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Clinical Features of the Patients with Chronic Lymphocytic Leukemia: Two Centers Experience

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Abstract

Objective: Chronic lymphocytic leukemia (CLL) is a hematologic malignancy characterized by the clonal proliferation of lymphocytes. The aim of the study was to analyze the demographic data, treatment indications, treatment responses and total survival data of patients with the diagnosis of CLL.

Methods: The study was conducted retrospectively in 183 patients who were followed up in the hematology departments of two centers between 1999 and 2014.

Results: The mean age of the patients was 64.72±11.40 years and 120 (65.6%) patients were male and 63 (34.4%) were female. Overall survival (OS) was not different between patients who had monoclonal gammopathy and those who did not (p=0.922). Among the patients, 105 received treatment while 78 of them were observed without a treatment. Chlorambucil was the most frequently (33%) used drug during the first line of chemotherapy. The difference between the distribution of male and female patients according to risk groups was statistically significant (p=0.018). Among patients who did not receive therapy and with higher Rai and Binet stages, overall and progression free survive were lower (p=0.0011). Furthermore, increases in β_2-microglobulin and sedimentation revealed lower rates of survival (p=0.001 and p=0.008 respectively).

Conclusion: It can be concluded that monoclonal bands are not associated with survival in CLL. Although the demographic information of our patients was similar to that of patients in other studies, OS was found to be less. This issue can be explained by the fact that the patients receiving chemotherapy were at a further stage.

Keywords: Chronic lymphocytic leukemia, monoclonal gammopathy, prognosis, survival

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of mature, typically CD5-positive B-cells in the blood, bone marrow, lymph nodes and the spleen because of clonal proliferation. CLL is the most common leukemia reported in most European and North American countries (1). Although there is no cure for treating CLL, survival rates have increased over time, increasing the 5-year survival to approximately 80% in Europe and North America (2-4).

CLL was defined as slowly progressive disease, but later it was shown that independent of the clinical phase, a group of CLL patients had rapidly progressive disease than expected. In other words, while some patients survive quite a long time without therapy, some patients require treatment shortly after the diagnosis. The total duration of survival can range between months and decades (5-7). The staging systems used as a standard in almost all medical centers were developed by Rai et al. (8) in 1975 and by Binet et al. (9) in 1977. But, during the last 50 years, beside Rai and Binet staging systems, the clinical, biological

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and molecular prognostic factors that can affect overall survival (OS) and the course of the disease have been identified (9). The aim of this retrospective study was to reveal demographic data, clinical and prognostic factors, the diversity of chemotherapy regimens, responses to treatment and OS rates of CLL patients in Antalya, Turkey.

METHODS

Study Design and Patients

This was an observational retrospective cohort study. It was conducted at University of Health Sciences Turkey, Antalya Training and Research Hospital Clinic of Hematology and Akdeniz University Faculty of Medicine Department of Hematology clinics. A total of 183 patients who were diagnosed with CLL between January 1999 and September 2014 were retrospectively examined. The demographics, clinical characteristics, prognostic markers, chemotherapy protocols, response rates to the therapy and OS were evaluated.

Patients files were analyzed according to age, gender, hemoglobin, hematocrit, white blood cell, lymphocyte count, B lymphocyte count, platelet count, erythrocyte sedimentation rate (ESR), glucose, urea, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase (LDH), total/direct bilirubin, total protein, albumin, immunoglobulin (Ig) and β_2-microglbulin (β_2-MG) levels and the results were recorded. Immunophenotyping of leucocytes and lymphocytes was performed by flow cytometry and paraproteins were detected by immunofixation electrophoresis. Modified Rai staging system was used for clinical staging and, disease stages, whether they received treatment or not were recorded. The chemotherapy protocols and drugs received by the patients and their responses to the treatments were also recorded. We applied chemotherapy protocols to our patients according to the National Cancer Institute-sponsored Working Group 1996 guidelines (10). This study was approved by the Local Ethical Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (decision no: 18/3, date: 02.05.2013). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical Analysis

Statistical package for evaluating the data for the Social Sciences (SPSS) 21.0 software was used. ANOVA analysis was run to reveal any statistical significance of the difference between means nominal and the differences between ordinal variables chi-square test to be placed between the arguments Mann-Whitney U and numerical features showing Wilcoxon tests and normal distribution Student's t-tests for evaluation of variables was used. For survival analysis Kaplan-Meier and Cox regression tests were used. For prognostic and predictive factors logistic regression test was used. Pearson's correlation test was used to analyze the relationships between parameters. $p<0.05$ was the level of significance for all statistical analyses.

