VIA MEDICA

ORIGINAL RESEARCH ARTICLE

Acta Haematologica Polonica 2022
Number 4, Volume 53, pages 277–284
DOI: 10.5603/AHP.a2022.0036
ISSN 0001–5814
e-ISSN 2300–7117

Assessment of two main therapeutic regimens of chronic lymphocytic leukemia in a major referral center in Syria

Lujain Hamdan*, Firas Hussein, Samer Akel

Tishreen University Hospital, Latakia, Syria

Abstract

Introduction: Due to the high cost of targeted therapy, chemoimmunotherapy regimens remain the standard therapy for chronic lymphocytic leukemia in many developing countries. In this study, we compare the treatment outcomes of the two main chemoimmunotherapeutic regimens.

Material and methods: Data was obtained from the oncology department archives at Tishreen University Hospital between 2016 and 2020. We enrolled previously untreated, fit patients with chronic lymphocytic leukemia who were treated with one of two regimens: either a fludarabine, cyclophosphamide, and rituximab regimen, or a bendamustine and rituximab regimen.

Results: 78 patients were enrolled in the study. 56.8% of the fludarabine, cyclophosphamide, and rituximab group achieved complete response versus 73.5% of the bendamustine and rituximab group. Progression-free survival was slightly shorter for fludarabine, cyclophosphamide, and rituximab than for bendamustine and rituximab [median 15.1 months (95% confidence interval {CI} 12.4–17.8] vs. 17.7 months (95% CI 15.4–20.1)] without statistical significance. In elderly patients (>65 years) median progression-free survival (PFS) was significantly (p = 0.046) longer with the bendamustine and rituximab treatment [median 19.9 months (95% CI 17.2–22.5)] than with the fludarabine, cyclophosphamide, and rituximab [median 11.6 months (6–17.2)]. Regarding overall survival, no significant difference between the two groups was documented. Delay and deletion of cycles, neutropenia and anemia were more frequent with the fludarabine, cyclophosphamide, and rituximab group. Furthermore, we found that elevated lactate dehydrogenase, positive expression of ZAP-70, stage C, and splenomegaly are all indicators of poor prognosis in correlation with PFS.

Conclusions: Our study found that the bendamustine and rituximab regimen is safer than, and has comparable efficacy to, the standard therapy of fludarabine, cyclophosphamide, and rituximab for previously untreated, fit patients with chronic lymphocytic leukemia.

Key words: chronic lymphocytic leukemia, chemoimmunotherapy, bendamustine, fludarabine

Acta Haematologica Polonica 2022; 53, 4: 277–284

*Address for correspondence: Lujain Hamdan, Tishreen University Hospital, Latakia, Syria, phone +96 39 357 83 604, e-mail: lujainhamdan93@gmail.com

Received: 16.04.2022 Accepted: 07.06.2022

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in developed countries [1]. It is a monoclonal B cell malignant disorder characterized by progressive accumulation of inefficient lymphocytes in the blood, the bone marrow, the lymph nodes and the spleen [2, 3].

CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease; in SLL, the disease is mainly nodal [4], while CLL is diagnosed when more than 5×10^9/L B-lymphocytes are present in the peripheral blood for at least three months [5], with a lymphocytic clonality confirmed by immunophenotyping [3].

CLL is mainly a disease of the elderly. The median age at diagnosis is 65–72 years [6, 7]. It is extremely heterogeneous in its clinical course [8].

CLL typically demonstrates a characteristic immunophenotype, expressing CD5, CD19, dim CD20, dim CD22, CD23, dim-to-negative CD79b and dim monoclonal surface immunoglobulin (Ig) [9].

Regarding therapy, combination chemoimmunotherapy (CIT) regimens such as FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) have been the frontline therapies for CLL [10] until recently, when targeted small molecular inhibitors were approved for all cases, preferably ones with del17 and defective p53 [11, 12]. The toxicity and cost differences between CIT and ibrutinib are significant. Moreover, due to financial demands, the availability of novel inhibitors is limited [13], especially in a resource-limited country like Syria.

