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Research Article

Retrospective Evaluation of Our Cases with Chronic Lymphocytic Leukemia: Single Centered Real Life Data

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Abstract

Objectives: Chronic Lymphocytic Leukemia (CLL) is a hematological malignancy characterized by clonal proliferation and accumulation of mature, typically CD5(+) B cells in peripheral blood, bone marrow, spleen and lymph nodes. We aimed to contribute to patient approach algorithms by examining the clinical and prognostic characteristics, treatment regimens used, treatment responses, that may be effective on survival of patients diagnosed with CLL who received follow-up and treatment in our center.

Methods: The study included 152 patients, who were diagnosed with CLL between January 2011 and December 2021in the Hematology Clinic of Zonguldak Bulent Ecevit University Faculty of Medicine Hospital and whose data could be accessed. Treatment responses, survival status and factors affecting overall survival (OS) were evaluated retrospectively.

Results: 152 patients (89 men, 63 women) were included in the study. The median age was 66.71±9.89 years. In our study, the survival of the patients in the group with advanced age, high LDH, high risk modified RAI and advanced Binnet was found to be low and statistically significant. The mean follow-up period in all our CLL cases was 53.44 months. During the follow-up period, 87 patients did not receive any treatment, while 65 patients received treatment. Five-year overall survival was 63.6%, and disease-free survival was found to be 59.3%.

Conclusion: In CLL patients the appropriate treatment should be selected at the appropriate time, taking into account the characteristics of the patient and the disease. In order to achieve complete remission, effective chemo-immunotherapy agents should be started at the right time in patients.

Keywords: Chronic lymphocytic leukemia, prognosis, overall survival, chemo-immunotherapy

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Chronic Lymphocytic Leukemia (CLL) is a hematological malignancy characterized by clonal proliferation and accumulation of mature, typically CD5(+) B cells in peripheral blood, bone marrow, spleen and lymph nodes.[1] It is the most common type of leukemia in Western society.[2] The diagnosis of CLL requires an absolute lymphocyte count above 5000 in peripheral blood for at least 3 months.[2] Median age at diagnosis is 70.[3] It is more common in men than in women (1.9:1).[3] It is estimated that there will be 21160 new cases of CLL and 4410 deaths, representing 1.1% of all new cancer cases in the United States in 2022.[4] The clinical course of CLL patients is highly variable, and most are asymptomatic at diagnosis.[5] Autoimmune cytopenias(AIC) may develop during the course of the disease, especially with the development of antibodies against blood cells.[6] Susceptibility to infections is common

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due to hypogammaglobulinemia (HG). Rai and Binet staging systems are generally used for staging purposes.[7, 8] The Rai classification was later modified and defined in 3 groups as low risk (RAI stage 0), intermediate risk (RAI stage 1,2) and high risk (RAI stage 3,4).[9] In addition to Rai and Binet staging systems, unfavorable prognostic factors affecting disease course and overall survival include male gender, advanced age, high lymphocyte count at diagnosis, short lymphocyte doubling time, presence of cytogenetic abnormalities, elevated LDH, β2 microglobulin and diffuse bone marrow involvement. With the advances in molecular biology, new prognostic markers of include increase in CD38, absence of somatic mutation in IgVH gene, 17p deletion [del(17p)]/TP53 abnormality are poor prognostic markers in CLL patients.[5] The presence of del 13q, del 11q, trisomy 12 is also important in predicting prognosis.[10]

In this study, our aim was to evaluate the results of our center regarding patients followed up with a diagnosis of CLL, to compare our real life data with the literature data and to contribute to the literature of our country.

Methods

The study included 152 patients, who were diagnosed with CLL between January 2011 and December 2021, whose data could be accessed. Male and female patients over 18 years of age were included in the study. Patients with CLL diagnosed by clinical, hemogram, peripheral smear, bone marrow aspiration, bone marrow biopsy, flow cytometry ± cytogenetic/FISH evaluation were included in the study. Demographic information, hemogram, biochemical parameters, peripheral smear findings, flow cytometry, bone marrow characteristics, lymphadenopathy (LAP) and organomegaly status, indications for treatment initiation, cytogenetic status, treatments and responses, and survival status of these patients were obtained retrospectively from the hospital data program. Factors affecting overall survival (OS) were also evaluated. The criteria for CLL diagnosis and response to treatment were based on the National Cancer Institute CLL Working Group (NCIWG -iWCLL) treatment indications, published in 1996 and revised in 2008.[11]

Ethics committee approval for the study was obtained from Zonguldak Bulent Ecevit University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee with the decision dated 08.06.2022 and numbered 2022/11.

