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Single-center Experience in Relapsed / REFRACTORY NON-HODGKIN'S lymphoma

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ABSTRACT

Non-Hodgkin's lymphomas are a heterogeneous malignancy group originating from lymphoid tissue and having an increasing frequency in the world in the last decade. Its clinic and response to treatment vary according to different sub-types. Today, the most compelling situation for a clinician is the patients with relapsed or refractory Non-Hodgkin's lymphoma. Its prognosis is poor even despite different treatments and autologous stem cell transplantation. The aim of the present study is to present the experiences in the diagnosis of relapsed/refractory Non-Hodgkin's lymphoma to the literature. A total of 193 patients, who were diagnosed and treated at Sivas Cumhuriyet University Medical Faculty Hospital between 2011 and 2021 were included in the study. 145 of these patients were not relapsed/refractory and 48 were relapsed/refractory. Rescue therapy was provided to the relapsed/refractory patients; however, autologous stem cell transplantation could only be applied to 25 patients. Of the stem cell transplantation patients, 17 are still alive. As a result, the best treatment under current conditions is the rescue therapy, followed by autologous stem cell transplantation. However, relapsed/refractory Non-Hodgkin's lymphomas have a quite poor prognosis; thus, new treatment agents are required.

***Keywords**:* Lymphoma, relapsed, refractory, stem cell transplantation

Relaps/REFRAKTER NON HODGKİN lenfomalarda Tek Merkez Deneyimi

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ÖZ

Non-Hodgkin lenfomalar, lenfoid dokudan kaynaklalan ve dünyada sıklığı son on yılda giderek artan heterejon karakterde bir malignite grubudur. Kliniği ve tedaviye yanıtları farklı alt tiplerine göre değişmektedir. Günümüzde klinisyeni en çok zorlayan ise relaps veya refrakter Non-hodgkin lenfoma hastalarıdır. Farklı tedaviler ve otolog kök hücre nakli ile bile prognozu çok kötüdür. Bu çalışmada amacımız relaps/refrater Non-Hodgkin lenfoma tanısındaki tecrübelerimizi literatüre sunmaktır. Çalışmaya2011-2021 yılları arasında Sivas Cumhuriyet Üniversitesi Tıp Fakültesi Hastanesinde tanısını koyup, tedavi ettiğimiz 145'i relaps/refrakter olmayan 48'i relaps/refrakter olan toplam 193 hasta dahil edilmiştir. Relaps/refrakter hastalara kurtarma tedavisi verilmiş ancak 25 hastaya otolog kök hücre nakli yapılabilmiştir. Kök hücre nakli yapılan hastaların da 17'si halen hayattadır. Sonuç olarak, günümüz koşullarında en iyi tedavi, kurtarma tedavisi ardından otolog kök hücre naklidir. Ancak relaps/refrakter Non-Hodgkin lenfomalar son derece kötü prognozlu olup yeni tedavi ajanlarına ihtiyaç duyulmaktadır.

***Anahtar sözcükler**:* Lenfoma, relaps, refrakter, kök hücre nakli

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Introduction

Non-Hodgkin's lymphomas (NHL) are one of the most frequent malignancies in the world and they are a heterogeneous group of malignancies originating from the lymphoid tissue and consisting of approximately 60 different sub-types having different clinical and biological features[1]. Even though NHL sub-type classification is very important for diagnosis and treatment, subtype-specific risk analysis is very difficult due to the limited number of cases and the rarity of each subtype[2]. The three most common subtypes of NHL that account for approximately two-thirds, are diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and follicular lymphoma (FL) originating from B cells. The most common subtype of NHLs caused by T cells is peripheral T-cell lymphoma (PTCL) (50%) [2]. Subtypes of NHLs give different responses to treatment since they have different biologies. The course of the disease can be aggressive or slowly progressive (indolent). Combination of rituximab, a monoclonal antibody targeting the CD20 antigen on B cells, with standard chemotherapy has positively affected the NHL treatment. Although rituximab-based regimes have high response rates, many patients may develop resistance to treatment or relapse after an initial response[3]. There are numerous factors determining the prognosis in NHL patients. These factors can include age, size of tumor, stage of tumor, performance score, serum LDH level, and bone marrow involvement [4].