RESULTS

General Characteristics of the Patients

A total of 183 patients, aged approximately 31-89 (mean 64.72±11.40), 120 (68%) were male and 63 (32%) were female were included in the study. Of all participants 88 (48.09%) patients were aged between 31 and 65 years, and 95 (51.91%) were equal or older than 65 years. Of the 183 cases, 131 (71.6%) were alive and 52 (28.4) died. In terms of gender, among the males there, 83 (69.2%) lived and 37 (30.8%) died. Among the females, 48 (76.2%) survived and 15 (23.8%) died. When the effect of gender on death or life status was examined, no statistically significant difference was found ($p=0.318$).

Laboratory Findings

The demographic data and laboratory values of the patients at the time of diagnosis are shown in Table 1. As seen in Table 1, lymphocytosis, especially type B lymphocytosis, is seen in our patients.

Lymphocyte immunophenotypes, frequency of monoclonal proteins and bone marrow biopsy in patients are shown in Table 2. Immunophenotyping of lymphocytes revealed that zeta-chain-associated protein kinase 70 (ZAP70) in 168 (91.8%) patients, CD38 expression in 158 (86.34%) patients and CD11c expression in 51.9% of patients were lower than 20%. However, CD20 expression was seen in 95.8% of patients were higher than 20%. Other immunophenotype rates are shown in Table 2. There was no statistically significant relationship between ZAP70, CD38, and CD11c and OS (p=ns). Bone marrow biopsy was performed in 14.8% of 183 patients that 59.3% showed diffuse bone marrow infiltration and 40.7% showed nodular bone marrow infiltration. There was no statistically significant difference between bone marrow diffuse or nodularity and OS ($p=0.345$). Immunofixation electrophoresis was performed in 74 patients and 47 (63.51%) of them revealed no monoclonal protein. However, monoclonal protein was detected in 27 (36.49%) patients. IgG kappa was seen in 12 (16.21%) patients, IgM kappa in 5 (6.76%) patients, and IgG

Table 1. Demographic data and laboratory values of chronic lymphocytic leukemia patients

Parameters	n	Min-max	Mean ± SD
Age	183	31-89	64.72±11.40
White blood cell (/mm^3)	183	8550-447470	61031.31±4613.46
Total lymphocyte (/mm^3)	183	6040-380000	49354±65027
B lymphocyte (/mm^3)	183	5010-309600	37728±50316
Hemoglobin (g/dL)	183	3.5-16.6	12.11±2.51
Platelet (mm^3)	183	5000-434000	185486±80839
Uric acid (mg/dL)	183	2.00-9.80	5.43±1.59
ALT (U/L)	183	3.00-139.00	20.19±14.49
AST (U/L)	183	9.00-67.00	21.48±9.23
Total protein (mg/dL)	183	3.00-11.00	6.88±0.084
Albumin (mg/dL)	183	2.20-6.10	4.31±0.51
Creatinine (mg/dL)	183	0.40-4.40	0.98±0.45
LDH (U/L)	183	53.00-2204.00	321.25±213.14
ESR (mm/h)	183	2.00-109.00	21.97±21.02
IgG (mg/dL)	134	190.00-5020.00	1013.99±633.34
IgM (mg/dL)	134	2.90-900.00	70.91±108.53
IgA (mg/dL)	134	17.00-924.00	134.43±108.53
β_2-microglobulin (mg/L)	183	0.22-16.40	4.06±2.13

SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation ratio, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M

Lambda in 3 (4.05%) patients. In the remaining 7 (9.46% patients, different monoclonal proteins were detected. OS was not different between patients who had monoclonal gammopathy and those who did not, (p=0.922).