Statistical Analysis

Statistical analyzes "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics were presented as n and % for categorical variables, and Mean±SD, median (IQR) for continuous variables. Kaplan Meier method was used to compare survival and disease-free survival times between RAI stage, Binnet stage and treatment groups. Finally, Univarite and Multivariete Cox Regression results are given on the risk of death from various clinical factors. $p<0.05$ was considered statistically significant.

Results

152 patients (89 men, 63 women) were included in the study. The median age was 66.71±9.89 years. It was observed that 116 patients were 60 years or older (Table 1). Examination of the laboratory data of the patients at the time of diagnosis revealed that the mean hemoglobin

Table 1. Clinical and Demographic findings (n=152)

Demographic variables	**n**	**%**
Sex		
Female	63	41.4
Male	89	58.6
Modified RAI staging		
Low risk	23	15.1
Intermediate Risk	98	64.5
High risk	31	20.4
Binet Stage		
A	59	38.8
B	69	45.4
C	24	15.8
1st line treatment		
R-FC	34	22.4
CHLORAMBUCIL	15	9.9
R-CVP	1	.7
R-B	15	9.8
None	87	57.2
2nd line treatment		
FCR	2	1.3
CHLORAMBUCIL	1	.7
R-CVP	1	.7
RB	14	9.2
None	134	88.2
Ex-Alive		
Alive	91	59.9
Ex	61	40.1
Comorbidity		
None	35	23.0
Available	117	77.00
Age group		
<60	36	23.7
≥60	116	76.3
	Mean±SD	**Median (IQR)**
Age	66,71±9,89	67,00 (14,75)

was 12.27±2.05 g/dL(7-16 g/dL), the mean leukocytes were 44085.52±51108.19 µL, and the platelet mean was 189513.69±84421.12 µL (Table 2). The diagnosis was made by peripheral blood flow-cytometric analysis in 148 patients and bone marrow biopsy in 4 patients.

At the time of diagnosis, 61 patients had LAP in ≥3 sites. Since β2 microglobulin was not checked in our hospital, the β2 microglobulin levels of the patients could not be obtained. When the stages of the patients at the time of diagnosis were evaluated, modified RAI stage was determined as low risk 15.1% (n=23), intermediate risk 64.5% (n=98), high risk 20.4% (n=31). According to BINET staging, stage A was 38.8% (n= 59), stage B was 45.4% (n= 69), and stage C was 15.8% (n= 24) (Table 1).

FISH was sent in 85 patients; 29 patients were 13q positive, 7 patients were 11q positive, 10 patients were trisomy 12 positive and FISH was not measured in 67 patients. Immune thrombocytopenic purpura (ITP) was noted in 3 patients and immune-hemolytic anemia (AIHA) in one patient.

Hepatitis serology was evaluated by ELISA in 152 patients. When the results were analyzed, HbsAg was negative in 102 patients, positive in 7 patients, not tested in 43 patients, antiHBs was not tested in 52 patients, negative in 92 patients, positive in 8 patients, antiHbcIgG was not tested in 55 patients, 69 patients were negative and 28 patients were positive. In the records, 21 of 28 patients with positive antiHbcIgG were given prophylaxis concurrently with chemotherapy, but one patient voluntarily discontinued prophylaxis and HBV reactivation occurred during the treatment period.

During the follow-up period, 87 patients did not receive any treatment, while 65 patients received treatment. When the indications for treatment were evaluated, it was seen that treatment was initiated for B symptom in 25 patients, LAP progression and organomegaly in 12 patients, shortened lymphocyte doubling time in 12 patients, splenomegaly exceeding 6 cm above the cervical arch in 13 patients, steroid-refractory AIHA in one patient and steroid-refractory ITP in 3 patients.