Relapsed disease refers to the occurrence of the disease during follow-up in the patients with a full response after initial the treatment and this is seen in 10-30% of the patients. Relapse is mostly seen between 1 and 5 years. Refractory disease refers to the disease progressing during the primary treatment or no change with the treatment[5].

The aim of the study is to evaluate the responses to treatment in relapsed/refractory (R/R) NHL patients according to the retrospective evaluation of the treatments, epidemiological characteristics of the patients, histological subtype, laboratory findings at the time of diagnosis, and stage of the disease.

Material and Methods

In the study, 193 patients, who were followed up with diagnosis of NHL between January 2011 and 2021 at the Sivas Cumhuriyet University, Faculty of Medicine, Department of Hematology, were retrospectively assessed. Approval of Sivas Cumhuriyet University, Non-Invasive Ethics Committee was obtained for the study. Patients who were aged 18 years and older and diagnosed with NHL at the hospital were included in the study. Patients diagnosed and/or treated at another hospital were excluded from the study. Age, gender, co-morbidities, stage at the time of diagnosis, bone marrow involvement, bulky disease, treatments, and treatment responses of 193 participants were recorded. The patients participating in the study were divided into two subgroups as patients with and without relapsed/refractory (R/R).

Statistical Analysis

Data of the study were uploaded in SPSS (ver. 22.0) software. Descriptive statistical criteria (mean, median, standard deviation, minimum and maximum values, percentiles) were utilized to evaluate the results of the study. Kolmogorov- Smirnov test was used to determine whether the data were normally distributed. In the comparison of the measurements, when the parametric test assumptions were fulfilled, the independent samples t test was used to determine the difference between the means of two independent groups, and the Mann-Whitney U test was used when the parametric assumptions were not fulfilled. Chi-square test was used to determine the correlation between the categorical groups. Significance level was accepted as 0.05 for the interpretation of the results.

Results

A total of 193 patients were included in the study. While 85 of these participants were female (44%), 108 were male (56%). Average age of the patients was 56.06±14.98 (min=18; max=84) years. When the subtypes of the disease were examined, the most common subtype was diffuse large b-cell lymphoma (n:124, 64.2%), followed by follicular lymphoma (n:17, 8.8%), mantle-cell lymphoma (n:13, 6.7%), and marginal zone lymphoma (n:11, 5.7%), whereas the other subtypes were also detected at lower rates. Table 1 shows the number and percentage of the subtypes of patients diagnosed with NHL included in the study.

The patients included in the study were divided in two subgroups as with R/R (n:145, 75.2%) and without R/R (n:48, 24.8%). When the groups were compared in terms of age and gender, no statistically significant difference was found between them. When the patients having bone marrow involvement at the time of diagnosis were compared with the patients without bone marrow involvement, no statistically significant difference was found in terms of relapse/refractoriness. However, the patients without bone marrow involvement mostly took place in the group without R/R. It is considered that this was caused by the smaller number of participants in the group with R/R and the difference may be significant in the further studies to be conducted with more cases. When the patients were compared according to the presence of a bulky mass at the time of diagnosis, no statistically significant difference was found between the groups with and without R/R. When patients with stage 1 and 2 are categorized as early stage according to Ann Arbor staging system, those with stage 3 and 4 are categorized as advanced stage.

Table 1. NHL subtype distribution in our study

Histological subtype	n	%
Diffuse large B-cell lymphoma	125	64.8
Follicular Lymphoma	17	8.8
Mantle cell lymphoma	13	6.7
Marginal zone lymphoma	12	6.2
T-cell lymphoma	9	4.7
Central nervous system lymphoma	5	2.6
Small lymphocytic lymphoma	3	1.6
ALK(-) anaplastic large cell lymphoma	2	1
Extranodal NK/T-cell lymphoma	2	1
Lymphoplasmacytic lymphoma	1	0.5
Plasmablastic lymphoma	1	0.5
Angioimmunoblastic lymphoma	1	0.5
Primary cutaneous anaplastic large cell lymphoma	1	0.5
Burkitt lymphoma	1	0.5
Total	**193**	**100**

Table 2. Comparison of groups according to gender, bone marrow involvement, bulky disease and stage at diagnosis