In this study, the effects of some risk factors on the OS of CLL patients are shown in Table 3. According to Modified Rai staging system, we compared the stages disease and OS rates. It was found that OS of low-risk group patients (stage 0) was 61.63±43.86 months, 47.53±30.00 months for patients in the intermediate risk group (stage 1-2), and 41.74±33.71 months for patients with high risk (stage 3-4). There was a statistical significance according to disease stage and OS and early diagnosis dramatically increased survival (p=0.034, Figure 1). Survival rates of male and female patients were 47.88±35.74 months and 47.66±31.35 months, respectively. It was shown that the effect of gender on OS was not statistically significant (p=0.967). OS in patients aged 31-65 years were 54.34±38.00 years and in patients over 65 years old, it was 41.76±29.18 years. When we examined the effect of age on OS in CLL, we found a statistically significant difference (p=0.013, Figure 2). β_2 -MG values ranged between 0.22 and 16.40 mg/dL (mean 4.06±2.13). The OS of patients whose β2-MG level below 4.06 mg/dL and equal or above the 4.06 mg/dL was 49.05±34.21 months and 45.31±33.30 months, respectively. According to the results, a statistically significant relationship was not found between OS and β_2-MG levels (p=0.506). The LDH values ranged between 53 and 2204 IU/L with a mean LDH value of 321.25±213.14 IU/L. The OS of patients below and above the mean LDH level was found to be 55.08±35.87 months and 43.60±32.62 months, respectively. According to these results, there is a statistically significant relationship between OS and LDH levels in the blood (p=0.028, Figure 3). ESR values of the

Table 2. Lymphocyte immunophenotypes, frequency of monoclonal proteins and bone marrow biopsy in patients

Lymphocyte immunophenotypes	Property (%)	n	%
ZAP70	<20	168	91.80
	≥20	15	8.20
CD38	<20	158	86.34
	≥20	25	13.66
CD11c	<20	95	51.91
	≥20	88	48.09
CD20	<20	9	4.92
	≥20	174	95.08
CD16	<5	162	88.50
	≥5	21	11.50
CD56	<5	119	65.00
	≥5	64	35.00
CD4	<5	66	36.10
	≥5	117	63.90
CD8	<5	87	47.50
	≥5	96	52.50
CD3	<5	74	40.40
	≥5	109	59.60
Bone marrow biopsy	Diffuse bone marrow infiltration	16	59.3
	Nodular bone marrow infiltration	11	40.7
Monoclonal protein condition (detected by immunofixation electrophoresis)	No monoclonal protein	47	63.51
	There is monoclonal protein - IgG Kappa - IgM Kappa - IgG Lambda *Others	27 12 5 3 7	36.49 16.21 6.76 4.05 9.46

*Others (IgM Lambda, IgA Kappa, IgG heavy chain, Kappa light chain, Lambda light chain, triclonal protein, multiclonal protein), ZAP70: Zeta-chain-associated protein kinase 70, IgG: Immunoglobulin G, IgM: Immunoglobulin M

Table 3. The effects of some risk factors on survival of chronic lymphocytic leukemia patients

Factors		Mean of survival time (month) Mean ± SD	p
*Disease stage	Low risk (0)	61.63±43.86	**0.034**
	Medium risk (1-2)	47.53 30.00	
	High risk (3-4)	41.74±33.71	
Gender	Male	47.88±35.74	0.967
	Female	47.66±31.35	
*Age	31-65 years old	54.34±38.00	**0.013**
	≥65 years old	41.76±29.18	
β_2-MG	0.1-4.06	49.05±34.21	0.506
	>4.061	45.31±33.30	
*LDH	≤321.25	55.08±35.87	**0.028**
	≥321.26	43.60±32.62	
ESR (mm/h)	High	43.63±29.90	0.210
	Normal	50.22±36.37	

*p<0.05, SD: Standard deviation, β_2MG: $\beta_2$microglobulin, LDH: Lactate dehydrogenase, ESR: Erythrocyte-sedimentation rate

