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ARAŞTIRMA / RESEARCH

Clinical and pathological characteristics of patients with non-Hodgkin lymphoma cases in Eastern Turkey

Türkiye'nin doğusunda non-Hodgkin lenfoma hastalarının klinik ve patolojik özellikleri

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Abstract

Purpose: This study aims to evaluate the epidemiological, demographic and clinical characteristics, and prognostic factors of the patients with non-Hodgkin lymphomas (NHL).

Materials and Methods: All patients diagnosed with NHL at the Department of Hematology of Inonu University Faculty of Medicine (Turkey) between 2000 and 2016 were evaluated for this study. Only patients older than 18 years were included in the study. Characteristics were evaluated by reviewing patients' records retrospectively.

Results: Of the 386 patients studied, 242 (62.7%) were male and 144 (37.3%) were female and the overall median age was 53 years (range: 18–92). The most common histological subtype of NHL was diffuse large B-cell lymphoma (DLBCL) (46.9%). In univariate analyses, advanced stage (III-IV), high-intermediate to high risk category disease based on IPI score, bone marrow involvement at diagnosis, haemoglobin levels below 10 g/dL, increased LDH levels, primary nodal involvement, the presence of B symptoms, the exigency of autologous bone marrow transplant, and not receiving rituximab-based chemotherapy regimens as the primary treatment were all associated with shorter overall survival.

Conclusion: The prevalence, clinical characteristics, histopathological subtypes, treatment responses, and overall survival rates may differ because NHL is a heterogeneous disease group and may vary according to a geographical area. Therefore, treatment should be individualized according to disease subtype.

Keywords:. Lymphoma, non-hodgkin lymphoma, diffuse large b-cell lymphoma

Öz

Amaç: Bu çalışmada non-Hodgkin lenfoma (NHL) hastalarının epidemiyolojik, demografik, klinik ve prognostik özelliklerini araştırmayı amaçladık.

Gereç ve Yöntem: İnönü Üniversitesi Tıp Fakültesi Hematoloji kliniğinde 2000 ile 2016 yılları arasında NHL tanısı ile takipli hastalar çalışmaya alındı. Çalışmaya 18 yaşından büyük hastalar dâhil edildi. Hasta özellikleri, kayıtlar retrospektif olarak gözden geçirilerek değerlendirildi.

Bulgular: Çalışmaya alınan 386 hastanın 242'si (%62.7) erkek, 144'ü (%37.3) kadın, ve tüm hastalarda ortanca yaş 53 idi. En sık NHL alt tipi Diffüz Büyük B Hücreli Lenfoma (DBBHL) (46.9) idi. Tek değişkenli analizde, hastaların ileri evrede (Evre III-IV) olması, IPI skoruna göre yüksek-orta ve yüksek riskli kategoride olması, kemik iliği tutulumu olması, hemoglobin düzeyinin 10 gr/dl'nin altında olması, LDH düzeyinin normalin üzerinde olması, primer tutulumunun nodal olması, B semptomların varlığı, otolog kemik iliği yapılması zorunluluğu ve birincil tedavi olarak rituximab bazlı kemoterapi rejimlerini almaması daha kısa genel sağkalım ile ilişkili bulundu.

Sonuç: NHL hastalığının insidansı, klinik özellikleri, histopatolojik alt tipleri, tedavi yanıtları ve genel sağkalım oranları coğrafi bölgelere göre farklılıklar gösterebilmektedir. Bu nedenle tedavi hastalık alt tip dağılımına göre bireyselleştirilmelidir.

Anahtar kelimeler: Lenfoma, non-Hodgkin lenfoma, diffüz büyük b hücreli lenfoma

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INTRODUCTION

Lymphomas are malignancies originating from various cells that comprise the immune system. Depending on the stage of differentiation from the cells where they originate, they develop different morphological, immunological, and clinical characteristics[1]. Recently the biology of the lymphomas has been better understood thanks to the contributions of immunohistochemistry and molecular genetics which have combined to identifying a number of new sub-types of lymphoma[2].

