Received: 01 Jun 2024 | **Accepted:** 03 Sep 2024 **Genel Tıp Derg. Volume** 34/**Issue** 5 (October), 671-679
DOI: 10.54005/geneltip.1493721

ORIGINAL ARTICLE

Immunosuppression-Based Lymphoproliferative Disease Features and Parameters Affecting Survival

İmmünsüpresyon Zemininde Gelişen Lenfoproliferatif Hastalik Özellikleri Ve Sağkalimi Etkileyen Parametreler

[1]Sabin Goktas Aydin, [2]Meliha Nalcaci, [2]İpek Yönal Hindilerden, [2]Sevgi Beşışık, [2]Mustafa Nuri Yenerel, [3]Ahmet Aydin

[1]İstanbul Kanuni Sultan Suleyman Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji, Türkiye
[2]İstanbul Üniversitesi İstanbul Tıp Fakültesi, Hematoloji Bilim Dalı, Türkiye
[3]Istanbul Medipol Üniversitesi, İç Hastalıkları Ana Bilim Dalı, Türkiye

Correspondence

Sabin Goktas Aydin
İstanbul Kanuni Sultan Suleyman Eğitim ve Araştırma Hastanesi, Tıbbi Onkoloji, Türkiye

E-Mail: drsabingoktasgmail.com

How to cite ?

Goktas Aydin S, Nalcaci M, Yönal Hindilerden İ, Beşışık S, Yenerel MN, Aydin A. Immunosuppression-Based Lymphoproliferative Disease Features and Parameters Affecting Survival. Genel Tıp Derg. 2024;34(5):671-79.

ABSTRACT

Aim: Lymphoid cell malignancies originate from the immune cells at various stages of differentiation, ranging from the slowest progressing ones to the most aggressive types. The immune deficiency-associated lymphomas are less frequently seen with worse prognoses, poor treatment responses, and high mortality rates than the primary lymphomas. In this study, we aim to evaluate the clinical and laboratory findings and to determine the survival rates, treatment responses, and the factors that may influence the mortality and survival rates in patients with immunodeficiency-associated lymphomas.
Material and Methods: The study included 15 patients with immunodeficiency-associated lymphomas and 49 patients with newly diagnosed primary lymphomas between January 2013 and January 2023. Patient characteristics, treatments, and mortality rates were retrospectively analyzed using data charts.
Results: The remission and partial remission rates after the treatment were significantly lower in the patients with immunodeficiency-associated lymphomas (p=0.025; OR=5.6 (1.4-22, 95%CI)). The International Prognostic Index (IPI) values of the primary lymphoma patients were significantly lower. Upon evaluating all patients in both groups collectively, a discernible trend indicated a deterioration in treatment responses correlating with escalating IPI values (p < 0.001). The levels of β-2 microglobulin were higher in the deceased patients (3.4±1.8mg/l vs 5.2±1.8mg/l; p<0.01). The Epstein-Barr Virus (EBV) DNA positivity rates were significantly higher in the deceased patients in the patient group with immunodeficiency-based lymphomas. Mortalities were observed in 5 (10.2%) patients with primary lymphomas and in 7 (46.7%) patients with immunodeficiency-associated lymphomas at the end of the follow-up period (p<0.01; OR=7.7). The mean progression-free survival rate was 30.8±1.8. The mean progression-free survival rate of the patients with immunodeficiency-associated lymphomas was 22.4±4.2 months (14.1-90.6 95%CI), whereas, in the primary lymphoma patients, it was 32.2±1.5 months (29.1-35.3 95%CI), leading to a significant difference between the two groups (p=0.004).
Conclusion: Our study demonstrated that immunodeficiency-associated lymphoma has a poorer prognosis, shorter survival rates, and higher mortality. In addition, IPI values, levels of β-2 microglobulin, and the outcomes of EBV serology tests are essential factors in determining this group of patients' prognoses and survival rates.

Keywords: non-Hodgkin lymphoma, Immunosuppression-related lymphoma survival, Prognosis

