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Original article

Evaluation of clinical and prognostic features and treatment outcomes in patients with chronic lymphocytic leukemia

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Abstract. *Objective:* We aimed to investigate the demographic and clinicopathologic characteristics, treatment responses, survival rates, and prognostic factors affecting survival in patients with chronic lymphocytic leukemia (CLL). *Material and Methods:* We retrospectively evaluated a total of 131 patients with CLL anddivided into two groups, alive and deceased, based on their situation at the time the data were collected for comparison. *Results:* The majority of the patients were male (n = 95; 72.5%) and the median age was 62 (35-82) at disease baseline. The mean follow-up time was 31.7 months and overall 3- and 5-year survival rates (OS) were 93.4% and 87.4%, respectively, for all patients. There were significant differences between the alive and deceased group with respect to age, platelet count, hemoglobin level, lactate dehydrogenase, albumin, Rai, modified Rai, and Binet stages, B symptoms, splenomegaly, hepatomegaly and autoimmune hemolytic anemia (AIHA) ($p < 0.05$). Regardless of treatment regimen, the treatment response rate in patients receiving first-line treatment was better in alive than in deceased ($p < 0.001$). Multivariate Cox regression analysis showed the following independent prognostic factors to affect both overall survival (OS) and treatment-free survival (TFS): age ≤ 64, Binet ≤ stage B, B symptoms, albumin > 4.1 g/dL, and presence of hepatomegaly. Also, AIHA was an independent prognostic factor affecting only TFS rates. *Conclusion:* The demographic characteristics of our patients were consistent with the literature, while our 3- and 5-year survival rates were higher. Notably, hepatomegaly and hypoalbuminemia were associated with low OS and TFS. The limitation of the study was the lack of a clear comparison between treatment regimens due to the uneven distribution of the number of patients receiving treatment.

Keywords: Chronic lymphocytic leukemia, prognostic factors, survival

Introduction

Chronic lymphocytic leukemia (CLL) a lymphoproliferative disease characterized by the accumulation of small mature lymphocytes (1). CLL is the most common type of leukemia in Western countries and comprises approximately 25-30% of all leukemias. It occurs predominantly in males, with a male/female ratio of 1.3:1-1.7:1 (2). Although CLL is generally a disease of advanced age, with incidence increasing with age, there are patients diagnosed at younger ages. A median age of 72 has been reported for the U.S. and Europe, whereas that of Turkey was only 63, with 24% of CLL patients under 55 years of age (3, 4).

Currently, CLL is typically diagnosed according to the criteria recommended by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) (5). Chromosomal anomalies are frequently detected in CLL by conventional cytogenetic or fluorescent in situ hybridization (FISH); these chromosomal anomalies have been found to be associated with treatment response and survival (6). The two staging

systems, Rai and Binet, have been used for a long time but they are not particularly effective for early detection of disease progression (7, 8). Treatment decision for CLL depends on the stage of the disease or the presence of active/symptomatic disease. Patients in asymptomatic early stage (Rai stage 0, Binet stage A) are followed without treatment unless there are signs of rapid progression; however, treatment should be initiated in patients with advanced stage (Rai III-IV, Binet C) or active/symptomatic disease (9, 10). The aim of the present study was to determine the demographic and clinicopathologic characteristics, prognostic features, treatment options, treatment response rates, and effects of these features on survival in CLL patients treated in our clinic.

Materials and methods

Patients

The study included 131 patients diagnosed with CLL in our hematology departmant between 2006 and 2018. Patient's datas were obtained retrospectively by examining patient files and information in the patient registry system. The diagnosis of CLL was reevaluated according to the IWCLL criteria. Patients were divided into two groups, alive and deceased, based on their situation at the time the data were collected for comparison.

