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Evaluation of PD-1 / PD-L1 Expressions in Patients with Diffuse Large B Cell Lymphoma and Chronic Lymphocytic Leukemia

Diffüz Büyük B Hücreli Lenfoma ve Kronik Lenfositer Lösemili Hastalarda PD-1 / PD-L1 Ekspresyonlarının Değerlendirilmesi

Cigdem Akkus[1], Sinan Demircioglu[2], Remzi Erten[3], Sinemis Cetin Dagli[4], Ali Dogan[5]

[1]Van Training and Research Hospital, Internal Medicine Clinic, Van,Türkiye
2 Necmettin Erbakan University Faculty of Medicine, Department of Hematology, Konya,Türkiye
3 Health Sciences University, Diyarbakır Gazi Yaşargil Trainning and Research Hospital, Department of Pathology, Diyarbakır,Türkiye
4 Van Yüzüncü Yıl University Faculty of Medicine, Department of Public Health, Van,Türkiye
5 Van Yüzüncü Yıl University Faculty of Medicine, Department of Hematology, Van,Türkiye

ÖZET

Amaç: Programlanmış ölüm 1 (PD-1) / PD-ligandı (PDL) yolu, T hücresi aracılı immün yanıtlarının düzenlenmesi için önemli bir kontrol noktasıdır. Kanserler ne yazık ki PD-1/ PD-L1 yolunun immünsüpresif etkilerinden de yararlanmaktadır. Yaygın Büyük B Hücreli Lenfoma (YBBHL) ve Kronik Lenfositer Lösemi (KLL)'de PD-1/ PD-L1'in önemi ile ilgili yeterli kanıt yoktur. Çalışmamızda YBBHL ve KLL'de PD-1/ PD-L1 ekspresyonun varlığını ve prognostik önemini değerlendirmeyi amaçladık.

Gereçler ve Yöntem: Hematoloji Kliniğinde Ocak 2010 ile Eylül 2018 tarihleri arasında takip edilen 18-80 yaş arası 26 YBBHL hastası ve 27 KLL hastası çalışmaya dahil edildi. İmmunhistokimyasal boyama için Tıbbi Patoloji Anabilim Dalı arşivinde bulunan hastalara ait parafin blokları kullanıldı. YBBHL hastalarının lenf bezi biyopsi materyalleri ve KLL hastalarının kemik iliği biyopsi materyalleri değerlendirildi. PD-1 neoplastik olmayan dokularda boyandı ve PD-L1 neoplastik hücrelerde boyandı. Boyanma yüzdesi %5'in üzerinde olanlar pozitif kabul edildi.

Bulgular: PD-1; YBBHL olgularının %65,4'ünde (n=17) pozitif, KLL olgularının %14,8'inde (n=4) pozitif saptandı. PD-L1; YBBHL olgularının %69,2'sinde (n=18) pozitif, KLL olgularının PD-L1 %3,7'sinde (n=1) pozitif saptandı. PD-1 ve PD-L1 ekspresyon ve boyanma sıklığı istatistiksel olarak anlamlı şekilde YBBHL'da daha yüksek bulundu (p=<0.001). PD-L1'de YBBHL tanılı olgularda evreler arasında ekspresyon açısında anlamlı fark bulundu (P=0,004).

Sonuç: Çalışmamızda YBBHL'de literatürden daha yüksek oranda PD-1/ PD-L1 ekspresyonu tespit edildi. KLL'de diğer çalışmalara göre daha düşük oranda PD-1/PD-L1ekspresyonu saptandı. PD-1/ PD-L1 ekspresyonun YBBHL'de KLL'den daha fazla olduğu gösterildi.

Anahtar Kelimeler: Yaygın Büyük B Hücreli Lenfoma, Kronik Lenfositer Lösemi, PD-1, PD-L1.

ABSTRACT

Aim: The programmed death 1 (PD-1) / PD-ligand (PDL) pathway is an important checkpoint for regulation of T cell mediated immune responses. Malignancies unfortunately also benefit from the immunosuppressive effects of the PD-1/PD-L1 pathway. There is not enough evidence regarding the importance of PD-1/ PD-L1 in Diffuse large B cell lymphoma (DLBCL) and Chronic lymphocytic leukemia (CLL). We aimed to evaluate the presence and prognostic significance of PD-1 / PD-L1 expression in DLBCL and CLL.