ÖZ

Amaç: Lenfoid hücre maligniteleri, en yavaş seyirliden en agresife kadar değişen, diferansiasyonun farklı seyrindeki immun sistem hücrelerinden ortaya çıkan malignitelerdir. İmmün yetersizlik zemininde gelişen lenfoma ise, primer lenfomaya kıyasla daha nadir gözlenen, prognozu ve tedaviye yanıtı kötü, mortalitesi yüksek bir hastalıktır. Biz bu çalışmada immün yetersizlik zemininde gelişen lenfoma hastalarının klinik ve laboratuvar özelliklerini değerlendirmeyi, bu hastalarda sağkalım oranlarını, tedavi yanıtlarını ve mortalite-sağkalım üzerine etkili olabilecek faktörleri değerlendirmeyi amaçladık.
Yöntem: Çalışmaya, Ocak 2013 ile Ocak 2023 tarihleri arasında başvuran, 15 immün yetersizlik zemininde gelişen lenfoma hastası ve aynı tarihte başvuran 49 primer yeni tanı lenfoma hastası dahil edildi. İmmünsüpresyon nedenleri, immünsüpresyon tedavileri ve süreleri, lenfoma evre ve tedavileri, tedaviye verilen yanıtları, mortalite oranları, sağkalım süreleri, laboratuvar değerleri poliklinik dosyaları ve yatış epikrizleri kullanılarak değerlendirildi.
Bulgular: Tedavi sonrası remisyon/kısmi remisyon gelişimi immünsüpresyon zemininde lenfoma gelişen olgularda anlamlı olarak daha düşüktü (p=0,025 OR 5,6 (1,4-22 %95CI)). Primer lenfomalı hastalarda international prognostic index (IPI) değeri anlamlı olarak daha düşük bulunmakla birlikte; her iki grup birlikte değerlendirildiğinde, IPI skoru yükseldikçe tedaviye verilen yanıt kötüydü (p<0,001). B2 mikroglobulin düzeyleri eksitus olan hastalarda daha yüksek olarak bulundu (3,4±1,8 mg/l vs 5,2±1,8 mg/l p<0,01). İmmünsüpresyon zemininde gelişen lenfoma hastalarından, eksitus gözlenenlerde Epstein-Barr Virus (EBV) DNA pozitiflik oranı anlamlı olarak daha yüksekti . Takip süresi sonunda, primer lenfoma olan hastaların 5'inde (%10,2) mortalite gözlenirken, immünsüpresyon zemininde gelişen lenfomalı hastaların 7'sinde (%46,7) mortalite gözlendi (p<0,01 OR7,7). Her iki grup birlikte değerlendirildiğinde, progresyonsuz ortalama sağkalım süresi 30,8±1,8 ay bulundu. İmmünsüpresyon zemininde gelişen lenfoma hastalarında, ortalama progresyonsuz sağkalım süresi 22,4±4,2 ay (14,1-90,6 %95CI) iken; primer lenfoma olanlarda ortalama progresyonsuz sağkalım süresi 32,2±1,5 ay (29,1-35,3 %95CI) olarak saptandı ve gruplar arasında anlamlı fark bulundu (p=0,004).
Sonuç: İmmünsüpresyon zemininde gelişen lenfoproliferatif hastalıkların, primer lenfomaya kıyasla prognozu kötü, sağkalımı kısa, mortalitesi yüksek bir hastalık olduğu çalışmamızda da gösterilmiştir. Ayrıca bu hastalarda sağkalım ve prognozu belirlemede IPI değeri, B2 mikroglobulin değeri ve EBV serolojisi önemlidir.

Anahtar Kelimeler: Uzun kodlamayan RNA, lncRNA, Laringeal kanser, miRNA, UCA1, miR138, CDK6

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - intihal.net
Complaints: geneltip@selcuk.edu.tr

Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
https://yayinevi.selcuk.edu.tr/

Introduction

Many factors are involved in the development of malignant diseases. However, it is known that the immune system's inability to recognize and eliminate tumor cells and disorders in programmed cell death due to various reasons also play a role. In individuals with immunodeficiency, a cell can become malignant, undergo clonal proliferation, and develop cancer more easily. Lymphoproliferative diseases are seen more frequently in people with congenital, acquired, or iatrogenic immunodeficiency than in the average population. The clinical and pathological features of lymphoproliferative disease that develop depending on the type and severity of immunodeficiency vary (1).

Lymphomas developing on an immunosuppressive background are of B-cell origin and have aggressive histopathological features. Epstein-Barr Virus (EBV) is often associated with these lymphomas. Compared to other lymphomas, extranodal involvement is more frequent, disease progression is rapid, treatment responses are poor, and complications are more common (2).

The World Health Organization (WHO) has categorized lymphoproliferative diseases developing on an immunosuppressive background into four groups: lymphoproliferative diseases developing on a primary immunodeficiency background, lymphomas associated with Human Immunodeficiency Virus (HIV) infection, Post-Transplant Lymphoproliferative Diseases (PTLD), and lymphoproliferative diseases developing after iatrogenic immunodeficiency (3).

Primary immunodeficiency is a group of diseases characterized by recurrent infections, usually with symptoms appearing in childhood. The treatment choice is similar to that for individuals without immunodeficiency but is determined according to the histological type (4,5).

HIV is a retrovirus that infects macrophages and T cells and can integrate into the host cell DNA by carrying the reverse transcriptase enzyme. It leads to chronic immunodeficiency and causes opportunistic infections and malignancy. In HIV-positive individuals, the development of lymphoma is due to polyclonal B cell proliferation due to chronic antigenic stimulation, impaired immune control of T lymphocytes, abnormal somatic mutations caused by immunodeficiency, and the presence of viral infections such as EBV and Human Herpes Virus-8 (HHV-8). Although the incidence of lymphoma has decreased with antiviral treatments, the survival time is short, and the prognosis is poor in patients who develop lymphoma (6).