Lymphomas are divided into two main groups: non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). Non-Hodgkin's lymphoma accounts for 70-75% of all lymphomas. The prevalence and histological subtype of NHL varies according to geographical region[3]. The heterogeneous properties of NHL are also reflected in the classification systems. Various classification systems have been used to determine the prognosis of lymphomas and treatment protocols. Today, the most widely used classification system is that developed by the World Health Organization (WHO)[4]. Although NHL usually develops in the lymph nodes, it may sometimes originate in an extranodal tissue or organ[5]. The stomach, intestines, bones, skin, lungs, salivary glands, breasts, central nervous system, oral cavity, and eyelid are the most common extranodal sites[6,7].

Among the various staging systems currently in use, the Ann Arbor staging system is the most common[8]. Treatment for NHL is determined on the basis of the patient's performance status, histologic type, and clinical stage of the disease. Treatment options vary from observation only to chemotherapy, chemotherapy plus radiotherapy, and/or high-dose chemotherapy with stem cell support autologous hematopoietic stem cell transplant[9]. The histologic type and stage of the disease significantly affect the prognosis and treatment response. The identification of high-risk classes is critical for the application of more intensive and aggressive treatment regimens. The International Prognostic Index (IPI) and its derivatives have been developed to demonstrate the relationship between clinical parameters and prognosis. The International Prognostic Index (IPI) is more useful for determining treatment than the Ann Arbor staging system[10,11].

According to the WHO National Cancer Research Center, although NHL is on the increase worldwide, it is more common in developed Western countries than in Asia and Africa. The clinical features and histopathological subtypes of NHL patients exhibit notable differences by geographical region. Similarly, prevalence of NHL varies according to age, geographical region, exposure to infectious agents, and ethnic/racial factors[12]. This study aims to define the epidemiological, demographic and clinical characteristics, and prognostic factors of the patients with NHL who live in eastern Turkey.

MATERIALS AND METHODS

This retrospective study was carried out by the Inonu University (IU), Faculty of Medicine, Department of Haematology, Malatya, Turkey. Patients diagnosed with NHL from January 2000 to December 2016 were included in this study. A total of 418 patient files were examined. Patients older than 18 years and diagnosed as NHL histopathologically were all included in the study. 32 patients with insufficient registration and follow-up information or under 18 age were excluded from the study. Approval for the study protocol was obtained from the Inonu University Faculty of Medicine Scientific Research Ethics Committee (ethics decision no. 2016/15-2). It was a retrospective study involing the review of patients medical records. All aspects of the study were performed according to the principles of the declaration of Helsinki (64th, 2013).

Parameters

Age, gender, complaint(s) at diagnosis, type of diagnosis, diagnostic history, histopathological subtype, presence of B symptoms, nodal and extranodal status, disease stage, IPI score, imaging results, biochemical tests, treatment protocols, treatment responses, and overall survival outcomes for each patient were assessed. Patients were categorised based on age as either under or over 60 years old. The diagnoses were recorded according to the WHO (2016) classification[4].

Involvements of sites were classified as nodal (cervical, axillary, inguinal, intraabdominal, mediastinal) and extranodal (stomach, skin, etc.). Patient performance status was categorized as either 0, 1 (< 2) or 2, 3, 4 (≥ 2) based on the Eastern Cooperative Oncology Group (ECOG) scale[13]. The disease was divided into 4 stages (I, II, III, and IV)

according to the Ann Arbor staging system[14]. Stages I-II was classified as early stage and III-IV as advanced stage. A temperature greater than 38 °C, night sweats, and weight loss exceeding 10% of body weight over the last 6 months were considered B symptoms. Lesions that were greater than 7 cm in any diameter were considered as bulky disease.

Prognostic findings were evaluated using the IPI scoring system. The IPI score was categorized as low (0-1), low-intermediate (2), high-intermediate (3), or high[4,5]. Treatment response was defined according to the International Working Formulation (IWF) standards. The final status of patients was identified as complete response (CR), unverified complete response (uCR), partial response (PR), unresponsive (stable disease), progression, relapse, exitus, or lost to follow-up.

Statistical analysis

The data obtained were analysed sing the Statistical Package for Social Sciences (SPSS) software (version 22.0). Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were presented as number (n) and percentage (%). Variables affecting survival were assessed using Kaplan-Meier analysis and the log-rank test. A value of $p \leq 0.05$ was considered statistically significant.

