognostic parameters and is itself a predictor of poor prognosis [17]. Similar to the current study results, Jeddi R et al. analysed the risk factors of septic shock in patients with hematological malignancies, including leukemia and lymphoma, and low Hb levels were found to be associated with septic shock [18]. In the logistic regression analysis of the current study, only LDH levels were found to be associated with IE. LDH is also a parameter of the IPI score that predicts prognosis in NHLs. High levels of LDH increase the IPI score that predicts aggressive disease and poor response to treatment that may cause high rates of infection. In another similar study investigating features associated with an increased risk of treatment-related death, serum LDH level was determined to be related to death in univariate analysis but not in the logistic regression model [19]. In respect of the HL cases, only 11 patients were determined with 12 IE and 3 patients with 3 FN episodes. This was a significantly lower rate than that of the NHL cases as was expected from current knowledge. It has been previously reported that neutropenia is a common complication of ABVD chemotherapy, but related complications including febrile neutropenia (FN), neutropenic sepsis, and death are much less frequent [20].

Conclusion

The risk of infection in patients with lymphoma was determined to be associated with central catheter usage, higher LDH levels and a diagnosis of PCNSL. Hematological parameters have no impact on the total incidence of IE. Patients with these risk factors should be monitored more carefully and the maximum level of infection prevention should be taken. There is a need for larger population-based studies to determine risk factors other than those already known.

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