Immunosuppressive therapy used after organ transplantation can increase the risk of infection and lead to neoplastic diseases. PTLD is usually seen with EBV infection and has a variety of clinical findings (7,8). The incidence of the disease varies depending on the organ type and treatment regimen and is usually seen in 2% of all organ recipients (9). The choice and duration of immunosuppressive therapy are important factors affecting the development of lymphoma. PTLD is different from classical lymphoma; it has extranodal location, variable morphological features, EBV association, lack of clear findings of monoclonality, low response to chemotherapy and radiotherapy, and spontaneous remission potential with reduction of immunosuppressive therapy (10). Although PTLD has a high mortality rate, spontaneous remission can be achieved in 42% of patients with early diagnosis and timely reduction or discontinuation of immunosuppressive therapy (11,12).

Lymphoproliferative disease also develops due to immunosuppressive therapy used in the treatment of autoimmune diseases, especially rheumatologic diseases. For the development of lymphoproliferative disease, the type of immunosuppressive drug used, the duration of treatment, and the underlying disease are important, as well as the patient's gender and genetic predisposition to lymphoproliferative disease. Methotrexate, thiopurines, and immunomodulatory drugs are the accused agents used in treatment. A significant proportion of patients can go into remission without the need for chemotherapy or radiotherapy by discontinuing immunosuppressive therapy (13).

This study aimed to evaluate patients with lymphoproliferative disease developing on an immunodeficiency background regarding the immunodeficiency causes, previous treatments, additional diseases, age and gender, stage, and clinical features. Additionally, we aimed to compare the characteristics of this group of patients with primary non-Hodgkin lymphoma (NHL) patients.

Material and Methods

This retrospective, cross-sectional, descriptive study included 64 patients diagnosed with NHL confirmed by biopsy between January 2013 and January 2023. Consent was obtained from the patients or their primary caregivers.

Of the patients included in the study, fifteen had lymphoma developing on an immunosuppressive background, while forty-nine had primary NHL diagnoses. The reasons for immunosuppression included HIV in five patients, Systemic Lupus Erythematosus (SLE) in two patients, Common Variable Immunodeficiency (CVID) in one patient, kidney transplantation in two patients, liver transplantation in four patients, and treatment for Hodgkin Lymphoma (HL) in one patient.

Immunosuppressive treatment, treatment durations, stages at lymphoma diagnosis, IPI, EBV serology, complete blood count values, gamma globulin, and B2-microglobulin levels were recorded from patients' charts. Staging (Costwold classification) and response evaluation were conducted using Positron Emission Tomography/Computed Tomography (PET/CT) or CT imaging.

Statistical Analysis

All statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics of the data included mean, median, standard deviation, minimum, maximum, 25th, and 75th percentiles, ratio, and frequency values. Categorical variables were compared using the chi-square test. The results of the variables were compared using the Mann-Whitney U test, Student T-test, and Wilcoxon test.

Progression-free survival (PFS) was defined as the time from the date of diagnosis to the date of disease progression or death. Overall survival (OS) was defined as the time from the date of diagnosis to the date of the last follow-up. Survival analysis and curves were performed using the Kaplan-Meier method and compared using the log-rank test. Survival times were presented as mean and standard deviation. The statistical significance level was set at $p<0.05$.

Results

Our study included 15 patients with lymphoma developed due to immunodeficiency (6 females, nine males) and 49 newly diagnosed NHL patients (21 females, 28 males) who applied to our clinic on the exact dates for comparison.

The mean age was 44.5±16.8 years in patients with lymphoma developed due to immunodeficiency and 54.5±16.6 years in patients with primary lymphoma (p=0.04). Gender distribution did not differ between the groups (p=0.9).

In the group receiving immunosuppressive therapy, 13 patients had diffuse large B-cell lymphoma, one patient had Kaposi's sarcoma, and one patient had Burkitt lymphoma.

The duration of treatment used before the development of lymphoma in patients receiving immunosuppressive therapy was a minimum of 12 months and a maximum of 312 months. The mean and median duration of immunosuppressive therapy was 97.8 and 62.5 months, respectively. In patients with HIV diagnosis, the mean duration of treatment they received until the diagnosis of lymphoma was 36 months. One of the patients with HIV infection was not included in the calculation of the treatment duration because he did not accept antiviral therapy. The patient developed NHL after 76 months of HL treatment, including radiotherapy and chemotherapy, with 12 months of duration (Table 1).

Table 1. The characteristics of the patients with immunodeficiency related lymphoma

Primary Disease	Female/Male	Mean Age (years)	Duration of immunosuppression treatment
Systemic lupus erythematosus	2/0	35,5	198
Post-liver transplant lymphoma	1/3	49	53
Post-kidney transplant lymphoma	1/1	68	111
Common variable immun deficiency	1/0	28	72
Human immunodeficiency virus	1/4	41	36
Hodgkin Lymphoma	0/1	27	76

B symptoms were present in 3 (20%) patients with lymphoma developed on an immunosuppressive background and in 20 (40.8%) patients with primary lymphoma (p=0.08, OR 2.7 (0.6-10 95%CI)).