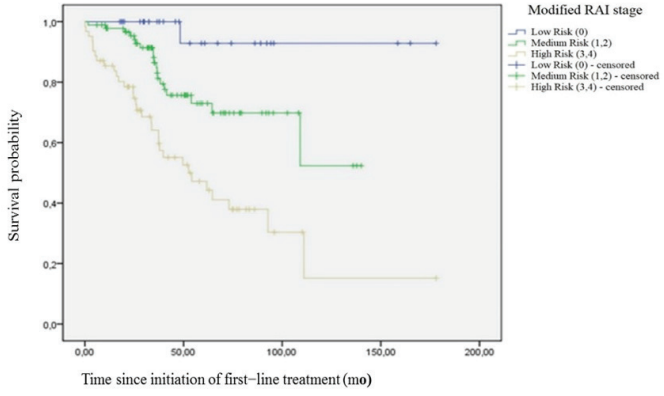

Figure 1. Survival analysis according to stage in our CLL patients
CLL: Chronic lymphocytic leukemia

patients ranged between 2.0 and 109.0, with a mean value of 21.97±21.02 mm/h (reference values as 0-20 mm/h). The OS of patients with high (≥20 mm/h) and a normal value (<20 mm/h) of ESR were 43.63±29.90 months and 50.22±36.37 months, respectively. According to the findings there is no statistically significant relationship between OS and ESR levels in the blood (p=0.210).

Clinical stages accordingly to the modified Rai system, mortality rates, the distribution of age groups, first line chemotherapy responses and treatment status of patients according to gender are presented in Table 4. Disease stage of the patients according

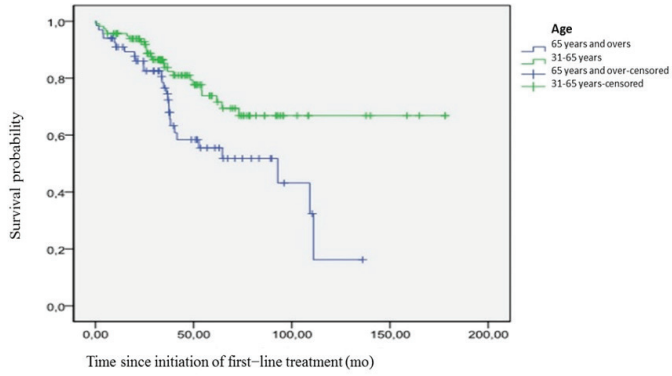

Figure 2. Survival analysis according to age in our CLL patients
CLL: Chronic lymphocytic leukemia

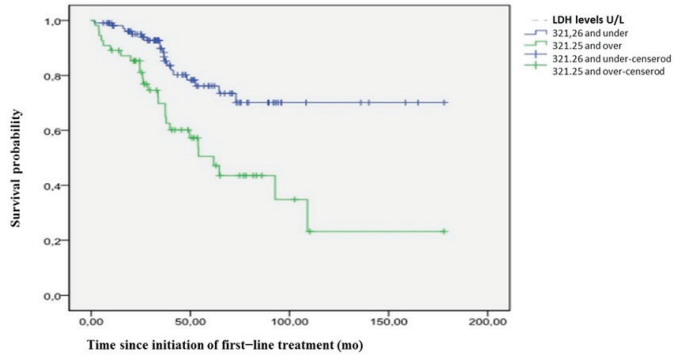

Figure 3. Survival analysis according to LDH in our CLL patients
LDH: Lactate dehydrogenase, CLL: Chronic lymphocytic leukemia

to gender was also examined at the time of diagnosis. According to this distribution, it was observed that the disease stage was concentrated in the low and medium groups in female patients, the high and medium-risk groups in men at the time of diagnosis. The difference between the distribution of male and female patients according to disease stage was found to be statistically significant (p=0.018). The patients were also divided 2 groups according to age that 88 (48.09%) patients were between 31 and 65 years and 95 (51.01%) were ≥65 years. There was no statistical difference between these two groups according to gender (p=0.826). The treatment needs of the patients were examined according to their gender. According to these results, it is seen that male patients need first-line chemotherapy treatment more than female patients. This result was statistically significant (p=0.011). Patients in need of treatment, the effect of gender on the first line chemotherapy response was examined. These results showed that first-line chemotherapy responses were not statistically different between male and female (p=0.969). During the study period, 52 of 183 patients died and 131 survived. The OS and mortality rates of the patients by gender were analyzed. The OS rate was 69.2% in male, while this rate was 76.2% in

female. There was no statistically significant difference between death and OS rates according to gender (p=0.318).