Table 1. Demographic features of patients and NHL subtype distribution according to WHO (2016) classification

Variable	n	%
Gender		
Female	144	37.3
Male	242	62.7
Median Age 53 years(range: 18–92)		
NHL Subtype		
DLBCL	181	46.9
Follicular lymphoma	36	9.4
Mantle cell lymphoma	34	8.9
MALT lymphoma	22	5.7
T-cell/histiocyte rich DLBCL	15	3.9
Primary CNS DLBCL	14	3.6
High-grade B-cell lymphoma	12	3.1
B-cell lymphoma unclassified (BCLU)	10	2.6
Large B-cell lymphoma	7	1.8
Small lymphocytic lymphoma	7	1.8
T-cell prolymphocytic leukemia	6	1.5
Nodal marginal zone lymphoma	6	1.5
Splenic marginal zone lymphoma	6	1.5
Burkitt lymphoma	5	1.3
Adult T-cell lymphoma/leukemia	5	1.3
ALK-negative anaplastic large T-cell lymphoma	5	1.3
Lymphoplasmocytic lymphoma	4	1.0
Peripheral T-cell lymphoma	4	1.0
Extranodal NK/T-cell lymphoma	3	0.8
ALK positive anaplastic large T-cell lymphoma	2	0.5
Other	2	0.5

Table 2. Primary extranodal involvement sites

Involvement site	n	%
Gastrointestinal system	37	41.6
Central nervous system	12	13.5
Bone	10	11.2
Liver	5	5.6
Eye lid	4	4.5
Other	21	23.6
Total	89	100

Table 3. Characteristics of patients and pretreatment variables predicting survival by univariate analyses

Characteristics	Overall distribution		5-year survival rate	
	(n)	(%)	(%)	*p value*
Gender				$p = 0.152$
Female	144	37.3	85.4	
Male	242	62.7	79.3	
Age				$p = 0.453$
< 60 years	199	51.6	80.9	
≥ 60 years	187	48.4	82.4	
Stage				$p = 0.012$
I-II	166	42.8	93.3	
III-IV	220	57.2	72.9	
Performance status (ECOG)				$p = 0.042$
0-1	315	81.6	98.1	
≥ 2	71	18.4	8.5	
IPI score				$p = 0.032$
0-1-2	272	70.5	94.4	
3-4-5	114	29.6	52.5	
B symptoms				$p = 0.021$
Present	173	44.8	70.5	
Absent	213	55.2	90.6	
Involvement site				$p = 0.018$
Primary Extranodal	92	24.1	91.0	
Nodal	294	75.9	78,8	
Extranodal sites				$p = 0.023$
< 2	358	92.7	82.4	
≥ 2	28	7.3	71.4	
Bone marrow involvement				$p = 0.041$
Present	55	14.2	72.7	
Absent	331	85.8	83.1	
Bulky lesion (diameter ≥ 7 cm)				$p = 0.352$
< 7	365	94.6	82.2	
≥ 7	21	5.4	71.4	
Lactate dehydrogenase				$p = 0.001$
≤ 240	191	49.5	91.1	
> 240	195	50.5	72.3	
Albumin (g/dL)				$p = 0.618$
≤ 3,5	186	48.2	81.7	
> 3,5	200	51.8	81.5	
Immunophenotype				$p = 0.815$
B-NHL	360	93.3	82.2	
T-NHL	26	6.7	73.1	
Hb (g/dL)				$p = 0.016$
≤ 10	67	17.4	65.7	
> 10	319	82.6	85	
Autologous stem cell trans-plant as secondary treatment				$p = 0.024$
Present	40	10.4	62.5	
Absent	346	89.6	83.8	
Organomegaly				$p = 0.232$
Present	132	34.2	77.3	
Absent	254	65.8	83.9	
First line chemotherapy response				*$p = 0.016$*
Present	285	73.8	83.7	
Absent	101	26.2	77.2	

RESULTS

There were 386 patients diagnosed with NHL during the study period who were included in the study. Of these, 242 (62.7%) were male and 144 (37.3%) were female. The median age for all patients was 53 years (range: 18–92). According to gender, median age for females was 51 and 54 as for males. The other clinical and laboratory characteristics of patients are shown in Tables 1, 2, and 3

