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IL-17 and IL-23 levels in patients with early-stage chronic lymphocytic leukemia

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ABSTRACT

OBJECTIVE: Cytokines produced by bone marrow mesenchymal stem cells are important components of the tumor microenvironment in chronic lymphocytic leukemia (CLL). The roles of IL-17 and IL-23 in both autoimmune diseases and tumor growth have been demonstrated. The role of the IL-17/23 axis in apoptosis has also been demonstrated in studies. Autoimmune cytopenias are common in CLL. In this study, we aimed to compare IL-17/IL-23 levels in early-stage CLL patients with healthy controls.

METHODS: After obtaining ethical approval from the local ethics committee, 22 patients with early-stage chronic lymphocytic leukemia and 21 healthy control groups were included in this study. IL-17 and IL-23 were analyzed using the enzyme-linked immunosorbent assay method.

RESULTS: The findings showed that the median IL-23 level was lower in men in the chronic lymphocytic leukemia group than women. There was a positive correlation between IL-17 and IL-23 levels in both the control group and the chronic lymphocytic leukemia group. There was no significant correlation between stage and IL-17 and IL-23 levels in chronic lymphocytic leukemia patients.

CONCLUSION: Results of studies conducted on IL-17 and/or IL-23 in chronic lymphocytic leukemia in the literature are not consistent. These inconsistent results can be explained by the fact that the immune system develops differently in each individual due to environmental factors, past infections, intestinal flora, vaccines, ethnicity, and even gender. Therefore, it can be hypothesized that the development and application of personalized immunotherapy strategies instead of standard therapy in chronic lymphocytic leukemia may increase therapeutic success rates.

Keywords: Chronic lymphocytic leukemia; interleukins; IL-17, IL-23.

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Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults worldwide [1]. It has been shown that the tumor microenvironment (TME) is critical for the survival and proliferation of CLL cells [2]. Cytokines produced by bone marrow mesenchymal stem cells (BMMSCs) are important components of TME in CLL. In CLL, BMMSCs provide a supportive niche for CLL cells and other blood cells [3, 4]. BMMSCs have been shown to protect CLL B cells from apoptosis and drug-induced cell death [5–7]. BMMSCs can release multiple cytokines and chemokines that are potentially important in regulating tumor cell growth [8, 9]. CLL cells can be directly stimulated by microenvironment elements or cytokines and chemokines. Interleukins and inflammatory cytokines play a role in promoting angiogenesis in CLL. Higher levels of IL-6 and IL-10 were observed in CLL patients than controls and were associated with shorter survival duration [10].

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Many studies have shown the role of the immune system in the development and spread of cancer [11, 12].

The main source of IL-17 is Th17 cells; however, CD8+ cells have also been shown to produce this cytokine; these are called "Tc17" [13]. It has been shown that IL-17 induces IL-6 in various cells. Zhu F et al. [14] have concluded in their study that the IL-17/IL-6 axis plays an important role in a mouse model of in vivo human CLL cell growth.

Interleukin-23 (IL-23) is a pleiotropic cytokine of the IL-6 superfamily that plays a role in bridging adaptive and innate immunity and tissue remodeling [15]. IL-23 has been shown to promote terminal differentiation and expansion of Th17 effector cells [16]. IL-17/IL-23 axis plays a role in many cancers. However, these roles are controversial in terms of prognosis [17, 18].

Although the role of IL-17 in CLL has been investigated in many studies, there are very few studies in the literature on IL-23 and IL-17/IL-23 in CLL.

The roles of IL-17 and IL-23 in both autoimmune diseases and tumor growth have been demonstrated [19, 20]. The role of the IL-17/23 axis in apoptosis has also been demonstrated in studies [21]. Autoimmune cytopenias are common in CLL. Therefore, we thought that IL-17 and IL-23 could play a role together in the pathogenesis of this disease. In this study, we aimed to compare IL-17/IL-23 levels in early-stage CLL patients with healthy controls.

MATERIALS AND METHODS

In this prospective study, after obtaining ethical approval of the ethics committee (Cukurova University Faculty of Medicine, 10.04.2020, 98/44), 22 patients who were diagnosed between 2018 and 2020, followed up without treatment, and 21 healthy controls were included in our study. The diagnosis of CLL was made according to iw CLL [22] and the patients were staged according to Rai staging system [23]. We included patients with early-stage (Stage 0–2) CLL who were not receiving treatment to exclude the effects of chemotherapy on IL levels. The data included gender, age, white blood cell (WBC) count, lymphocyte count, hemoglobin level, and platelet count. We measured the complete blood count (CBC) by using Unicel DxH 800 Cellular Analysis system (Beckman Coulter, Brea, CA).