Material and methods

Study design and participants

This was a retrospective, cohort study. Data was obtained from the oncology department archives at Tishreen University Hospital in Latakia, Syria between 2016 and 2020. We enrolled previously untreated, fit patients with chronic lymphocytic leukemia who required treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria [14] and had an Eastern Cooperative Oncology Group (ECOG) status of 0–2. Staging was decided according to the Binet staging system. Patients had to have an advanced clinical stage (Binet C) or confirmed active disease requiring treatment [14]. The main exclusion criteria were impaired renal function, previous therapy for chronic lymphocytic leukemia (except steroids), Richter transformation, and active secondary malignancy requiring treatment. The patient's initial data at diagnosis was obtained from the department's archives, including demographic characteristics, laboratory parameters, radiological findings, staging and immunophenotyping results. Patients were treated with one of two regimens, either the FCR or the BR regimen, where six 28-day cycles of rituximab, fludarabine and cyclophosphamide were compared to six 28-day cycles of bendamustine and rituximab. Intravenous fludarabine (25 mg/m^2 per day) and cyclophosphamide (250 mg/m^2 per day) were administered on the first three days of each cycle, while bendamustine (90 mg/m^2 per day) was administered intravenously on the first two days of each cycle. Rituximab 375 mg/m^2 was given intravenously to both groups on day 1 of each cycle. There was no prophylactic use of antibiotics or growth factors. An assessment of initial response was done one month (give or take seven days) after the beginning of the last cycle of treatment. Response to treatment was classified according to the iwCLL response criteria [14]. All adverse events, including neutropenia, anemia, thrombocytopenia, delay or deletion of cycles and hospitalization, were reported. Afterwards, patients were followed for two years.

Outcomes

The primary objective of this study was to compare the efficacy and safety of bendamustine and rituximab to the standard treatment of fludarabine, cyclophosphamide, and rituximab with regard to a primary endpoint of progression-free survival (PFS), defined as the time from diagnosis until progression or death from any cause. Secondary endpoints were overall survival (OS; defined as the time from diagnosis until death from any cause), the proportion of patients who achieved an overall response (OR), defined as the proportion of patients having achieved a complete remission or partial remission as a response to study treatment. We also evaluated the prognostic value of some demographic, clinical, and laboratory variables with regard to PFS. The sample was divided into two groups. The first included patients who achieved PFS ≥24 months and the second included patients with PFS <24 months.

Statistical analysis

Statistical analysis methods included descriptive statistics such as quantitative variables expressed by measures of central tendency and measures of dispersion, and qualitative variables expressed as frequencies and percentages, while inferential statistics included other tests. For natural distribution of data, we used a Kolomogorov-Smirnov test. For the difference between two independent groups (the two treatment groups as well as the two prognostic groups) we used an Independent T student test in case the distribution was natural, and a Mann-Whitney U test in case it was unnatural, while for the relation between qualitative variables we used a Chi-square test. As for survival time analysis, we used Kaplan-Meier curves according to Breslow. The results were considered statistically significant when the *p*-value was less than 0.05. The IBM SPSS Statistics (Statistical Package for the Social Sciences for Windows; Version 20) program was relied upon to calculate the statistical parameters and analyze the results.

Table I. Comparison between demographic and clinical characteristics, laboratory results and radiological findings between groups at diagnosis

Variable		FCR (n = 44)	BR (n = 34)	*p* value
Sex	Male	30 (68.2%)	22 (64.7%)	0.747
	Female	14 (31.8%)	12 (35.3%)	
Age		59.3 ± 8.1	61.4 ± 10.9	0.344
	≤65	33 (75%)	22 (64.7%)	0.323
	>65	11 (25%)	12 (35.3%)	
Laboratory results	WBC	75.1 ± 69.3	58.4 ± 79.1	0.313
	LYM	58.6 ± 56.7	48.1 ± 66	0.454
	Hb	10.9 ± 2.3	11.5 ± 2.5	0.274
	PLT	150.5 ± 90.8	159.5 ± 80.9	0.653
	LDH	438.1 ± 193.3	405.5 ± 160.4	0.428
Splenomegaly		34 (77.3%)	20 (58.8%)	0.080
Binet staging	Stage B	20 (45.5%)	20 (58.8%)	0.241
	Stage C	24 (54.5%)	14 (41.2%)	
Overall response	CR	25 (56.8%)	25 (73.5%)	0.312
	PR	15 (34.1%)	7 (20.6%)	
	Progression	4 (9.1%)	2 (5.9%)	

WBC — white blood cells; LYM — lymphocytes; Hb — hemoglobin; PLT — platelets; LDH — lactate dehydrogenase; CR — complete response; PR — partial response

Results

Patients

One hundred and fifty cases of CLL were diagnosed in the oncology department between 2016 and 2020, 88 of whom were treated with either FCR or BR. The other most used first-line regimens were chlorambucil, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), and R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), in that order. In addition, a large proportion of patients did not need any treatment at diagnosis. We excluded 10 patients from the study because they did not fulfill the inclusion criteria.