Materials and Methods: 26 DLBCL patients and 27 CLL patients aged between 18-80 years, who were followed up between January 2010 and September 2018 in Hematology Clinic, were included. For immunohistochemical staining, paraffin blocks belonging to the patients in the archive of Medical Pathology Department were used. Lymph node biopsy materials of DLBCL patients and bone marrow biopsy materials of CLL patients were evaluated. PD-1 was stained in non-neoplastic tissues and PD-L1 was stained in neoplastic cells. Those whose staining percentage was above 5% were considered positive.

Results: PD-1; It was detected positive in 65.4% (n=17) of DLBCL cases and 14.8% (n=4) of CLL cases. PD-L1 was detected positive in 69.2% (n=18) of DLBCL cases, and PD-L1 was positive in 3.7% (n=1) of CLL cases. The frequency of PD-1 and PD-L1 expression and staining was found to be statistically significantly higher in DLBCL (p=<0.001). In PD-L1, a significant difference in expression was found between stages only in cases diagnosed with DLBCL (P=0,004).

Conclusion: In our study, a higher rate of PD-1/ PD-L1 expression was detected in DLBCL than in the literature. A lower rate of PD-1/ PD-L1 expression was detected in CLL compared to other studies. It has been shown that PD-1/ PD-L1 expression is higher in DLBCL than in CLL.

Keywords: Diffuse large B cell lymphoma, Chronic lymphocytic leukemia, PD-1, PD-L1.

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Sorumlu Yazar/Corresponding Author: Sinan Demircioğlu, Necmettin Erbakan University, Faculty of Medicine, Department of Hematology, Konya, Türkiye
e-mail: sinandemircioglumd@gmail.com

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INTRODUCTION

The programmed death 1 (PD-1)/PD-ligand (PDL) pathway is important for the regulation of T cell-mediated immune responses (1). The complex consists of the transmembrane protein PD-1/CD279 and its two ligands PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273). PD-1 is expressed on activated T cells, B cells, natural killer cells, macrophages, as well as a large proportion of tumor-infiltrating lymphocytes (TIL) (2). PD-1 functions as an important immune checkpoint in the regulation of T cell-mediated responses. PD-L1 is expressed mainly by antigen-presenting cells (APCs) as well as various non-hematopoietic cells and tumor cells (3).

PD-L1 is activated by PD-1 and causes reversible inhibition of T cell activity and proliferation (4–6). Malignant cells can also exploit the immunosuppressive effects of the PD-1-PD-L1 pathway (7). Many tumors are known to express PD-L1 as a line of defense against TILs (8). The importance of PD-1/PD-L1 expression in some solid tumors and in Hodgkin's lymphoma (HL), a hematological neoplasm, is well known. Anti-PD-1/PD-L1-directed treatments have begun to be used successfully in the clinics (9). However, there is insufficient evidence regarding the importance of PD-1/PD-L1 in Diffuse large B cell lymphoma (DLBCL) and Chronic lymphocytic leukemia (CLL). In the current study, we aimed to evaluate the presence and prognostic significance of PD-1/PD-L1 expression in DLBCL and CLL.

MATERIALS AND METHODS

Patients

The current study included 26 DLBCL and 27 CLL cases who received chemotherapy and were followed up at the Hematology Clinic between January 2010 and September 2018, and whose post-chemotherapy response data was available. Lymph node biopsy materials of DLBCL patients and bone marrow biopsy materials of CLL patients were evaluated. Patients between the ages of 18 and 80 years were included in the study. DLBCL disease stage at diagnosis was determined according to the Ann Arbor staging system, and risk scoring was calculated according to the International Prognostic Index (IPI) score. CLL staging was carried out according to the RAI classification. Stage at diagnosis and risk scores were determined from patient files. The study was approved by Non-Interventional Clinical Research Ethics Committee (Decision no: 08, Date: 09.11.2018). Financial support for the study was obtained from the Scientific Research Project unit (project number TTU-2019-7741).