Bone marrow involvement, evaluated by bone marrow biopsy, was found in 3 (20%) patients with lymphoma developed on an immunosuppressive background and in 9 (18.4%) patients with primary lymphoma (p=0.7). Splenomegaly was present in 6 (40%) patients with lymphoma developed on an immunosuppressive background and in 15 (30.6%) patients with primary lymphoma (p=0.8).

EBV serology was positive in 60% of patients with lymphoma developed on an immunosuppressive background. EBV serology was positive in 71% of patients who died during the follow-up period. The mean survival time was 5.2 months for patients with EBV-positive lymphoma who died and 11 months for

EBV-negative patients.

Patients with primary lymphoma received 6±2 cycles of chemotherapy, while the patients with immunosuppression received 5.5±4 cycles (p=0.6).

The remission rate after the first treatment regimen applied in patients with primary lymphoma was 79.6%, while this rate was 46.6% in the group with lymphoma developed on an immunosuppressive background (p=0.025 OR 5.6 (1.4-22 95%CI)).

When patients with lymphoma developed on an immunosuppressive background were grouped according to their primary disease, complete remission was observed in one of the two patients with SLE diagnosis, complete/partial remission in two patients with liver transplantation, complete remission in two of the five patients with HIV, and one patient's treatment is still ongoing. Remission could not be achieved in two patients with kidney transplantation.

The frequency of stage III-IV disease was 73.3% in patients with lymphoma developed on an immunosuppressive background and 49% in primary lymphomas (p=0.09). The remission rate was 82.7% in stage I-II tumors and 62.8% in stage III-IV patients (p=0.08 OR 3.3 (0.8-3,1 95%CI)). No statistically significant relationship was found between stage and treatment response. The treatment responses are summarized in Table 2.

Table 2. Response to treatment according to different categories

	Response to Treatment	
	Complete / Partially Response N (%)	Progression N (%)
Primary lymphoma	39 (79,6)	10 (%20,4)
Immunosuppression related lymphoma	7 (%46,6)	8 (%53,4)
Stage I-II	24 (%82,7)	5 (%17,2)
Stage III-IV	22 (%62,8)	13 (%37,2)
International prognostic index		
0	5 (%100)	0
1	19 (%100)	0
2	13 (%72,2)	5 (%27,3)
3	9 (%47,3)	10 (%52,7)
4	0	3 (%100)

The median IPI score was 2.5 ± 2 in patients with lymphoma developed on an immunosuppressive background and 2 ± 2 in newly diagnosed primary lymphoma (p=0.04). When both groups were evaluated together, 7.8% of the patients had an IPI score of 0, 29.6% had an IPI score of 1, 28.1% had an IPI score of 2, 29.6% had an IPI score of 3, and 4.9% had an IPI score of 4. The treatment response worsened as the IPI score increased (p<0.001).

Although the relapse rate was lower in patients with lymphoma developed on an immunosuppressive background, the difference was not statistically significant. One patient with lymphoma developed on an immunosuppressive background experienced relapse, while relapse was observed in six patients with primary newly diagnosed lymphoma.

Extranodal involvement was present in a similar proportion of patients with lymphoma developed on an immunosuppressive background (60%) and those with primary lymphoma (65.3%). The most common extranodal sites in patients with lymphoma developed on an immunosuppressive background were the spleen and the gastrointestinal system. Notably, extranodal disease was present in a high proportion (85.7%) of the patients in this group who died. The stomach was the most common extranodal organ involved in the primary lymphoma group, and extranodal disease was present in 3 (60%) of the patients who died.

The detailed laboratory parameters for patients in both groups are presented in Table 3. The mean Lactate Dehydrogenase (LDH) level was significantly higher in patients with lymphoma developed on an immunosuppressive background who died compared to those who did not die (828.4±303.9 U/L vs 439.4±72.9 U/L). A similar trend was observed in patients with primary lymphoma, where the mean LDH level was higher in patients who died (681.2 ± 124.8 U/L) compared to surviving patients (355.4±211.3 U/L).

Table 3. The laboratory parameters in the total cohort with mean ± SD values

	Immunosuppression related lymphoma	Primary lymphoma	P value
White blood cell (/mm^3)	6660±3862,2	8159,3±8052	0,7
Lymphocyte (/mm^3)	1282±819,7	2887,7 ±5877,5	0,09
Neutrophil (/mm^3)	5026,6±3930,5	4953,2±1974,7	0,6
Hemoglobin (gr/dl)	10,5±2	11,8±1,6	0,9
Platelet (/mm^3)	200533,3±95120,1	272000±89233,3	0,4
Gamma globulin (g/dL)	0,9±0,1	1 ±0,2	0,08
Lactate Dehydrogenase (U/L)	621,1±319,4	424±304,7	0,2
B2 microglobulin (mg/L)	3,4±1,6	3 ±2,1	0,1

B2 microglobulin levels were consistently higher in patients who died compared to those who were alive, regardless of whether they had lymphoma developed on an immunosuppressive background or primary

lymphoma. This difference was statistically significant (p=0.01). When the effect of the B2 microglobulin level on survival was investigated, it was observed that survival decreased significantly as the B2 microglobulin level increased.