Table 2. Laboratory information of patients (n=152)

Biochemical findings	Mean±SD	Median (IQR)
HB	12.27±2.05	12.60 (2.65)
WBC	44085.52±51108.19	27750.00 (30000.00)
Thrombocyte	189513.69±84421.12	185000.00 (100500.00)
Lymphocyte	35091.44±45246.57	21250.00 (26150.00)
ALT	15.55±9.78	12.50 (7.00)
AST	20.80±10.38	18.00 (8.00)
LDH	239.42±65.64	225.00 (79.25)

When first-line treatments were analyzed, 34 patients (22.4%) received Rituximab- Fludarabine, Cyclophosphamide (R-FC), 15 patients (9.8%) received Rituximab-Bendamustine (R-B), 1 patient (0.7%) received Rituximab-Cyclophosphamide, Vincristine, Prednisolone (R-CVP), and 15 patients (9.9%) received Chlorambucil (Table 1). In the follow-ups of the patients who received one line of treatment, it was determined that 32 patients died and 33 patients survived. When the response rates of our 34 patients who received R-FC treatment were analyzed, it was seen that 22 patients had a complete response and survived, 12 patients died and overall survival was 64.7%. It was observed that all 15 patients who received RB responded, and 6 patients died of causes other than CLL. It was observed that 15 patients received chlorambucil due to age and performance, and 13 of these patients died, with an average age of 78.6 years. Of the 18 patients who received second-line treatment; it was observed that 14 took RB, 2 took R-FC, 1 R-CVP, and 1 patient took chlorambucil (Table 1). It was observed that 8 of 15 patients who received second-line treatment died. 4 patients received ibrutinib in 3rd line treatment and 2 patients received venotoclax treatment after ibrutinib treatment. One of these patients died in 2021 due to Covid-19 infection.

In addition, it was observed that one patient was given R-FC in the first-line treatment, but due to Covid-19 infection after the second cycle, Ibrutinib treatment was started by obtaining off-label application approval from the Ministry of Health. No adverse events were observed in patients on ibrutinib and all patients were evaluated by cardiology for cardiac issues before starting treatment. In total, there were 36 patients below 60 years of age, who received treatment, and 50 of 116 patients aged 60 years and above received treatment. Age, LDH, RAI and Binnet staging variables were found to be statistically significant in terms of risk of death ($p<0.05$) (Table 3). It was observed that those aged 60 years and over and the increase in LDH values increased the risk of death ($p<0.001$). While 95.7% of patients with low risk RAI stage did not receive treatment, only one patient received treatment Of the patients with intermediate risk, 62.2% did not receive treatment and 37.8% received treatment. While 90.3% of high-risk patients received treatment, 9.7% did not receive treatment (Table 4). Among patients with Binnet stage A, 89.8% did not receive treatment, while 10.2% received treatment. Of those with stage B, 47.8% did not receive treatment, 52.2% received treatment All patients with stage C received treatment (Table 4). Overall survival was determined as 108 months. While 2-year survival was 82%, 5-year survival was 63.6% (Fig. 1). Overall survival times according to RAI stages were found to be statistically significant ($p<0.001$). The overall survival was found to be 108

Table 3. Univariate and Multivariete Cox Regression Results for Various Clinical Variables

Variables	Univariate HR (95%CI)	p	Multivariete HR (95%CI)	p
Age (Ref:60<)	3.29 (1.41)-7.66)	0.006	1.06 (1.03)-1.10)	<0.001
LDH	1.00 (1.00)-1.02)	<0.001	1.01 (1.01)-1.02)	<0.001
Comorbidity (Ref:None)	1.81 (0.88)-3.69)	0.102	1.63 (0.78)-3.40)	0.189
RAI staging (Ref: low risk)		0.002		0.510
Intermediate Risk	2.58 (0.79)-8.36)	0.113	2.07 (0.59)-7.21)	0.252
High risk	5.79 (1.72)-19.53)	0.005	1.87 (0.34)-10.09)	0.465
Binnet staging (Ref:A)		0.010		0.928
B	1.51 (0.83)-2.77)	0.183	1.14 (0.57)-2.27)	0.700
C	2.96 (1.46)-6.01)	0.003	1.12 (0.31)-3.97)	0.855
			p<0.001, -2 loglikelihood=506.15	

Table 4. Modified RAI and Binet distributions in treated and untreated patients

	Untreated n (%)	Treated n (%)
RAI staging		
Low risk	22 (95.7)	1 (4.3)
Intermediate Risk	61 (62.2)	37 (37.8)
High risk	3 (9.7)	28 (90.3)
Binnet Stage		
A	53 (89.8)	6 (10.2)
B	33 (47.8)	36 (52.2)
C	0 (0.0)	24 (100.0)