Diagnosis moment	Non-R/R	R/R	Total	p
Bone marrow involvement				
Yes	38 (%67.9)	18 (%32.1)	56 (%100)	.135
No	107 (%78.1)	30 (%21.9)	137 (%100)	
Bulky mass				
Yes	17 (%81)	4 (%19)	21(%100)	.513
No	128 (%74.4)	44 (%25.6)	172 (%100)	
Gender				
Female	65 (%76.5)	20 (%23.5)	85 (%100)	.702
Male	80 (%74.1)	28 (%25.9)	108 (%100)	
Stage				
Early	55 (%75.3)	18 (%24.7)	73 (%100)	.957
late	90 (%75)	30 (%25)	120 (%100)	

When comparing the patients in terms of this system, no statistical significant difference was determined between the groups with and without R/R. Table 2 shows the comparison results of the groups with and without R/R in terms of gender, bone marrow involvement at the time of diagnosis, bulky disease, and stage of the disease.The groups with and without R/R were compared according to their laboratory data at the time of diagnosis. As a result of the normal distribution analysis of the measurements, the values other than MPV did not show a normal distribution. MPV showed a normal distribution. Total leucocyte count, neutrophil count, lymphocyte count, platelet count, hemoglobin concentration, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), erythrocyte sedimentation rate (ESR), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), and lactate dehydrogenase (LDH) of both groups at the time of diagnosis were recorded and compared. The difference between LDH and ESH values was found to be statistically significant (p values of 0.007 and 0.00, respectively). In other words, ESR and LDH values of the group with R/R at the time of diagnosis were significantly higher than those of the group without R/R. In the group with R/R, mean LDH level was 379.97±231.15 U/L and ESH was 56.25±29.80 mm/h and in the group without R/R, LDH was 310.73±171.95 U/L and ESH was 39.75±25.94 mm/h. No statistically significant difference was determined between the groups in terms of the other laboratory values. Table 3 shows the comparison of the groups according to the age and laboratory data at the time of diagnosis.

The number of R/R patients was 48 and autologous stem cell transplantation was performed in 24 (50%) of these patients. This procedure could not be applied to the remaining 24 patients (50%) due to poor performance or death. Of the patients with R/R, 31 (64.5%) are not alive and 17 (35.4%) are alive. Among the patients without R/R, 116 (80%) are still alive and 29 (20%) died due to the reasons other than the relevant disease.

Table 3. Comparison of the groups according to age and laboratory values at the time of diagnosis

Diagnosis moment	Groups	n	Mean	SD	Median	Test	p
Age	Non-R/R	145	56.6414	15.04146	98.94	3139.0	.402
	R/R	48	54.3125	14.83836	91.15		
WBC 10^6/L	Non-R/R	145	6920.62	2519.58	94.81	3162.5	.344
	R/R	48	7449.79	2963.11	103.61		
Neutrophil 10^6/L	Non-R/R	145	4722.48	1981.45	95.84	3311.5	.615
	R/R	48	5115.00	2567.95	100.51		
Lymphocyte 10^6/L	Non-R/R	145	1550.17	1354.49	99.61	3102.0	.260
	R/R	48	1479.39	1348.85	89.13		
Hemoglobin (g/dL)	Non-R/R	145	12.76	4.60	100.84	2923.0	.097
	R/R	48	11.91	1.79	85.40		
Platelet (/mm^3)	Non-R/R	145	250137.93	106697.17	99.38	3134.5	.303
	R/R	48	229920.83	102877.67	89.80		
MPV fL	Non-R/R	145	9.04	1.20	97.67	-.160	.873
	R/R	48	9.07	1.42	94.98		
PCT %	Non-R/R	145	.23	.10	97.20	3451.0	.931
	R/R	48	.22	.09	96.40		
PDW fL	Non-R/R	145	20.62	11.76	99.29	3147.5	.321
	R/R	48	19.06	10.33	90.07		
ESR (mm/h)	Non-R/R	145	39.75	25.94	88.94	2311.5	.000*
	R/R	48	56.25	29.80	121.34		
Creatine (mg/dL)	Non-R/R	145	.81	.25	96.68	3433.0	.888
	R/R	48	.79	.21	97.98		
ALT (U/L)	Non-R/R	145	28.55	26.64	96.68	3433.0	.889
	R/R	48	25.10	15.52	97.98		
AST (U/L)	Non-R/R	145	26.68	15.80	95.64	3282.5	.556
	R/R	48	27.77	18.64	101.11		
ALP (U/L)	Non-R/R	145	93.05	38.60	94.23	3078.0	.231
	R/R	48	115.16	79.79	105.38		
GGT (U/L)	Non-R/R	145	46.06	37.11	94.50	3118.0	.280
	R/R	48	49.06	37.05	104.54		
LDH (U/L)	Non-R/R	145	310.73	171.95	90.79	2580.0	.007*
	R/R	48	379.97	231.15	115.75		