Immunohistochemical Analysis

Paraffin blocks of specimens collected from patients diagnosed with DLBCL and CLL were used for immunohistochemical staining. The appropriate paraffin blocks were selected from Hematoxylin - Eosin sections. The presence of sufficient tissue from the paraffin blocks for immunohistochemical examination was first evaluated. Next, 4 micrometer thick sections were obtained from the selected paraffin blocks with a Leica RM® 2135 (Leica MICROSYSTEMS, GERMANY) brand rotary microtome device and placed on poly-L-lysine coated slides. Primary antibodies against PD-1 (NAT105) and PDL-1 (SP263) were used. The sections were stained with these antibodies using the Ventana Benchmark XT immunohistochemistry automatic staining system and Ventanaultra View Universal DAB Detection Kit (REF 760-500, Ventana Medical Systems, Inc., Arizona, USA) accompanied by appropriate positive controls. The stainings were evaluated at different magnifications on an Olympus BX53F (Olympus, Tokyo, Japan) light microscope. The staining intensity was evaluated in non-neoplastic tissues for PD-1 and in neoplastic cells for PD-L1 as follows:

Table 1. Laboratory Data

	DLBCL Mean±SD	CLL Mean±SD
Hb (g/dl)	12.5 ± 2.1	12.1 ± 2.98
WBC (x109/L)	7.68 ± 3.16	7.53 ± 8.81
PLT(x109/L)	220.23 ± 103.27	152.51 ± 85.73
Neutrophil count (x109/L)	5.37 ± 2.84	8.05 ± 7.86
Lymphocyte count (x109/L)	1.59 ± 1.85	59.99 ± 74.61
Eosinophil count (x109/L)	0.90 ± 0.87	0.33 ± 0.60
Monocyte count (x109/L)	0.51 ± 0.43	5.99 ± 11.84
MCV(fL)	86.23 ± 5.36	91.59 ± 7.99
Glucose (mg/dl)	112.07 ± 61.23	102 ± 24.11
ALT (U/L)	28.65 ± 27.09	20.55 ± 14.10
AST (U/L)	35.03 ± 6.68	23.44 ± 7.94
Uric acid (mg/dl)	5.15 ± 2.20	5.35 ± 1.55
Creatine (mg/dl)	1.06 ± 0.50	0.83 ± 0.265
Urea (mg/dl)	1,03 ± 2,05	3,31 ± 6,06
Ferritin(ng/ml)	318.39 ± 410.92	151.19 ± 265.69
Sedimentation (mm/h)	33.26 ± 26.16	27.33 ± 29.20
CRP (mg/L)	49.19 ± 5.,69	19.13 ± 29.64
Albumin (g/dl)	3.56 ± 0.67	4.13 ± 0.762
Ki-67(%)	67.11 ± 22.27	12.03 ± 10.917

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, Hb: hemoglobin, PLT: platelet count, MCV: Mean corpuscular volume, WBC: white blood cell, DLBCL: Diffuse large B cell lymphoma, CLL:Chronic lymphocytic leukemia

(-) or (0): No staining
(+) or (1): Weak staining
(++) or (2): Moderately strong staining
(+++) or (3): No strong staining

The sections with a staining percentage above 5% were considered positive, and those below 5% were considered negative.

Table 2. PD-1 / PD-L1 expression frequency and staining intensity in DLBCL-CLL.

	DLBCL (n:26)		CLL (n:27)		P value
	N	%	N	%	
PD-1 expression					
Positive	17	65.4	4	14,8	
Negative	9	34.6	23	85,2	<0.001
PD-1 staining intensity					
-(0)	7	26.9	19	70,4	
+ (1)	3	11.5	5	18,5	0,001
++ (2)	13	50	3	11,1	
+++ (3)	3	11.5	0	0	
PD-L1 expression					
Positive	18	69.2	1	3,7	
Negative	8	30.8	26	96,3	<0.001
PD-L1 staining intensity					
-(0)	7	26.9	26	96,3	
+ (1)	0	0	0	0	
++ (2)	1	3,8	0	0	
+++ (3)	18	69.2	1	3,7	<0.001

Those with a staining percentage above 5% were considered positive, and those below were considered negative. DLBCL: Diffuse large B cell lymphoma, CLL:Chronic lymphocytic leukemia

Table 3. Prognostic significance of PD-1 / PD-L1 in DLBCL.