Data collection

Age, gender, comorbidities, haemogram parameters, lactate dehydrogenase (LDH), β2-microglobulin, creatinine, albumin, globulin and uric acid levels were all recorded at the time of diagnosis. A β**2**-microglobulin level exceeding 2.4 mg/L was considered high. Bone marrow biopsy and aspiration results were evaluated in some patients for further examination and, due to their effect on the prognosis, an assessment was made regarding the presence of nodular involvement or diffuse involvement. The results of the chromosome analyses and cytogenetic abnormalities were recorded. The presence of B symptoms (which include a decrease in body weight of more than 10% in the last 6 months, fever exceeding 38 degrees for 2 weeks or more without any sign of infection, and night sweats lasting one month or longer with no indications of infection), and hepatomegaly, splenomegaly or lymphadenopathy (LAP) as indicated by physical examination or imaging techniques, were determined.

Staging, induction therapies, and treatment responses

Disease staging was made according to the Rai, modified Rai, and Binet staging systems. Treatment protocols were classified. Treatment indications for each step were evaluated according to the IWCLL guidelines and treatment response statuses were also recorded based on the IWCLL guidelines.

Ethics

The study was approved by the research ethics committee of the university. (Date / reference number: 31.01.2018/002). All aspects of the study, including periodical clinical and laboratory checkups, were performed according to the principles of the Declaration of Helsinki (64th, 2013).

Statistical Analysis

Statistical analysis of the data was carried out using SPSS 25.0 (IBM Corparation, Armonk, New York, United States). The Shapiro-Wilk test was used to determine whether the data exhibited normal distribution and variance homogeneity was assessed using the Levene test. The Independent-Samples t-test and Mann-Whitney U test were used to compare two independent groups based on quantitative data. Categorical variables were compared using the Pearson Chi-Square and Fisher-Freeman-Holton tests. The cut-off value, sensitivity, and specificity of mortality-related parameters were analyzed by Receiver Operating Curve (ROC) curve analysis. The Stepwise-Wald method was used in the Multivariant Cox Regression analysis to demonstrate the effect of survival-related prognostic variables on survival. Quantitative variables were expressed as median ± SD (standard deviation) and minimum-maximum, while categorical variables were expressed as n (%). Variables were examined

within a 95% confidence interval and a p-value of less than 0.05 was considered significant.

Results

Demographic characteristics and laboratory tests

The study flow chart is presented in Fig. 1. Of the 131 patients included in the study, 36 (27.5%) were female and 95 (72.5%) were male. The median age of the patients was 62 (35-82) and individuals under 55 years of age comprised 25.1% (n = 33) of the total. Haemogram parameters and other laboratory tests results for the total patient population at the time of diagnosis are shown in Table 1. A statistically significant differences between alive and deceased groups were found with respect to age (p < 0.001), platelet count (p = 0.001), hemoglobin level (p = 0.002), LDH (p = 0.004), and albumin (p = 0.008) (Table 1).

Staging, cytogenetic and clinical characteristics

There were significant differences between the two groups with regard to the Rai, modified Rai, and Binet staging systems (p = 0.002, p = 0.002, and p = 0.001, respectively). The incidence of B symptoms in the deceased group was significantly higher compared with the alive group (p = 0.007). Splenomegaly and hepatomegaly also were present at significantly higher rates in the deceased group than in the alive group (p = 0.003 and p = 0.001, respectively), as did incidence of autoimmune hemolytic anemia (AIHA) (p = 0.031). Cytogenetic analysis of 90 patients revealed that 8 (8.9%) patients were 17 p deletion-positive and 2 (3.2%)