Table 5. OVS and PFS comparisons of patients

Overall Survive (months)	Median (%95 CI)	p
General	108.00 (76.66)-139.33)	
RAI staging		
Low risk	-	<0.001
Intermediate Risk	108.00 (70.39)-145.60)	
High risk	36.00 (27.26)-44.73)	
Binnet Staging		
A	-	
B	84.00 (58.49)-109.51)	0.005
C	36.00 (13.79)-58.20)	
Treatment status		
None	-	0.001
Available	60.00 (41.91)-78.08)	
PFS (months)	**Median (%95 CI)**	
General	120.00 (73.59)-166.40)	

Kaplan Meier curve, Long rank test, p<0.05 statistically significant.

months in those with intermediate risk and 36 months in those with high risk (Table 5). A statistically significant difference was also found between intermediate risk and high risk in terms of overall survival times (p=0.002). In the low risk group, 2-year survival was 90% and 5-year survival was 82.5%. While 2-year survival was 85.2% and 5-year survival was 74.5% in the intermediate risk group, 2-year survival was 67.1% and 5-year survival was 37.1% in the high-risk group (Fig. 2). Overall survival times according to Binnet stages were found to be statistically significant (p<0.001). The overall survival was found to be 84 months in those with stage B and 36 months in those with stage C (Table 5). A statistically significant difference was found between stage B and C in terms of overall survival (p=0.022). In stage A group, 2-year survival was 83.4% and 5-year survival was 74.1%; in stage B group, 2-year survival was 86.6% and 5-year survival was 64.7%; in stage C group, 2-year survival was 65.8% and 5-year survival was 36.5% (Fig. 3). Overall survival periods according to treatment status were found to be statistically significant (p<0.001). Overall survival in those treated was 60 months. In those who did not receive treatment, 2-year survival was 87.8% and 5-year survival was 76.6%, while 2-year survival was 83.2% and 5-year survival was 49.5% in those who received treatment (Fig. 4). While the mean follow-up time was 53.44 ±36.66 in all our CLL cases, it was 53.16±36.42 months in those who did not receive treatment. Overall disease-free survival was 120 months, and 2-year disease-free survival was 69.3.5% and disease-free survival was 59.3% (Fig. 5). When the patients were evaluated in terms of comorbidities, 117 patients had at least one comorbidity, while 13 patients had a second malignancy. Malignancies included bladder malignancy in 1 patient, prostate malignancy in 3 patients, basal cell skin in 1 patient, ovarian malignancy in 1 patient, thyroid malignancy in 1 patient, chronic myeloproliferative disease in 1 patient, plasmacytoma in 1 patient, malignant melanoma

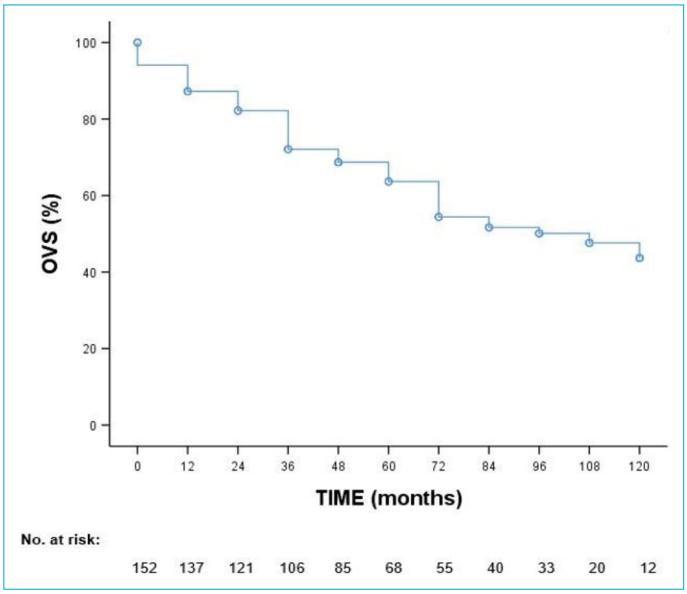

Figure 1. Survival curve of all patients.