The chemotherapy protocols and response to treatment are presented in Table 5. Chlorambucil plus the methylprednisolone was the most used drug in our unit (33%), cyclophosphamide plus fludarabine (FC) was at the second frequency (21.9%). The mean duration between the diagnosis and the first treatment was 18 months. During the first-line treatment, among these 105 patients, 35 were treated with chlorambucil plus methylprednisolone, 9 were treated with only FC, 23 were treated with FC, 13 were treated with fludarabine-cyclophosphamide-rituximab (FCR), 22 were treated with cyclophosphamide-vincristine-prednisolone or cyclophosphamide-prednisolone, and 3 were treated with a high dose of methylprednisolone. As seen in 39.1% of the patients gave a complete response to first-line chemotherapy and 21.9% of the patients gave a complete response to second and subsequent chemotherapy regimens. For 105 (57.4%) patients needing treatment, the effect of gender on the duration of first-line treatment (TFS) was examined. TFS was 17.53±26.9 months for male and 21.09±28.3 months for females. Statistically, the effect of gender on TFS duration was not found to be significant (p=0.570).

DISCUSSION

Generally, CLL is not an aggressive disease, but it might result in morbidity and mortality in some major complications. This study revealed that the number of male patients was twice higher than that of female patients. Our results were comparable to those of previous studies (11,12). Moreover, CLL is more common in elderly patients and the average age was found to be 70 years but in the present mean age of our patients was 64.7 years (13). Today, we think that the age of CLL seen is gradually decreasing. The disease stage and the rate of needing treatment at admission were found to be significantly higher in males than in women. However, OS rates did not differ significantly between males and females. Patients with high disease stage, LDH and older age regardless of gender, showed lower OS rates.

While ZAP70 was negative in 168 (91.8%) of our patients, it was found positive in only 15 (8.2%) patient. However, CD38 was negative in 158 (86.34%) patients and positive in 25 (13.66%) patients. Previous studies revealed that ZAP70 is not expressed in normal "B" lymphocytes but overexpressed in Ig heavy-chain genes unmutated CLL and demonstrated an equivalent clinical value to Ig heavy-chain genes mutational status about disease progression and survival (8,14). CD38 expression, as well as ZAP70 and the mutation status of Ig variable region heavy chain, are

Table 4. Modified Rai stages, mortality rates, distribution of age groups, first line chemotherapy responses and treatment status of patients according to gender

Gender		Male n (%)	Female n (%)	Total n (%)	p
*Stage	Low risk (0)	16 (13.30)	13 (20.60)	29 (15.80)	**0.018**
	Medium risk (1-2)	56 (46.70)	36 (57.10)	92 (50.30)	
	High risk (3-4)	48 (40.00)	14 (22.20)	62 (33.90)	
	Total	120 (100)	63 (100)	183 (100)	
Age	31-65 years old	57 (47.50)	31 (49.20)	88 (48.09)	0.826
	≥65 years old	63 (52.50)	32 (50.80)	95 (51.91)	
	Total	120 (100)	63 (100)	183 (100)	
*Treatment status	Treated	77 (64.20)	28 (44.40)	105 (57.40)	**0.011**
	No treated	43 (35.80)	35 (55.60)	78 (42.60)	
	Total	120 (100)	63 (100)	183 (100)	
Response to first-line therapy	Complete remission	31 (40.30)	10 (35.70)	41(39.00)	0.969
	Partial remission	32 (41.60)	15 (53.60)	47 (44.80)	
	Refractory	13 (16.90)	2 (7.10)	15 (14.30)	
	Progressive	1 (1.30)	1 (3.60)	2 (1.90)	
	Total	77 (100)	28 (100)	105 (100)	
Life status	Living	83 (69.20)	48 (76.20)	131 (71.60)	0.318
	Dying	37 (30.80)	15 (23.80)	52 (28.40)	
	Total	120 (100)	63 (100)	183 (100)	

*p<0.05

Table 5. Treatments for patients with chronic lymphocytic leukemia and distribution of patients' responses to applied treatment

Drugs	First order treatment (n=105) n (%)	Second and other order treatments (n=75) n (%)
Chlorambucil plus MP	35 (33.3)	13 (17.3)
Fludarabine	9 (8.6)	4 (5.3)
FC	23 (21.9)	7 (9.3)
FCR	13 (12.4)	17 (22.7)
CVP or CP	22 (21.0)	11 (14.7)
High-dose MP	3 (2.9)	3 (4.0)
Other treatments	-	20 (26.7)
Response rates		
Complete remission	41 (39.1)	23 (21.9)
Partial remission	47 (44.8)	42 (40.0)
Refractory	15 (14.3)	5 (4.8)
Progressive	2 (1.9)	1 (0.95)