During the follow-up period, which averaged 16.1±10.2 months, twelve patients (18.8%) died. The cause of death was an infection in 63.5% of patients, while disease progression-related death occurred in 31,7% of patients. The remaining patients died due to treatment-related side effects. Mortality was significantly higher in patients with lymphoma developed on an immunosuppressive background (46.7%) compared to patients with primary lymphoma (10.2%). The mean PFS was also shorter in patients with lymphoma developed on an immunosuppressive background (22.4±4.2 months) compared to patients with primary lymphoma (32.2±1.5 months). In the primary lymphoma group, the average survival time for patients who died was 16 months. Interestingly, no statistically significant relationship between stage and mortality was found when both groups were evaluated. However, when only patients with lymphoma developed on an immunosuppressive background were assessed, the mortality rate was significantly higher in advanced-stage patients compared to early-stage patients.

Discussion

NHL is a heterogeneous disease with many subtypes within the group of lymphoproliferative disorders. While the median age of diagnosis for NHL is 60 years (range 14-98), the age of onset in patients with lymphoproliferative diseases arising in the setting of immunosuppression is highly variable (14). Diffuse large B-cell lymphoma constitutes 30-58% of all NHL cases in developed countries (15).

In our study, the median age in the newly diagnosed primary lymphoma group was 54 years, with 57% being male. In the other group, the median age was 50, and 60% were male. When both groups were evaluated together, similar to the literature, diffuse large B-cell lymphoma was diagnosed in 75% of patients, and marginal zone lymphoma was diagnosed in 9%.

Few studies investigate the relationship between immunosuppressive therapy, treatment duration, and lymphoma development. An analysis of 140 patients with post-transplant lymphoma reported a five-year relative risk of NHL development of 29.2 for liver transplantation and 17.4 for kidney transplantation (11). Another study found the median duration of immunosuppression to be 133 months, and azathioprine-containing regimens were identified as carrying the highest risk of lymphoma development (16). Ciftciler et al. discovered that 6 patients with immunosuppression out of 52 patients with atypical lymphoproliferative disorder developed lymphoproliferation after a median of 2.3 months (17). In our study, NHL developed after an average of 53 months of immunosuppressive therapy in four patients who received liver transplants and after an average of 111 months in two patients who received kidney transplants.

The incidence of lymphoma in patients with CVID ranges from 1.8% to 2.2%, with the disease typically presenting between the ages of 20 and 40 and lymphoma developing between 40 and 70 (14). The patient with CVID included in our study was diagnosed at 28, and NHL was diagnosed 72 months after the initial diagnosis.

NHL develops in 10% of HIV-positive patients, and the time interval between diagnosis and lymphoma development varies across studies (18). In our research, this period was found to be 36 months.

In an evaluation of nine patients receiving immunosuppression for rheumatologic disease, the average duration of immunosuppressive therapy was 48 months (19). In our study, NHL developed after an average of 198 months in two patients with SLE receiving immunosuppressive therapy.

EBV is frequently associated with lymphoma development (20). A prospective study that followed 98 lymphoma patients who developed the disease in the setting of immunosuppression for various reasons for a median of 7.6 years found EBV serology positive in 83% of patients (21). A study investigating the association between EBV and mortality in PTLD examined 288 patients who underwent umbilical cord transplantation. EBV-positive PTLD developed in 22 patients, and the survival time was statistically significantly shorter in patients with EBV-positive PTLD (22). A study conducted on HIV-positive lymphoma patients showed that the impact of EBV seropositivity on two-year mortality was more significant than only an elevated IPI score (23). The role of EBV in the pathogenesis of SLE is well-known. Cohort studies have observed a significantly higher EBV positivity rate (50-70%) in patients with lupus compared to the average population (24).

In our study, EBV serology was positive in 60% of

patients who developed lymphoma in the setting of immunosuppression. When examining EBV serological positivity according to the primary disease, the rates were as follows: 100% in patients with SLE, 75% in PTLD following liver transplantation, 100% in PTLD following kidney transplantation, 40% in HIV-positive patients, negative in the patient with CVID, and negative in the patient who developed NHL following HL chemotherapy. Additionally, EBV serology was positive in 71% of the patients who died during the follow-up period. The median survival time for patients with EBV-positive lymphoma who died was 5.2 months, while the median survival time for patients with EBV-negative lymphoma who died was 11 months. Although statistical significance was not determined due to the heterogeneity of the primary disease and limited data, our study also observed a high rate of EBV seropositivity in patients with lymphoma arising in the setting of immunosuppression, similar to the studies conducted in the literature. Additionally, we observed shorter survival times and higher mortality rates in patients with EBV-positive disease.