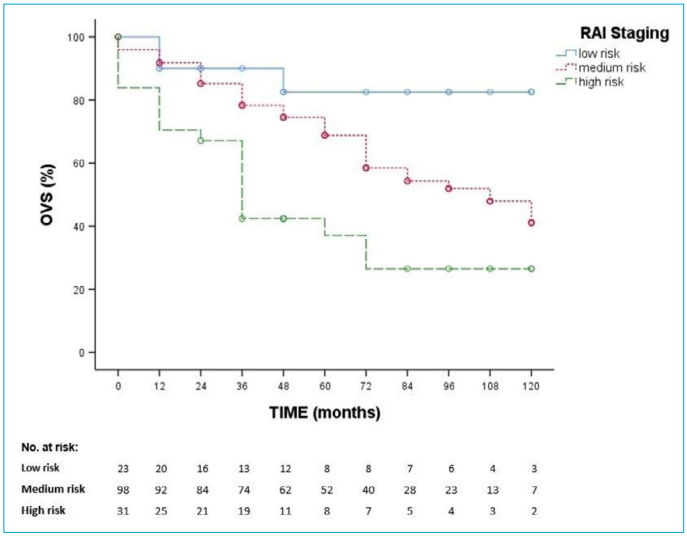

Figure 2. Survival status by modified RAI stage.

in 1 patient, chronic myeloid leukemia in 1 patient, myelodysplastic syndrome in 1 patient and prostate malignancy, multiple myeloma and chronic lymphocytic leukemia in 1 patient.

Discussion

CLL accounts for approximately 30% of adult leukemias. The mean age at diagnosis is 70, and it is more common in men.[3] The mean age was reported as 64 in one of the studies conducted in our country while it was[12] reported as 63 in another study.[13] In our study, the mean age of diagnosis was 66, and the male/female ratio was 1.4. The most prominent feature of the disease, which is usually diagnosed in the asymptomatic period, is the increased lymphocyte percent-

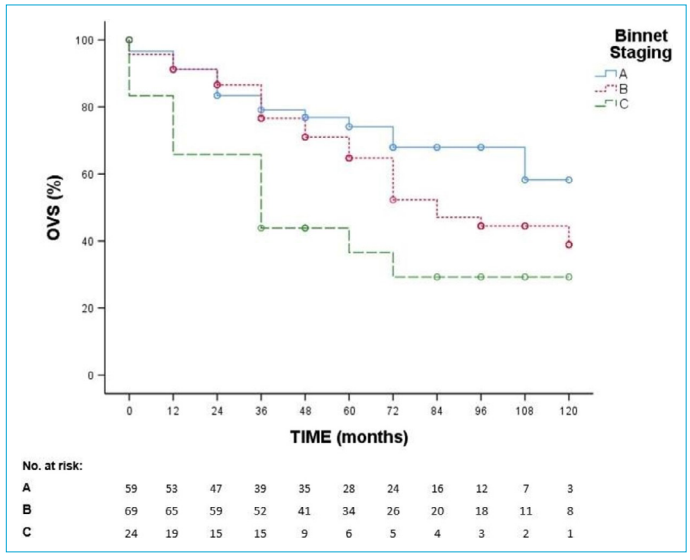

Figure 3. Survival status by modified BINET stage.

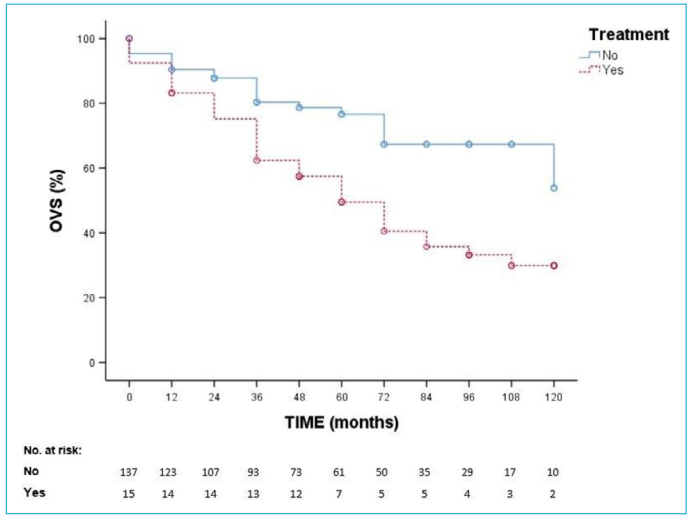

Figure 4. Survival in the treated and untreated group.