		PD-1			PD-L1		
	n	Positive (%)	Negative (%)	P value	Positive (%)	Negative (%)	P value
Stage							
1	6	4 (66,6)	2 (33,3)		4 (66,7)	2 (33,3)	
2	5	2 (40)	3 (60)	0,058	2 (40)	3 (60)	0,004
3	11	10(90,9)	1 (9,1)		11 (100)	0 (0)	
4	4	1 (25)	3 (75)		1 (25)	3 (75)	
ECOG Performance Status							
1	11	8 (72,7)	3 (27,3)		8 (72,7)	3 (27,3)	
2	3	2 (66,7)	1 (33,3)	0,615	2 (66,7)	1 (33,3)	0,962
3	5	2 (40)	3 (60)		3 (60)	2 (40)	
4	7	5 (71,4)	2 (28,6)		5 (71,4)	2 (28,6)	
IPI score							
Low risk	9	7 (77,8)	2 (22,2)		7 (77,8)	2 (22,2)	
Low-intermediate risk	2	0 (0)	2 (100)	0,131	0 (0)	2 (100)	0,145
High-intermediate risk	9	5 (55,6)	4 (44,4)		6 (66,7)	3 (33,3)	
High risk	6	5 (3,3)	1 (16,7)		5 (83,3)	1 (16,7)	
Disease subtype							
Germinal Center	6	5 (83,3)	1 (16,7)		4 (66,7)	2 (33,3)	
Non-Germinal	20	12 (60)	8 (40)	0,380	14 (70)	6 (30)	1,00
Ki 67 index							
<30	1	1 (100)	0 (0)		1 (100)	0 (0)	
>30	25	16 (64)	9 (36)	1,00	17 (68)	8 (32)	1,00
Treatment response							
Complete response	5	4 (80)	1 (20)		4 (80)	1 (20)	
Partial response	8	4 (50)	4 (50)	0,505	4 (50)	4 (50)	0,263
Unresponsive	9	7 (77,8)	2 (22,2)		8 (88,9)	1 (11,1)	
Stable disease	4	2 (50)	2 (50)		2 (50)	2 (50)	

ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, PD-1: Programmed death 1, PD-L1: Programmed death ligand-1, DLBCL: Diffuse large B cell lymphoma,

Table 4. Prognostic significance of PD-1/PD-L1 in CLL.

		PD-1			PD-L1		
	n	**Positive (%)**	**Negative (%)**	**P value**	**Positive (%)**	**Negative (%)**	**P value**
Stage							
0	1	0 (0)	1 (100)	0,710	0 (0)	1 (100)	0,842
1	6	1 (16,7)	5 (83,3)		0 (0)	6 (100)	
2	5	0 (0)	5 (100)		0 (0)	5 (100)	
3	15	3 (20)	12 (80)		1 (6,7)	14 (93,3)	
4	0	0 (0)	0 (0)		0 (0)	0 (0)	
ECOG Performance Status							
1	8	2 (25)	6 (75)	0,708	0 (0)	8 (100)	0,397
2	7	1 (14,3)	6 (85,7)		1 (14,3)	6 (85,7)	
3	4	0 (0)	4 (100)		0 (0)	4 (100)	
4	8	1 (87,5)	7 (12,5)		0 (0)	8 (100)	
Ki67 index							
<30	23	2 (8,7)	21 (91,3)	0,92	1 (4,3)	22 (95,7)	1,00
>30	4	2 (50)	2 (50)		0 (0)	4 (100)	
Treatment response							
Complete response	11	2 (18,2)	9 (81,8)	0,358	0 (0)	11 (100)	0,206
Unresponsive	5	0 (0)	5 (100)		1 (20)	4 (80)	
Stable disease	3	0 (0)	3 (100)		0 (0)	3 (100)	
Progressive disease	8	2 (25)	6 (75)		0 (0)	8 (100)	

ECOG: Eastern Cooperative Oncology Group, IPI: International Prognostic Index, PD-1: Programmed death 1, PD-L1: Programmed death ligand-1, CLL:Chronic lymphocytic leukemia