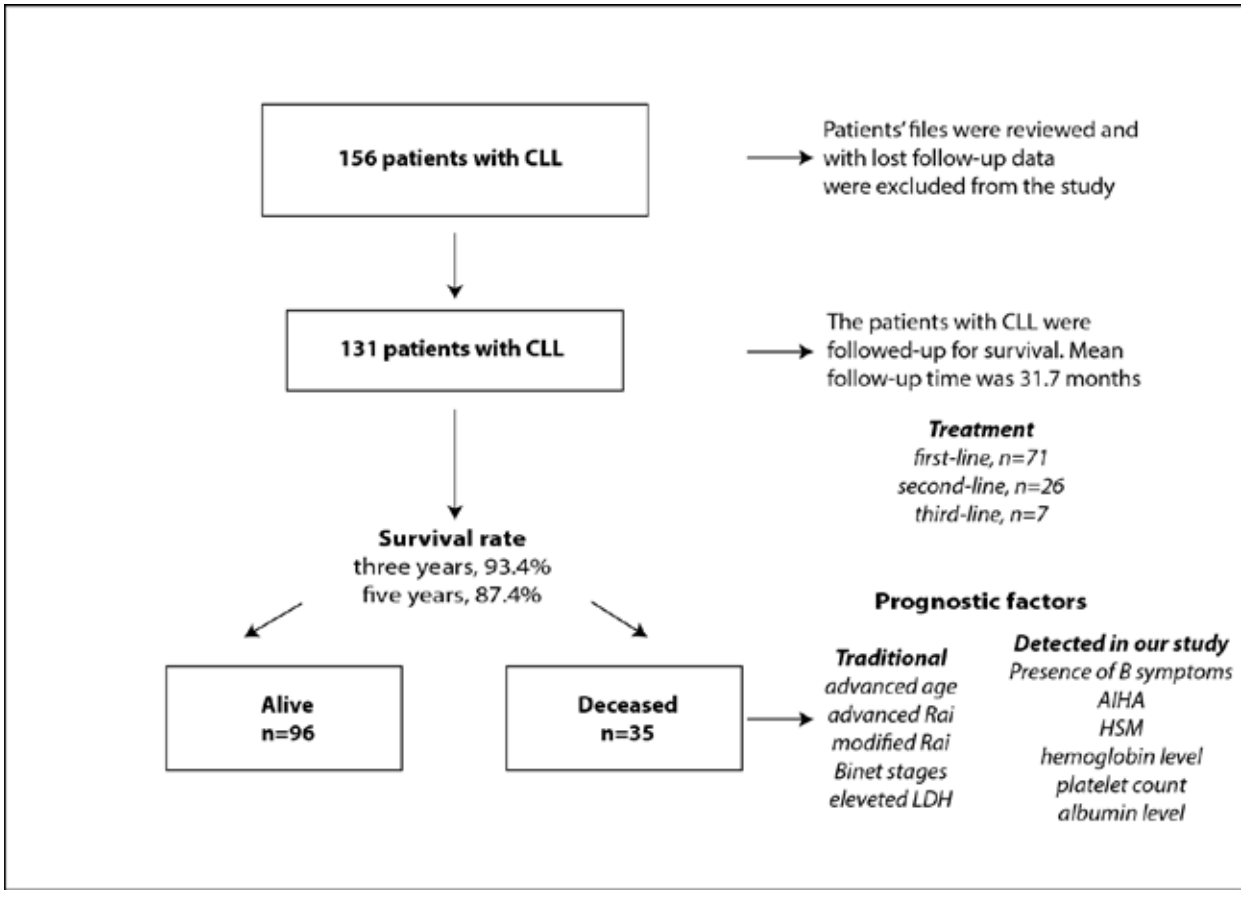

Fig.1. The study flow chart. Abbreviations: CLL, chronic lymphocytic leukemia; AIHA, autoimmune hemolytic anemia; HSM, hepatosplenomegaly; LDH, lactate dehydrogenase.

Table 1. Demographic characteristics and laboratory features of patients with CLL