At the time of the study, 285 patients (73.8%) were in remission, 71 (18.4%) had died, 7 (1.8%) were stable, and 23 patients (6.0%) were continuing treatment. Fifty-five patients (14.3%) experienced at least one relapse, and disease progression was observed in 54 patients (14%).Based on survival analysis, 71 patients (18.4%) died. Median overall survival time was 151.2 ± 5.7 months and the 5-year overall survival rate was 81.6%. The 5-year overall survival rate of males was 79.3% while that of females was 85.4%. In univariate analyses, no statistically significant difference in overall survival on the basis of gender, age, the presence of bulky lesions, albumin levels, immunophenotype characteristiics, platelet count, or the presence of organomegaly was observed (Table 3).

The overall survival rates were significantly different with respect to stage based on the Ann Arbor staging system, EGOC performance score, IPI score, presence of B symptoms, autologous stem cell transplantation as second line therapy, primary nodal involvement, bone marrow involvement, serum LDH level, hemoglobin level, and rituximab-based chemotherapy regimen were all significantly associated with overall survival (Table 3).

DISCUSSION

NHL is a disease characterized by the malignant monoclonal proliferation of lymphoid cells. Worldwide, NHL is more common in men than in women. The male: female ratio has been reported as 1.43 in the United States, 1.23 in Europe, 1.52 in Austria, and 1.7 in the United Arab Emirates[15,16,17,18]. Previous reports from Turkey indicate the male:female ratio varies between 1.39 and 1.8[19,20]. Similarly, in this study the male:female ratio is 1.69, comparable to the previous reports.

The median age of the patients in this study was similar to reports from Western countries, although higher when compared with other studies from Turkey[19,20]. The prevalence of B symptoms in our study was 44.8%. This rate is similar with studies reported in Western countries as well as in Turkey[20,21].

The rate of primary extranodal lymphoma as reported in the literature is 22-25% in the United States, 27% in the United Kingdom, 27% in Canada, 33% in Denmark and the Netherlands, and 42% in France[5]. Based on case series studies conducted in Turkey, the rate of primary extranodal lymphoma has been reported to vary between 25% and 57%[19,20]. In the present study, the rate of primary extranodal lymphoma was 24.1%, similar to values reported for Western countries and for Turkey. This is not surprising as the socio-economic status of Turkey is similar to most western countries.

According to data reported in the literature for the United States as well as for Middle Eastern and Asian countries, the most common primary extranodal disease is gastric lymphoma[5]. The same finding has been reported for Turkey[19]. The results of this study support the literature findings, as primary extranodal involvement was most often observed in the stomach. This may be due to the same biology of the disease all over the world.

Natural killer (NK)/T-cell lymphomas are rare and comprise only 10-15% of all cases of NHL. T-cell NHL rates of 12% in the United States and 9.5% - 13.6% in Europe have been reported[7], while rates reported for Turkey are between 8% and 16%[20]. In the present study, T-cell NHL accounted for 6.7% of all NHL cases, lower than the aforementioned rates reported in the literature. This may be due to some genetic and geographic difference with some western countries.

Diffuse large B-cell lymphoma, the most common type of NHL according to the WHO classification, is known to constitute approximately 30-40% of all NHL cases[22]. The rates of DLBCL in NHL case are 22.3% in the United States and 25-53% in Europe[23]. Turkish data reported DLBCL comprises 38.3-66% of all NHL cases[19,20]. This study identified DLBCL as the most common histopathological type of NHL in Eastern Turkey, with a rate of 46.9%, similar to other reports for Turkey, Europe, Asia, and Middle East reports.

The second most common lymphoma is follicular lymphoma (FL). While prevalence of FL in the United States and Western Europe approaches 20-

33%, this rate is lower in Asian and Middle Eastern countries, and is only 4-11% in Turkey[20,21]. In the present study FL ranked third among the NHL subtypes, at 9.4%. This rate is much lower than those reported for the United States and Western Europe but similar to data reported from Asian and Middle Eastern countries.