Statistical Analysis

The data were evaluated with the SPSS 22.0 statistical program. Frequency distributions were examined. Descriptive statistics are given as percentages and averages. Chi-square and Fisher's exact test were used for categorical variables. The suitability of numerical variables for normal distribution was evaluated with the Kolmogorov-Smirnov test. When parametric test conditions were met for numerical variables, Student-t test was used for binary variables, analysis of variance (ANOVA) was used in groups with more than 2 variables, Mann-Whitney U test was used when parametric conditions were not met, and Kruskal Wallis test was used in groups with more than two variables. The study was conducted with a 95% confidence interval, and $p<0.05$ was considered to be statistically significant.

RESULTS

The average age of the DLBCL cases at diagnosis was 56.4 ± 17.26 years; 46.2% (n=12) were female and 53.8% (n=14) were male. The average age of CLL cases at diagnosis was 61.40 ± 10.95 years, 44.4% (n=12) female and 55.6% (n=15) male. The distribution of the age at diagnosis of DLBCL and CLL was evaluated with the Mann-Whitney U test; no statistically significant difference was detected (p= 0.130). The mean leukocyte count was found to be higher in CLL patients (75326/µL) than in DLBCL patients (7683/µL). The Ki-67 index was found to be higher in DLBCL (67.11%) compared to CLL (12.03%). All other laboratory data are shown in Table 1.

The expression of PD-1/PD-L1 and their staining intensities in DLBCL and CLL (Table 2) were evaluated with the Pearson Chi-Square test; the proteins were found to be expressed statistically significantly more in DLBCL than in CLL (p=0.00) (Table 2). We observed that PD-1 was expressed in 65.4% and PD-L1 in 69.2% of the patients with DLBCL, while PD-1 was expressed in 14.8% and PD-L1 in 3.7% of the patients with CLL. No statistically significant difference in Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) score, IPI score, disease subtype, Ki67 index, treatment response and PD-1 expression could be identified in the cases diagnosed with DLBCL (P>0.05). A significant difference in PD-L1 expression was identified; additionally, a significant difference could be identified in the expression of PDL-1 between Ann Arbor stages (P=0.004) (Table 3).

We also evaluated the relationship between the expression of PD-1 and PD-L1 and RAI stage, ECOG score, IPI, Ki67 index, and treatment response in the cases diagnosed with CLL using the Chi-Square test. No statistically significant difference could be identified for either PD-1 or PD-L1 (Table 4).

DISCUSSION

The current study was designed to evaluate the expression of PD-1 and PD-L1 in patients with DLBCL and CLL. Yang et al. evaluated the plasma levels of PD-L1 in patients with B-cell lymphoma. The highest PD-L1 expression was found in DLBCL, followed by small lymphocytic lymphoma, mucosa-associated lymphoid tissue lymphoma, mantle cell lymphoma; the lowest expression of PD-L1 was detected in follicular lymphoma (10). Corroborating these data, we also observed stronger PD-L1 expression in DLBCL compared to CLL.

In one of the largest studies reported to date, PD-L1 and PAX5 were analyzed together in biopsy samples from 1253 DLBCL patients. PD-L1 was reported to be positively expressed in 11% of the tumor cells while PD-L1 (mPD-L1) was expressed in the tumor microenvironment in 15.3% of the cases. Both

tumor PD-L1(+) and mPD-L1(+) DLBCL were associated with non-germinal center B-cell type and Epstein-Barr virus (EBV) positivity. Patients with PD-L1(+) DLBCL had lower overall survival (OS) compared to patients with PD-L1(-) DLBCL. Contrary to our findings, a previous study has reported no significant difference in OS between mPD-L1(+) and mPD-L1(-) DLBCL (11). Another study investigated the relationship between the prognosis of DLBCL patients and PD-1 expression on the surface of CD4+ T cells. Patients with ≥30.25% PD-1 expression on CD4+ T cells had significantly lower event free survival (EFS) and OS compared to patients with <30.25% PD-1 expression on CD4+ T cells (10, 12). Kwon et al. reported that 61.1% of tumor cells in patients diagnosed with DLBCL showed expression of PD-L1. Strong PD-L1 expression on tumor cells was significantly associated with the presence of B symptoms and EBV infection and tended to be higher in activated B cell-like cells (16.7%) compared to the germinal center B cell (GCB)-like immunophenotype (2.5%). Increased infiltration of PD-1(+) cells was associated with prolonged progression-free survival (PFS) (P = 0.005) and OS (P = 0.026) in DLBCL patients treated with rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP). The prognostic significance of PD-L1 expression, however, was not reported in the study (13).