Parameters	All Patients Median (Range)	Alive Group Median (Range)	Deceased Group Median (Range)	*p*-value
Gender, n (%)	31 (100)	96 (73.3)	35 (26.7)	0.659
Female	36 (27.5)	25 (26.1)	11 (31.46)	
Male	95 (72.5)	71 (73.9)	24 (68.64)	
Age	62.2 (35-82)	59 (35 - 82)	68 (51-82)	<0.001
Leukocyte count (10^9/L)	54.1 (2.6-368)	30.5 (2.6-368)	318 (9.9-276)	0.925
Lymphocyte count (10^9/L)	41.5 (1.1-283)	41.5 (1.1-283)	22.7 (5.5 /237)	0.882
Platelet count (10^9/L)	177 (100-565)	182.5 (19.7-474)	130 (10-565)	0.001
Hemoglobin level (g/dL)	13.4 (6.1-17)	14.15 (6.1-17)	13.1 (6.6-16)	0.002
2-microglobulin (mg/L)	4.1 (2.4-8)	3.7(2.4-5)	4.2 (3.6-8)	0.637
LDH (IU/L)	341(82-1740)	310 (82-643)	409 (202-1740)	0.004
Albumin (g/dL)	4.1(2.8-5.5)	4.4 (2.9-5.5)	4 (2.8-4.9)	0.008
Globulin (g/dL)	2.6 (1.3-7.4)	2.6 (1.3-5.2)	2.3 (1.8-7.4)	0.254
Uric acid (mg/dL)	5.43 (2-6-12.8)	5.05 (2.6-9.1)	4.8 (2.7-12.8)	0.492
Creatinine (mg/dL)	0.83 (0.4-.1.7)	0.8 (0.4-1.7)	0.8 (0.4-1.5)	0.584

were 11q deletion-positive. CD38 and CD5 levels, accepted as prognostic factors in flow cytometric examination, were included in the study. CD38 was positive in 8 (17.4%) of 46 patients, while CD5 was detected in 106 patients, 79 (74.5%) of whom were positive. There were no statistically significant differences with respect to the presence of 17p deletion or CD38 and CD5 expression levels between alive and deceased groups. Data analysis could not be performed for the 11q deletion (Table 2).

Primary treatment decisions, treatment regimens and response rates

Of 131 patients, 71 (54.2%) underwent at least one line of treatment for various indications. At the start of first-line treatment, most patients had more than one indication for treatment. Of these patients, findings of progressive bone marrow insufficiency (Rai stage III-IV) were detected in 60 (84.5%), 39 (54.9%) had B symptoms, and 17 (23.9%) met the criterion for massive splenomegaly, with the spleen extending past the costal margin by > 6 cm. Mass lymphadenopathy (LAP) was found in 10 patients (14.1%), AIHA in 8 patients (11.3%) and progressive lymphocytosis, was also detected in 8 patients (11.3%). The treatment regimens given to patients and their response rates are presented in Table 3. Treatment response rates were significantly higher in alive group receiving first-line treatment compared to deceased group ($p < 0.001$).

Multivariate analysis

The mean follow-up time was 31.7 month and three-year and five-year overall survival rates (OS) were 93.4% and 87.4%, respectively. The three-year

Table 2. Demographic characteristics and laboratory features of patients with CLL

Parameters	All patients n (%)	Alive Group n (%)	Deceased Group n (%)	*p*-value
Stage, Rai				**0.002**
Rai-0	**37 (28.2)**	**33 (34.41)**	**4 (11.44)**	
Rai-I	**36 (27.5)**	**29 (30.24)**	**7 (20.02)**	
Rai-II	**34 (26)**	**24 (25.03)**	**10 (28.60)**	
Rai-III	**3 (2.3)**	**2 (2.09)**	**1 (2.86)**	
Rai-IV	**21 (16)**	**8 (8.34)**	**13 (37.18)**	
Stage, Modified Rai				**0.002**
Low	**37 (28.3)**	**33 (34.41)**	**4 (11.44)**	
Intermediate	**70 (53.4)**	**53 (55.26)**	**17 (48.62)**	
High	**24 818.3)**	**10 (10.43)**	**14 (40.04)**	
Stage, Binet				**0.001**
Binet-A	**39 (29.8)**	**35 (36.49)**	**4 (11.44)**	
Binet-B	**68 (51.9)**	**51 (53.18)**	**17 (48.62)**	
Binet-C	**24 (18.3)**	**10 (10.43)**	**14 (40.04)**	
B symptoms				**0.007**
Absence	**88 (67.2)**	**71 (74.03)**	**17 (48.62)**	
Presence	**43 (32.8)**	**25 (26.07)**	**18 (51.48)**	
Splenomegaly				**0.003**
Absence	**70 (53.4)**	**59 (61.52)**	**11 (31.46)**	
Presence	**61 (46.6)**	**37 (38.58)**	**24 (68.64)**	
Hepatomegaly				**0.001**
Absence	**76 (58.1)**	**64 (66.73)**	**12 (34.32)**	
Presence	**55 (41.9)**	**32 (33.37)**	**23 (65.78)**	
Bone marrow involvement				0.068
Absence	**6 (16.7)**	**6 (30.03)**	**0 (0)**	
Nodular	**11 (30.5)**	**5 (25.03)**	**6 (37.54)**	
Diffuse	**19 (52.8)**	**9 (45.05)**	**10 (62.56)**	