ESR: Erythrocyte Sedimentation Rate WBC:White blood cell (10^6/L), MPV:Mean platelet volüme, PCT: Platecrit, PDW:Platelet Distribution Width, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyltransferase and LDH: Lactate Dehydrogenase

Table 4. Treatment protocols received by the groups in first and second steps

Protocols used in first step	n	%	Protocols used in second step	n	%
RCHOP	138	71.5	R-DHAP	22	11.4
CHOP	12	6.2	R-ICE	8	4.1
R-CVP	9	4.7	DHAP	3	1.6
R-Bendamustine	6	3.1	ICE	3	1.6
HD-MTX	5	2.6	HD-MTX	4	2.1
R-CNOP	5	2.6	R-Bendamustine	2	1
R-EPOCH	4	2.1	Ibrutinib	1	0.5
Isolated RT	3	1.6	R-Ibrutinib	1	0.5
CNOP	2	1	De Angeles	1	0.5
R-FC	2	1	CHOP	1	0.5
RCHOP+R-DHAP	2	1	R-CVP	1	0.5
R-mini CHOP	2	1	Pralatrexate	1	0.5
EPOCH+Bortezomib	1	0.5			
FC	1	0.5			
100 mg MTX weekly	1	0.5			
Total	193	100	Total	48	24.9

R-CHOP: Rituximab+Cyclophosphamide+Adriamycin +Vincristine+ Prednisolone; CHOP: Cyclophosphamide+Adriamycin +Vincristine+ Prednisolone CNOP: Cyclophosphamide+ Mitoxantrone+Vincristine+ Prednisolone; R-CVP: Rituximab+Cyclophosphamide +Vincristine+ Prednisolone; R FC: Rituximab+Fludarabine+Cyclophosphamide; EPOCH: Etoposide+ Prednisone+Doxorubucin Vincristine+ Cyclophosphamide; GVD:Gemsitabin+Vinorelbin+dexametazon; HD MTX: yüksek doz metotrexat; R DHAP: Rituximab+ Cisplatin+ Cytarabine+ Dexamethazone; R-ICE: Rituximab+ Etoposide+ Carboplatine+ Ifosfamide; RCD: Rituximab+: Cyclophosphamide+ Dexamethazone; De Angeles protokolü [16]

Discussion

NHL is a hematologic malignancy with an increasing prevalence throughout the world. While it is diagnosed in early decades in countries of the Middle East and Asia, it is generally diagnosed in Europe generally in the 6-7 decades on average[6]. In the current study, the diagnosis age of NHL was found to be averagely 56.06 ±14.98 years. NHL is more frequently detected in men. In the current study, it was also diagnosed in 44% of women and 56% of men. Even though this difference was not statistically significant, it is compatible with the literature[7]. NHLs are a heterogeneous group of diseases that occur in a wide spectrum ranging from mild to aggressive disease in terms of histology, pathogenesis and clinical course. The most common indolent subtype is follicular lymphoma (FL) in B-cell origin and cutaneous T-cell lymphoma (CTCL) in T-cell origin, while the aggressive subtypes are diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma (PTCL) and constitute about 80% of all NHL diagnoses in adults[8]. The clinical course in NHLs frequently varies from patient to patient. However, NHL relapses in a significant part of the patients or they are resistant to primary care. Till now, conventional primary care has included rituximab in combination with doxorubicin, cyclophosphamide, vincristine, and prednisone. Although it has been proven that these treatments are beneficial, their five-year survival rate does not exceed 70%, and synchronously, almost half of the patients are resistant to the treatment or the disease relapses after the treatment. In such situations, median general survival considerably decreases and does not exceed 10 months[9]. Although good clinical responses are achieved after rituximab treatment in NHLs, patients with relapsed/refractory NHL have a poor prognosis in general and it is very difficult to manage the disease clinically[10].