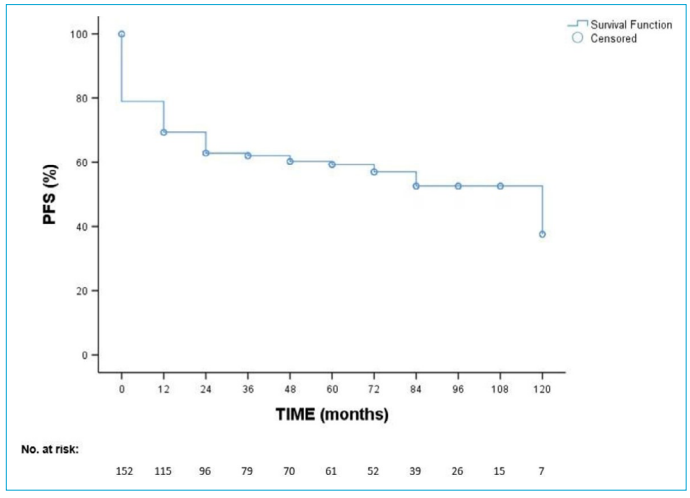

Figure 5. Disease-free survival of all patients.

age. The iwCLL group has specified how to diagnose CLL in the guidelines.[1] The diagnosis of CLL is mostly made by hemogram, peripheral smear and immunophenotyping. Peripheral blood should contain ≥5000 B-lymphocytes/μL for at least 3 months and clonality of these lymphocytes should be confirmed by flow cytometry. Mature lymphocytes with small narrow cytoplasm and basket cells are seen in peripheral smear. The diagnosis was made by peripheral blood flow-cytometric analysis in 148 patients and by bone marrow biopsy in 4 patients. It is known that the mortality rate is also high in patients who initially consulted with a high lymphocyte count.[14] the mean lymphocyte count was found to be 31000 by Serel et al.[6] and 34.000 by Demir et al.[12] while we found 44085. In our study, we observed that mortality increased as the lymphocyte count increased. The most common finding on physical examination is LAP, followed by splenomegaly. In our study; 40.1% of the patients had ≥3 sites of LAP, and 8.5% had splenomegaly.

All other causes of anemia and thrombocytopenia such as immune hemolysis, bleeding, hypersplenism, iron and vitamin deficiencies and myelosuppression should be excluded when deciding on advanced stage in CLL.[15] Therefore, if necessary, the disease status should be evaluated with bone marrow examination. Autoimmune cytopenias (AIC), which can be seen as AIHA, ITP, pure red cell aplasia or autoimmune granulocytopenia, are seen in 5-9% of CLL follow-ups. Treatment of CLL-associated AIC is usually directed towards autoimmunity, whereas CLL-specific treatment is given in refractory disease or disease progression.[16] In a study conducted in 2008, the frequency of ITP was found to be 5%,[17] in another study in 2010, ITP was found to be 2%, AIHA 5-10%.[18] In our study, one patient had AIHA and three patients had ITP. Secondary hypogammaglobulinemia (SHG) is an important complication of CLL associated with recurrent and severe infections.[19, 20] Although it is seen during the natural course of CLL, it can also develop due to CLL treatments. Anti-CD20 antibodies, BTK inhibitors and phosphoinositide 3 kinase δ inhibitors used in CLL treatment can cause SHG.[21, 22] Çelik et al.[19] reported that there was a significant decrease in the level of IgG in patients who received ibrutinib monotherapy in their study. In many studies, it has been reported that the incidence of HG development in CLL patients is between 20-70%.[23, 24] This rate was 20% in our study. Infections are the most important cause of mortality and morbidity in CLL patients and cause 30-50% of deaths.[25] Ig replacement (IVIG) has been shown to reduce major infections in SHG.[26] In our study, it was seen that the patients were given IVIG prophylaxis. When our cases were evaluated in terms of the infections they had, the most common infection was pneumonia. In the follow-ups between 2020-2021, it was observed that 14 of our patients had Covid-19 infection and one patient died. Hepatitis B virus (HBV) is an important cause of morbidity and mortality, especially in those receiving anti-CD20 therapy. Since chemoimmunotherapy may lead to HBV reactivation in patients who have previously been exposed to HBV, all guidelines recommend that all patients with HBsAg/Anti-HBcIgG positive should start prophylactic antiviral agents before starting chemotherapy regimens, especially rituximab-containing chemotherapy regimens, and that this treatment should be continued for 6 to 12 months after completion of chemotherapy.[27] In our study, HbsAg was positive in 7 patients and antiHbcIgG was positive in 28 patients, but 21 patients were given antiviral prophylaxis concurrently with chemotherapy; one patient died due to HBV reactivation as a result of voluntary discontinuation of prophylaxis. Eight of our patients were vaccinated. While RAI and Binet are commonly used in prognostic staging of CLL, the CLL International Prognostic Index (CLL-IPI) was defined in 2016. CLL-IPI is an index that determines risk according to age, clinical stage, TP53 status, IGHV mutation status, serum B2 microglobulin parameters.[28, 29] We used the modified RAI and Binet staging system in our study. When our cases were evaluated according to the stages, the modified RAI was found to be 15.1% in the low-risk group, 64.5% in the intermediate-risk group, and 20.4% in the high-risk group; in the literature while RAI et al.[8] determined the low risk group as 31%, the intermediate risk group as 61% and the high risk group as 8%. In our study of distribution according to BINET stage, stage A was 38.8%, stage B was 45.4%, stage C was 15.8%, and in the study of BINET et al.,[7] stage A was found to be 55%, stage B 30%, and stage C 15%. When our patients were evaluated prognostically, age, LDH, RAI and Binnet staging variables were found to be statistically significant ($p<0.05$) in terms of mortality risk. Every patient with a diagnosis of CLL should be evaluated in terms of treatment indication during the diagnosis period. iwCLL guidelines are recommended for both treatment indication and evaluation of response to treatment.[3, 11] Chlorambucil is one of the first agents in the treatment of CLL.[30] Currently, chlorambucil monotherapy is still used as an option to provide palliation in elderly patients who are not suitable for intensive chemotherapy.[3] In our study, it was observed that 15 patients received chlorambucil and their mean age was 78.6 years. R-FC is standard first-line therapy for CLL patients.[31, 32] Tam et al.[33] reported a complete response rate of 72% in patients who underwent R-FC in their study; we found this rate as 64.7% in our study. In another study of 117 patients with chemo-immunotherapy, total response was 88%, complete response was 23%, 90.5% of the patients were alive and PFS was 33.9 months at 27 months follow-up.[34, 35] When the other treatments received by our patients were evaluated, it was seen that ibrutinib was given in the third-line treatment in 4 re-