(*continued*)

AIHA				**0.031**
Absence	**123 (93.9)**	**93 (96.97)**	**30 (85.80)**	
Presence	**8 (6.1)**	**3 (3.13)**	**5 (14.30)**	
17p Deletion				**0.196**
Negative	**82 (91.1)**	**63 (94.1)**	**19 (82.6)**	
Positive	**8 (8.9)**	**4 (5.9)**	**4 (17.4)**	
11q Deletion				**ND**
Negative	**60 (96.8)**	**44 (100)**	**16 (88.9)**	
Positive	**2 (3.2)**	**0 (0)**	**2 (11.1)**	
CD38				**0.982**
Negative	**38 (82.6)**	**32 (82.1)**	**6 (85.8)**	
Positive	**8 (17.4)**	**7 (17.9)**	**1 (14.3)**	
CD5				**0,793**
Negative	**27 (25.5)**	**22 (26.22)**	**5 (22.7)**	
Positive	**79 (74.5)**	**62 (73.88)**	**17 (77.3)**	

Table 3. Treatment regimens and response rates of patients with CLL

Variables	**All patients n (%)**	**Alive Group n (%)**	**Deceased Group n (%)**	***p*-value**
First-line treatment regimens				ND
B or B-R	7 (9.5)	7 (15.7)	0 (0)	
CVP	8 (11)	1 (2.2)	7 (25)	
FC	2 (2.7)	1 (2.2)	1 (3.6)	
FC-R	28 (38.4	23 (51.1)	5 (17.7)	
Chlorambucil	14 (19.2)	6 (13.3)	8 (28.7)	
R-CVP	14 (19.2)	7 (15.5)	7 (25)	
Response to first-line treatment				<0.001
Complete remission	28 (38.4)	26 (56.5)	2 (7.41)	
Partial remission	18 (24.7)	12 (26.1)	6 (22.24)	
Stable disease	16 (21.9)	7 (15.2)	9 (70.44)	
Refractory disease	7 (9.6)	0 (0)	7 (86.75)	

Progressive disease	4 (5.4)	1 (2.2)	3 (54.60)	
Second-line treatment regimens				ND
B-R	5 (19.3)	1 (9.1)	4 (26.6)	
FC	1 (3.8)	0 (0)	1 (6.7)	
FC-R	10 (38.6)	6 (54.5)	4 (26.6)	
Ibrutinib	1 (3.8)	1 (9.1)	0 (0)	
R-HDMP	1 (3.8)	0 (0)	1 (6.7)	
R-Chlorambucil	1 (3.8)	0 (0)	1 (6.7)	
R-CHOP	1 (3.8)	0 (0)	1 (6.7)	
R-CVP	6 (23.1)	3 (27.3)	3 (20)	
Response to second-line treatment				ND
Complete remission	6 (20)	5 (45.5)	1 (5.3)	
Partial remission	7 (23.3)	6 (54.5)	1 (5.3)	
Stable disease	0 (0)	0 (0)	0 (0)	
Refractory disease	13 (43.4)	0 (0)	13 (68.3)	
Progressive disease	4 (13.3)	0 (0)	4 (21.1)	

ND; Not Done, R; Rituximab, B; Bendamustine, B-R; Bendamustine-Rituximab, FC; Fludarabine-Cyclophosphamide, FC-R; Fludarabine-Cyclophosphamide-Rituximab, CVP; Cyclophosphamide-Vincristine-Prednisolone, R-CVP; Rituximab-Cyclophosphamide-Vincristine-Prednisolone, R-CHOP; Rituximab-Cyclophosphamide-Doxorubicin-Vincristine-Prednisolone, R-HDMP; Rituximab-high dose methylprednisolone.

and five-year treatment-free survival (TFS) for all patients were 85.1% and 71%, respectively. Multivariate Cox regression analysis showed the following prognostic factors to affect both OS and TFS: age ≤ 64 as positively, Binet ≤ stage B as positively, albumin >4.1 g/dL as positively, B symptoms as negatively, and presence of hepatomegaly as negatively (Table 4 and 5). Also, AIHA was a prognostic factor affecting only TFS rates as negatively (Table 5).