Taborelli et al. reported a 5-year OS rate of 64% in their study, whereas Murray et al. found a statistically significantly lower OS in patients with PTLD (25, 26). Another study following 45 patients with post-liver transplant lymphoma for a median of 27 months found a median OS of 50 months (27). In our study, the average OS for the four patients who developed lymphoma after liver transplantation was eight months. The two patients who developed lymphoma after kidney transplantation had an OS of 5 months and died. Both PTLD patients received reduced-dose immunosuppressive therapy and chemotherapy. The patients who died after transplant were over 60 years old, had stage III-IV disease, and had an IPI score of 3-4.

Studies investigating HIV-associated lymphoma have identified high active antiretroviral therapy and IPI score as statistically significant independent factors affecting OS (28). Another study included 119 HIV-positive patients who developed non-Kaposi's sarcoma malignancies. After a median follow-up of 38.5 months, 82.5% of the patients developed NHL, and 56% of these patients had stage IV disease. The median OS for the 78 chemotherapy-eligible patients in the NHL group was six months (29). Our study included five HIV-positive lymphoma patients. Two patients (40%) died. The patient diagnosed with Burkitt's lymphoma died after 14 months, and the patient diagnosed with Kaposi's sarcoma died after three months. Three HIV-positive patients were diagnosed with diffuse large B-cell lymphoma whose PFS was an average of 24 months. Despite the small sample size, their survival time was similar.

There are limited studies and case reports on the development of lymphoma associated with CVID, and most involve the pediatric population. A retrospective study conducted between 1986 and 1997 found that 19 of the 413 patients with NHL who presented had CVID-associated lymphoma. Three of these patients died from progression, three from sepsis, one from treatment-related toxicity, and one from a second malignancy (30). In our study, one patient with CVID developed diffuse large B-cell lymphoma 78 months after diagnosis. Their PFS was 26 months.

Bernardsky et al. found that lymphoma developed an average of 12.4 years after the diagnosis of SLE in their study. The median age of the patients was 57, and 22% of the patients died within a median of 1.2 years (31). Our study included two patients with SLE. The first patient had a PFS of 32 months. Upon detailed examination, the patient was found to have early-stage disease and an IPI score of 1. The other patient died five months after diagnosis.

Statistically, providing an average value for OS was the main limitation of this study. Therefore, it was not appropriate to compare survival times with historical studies. However, this did not pose a problem when comparing the two groups within the study. Consistent with the literature, our study found that patients with lymphoma arising from immunosuppression had a significantly lower OS and a significantly higher mortality rate compared to patients with primary lymphoma. The average PFS was 22.4 ± 4.2 months in patients with lymphoma arising from immunosuppression and 32.2 ± 1.5 months in patients with primary lymphoma.

A study conducted at Istanbul University Cerrahpaşa Faculty of Medicine between 2000 and 2011 showed a significant correlation between the calculated IPI score and OS and PFS in 312 NHL patients diagnosed and followed. The PFS rates were 85%, 80%, 57%, and 51% for patients with IPI scores of 0-1, 2, 3, and 4-5, respectively (32). In our study, similar to the literature, the IPI score of patients with primary lymphoma was significantly lower than that of patients with lymphoma from immunosuppression. When both groups were evaluated together, an increase in the IPI score was shown to have a statistically significant effect on

mortality. The remission and partial remission rates were also statistically significantly higher in patients with lower IPI scores. Remission rates were 100%, 72%, and 47.3% for patients with IPI scores of 0-1, 2, and 2-3, respectively. Progression or death was observed in 52.7% of patients with an IPI score of 3 and 100% of patients with an IPI score of 4.

One of the IPI parameters, LDH, has prognostic significance (33). In our study, when both groups were evaluated separately, the LDH value was significantly higher in patients with mortality. Similar to the literature, the LDH value was found to be significantly higher in patients with lymphoma arising from immunosuppression, as expected, as the IPI value was significantly higher, mortality was higher, and survival was lower.

A study conducted at Trakya University with 114 NHL patients investigated treatment, response to treatment, and survival. The median survival for patients with stage IV disease at diagnosis was 26 months, 86 months for stage II, and 96 months for stage III. It was observed that patients with B symptoms, extranodal and bone marrow involvement at diagnosis, those who did not respond to first-line treatment, and those with IPI>2 had statistically significantly shorter survival than others (34).

In our study, no statistically significant relationship was found between stage, treatment response, and mortality when both groups were evaluated. However, when patients with lymphoma arising from immunosuppression were assessed, the mortality rate was significantly higher in patients with advanced-stage disease compared to early-stage patients. When the primary lymphoma group was evaluated, 60% of the patients with mortality were found to be stage I-II. This difference can be explained by the fact that the patients with mortality in the primary lymphoma group had a higher IPI score, a higher B2 microglobulin value, and were older.

It is known that B2 microglobulin levels are higher in NHL patients than in the average population. In a prospective study, 287 NHL patients were followed for seven years, and PFS was calculated according to high and low B2 microglobulin levels. Three models were created using the Cox model, including IPI. As a result, a strong and statistically significant relationship was found between B2 microglobulin elevation and mortality. It was also shown that the mortality of patients with high serum B2 microglobulin and IPI was significantly higher than that of patients with only high B2 microglobulin or only high IPI (35). In a retrospective study of 312 newly diagnosed, untreated NHL patients, the optimal cut-off value for serum B2 microglobulin level was 3.2 mg/L. It was shown that patients with B2 microglobulin value ≥3.2 mg/L had significantly lower PFS and OS than patients with <3.2 mg/L (36).