Blood samples were drawn from the subjects and centrifuged at 4000 rpm for 10 minutes and stored at −80°C as serum until use.

Highlight key points

- IL-17/IL-23 axis plays a role in many cancers and autoimmunity.
- IL-17 and IL-23 differ between gender in the CLL group.
- Determining the role of interleukins in chronic lymphocytic leukemia will be a guide in new treatment strategies to be developed.

Human IL-17 and IL-23 serum levels were determined by ELISA (enzyme-linked immunosorbent assay) method using a commercial ELISA kit (Bioassay Technology Laboratory), automatic ELISA reader (Thermo Scientific, FINLAND), and computer software (Scanlt for Multiscan FC 2.5.1). Sensitivity for IL-17 was 1.06 ng/L, and the assay range was 2 –600 ng/L. Sensitivity for IL-23 was 1.52 ng/L, and the assay range was 3 –900 ng/L. Intra-assay %CV was <8%, and Inter-assay %CV was <10%. Results were expressed in ng/L.

Patients with different known hematological or solid malignancies, active infection, or any inflammatory rheumatism and those using immunosuppressive or anti-inflammatory drugs were excluded from the study.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) and MedCalc software. The normal distribution of the data was evaluated using the Kolmogorov–Smirnov test. Among the numerical variables, those with normal distribution were shown as mean±standard deviation, and those without normal distribution were shown as the median (min–max). Categorical variables were expressed as numbers and percentages. Statistical significance of numerical variables between the control group and CLL groups was evaluated by T-test (for numerical variables with normal distribution) and Mann–Whitney U test (for numerical variables without normal distribution) in independent samples. The statistical significance of IL-17 and IL-23 levels between two groups was evaluated using Mann–Whitney U test, and the statistical significance between three or more groups was evaluated using Kruskal–Wallis H test (for numerical variables without normal distribution). Chi-Square and Fisher's exact chi-square test were used for the comparison of categorical data. In statistical analysis, $p<0.05$ was considered significant.

Table 1. Distribution of demographic and laboratory findings

Variables	CLL n=22	Control n=21	p
Gender, %			
Female	36.4	47.6	0.543
Male	63.6	52.4	
Age, years	57.7±7.6	59.5±9.2	0.488
Stage, %			
0	31.8	–	–
1	40.9	–	
2	27.3	–	
WBC (x10^3/µl)	28.6 (13.7–216)	7.9 (2.6–13.2)	<**0.001***
Hemoglobin	13.5±2	13.1±1.9	0.460
Neutrophils (x10^3/µl)	4.7 (2.8–8.5)	4.8 (1.9–10.7)	0.269
Lymphocytes (x10^3/µl)	19.2 (4.3–204.7)	1.8 (0.4–3.2)	<**0.001***
Platelets (x10^3/µl)	223.5 (115–463)	240 (100–630)	0.846
DC			
Positive %	18.2	–	–
Negative %	81.8	–	
IL-17 (ng/L)	18.5 (11–413.6)	18.3 (11.1–213.7)	0.576
IL-23 (ng/L)	17.4 (6–428.2)	20.7 (6–533.8)	0.846

Numerical variables were shown as mean±standard deviation or median (min–max) according to normality distribution. Categorical variables were shown as numbers (%).
*: p<0.05 shows statistical significance; CLL: Chronic lymphocytic leukemia; WBC: White blood counts; DC: Direct coombs; IL-17: Interleukin -17; IL-23: Interleukin-23.

RESULTS

The study population consisted of 43 subjects, including 21 controls and 22 CLL patients. The age range of the entire study population was 45–73 years, with a mean age of 58.6±8.3 years. There was no significant difference in mean age and gender distributions between CLL and control groups (Table 1).

The median WBC level (28.6×10^3 vs. 7.9×10^3; p<0.001) and the median lymphocyte level (19.2×10^3 vs. 1.8×10^3; p<0.001) were higher between the CLL group and the control group. There was no significant difference in median IL-17 (18.5 vs. 18.3; p=0.576) and median IL-23 (17.4 vs. 20.7; p=0.846) levels between the CLL group and the control group. There was no significant difference in the distribution of other laboratory results between the CLL group and the control group (Table 1).

Although it was not statistically significant in the control group, mean IL-17 and IL-23 levels were higher in men than in women. There was no significant relationship between IL-17 and IL-23 levels and age in the CLL group. On the contrary, IL-17 was numerically higher in women than in men in the CLL group (again, although not statistically significant). In addition, median IL-23 levels were lower in men than women in the CLL group (12.7 vs. 64.1; p=0.029) (Table 2).