Discussion

A disease of advanced age, chronic lymphocytic leukemia, is a lymphoproliferative disease that rarely occurs at a young age. According to the results of an earlier study conducted in our country (Turkey) examining CLL patients, the male/female ratio was 1.5:1 (11). In our study, with 72.5% of the patients being male and 27.5% female, the male/female ratio was 2.5:1. The median age of our patients was similar to those of other studies conducted in our country.

Age is considered an important prognostic factor in CLL. Shanafelt et al. categorized patients based on age when they investigated the prognostic effects of age, finding that mortality and total survival rates were significantly different between age groups (12). In a study by Pamuk et al., patients were classified as young (under 60 years) and old (over 60 years); analysis of the data revealed a median overall survival of 118 months for young group and 132 for the old group (11). In our

Table 4. Multivariate analysis of overall survival in patients with CLL

Variables	B	Se	OR (95% CI)	*p*-value
Age ≤64	-1.177	0.383	3.25 (1.53-6.87)	0.002
Binet ≤ stage B	-1.635	0,611	5.13 (1.55-6.99)	0.008
B symptoms	-0.770	0.383	2.16 (1.02-4.58)	0.044
Albumin >4,1 gr/dL	-0.840	0.356	2.31 (1.15-4.64)	0.018
Hepatomegaly	-1.110	0.388	3.03 (1.41-6.49)	0.004

B; regression coefficient, Se; Standard error, CI; Confidence Interval, OR; Odss Ratio

Table 5. Multivariate analysis of treatment-free survival in patients with CLL

Variables	B	Se	OR (95% CI)	*p*-value
Age ≤64	-1.021	0.385	2.78 (1.30-5.91)	0.008
Binet ≤ stage B	-3.273	0.677	6.40 (7.00-9.61)	<0.001
B symptoms	-0.872	0.384	2.39 (1.12-5.07)	0.023
Albumin >4.1 gr/dL	-0.781	0.383	2.18 (1.01-4.62)	0.041
Hepatomegaly	-1.209	0.442	3.35 (1.41-7.96)	0.006
AIHA	-1.871	0.574	6.49 (2.10-20.02)	0.001

AIHA; autoimmune hemolytic anemia, B; regression coefficient, Se; Standard error, CI; Confidence Interval, OR; Odss Ratio

study, the median age in the alive group was significantly lower than the deceased group ($p < 0.001$).

Another important prognostic factor in CLL is disease stage (13). Binet et al., showed that, the total survival of patients with Binet stage-C was 2 years, that of patients with Binet stage-B was 7 years, while the survival of patients with Binet stage-A was similar with the sex- and age-matched population (7). In the present study, the OS was 121.1 months in patients with Binet stage-A, 101.6 months in patients with Binet stage-B, and 63.9 months in patients with Binet stage-C. Similarly, OS was found to decrease with increasing Rai and modified Rai stage.

In two previous studies, B symptoms were observed in 25% and 22% of patients with CLL (14, 15). In this study, the incidence of B symptoms was 32.8%, and a statistically significant relationship was found between the presence of B symptoms and mortality. The rate of B symptoms in the deceased group was 3.01 times higher than that of the alive group (95% CI; 1.3-6.7; $p = 0.007$). The OS and TFS of the patients with B symptoms were found to be significantly shorter than the patients without B symptoms ($p = 0.001$ and $p < 0.001$, respectively).