International prognostic index is used in the world to determine the prognosis of NHL. Within this index, age (>60), advanced stage (III and IV), extranodal involvement, performance status (>2), and high LDH take place[11]. numerous studies have reported that high serum LDH is found to be associated with poor prognosis in lymphomas. In a study conducted with patients with DBBHL, serum LDH values higher than the normal limit were found to be associated with a shorter general and progression-free survival time[12-14]. In the current study, it was found that LDH level at the time of diagnosis was significantly high in the group with R/R compared to the group without R/R and this was correlated with poor prognosis. High ESR is not stated in the international prognosis index. However, in the present study, ESR was statistically significant higher in the group with R/R than the group without R/R and was correlated with poor prognosis. Stage of the patient at the time of diagnosis is included in the prognostic index. Poor prognosis is expected in the patients at advanced stage (III and IV). In the current study, a total of 73 patients were diagnosed at early stage and of these patients, 75.3% (n:55) were in the group without R/R and 24.7% (n:18) in the group with R/R. 75% of 120 patients diagnosed at advanced stage (n:90) were in the group without R/R and 25% (n:30) in the group with R/R. This difference was not statistically significant and did not have a prognostic value. Bone marrow involvement at the time of diagnosis has a prognostic value. However, it was found in the present study that while 56 (29%) patients had bone marrow involvement at the time of diagnosis, 137 (71%) did not have bone marrow involvement at the time of diagnosis. Of the patients with bone marrow involvement, 67.9% (n:38) were in the group without R/R and 32.1% (n:18) in the group with R/R. This difference was not statistically significant. We think that the low number of cases in the present study, especially the low number of the participants in the group with R/R, affected the results.

Management of R/R NHL is quite difficult for many clinicians. The best approach under current conditions is high-dose chemotherapy with the least partial response followed by autologous stem cell transplantation (autologous SCT) after the rescue therapy is applied to the patient with R/R. The patients responded to the rescue therapy partially or completely can be candidates for autologous SCT. The most frequently preferred protocols for rescue therapy are DHAP ± Rituximab and ICE ± Rituximab. Similar clinical results have been obtained with these protocols. However, 3-year survival in the patients with a relapse earlier than 12 months is 20% and its prognosis is quite poor[15]. Rescue therapy was administered to 48 patients with R/R followed up at our clinic during secondary care. DHAP ± Rituximab was given to 25 (52%) patients and ICE ± Rituximab to 11 (22.9%) patients. The protocols could not be compared with one another in the study due to the insufficient number of patients. Table 4 shows the chemotherapy protocols given in primary and secondary care. Of 48 patients with R/R, autologous SCT was performed in 24 (50%) and this procedure could not be applied to the remaining 24 patients (50%) due to poor performance or death.

While the majority of patients with chemosensitive aggressive B-cell lymphoma can be treated with immunochemotherapy or autologous stem cell transplantation, the prognosis for R/R disease, mantle cell lymphoma or advanced stage indolent lymphoma, and peripheral T-cell lymphoma is quite poor. Allogeneic stem cell transplantation (Allogeneic SCT) can be a treatment option for such patients. Despite allogeneic SCT is a treatment option, the patients should be well-examined due to the high morbidity and mortality rates after transplantation. In the current study, allogeneic SCT was applied to a patient diagnosed with R/R DBBHL due to the relapse after autologous SCT. The patient is in the first year of stem cell transplantation and is still in remission. Of 24 patients to whom autologous SCT was applied, 17 (35.4%) are still alive. Among the patients without R/R, 116 (80%) are still alive and 29 (20%) died due to the reasons other than the lymphoma.

Conclusion

The use of rituximab in combination with the chemotherapeutic agents is standard in primary care for B-cell NHLs and it has rather improved the prognosis. However, rituximab resistance has been reported in several NHL subtypes including relapsed FL or low-grade NHL and it is correlated with poor prognosis. T-cell lymphomas generally have a poor prognosis and a worse prognosis in case of relapse. Relapse generally emerges within the first 2 years after the completion of the treatment[15]. Clinical management of R/R NHLs is quite difficult. The most important criterion in the treatment selection for R/R NHL is to evaluate the compatibility of the patient for autologous SCT. Autologous SCT is an important treatment alternative in R/R lymphomas and the response of the patients to the rescue regimens is quite important to reach this treatment option. Autologous SCT can be applied in the patients with at least a partial response to the rescue therapy. Prognosis of the patients may progress as poor even after the stem cell transplantation. New treatment agents for the patients with R/R NHL and different clinical studies with more cases are needed in this field.

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