Similar to the literature, in our study, B2 microglobulin levels were statistically significantly higher in patients who died when both groups were analyzed separately and all patients together. In both groups, the average B2 microglobulin level of patients with mortality was 5.2±1 mg/L, while the average for patients alive was 3.4±1.8 mg/L. When the cut-off value of 3.2 mg/L, referenced in the studies, was accepted, the PFS was 27.1 months for patients with B2 microglobulin level <3.2 mg/L and eight months for patients with ≥3.2 mg/L.

One of the most important limitations of our study is that the primary diseases and, therefore, the immunosuppressive treatments used in the patient population with lymphoma arising from immunosuppression were very variable. Including solely one Kaposi's sarcoma with lymphoma patient could introduce heterogeneity. Another limitation is that the number of patients was insufficient to evaluate the characteristics and survival of lymphoma for each primary disease.

Despite these limitations, the study will contribute to the literature by presenting the single-center experience of a relatively rare group of patients in our country and compiling the studies. Future studies with larger patient populations are needed to investigate further the relationship between lymphoma arising from immunosuppression, stage, treatment response, B2 microglobulin level, and other factors.

Conclusion

Compared to patients with newly diagnosed primary lymphoma, patients with lymphoma arising from immunosuppression were shown to have statistically significantly higher IPI scores, worse treatment responses, higher LDH and B2 microglobulin values, shorter mortality, and PFS. This study supports that treating lymphoproliferative disease developing on an immunosuppressive basis is more complex; the prognosis is worse, the mortality is higher, and the survival is lower. Serum B2 microglobulin, serum LDH, IPI score, and EBV DNA status can also help to determine the prognosis of lymphoproliferative disease developing on an immunosuppressive basis.

Patients receiving immunosuppressive therapy should be closely monitored for the development of lymphoma. More intensive chemotherapy regimens may be considered for patients with laboratory findings that indicate a poor prognosis.

Acknowledgments

This study was Sabin Göktaş Aydın's Internal Medicine Thesis. It has not been previously published in another journal or publishing house.

Ethical Committee Approval Information

Approving Committee

Consent was obtained from the patients or their first-degree relatives. The ethics committee approved the study with decision number E-10840098-202.3.02-3213.

Researcher Contribution Statement

Idea and design: M. Nalcaci; Data collection and processing: S. Göktaş Aydin, A Aydin; Interpretation of the data: M. Nalçacı, S. Göktaş Aydın; Writing significant sections of the article: M. Nalçacı, S. Göktaş Aydın, A. Aydin; Reviewing and evaluating the article: S. Besısisk, İ. Onal, M. Yenerel.

Conflict of Interest Statement

The authors declare no conflict of interest.

There is no funding.

References:

1.Tran H, Nourse J, Hall S et al. Immunodeficiency Associated Lymphomas. Blood Reviews; 2008;22:261-281.

2.Yarbo JW. The Epstein Barr virus and the distinction between benign and malignant lymphoproliferative processes. Semin Oncol 1993; 20:658-661.

3.Swerdlow S, Campo E, Harris N et al. WHO Classification of tumors of haematopoetic and lymphoid tissue. 4th ed. Bosman F, Jaffe E, Lakhani S, Ohgaki H. editors Lyon, France International Agency for Research on Cancer (IARC); 2008.

4.Salavoura K, Kolialexi A, Tsangaris G et al.Development of cancer in patients with primary immunodeficiencies. Anticancer Res; 2008;28:1263-1269.

5.Leechawengwongsa E, Shearerb WT. Lymphoma complicating primary immunodeficiency syndromes. Curr Opin Hematol 2012; 19:305-312.

6.Kaplan LD. HİV-associated lymphoma. Best Practice & Research Clinical Haematology 2012;25:101-117.

7.Morrison VA, Dunn DL, Maniel JC et al. Clinical characteristics of posttransplant lymphoproliferative disorders. Am J Med 1994;97:14-24

8.Lebland V, Sutton L, Dorent R et al. Lymphoproliferative disorders after organ transplantation: A report of 24 cases observed in a single center. J Clin Oncol 1995; 13:961-968.

9.Craig FE, Gulley ML, Banks PM. Posttransplantation lymphoproliferative disorders. Am J Clin Pathol 1993; 99:265-276

10.Nalesnik MA, Starzl TE. Epstein-Barr virus, infectious mononucleosis, and post- transplant lymphoproliferative disorders. Transplantation Science 1994;4:61-79.

11.Fararjeh FA, Mahmood S, Yallop D et al. A retrospective analysis of post-transplant lymphoproliferative disorder following liver transplantation. Eur J Haematol. 2018;100(1):98-103.