DLBCL is divided into two subtypes: GCB type, which generally has a good prognosis, and the non-GCB (activated B cell-like (ABC)) type, which shows poor prognosis. Compared with classical HL, the expression of PD-L1 is known to be much lower in DLBCL (except for some specific subtypes). Only 10-24% of DLBCL cases are known to be positive for PD-L1; of these, PD-L1 expression is observed more frequently in non-GCB than in the GCB subtype. Moreover, PD-L1 expression is detected more frequently in de-novo DLBCL than in transformed DLBCL. PD-L1 expression is seen in approximately two-thirds of EBV+ DLBCLs, while it is seen in 5–10% of EBV-negative DLBCLs (11, 14–16). In the current study, we observed more PD-L1 expression in the GCB arm (83.3%) compared to the non-GCB arm (60%), although the difference was not statistically significant.

PD-L1 was reported to be expressed in 70% of classical HL, 54% of nodular lymphocyte-predominant HL, 35% of primary mediastinal B-cell lymphomas, and 31% of primary DLBCL (17). Gassner et.al reported that T cells express high levels of the inhibitory exhaustion markers PD-1 and lymphocyte-activation gene 3 (LAG3), whereas CLL cells express high levels of PDL-1. The fraction of exhausted T cells was shown to increase with the progression of CLL. The same study also demonstrate that exhausted T cells could be reinvigorated and show CLL cytotoxicity by the inhibition of PD-1/PD-L1 interaction in vivo (18).

Grzywnowicz et.al demonstrated the expression of PD-1 and PD-L1 on the surface of CLL cells and reported that the expression of PD-1 was higher in CLL cells compared to healthy donors. However, the relationship between PD-1 and PD-L1 with time to progression and OS could not be demonstrated (19). Similarly, another study also reported higher expression of PD-1/PD-L1 in CLL patients compared to the control group; this high expression was associated with RAI stage, CD38, ZAP-70, chromosome karyotype (20). Another study that evaluated the effect of EBV status on CLL prognosis also reported a higher expression of PD-1/PD-L1 in the patient group compared to the control group. High expression of PD-1/PD-L1 was associated with poor prognostic markers (RAI stages of CLL, del 17p13, ZAP70 and CD38 expression), failure of complete remission, shorter PFS and OS (21). In the current study, we detected PD-1/PD-L1 expression in CLL cells; however, contrary to the literature, we could not identify any significant relationship between PD-1/PD-L1 expression and stage, ECOG, IPI, disease type, Ki67 index, and treatment response.

A Phase Ib study using Nivolumab in patients with relapsed/refractory hematological malignancies reported an objective response of 40% in follicular lymphoma, 36% in DLBCL, 15% in Mycosis Fungoides, 40% in peripheral T-cell lymphoma and 4% in Multiple myeloma. Genetic alterations of PD-L1 and PD-L2 were rare among the Non-Hodgkin's lymphoma patients evaluated in the referred study (22).

Study Limitations

One of the limitations of the current study is the short follow-up period after treatment. CLL and DLBCL are diseases that are known to have high treatment response and longer survival compared to other malignancies. Another limitation of our study is that the number of patients in both DLBCL and CLL was too small to show statistically significant differences in subgroup analyses.

CONCLUSION

Higher PD-1 and PDL-1 expression and staining intensity were observed in DLBCL patient samples compared to the cases diagnosed with CLL. The current study suggests that PD-1/PD-L1 expression in B-cell lymphomas can be used diagnostically and may be a target for immunotherapy, especially in DLBCL.

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Address correspondence to: *Sinan Demircioğlu, Necmettin Erbakan University, Faculty of Medicine, Department of Hematology, Konya, Türkiye*

e-mail: *sinandemircioglumd@gmail.com*

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