The presence of anemia and thrombocytopenia in CLL patients is rarely associated with immune cytopenias. They usually occur as a result of bone marrow infiltration and are considered indications for starting treatment. Studies have reported both to be associated with survival (15, 16). The median hemoglobin values in our study were higher than those of these studies and mortality was 2.9 times higher when the hemoglobin level was ≤ 13.8 g/dL (95% CI; 1.3-6.6; $p = 0.006$). Similarly, when the platelet count was ≤ 130 × 109/L, the mortality rate was 4.5 times higher (95% CI; 2.0-10.3; $p = 0.003$).

The category of prognostic factors for CLL includes β2-microglobulin and LDH, which are considered indicators of tumor load. Studies investigating the relationship between survival and LDH or β2-microglobulin have shown both to be associated with short survival time at elevated levels (15, 17). In addition, elevated LDH and a progressive increase in LDH are stimulus parameters for Richter's transformation. In our study, mortality in patients with high LDH levels was 3.5 times greater than in patients with normal LDH levels, and both OS and TFS were shorter (respectively, p = 0.002 and p = 0.016). However, in this study, although the median β2-microglobulin level in the deceased group was higher than in the alive group, the difference was not significant, and no significant relationship was detected between β2-microglobulin levels and OS and TFS.

Since there are a number of factors affecting albumin levels, the use of albumin as a prognostic parameter is not always appropriate. In particular, albumin levels are reduced in the presence of acute inflammatory conditions, protein malnutrition, and chronic liver or kidney diseases. Levis et al. detected a significant relationship between hypoalbuminemia and survival (18). In our study, an albumin level ≤ 4.1 g/dL was associated with a 3.1 times increase in mortality (95% CI; 1.4-6.9; p = 0.010).

Bone marrow biopsy is not a mandatory test for the diagnosis of CLL, however it could been done in patients who cannot be diagnosed or whose diagnosis is uncertain. In a study by Rozman et al., bone marrow infiltration type was determined to be an independent prognostic factor affecting survival (19). In our study, no statistically significant association between bone marrow infiltration pattern and mortality was detected.

Studies examining the relationship between splenomegaly/hepatomegaly and survival have reported different results. In some studies, there was no association between hepatosplenomegaly and survival (13), whereas in other studies, the presence of hepatomegaly/splenomegaly was found to be significantly associated with short survival time (15). In our study, the presence of splenomegaly/hepatomegaly was associated with both shorter OS and TFS.

Recent studies have investigated the frequency of cytogenetic abnormalities in CLL, their effect on treatment response, and their relationship with survival. The presence of 17p deletion has generally been associated with poor treatment response and short survival time (20,21). In our study, interestingly, there was no statistically significant relationship between 17p deletion and mortality. In a study by Demir et al. on CD5-negative CLL patients, survival time did not change when CD5 was negative (22). Ibrahim et al., in their study on CD38 levels, reported shorter survival time, more frequent lymph node infiltration and hepatomegaly, lower hemoglobin levels and higher β2-microglobulin levels in patients with CD38 positivity and the patients also exhibited more aggressived forms of the disease regardless of the disease stage (23). Although the rate of CD5 negativity was higher in our study, nonetheless there was no effect on survival, the rate of CD38 positivity was low compared with other studies, and it was not associated with survival.

The existence and use of anti-CD20 monoclonal antibodies has led to drastic changes in the treatment of CLL. The first monoclonal antibody used in patients with CLL was rituximab, the first study of which showed a pronounced benefit in survival with the addition of rituximab to FC chemotherapy in untreated CLL patients (24,25). In our patient groups, the first-line treatment regimens were not evenly distributed, and therefore no comparison could be made between the groups. However, there was a statistically significant difference between alive and deceased groups with respect to the first-line treatment response. The data were not suitable for analysis of the relationship between survival rates and second- and/or third-line treatment regimens.

In conclusion, in this study the median age of patients was lower, male predominance was more prominent, and the proportion of advanced stage patients was higher compared those of previous studies reported in the literature. In addition to the traditional prognostic parameters (advanced age, advanced Rai, modified Rai and Binet stages, and elevated LDH), the presence of B symptoms, AIHA and hepatosplenomegaly, hemoglobin level, platelet count, and albumin levels also affected survival negatively or positively.

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