According to the American Cancer Society, 5-year overall survival rate for NHL was 67% in the United States and 55.2% in China[24]. Data from Korea showed a 5-year overall survival rate of 74.4% for B-cell NHL and 50% for NK/T NHL[16]. The 5-year overall survival rates of NHL patients in Turkey have not received much attention from researchers. In a study conducted at Pamukkale University in 2011, 5-year overall survival was 79% for NHL patients as whole, 81% for B-cell NHL, and 61% for NK/T cell NHL[20]. The 5-year overall survival rate in the present study was 81.6% for all patients, 82.2% for B-cell NHL, and 73.1% for NK/T cell NHL. The 5-year overall survival rates observed in the present study were higher than the worldwide rates, but close to the Turkish rates. However, no statistically significant difference in terms of 5-year overall survival was found between immunophenotypes.

In patients with NHL, a number of factors have been identified that can affect prognosis and response to treatment. The most important of these are age, performance status, presence of B symptoms, tumor size, tumor stage, nodal and extranodal involvement, presence of bone marrow involvement, and serum LDH level[25]. In the current study, advanced stage (stage III-IV), poor performance status (ECOG score of 2 or higher), a high-intermediate or high risk IPI score, presence of B symptoms, bone marrow involvement, Hb level less than 10 g/dL, LDH level above normal, and nodal involvement sites were all associated with shorter overall survival, consistent with the literature.

Several studies have reported that the presence of two or more extranodal involvement sites is associated with short survival time[26]. However, in the present study, unlike in the literature, there was no significant relationship between the number of extranodal involvement sites and overall survival. In NHL, bone marrow involvement is known to be a criterian of poor prognosis. Bone marrow involvement has been associated with short survival times in a number of studies[26]. The findings of the present study are consistent with the literature, having found bone marrow involvement to be associated with shorter survival time.

Bulky lesions are defined as tumor masses of 7 cm or more in diameter in some studies, and as 7.5 cm or larger in other studies[26]. Data concerning the relationship between bulky disease and survival also vary. According to some studies, bulky lesions are associated with short survival[22]. However, no significant relationship between bulky lesions and survival has been reported in Turkish studies[27]. In the current study, the relationship between bulky lesions and survival was not significant, similar to the finding of other Turkish studies.

Natural killer (NK)/T-cell NHL cases account for approximately 10-15% of aggressive lymphomas in the United States and Europe[17], and are higher in Asia and the Middle East. Comparing NK/T-cell NHL to B-cell NHL, the former is more aggressive and has a worse prognosis[28]. While they are similar with regard to pretreatment characteristics and IPI scores, T-cell immunophenotype has been shown to have a negative effect on overall survival[29]. In the present study, however, the effect of T-cell immunophenotype on overall survival was not significant.

Serum LDH levels, which become elevated as a sign of increased cell turnover in neoplastic diseases, have been reported to adversely affect overall survival rates[19]. In this study, high serum LDH levels had a statistically significant negative effect on overall survival, consistent with the literature. The presence of anemia has been demonstrated to be a poor prognostic factor in lymphomas[20]. Low hemoglobin levels in the current were associated with a short survival time, similar to findings in the literature.

The distribution of NHL patients in this study was very heterogeneous and the number between groups was very different. Therefore, the analysis of sub-groups could not be made as the main limitation of this study.

As a concluion in Eastern Turkey more males than females develop NHL with DLBCL constituting the most common histological type. The prevalence, clinical characteristics, histopathological subtypes, treatment response, and overall survival rates of NHL may vary according to geographical region, and even in different regions of the same country. We therefore believe that the results of this study, which provide further evidence of this variability, represent

a meaningful contribution to the existing medical literature.

Yazar Katkıları: Çalışma konsepti/Tasarımı: AD, NYD, MAE, ÖE, İK, EK; Veri toplama: AD, NYD, MAE, ÖE, İK, EK; Veri analizi ve yorumlama: AD, NYD, MAE, ÖE, İK, EK; Yazı taslağı: AD, NYD, MAE, ÖE, İK, EK; İçeriğin eleştirel incelenmesi: AD, NYD, MAE, ÖE, İK, EK; Son onay ve sorumluluk: AD, NYD, MAE, ÖE, İK, EK; Teknik ve malzeme desteği: AD, NYD, MAE, ÖE, İK, EK; Süpervizyon: AD, NYD, MAE, ÖE, İK, EK; Fon sağlama (mevcut ise): yok.
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