lapsed refractory patients. It is known that significant results have been achieved with Ibrutinib treatment in high-risk CLL such as 17p del.[36] Minimal residual disease (MRD) status is one of the important factors affecting prognosis in disease follow-up. Studies have reported increased treatment responses and survival rates in CLL patients with 17 p mutations with treatment strategies and new drugs according to MRD.[37] The frequency of secondary malignancies (solid and hematological malignancies) in CLL has been reported in previous studies. A broad spectrum of solid malignancies has been described, including gastric, colon, breast and kidney carcinomas. It has also been reported that different hematologic malignancies such as myeloproliferative neoplasms (MPNs), myelodysplastic syndrome (MDS), acute leukemia, multiple myeloma (MM) occur during, before or simultaneously with the course of the disease in CLL patients.[38, 39] In our study, 9 patients had solid organ malignancy, 3 patients had hematologic malignancy, and 1 patient had both solid organ and hematologic malignancy. Compared to studies conducted in our country, we found that our mortality rate was higher in our study. We believe that this is due to the fact that 76.3% of the patients included in the study were 60 years or older and 77% had at least one comorbidity. Other limitations of our study are that genetic tests and B2 microglobulin levels could not be performed in all patients due to hospital conditions, and the small number of patients.

Conclusion

CLL is a disease of elderly. Patients comorbidities, quality of life, and performance status affect treatment options. For this reason, patients should be evaluated in detail in terms of comorbidity in the selection of treatment. In patients with CLL, appropriate treatment should be planned for the patient by staging, cytogenetic and prognostic evaluation with FISH. In our study, we wanted to contribute to the studies in this field in our country with our real life data by examining the prognostic status, treatment responses and survival status of our patients diagnosed with CLL.

Disclosures

Ethics Committee Approval: Ethics committee approval for the study was obtained from Zonguldak Bulent Ecevit University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee with the decision dated 08.06.2022 and numbered 2022/11.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A.A., S.E.; Design – M.A.A., S.E.; Supervision – M.A.A., S.E., S.Y.; Materials – M.A.A., S.Y.; Data collection &/or processing – M.A.A.; Analysis and/or interpretation – M.A.A., S.E., S.Y.; Literature search – M.A.A., S.Y.; Writing – M.A.A.; Critical review – M.A.A., S.E., S.Y.

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