MP: Methyl prednisolone, FC: Fludarabine-cyclophosphamide, FCR: Fludarabine-cyclophosphamide-rituximab, CP: Cyclophosphamide-prednisolone, CVP: Cyclophosphamide-vincristine-prednisolone

important prognostic indicators in CLL. The advantage of CD38 is its easy measurement (15,16). In our study, CD38 was found to be positive at a rate of 13.66%. Today, anti-CD38 antibody treatments are on the agenda (17). This result shows that 13.66% patients with CLL can benefit from anti-CD38 antibody treatments. Previous studies have confirmed the importance role of ZAP70 in CLL prognosis. One of these studies showed that ZAP70 is an independent prognostic factor that physicians must consider in determining the best treatment strategy and prognosis for patients with CLL (18). Second of these studies suggested that ZAP70 inhibitors possess significant potential for the treatment of autoimmunity, organ transplant rejection, graft-versus-host disease, and B-cell CLL (19).

Bone marrow biopsy was performed in 27 (14.8%) of 183 patients that 59.3% showed diffuse bone marrow infiltration and 40.7% showed nodular bone marrow infiltration. Since very few patients underwent bone marrow biopsy, it was not very suitable for evaluation in this study. However, it can be said that the diffuse involvement is more. Accordingly, monoclonal gammopathy was investigated in 74 of the patients. Among these patients 27 (36.5%) were identified with monoclonal gammopathy, whereas 63.5% were not. Of the patients who had monoclonal gammopathy, 12 of them had IgG Kappa, 5 had IgM Kappa, 3 had IgG Lambda and 7 had other band. When the effect of having monoclonal gammopathy on total survival was examined, results showed that having monoclonal gammopathy did not have any effect on the total duration of survival (p=0.922). No relationship was found between the monoclonal protein and OS. This result has not been previously reported in the literature. Therefore, it was not appropriate to evaluate the relationship between monoclonal proteins and OS.

The most used prognostic parameter is the Rai staging system (8). Although 30 years after its development, this staging system still has significant use in CLL. The collection of information on age, sex, and performance status are adjuncts to prognosis but are not sufficiently useful to permit accurate prognostic counseling for a given patient. Other easily monitored prognostic markers include LDH, β_2-MG, serum thymidine kinase and lymphocyte doubling times are found. The sign of widespread bone marrow infiltration is a lower indicator of survival (14,20). The relationship of β_2-MG to disease mass is controversial. One retrospective series of 302 untreated patients found it to be the strongest predictor of 5-year survival on multivariate analysis (21), but another study in a prospective trial (n=106) did not find it to be a significant predictor of survival using multivariate analysis (22). Some risk factors affect CLL regardless of gender in this study. When evaluated according to these risk factors, disease stage, age and LDH levels were found to be effective risk factors in this study. However, gender, β_2-MG and ESR were not found to be effective.

According to the modified Rai staging system, the ratios of patients in the low-risk group (stage 0), intermediate-risk group (stage 1 and 2), and high-risk group (stage 3 and 4) were 15.8%; 50.3% and 33.9% respectively. In some studies, in the literature, it has been reported that the number of patients in the high-risk group is less and that patients are usually diagnosed at an early age (23,24). In our study, at the time of diagnosis, female patients were mostly in low and intermediate risk groups whereas male patients were mostly in intermediate and high-risk groups and this finding was statistically significant. This result shows that the disease can progress worse in male patients. Therefore, male patients may have accepted treatment more than female.

Advanced age alone is a high-risk factor for cancer. Age is reported as an independent negative factor for the survival of most studies of CLL patients (4,25-28). However, it should be kept in mind that CLL and other age-related diseases are the most common cause of death in most elderly patients. Older patients have been treated less frequently than younger patients and are often not given heavy chemotherapy. This resulted in a significantly lower complete response rate and a shorter survival rate. However, mortality attributable to the disease was not significantly different between young and older patients. In our

study, patients were grouped according to their age as 31-65 years and equal and over 65 years old. No statistical difference was found between these two groups according to gender (p=0.826).