There was a positive correlation between IL-17 and IL-23 levels in both the control group and the CLL group (control → r=0.805; p<0.001; CLL → r=0.783; p<0.001, respectively). There was no significant relationship between other laboratory results and IL-17 and IL-23 levels (p>0.05). There was no significant correlation between stage and IL-17 and IL-23 levels in CLL patients (p>0.05) (Table 3).

There was no significant correlation with IL-17 and IL-23 levels in CLL patients based on Stage and DC test results (p>0.05) (Table 4).

DISCUSSION

In our study, there was no significant difference between median IL-17 and median IL-23 levels of the CLL group and the control group. However, there was a positive correlation between IL-17 and IL-23 levels

Table 2. Distribution of IL-17 and IL-23 levels according to demographic findings in CLL

Group	Variables	IL-17 (ng/L)	p	IL-23 (ng/L)	p
CLL					
Gender	Female	51.0 (11.2–413.5)	0.238	64.1 (12.0–428.2)	**0.029***
	Male	16.9 (11.0–97.5)		12.7 (6.0–108.8)	
	Age	r=0.117	0.605	r=0.230	0.304
Control					
Gender					
	Female	14.6 (11.2–46.1)	0.468	13.1 (6.0–55.1)	0.282
	Male	22.0 (11.1–213.7)		21.9 (9.9–533.8)	
	Age	r=0.001	0.999	r=0.095	0.683

Numerical variables were shown as median (min–max) according to normality distribution. r: Spearman correlation coefficient; *: p<0.05 shows statistical significance; CLL: Chronic lymphocytic leukemia; DC: Direct coombs; IL-17: Interleukin -17; IL-23: Interleukin-23.

Table 3. Laboratory findings related to IL-17 and IL-23 levels

Group	Variables	IL-17		IL-23	
		r	p	r	p
Control	WBC	0.114	0.622	0.185	0.422
	Hemoglobin	-0.209	0.363	-0.108	0.642
	Neutrophils	0.040	0.864	0.077	0.739
	Lymphocytes	0.178	0.439	0.187	0.417
	Platelets	-0.099	0.668	-0.020	0.931
	IL-23	0.805	<**0.001***	–	–
CLL	EVRE	0.178	0.428	0.147	0.513
	WBC	0.251	0.259	0.119	0.599
	Hemoglobin	-0.126	0.575	-0.268	0.228
	Neutrophils	-0.067	0.766	-0.002	0.992
	Lymphocytes	0.141	0.532	0.010	0.964
	Platelets	-0.057	0.801	0.181	0.421
	IL-23	0.783	<**0.001***	–	–

r: Spearman correlation coefficient; *: p<0.05 shows statistical significance. CLL: Chronic lymphocytic leukemia; WBC: White blood counts; DC: Direct coombs; IL-17: Interleukin -17; IL-23: Interleukin-23.

in both the control group and the CLL group. This correlation shows the strong correlation of IL-17 and IL-23 with each other, which is consistent with the literature. While there was no significant relationship between IL-17 and IL-23 levels and gender in the control group, the median IL-23 level was lower in men than women in the CLL, which is an interesting result of our study. There are no such literature data in studies on IL-23 in CLL. Although not statistically significant, IL-17 levels were also numerically higher in female patients with CLL than in men.

The role of the immune system in cancer development is very important; however, it is still not fully understood. The effects of cytokines in the microenvironment may vary based on the tumor or even the host. For example, the Th17/IL-17 axis may play pro- and antitumor roles depending on the type of malignancy investigated [14, 24].

In the literature, the results of studies conducted on cytokines in CLL are highly inconsistent. For example, Tang et al. [25] reported in their study that the frequency of Th17 increased in CLL than healthy controls and that high IL-17 levels were associated with poor clinical outcomes. Again Zhu et al. [14] showed in their study that IL-17 and IL-6 were higher in plasma of both treated and untreated CLL patients than healthy controls. Sherry et al. [24] showed that Th17 cells increased in CLL and this increase correlated with better outcome. Furthermore, Hus et al. [26] claimed that Th17/IL-17 played a protective role and that CLL patients with more advanced disease stage had lower Th17/IL-17 levels. Similarly, Jain et al. [27] showed that Th17 cells increased in CLL patients with better prognostic markers and were associated with longer survival. Jadidi-Niaragh et al. [28] also reported that down-regulation of IL-17-producing T cells and expansion of Treg cells were associated with the progression of CLL. Kouzegaran et al. [29] showed in their study that IL-17A plasma level was significantly