12.Benkerrou M, Durandy A, Fischer A. Therapy for transplant-related lymphoproliferative diseases. Hematol Oncol Clin North Am 1993; 7:467-475.

13.Hasserjian RP, Chen S, Perkins SL et al. Immunomodulatuar agent related lymphoproliferative disorders. Mod Pathol 2009;22:1532-1540.

14.Shapiro RS. Malignancies in the setting of primary immunodeficiency. İmplications for hematologists/oncologists. Am J Hematol 2011;86:48-55.

15.Wagner N, Bartlett N. Lymphoma. In: Govindan R, Arqueta M, editors. The Washington Manual of Clinical Oncology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 278-97,57.

16.Cheung CY, Ma MKM, Chau KF et al. Posttransplant lymphoproliferative disorders in kidney transplant recipients: retrospective cohort analysis over twodecades in Hong Kong. Oncotarget. 2017;8(57):96903-96912.

17.Ciftciler R, Ciftciler AE, Saglam EA et al. Follow-up of Patients with Atypical Lymphoproliferation in Bone Marrow or Lymph Node Biopsy. Acta Medica, 52(1), 37–42

18.Longa J L, Engelsa E A, Moorea R D et al. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HİV-infected individuals. AIDS 2008;22:489-496

19.Kawano N, Ono N, Kawano S et al. New concepts in EBV-associated B, T, and NK cell lymphoproliferative disorders. Virchows Arch. 2023;482(1):227-244.

20.Taj MM, Hadzic N, Height SE et al. Long term outcome for immune suppression and immunerelated lyphoprolifreative disorder prospective data from the United Kingdom Children's Leukaemia and Cancer Group registry 1994-2004. Leuk Lymphoma. 2012;53(5):842-8.

21.Sanz J, Arango M, Senent L et al. EBV associated postransplant lymphoproliferative disorderafter umbilical cord blood transplantation in adults with hematological diseases. Bone Marrow Transplant. 2014;49 (3):397-402.

22.Carbone A, Volpi CC, Gualeni AV et al. Epstein Barr virus associated lymphomas in people with HIV. Curr Opin HİV AIDS. 2017;12(1):39-46.

23.Chougule D, Nadkar M, Rajadhyaksha A et al. Association of clinical and serological parameters of systemic lupus erythematosus patients with Epstein-Barr virus antibody profile. J Med Virol. 2018;90(3):559-563.

24.Taborelli M, Piselli P, Ettorre GM et al. Italian Transplant and Cancer Cohort Study. Survival after the diagnosis of de novo malignancy in liver transplant recipients. Int J Cancer. 2019;144(2):232-239.

25.Murray SL, O'Leary E, De Bhailís ÁM et al. Cancer survival in kidney transplant recipients in Ireland. Nephrol Dial Transplant. 2020;35(10):1802-1810.

26.Mukthinuthalapati PK, Gotur R, Ghabril M . Incidence, risk factors and outcomes of de novo malignanciespost liver transplantation. World J Hepatol. 2016;8(12):533-44.

27.Mounier N, Spina M, Gabarre J et al. AIDS-related non-Hodgkin lymphoma: final analysis of 485patients treated with risk-adapted intensive chemotherapy. Blood. 2006;107(10):3832-40

28.Oriol A, Ribera JM, Esteve J et al. PETHEMA Group, Spanish Society of Hematology. Lack of influence of human immunodeficiency virus infection status in the response to therapy and survival of adult patients with mature B-cell lymphoma or leukemia. Results of the PETHEMA-LAL3/97 study. Haematologica. 2003;88(4):445-53

29.Seidemann K, Tiemann M, Henze G et al. Therapy for non-Hodgkin lymphoma in children with primaryimmunodeficiency: analysis of 19 patients from the BFM trials. Med Pediatr Oncol. 1999;33(6):536-44

30.Bernatsky S, Velásquez García HA, Spinelli JJ et al. Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma.

31.Ozbalak M, Ar MC, Tuzuner N et al. Detailed analysis of diffuse large B cell lymphoma patients: a single center, retrospective study. ISRN Hematol. 2013;2013:908191.

32.Yadav C, Ahmad A, D'Souza B et al. Serum Lactate Dehydrogenase in Non-Hodgkin's Lymphoma: A Prognostic Indicator. Indian J Clin Biochem. 2016;31(2):240-2

33.Pamuk G.E, Harmandar F, Hrmandar O et al. Non-Hodgkin Lenfoma Vakalarımızın Klinik Özelliklerinin Değerlendirilmesi .International Journal of Hematology and Oncology 2006;16(4):185-94.

34.Wu L, Wang T, Gui W et al. Prognostic Significance of Serum Beta-2 Microglobulin in Patients with Non-Hodgkin Lymphoma Oncology 2014;87:40-47

35.Kanemasa Y, Shimoyama T, Sasaki Y et al. Beta-2 microglobulin as a significant prognostic factor and a new risk model for patients with diffuse large B-cell lymphoma. Hematol Oncol. 2017;35(4):440-446.