The number of patients who required chemotherapy in our study was 105. It was observed that 64.2% of the male patients needed treatment, while 35.8% did not need treatment. However, it was observed that 44.4% of the female patients needed treatment, whereas 55.6% did not need treatment. It was found statistically significant that male gender was effective in the need for treatment and that male patients had more treatment requirements than female patients.

Chemotherapy protocols and responses were critically important issues in our study. CR was achieved 41 of these patients after 1st line chemotherapy. However, after the first line chemotherapy, 47 patients had PR, 15 patients had refractory and 2 patients had progression. Gender is important in the diagnosis and diagnosis of CLL. The occurrence of CLL in male and female is drastically different (29). For example, the incidence of US CLL in 1975-2001 was 5.0 per 100,000 per year for men and 2.5 for women (30). Additionally, female CLL patients have better 10-year survival and a better response to treatment (31). Understanding the mechanism behind these gender differences will provide valuable information about CLL. In the current study, some patients had refractor disease (14.3%), but only a few showed progression of the illness (1.9%) after first-line chemotherapy. TFS and OS are the same as male, although female is detected at a lower stage, according to our results. These results made us think of 2 hypotheses. First, the female have a worse course of CLL, even if they are lowly staged. Second, because females are at a low stage, they have a lower TFS or OS without treatment because they are less treated.

At the end of the study, of 183 patients, 131 (75.6%) were alive and 52 (24.4%) died. The causes of death differed with the most frequent causes are pneumonia (38.6%), sepsis (26.9%), heart disease (11.7%) and other causes (22.8%). Previous studies revealed the prognostic factors that affect survival were; male gender, high level of lymphocytes in the blood at the time of diagnosis, lymphocyte doubling time, CD38-positive cell count being more than 30%, positivity of ZAP70, existence of some cytogenetic abnormalities, serum LDH, high level of β_2-MG and bone marrow diffuse involvement (32-38).

Some of the previously conducted studies revealed a ratio of CR between 4 and 10%, and a PR ratio between 36 and 50% (24,39-42). In the current study, CR was achieved 41 of these patients after 1st-line chemotherapy, and 23 patients achieved CR with 2nd, 3rd, 4th, and 5th line of chemotherapy. In total, 63 patients achieved CR. Although the treatments applied in this study were significantly successful and the participating patients had similar demographic characteristics with the patients in previous studies, the OS time was less in the patients who received the treatment. These treatments were successfully implemented in the other studies, such as first-line treatment with FCR is associated with a response rate of 90-95% and a CR rate of 40-75%. The patients analyzed in this study were treated between 1999 and 2014. The most important first line chemotherapy protocols applied at that time were chlorambucil plus methylprednisolone, FC and FCR. Although new treatment approaches have been discovered, FCR is still an important protocol for treating CLL (43-45).

Study Limitations

This study has several limitations. A limitation of our study is that the number of patients is low, and the second is to conduct our study in patients diagnosed since 1999. Because after 1999 there have been many changes in the diagnosis and treatment of CLL. In more patients, the monoclonal protein should be evaluated.

CONCLUSION

Although this study examined CLL patients with similar demographic data as to other CLL studies, differences were observed in the agents used for chemotherapy due to the period covered by the study. In our study lymphocyte immunophenotypes such as ZAP70, CD38, CD11c, and other lymphocyte immunophenotypes were not associated with OS. However, large series of studies with anti-CD38 and other antibodies are needed for treatment response relationships. As in the literature, we have shown that disease stage, age and LDH is associated with OS. At the end of our study, it was observed that the disease stage was more advanced in men. Simultaneously, our study showed that men need more treatment than women. Additionally, advanced cytogenetic analysis and prognostic markers can be used at the time of diagnosis, CLL treatment and follow-up. It will enable them to do better and extend their survival.

Ethics

Ethics Committee Approval: This study was approved by the Local Ethical Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (decision no: 18/3, date: 02.05.2013).

Informed Consent: Informed consent was obtained from the patients after a detailed explanation on the objectives and scope of the study was provided, in line with the principles of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.E.D., E.K., A.T., Concept: F.E.D., E.K., A.T., Design: F.E.D., E.K., A.T., Data Collection or Processing: F.E.D., Analysis or Interpretation: F.E.D., E.K., A.T., Literature Search: F.E.D., Writing: F.E.D.

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