Table 4. Distribution of IL-17 level according to stage and DC positivity in CLL

Variables	CLL	IL-17			IL-23		
	%	Median	Min.–Max.	p	Median	Min.–Max.	p
Stage (n=22)							
0	31.8	13.2	11.0–53.7	0.070	12.7	6.0–65.4	
1	40.9	91.7	11.5–413.6		95.7	7.9–428.2	0.083
2	18.2	18.4	11.9–48.3		16.1	8.4–62.7	
DC (n=22)							
Positive	18.2	21.7	12.3–403.4	0.774	21.0	12.7–428.2	0.434
Negative	81.8	18.5	11.0–413.6		14.4	6.0–328.8	

Min.: Minimum; Max.: Maximum; CLL: Chronic lymphocytic leukemia; DC: Direct coombs; IL-17: Interleukin -17; IL-23: Interleukin-23.

higher than healthy control subjects; however, there was no significant relationship between IL-17A levels and different stages of the disease.

It can be concluded that in patients with the same disease, differences in the microenvironment may modulate the types of cytokines secreted by Th17 cells (and other T cell subsets) and thus affect the outcome differently [24].

It is possible that Th17 function may vary depending on the cause, type, and location of cancer and the stage of the disease, as collective evidence suggests that Th17 cells may cause inflammation and promote the initiation and early growth of certain tumors [26, 30, 31].

Cutrona G et al. [15] described an autocrine/paracrine cycle represented by the IL-23 complex expression and IL-23 production required for the clonal expansion of CLL cells. They demonstrated that inhibition of this cycle with the appropriate mAb resulted in viability and insufficiency for CLL cell proliferation in vitro and prevented the prolonged remission of the disease and the expansion of leukemic clones in NOD-SCIDγcnull (NSG) mice, and therefore, they argued that the IL-23R/IL-23 axis could represent a suitable target for the treatment of CLL. In the study conducted by Sherry et al. [24], serum IL-23 levels were significantly higher in CLL patients than healthy controls, and significant heterogeneity was observed in serum IL-23 levels in different CLL patients.

Karmali et al. [32] found in their study with 28 CLL patients that serum IL-23 and IL-17 levels were lower than healthy controls. As with IL-17 in CLL, the results of studies with IL-23 are also inconsistent.

In our study, there was no significant difference in median IL-17 and median IL-23 levels between the CLL group and the control group. This result is probably due to the early stage of the disease in our patients. However, there was a positive correlation between IL-17 and IL-23 levels in both the control group and the CLL group. This correlation shows the strong correlation of IL-17 and IL-23 with each other, which is consistent with the literature.

While there was no significant relationship between IL-17 and IL-23 levels and gender in the control group, the median IL-23 level was lower in the men group than women in the CLL, which is an interesting result of our study. There are no such literature data in studies with IL-23 in CLL. We do not know why women with CLL have higher IL-23 levels than men. However, women and men have different immune structures; for example, women typically develop higher antibody responses to vaccines and experience more adverse reactions following vaccination than men [33]. IL-23 and IL-12 function as complementary cytokines in protection against infectious agents [34]. Autoimmune diseases are more common in women than in men, and the role of IL-23 in autoimmune diseases has been demonstrated in studies [35].

In the light of this information, we can conclude that in our study, female patients with CLL had higher levels of IL-23 than male patients due to their excessive immune response to the tumor. More comprehensive studies are needed to answer this question.

The low number of cases in our study is our most important limitation. Another limitation is that IL-17 and

IL-23 levels were not studied at all stages of CLL, and markers indicating good prognosis and poor prognosis for the disease were not examined.

The results of studies on IL-17 and/or IL-23 in CLL in the literature are not consistent. Future studies will also potentially show different results. These inconsistent results can be explained by that the immune system develops differently in each individual due to environmental factors, previous infections, intestinal flora, vaccines, ethnicity, and even gender [11, 33, 36].

Conclusion

We can conclude that in our study, female patients with CLL had higher levels of IL-23 than male patients due to their exessive immune response to the tumor. Therefore, we hypothesize that the development and application of personalized immunotherapy strategies instead of standard therapy in CLL may increase therapeutic succes rates and would like to point out that interleukins are molecules worth investigating for tumor immunotherapy. More comprehensive studies on this subject will add valuable information to the literature.

Ethics Committee Approval: The Cukurova University Research Ethics Committee granted approval for this study (date: 10.04.2020, number: 98).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – DYA, MB; Design – DYA; Supervision – DYA; Fundings – DYA, MB; Materials – DYA, MB; Data collection and/or processing – DYA; Analysis and/or interpretation – DYA; Literature review – DYA, MB; Writing – DYA; Critical review – DYA, MB.

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