Eventually, 78 patients with CLL were enrolled in the study. Males were predominant with 52 (66%) patients. The ages of patients at diagnosis ranged between 39 and 81 years, median 60.2 ± 9.4. The FCR group included 44 patients, while the BR group had 34 patients. Fifty-five patients of the entire sample were ≤65 years, 33 patients in the FCR group and 22 in the BR group. Likewise, the proportion of patients older than 65 years was higher in the FCR group than in the BR group. All patients in both groups had ≥3 lymphadenopathy areas (the areas of involvement considered are: a) head and neck, including the Waldeyer ring; b) axillae; and c) groins, including superficial femoral) [3]. Only five patients in the entire sample had hepatomegaly, therefore these variables were not included in the study. Patients were distributed almost equally between stages B and C with 40 and 38, respectively. No patient in either group was in stage A. Laboratory results and demographic characteristics did not show any statistical value between the two groups. 56.8% of the FCR group achieved complete response vs. 73.5% of the BR group; four patients from the FCR group and two patients from the BR group had a progressive disease while being on treatment; and no cases of stable disease were documented (Table I, Figure 1).

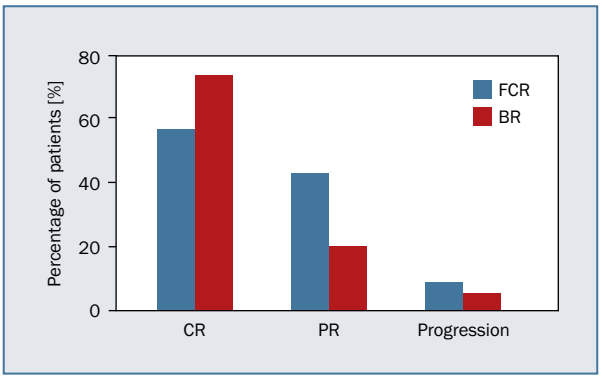

Figure 1. Bar chart demonstrates overall responses of patients between the two treatment groups; CR — complete response; PR — partial response; FCR — fludarabine, cyclophosphamide, rituximab; BR — bendamustine, rituximab

Response to treatment

Although the differences in complete responses among most prognostic subgroups were clinically higher in the BR group, none of it was significant with the exception of patients with expression of CD22 (Table II).

Table II. Overall response and complete response in FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) groups according to different variables

Variable	Response	FCR	BR	*p* value
Male (52)	CR	16 (53.3%)	17 (77.3%)	0.208
	OR	27 (90%)	21 (95.5%)	0.466
Female (26)	CR	9 (64.3%)	8 (66.7%)	0.976
	OR	13 (92.9%)	11 (91.7%)	0.910
Age ≤65 years (55)	CR	20 (60.6%)	17 (77.3%)	0.197
	OR	29 (87.9%)	20 (90.9%)	0.724
Age >65 years (23)	CR	5 (45.5%)	8 (66.7%)	0.305
	OR	11 (100%)	12 (100%)	1.0
Binet staging				
Stage B (40)	CR	12 (60%)	17 (85%)	0.077
	OR	18 (90%)	19 (95%)	0.548
Stage C (38)	CR	13 (54.2%)	8 (57.1%)	0.859
	OR	22 (91.7%)	13 (92.9%)	0.869
CD22 expression (n = 43)	CR	10 (47.6%)	17 (77.3%)	**0.044**
	OR	19 (90.5%)	21 (95.5%)	0.522
CD23 expression (n = 50)	CR	18 (53.9%)	12 (75%)	0.137
	OR	32 (94.1%)	15 (93.8%)	0.959
CD38 expression (n = 32)	CR	9 (50%)	10 (71.4%)	0.221
	OR	16 (88.9%)	14 (100%)	0.198
ZAP-70 expression (n = 23)	CR	5 (41.7%)	7 (63.6%)	0.292
	OR	11 (91.7%)	11 (100%)	0.328

CR — complete response; OR — overall response

Toxicity

The number receiving less than six treatment cycles was 21 (47.7%) with FCR and nine (26.5%) with BR ($p = 0.05$). Reasons for treatment discontinuation or delay in the FCR group were severe myelosuppression in 26 (66.7%) patients, early complete response in seven (17.9%) patients, death in two (5.1%) patients, renal failure in two (5.1%) patients, and two patients had a progressive disease. In the BR group, we found severe myelosuppression in 12 (75%) patients, early complete response in two (12.5%) patients, and two patients died.

Neutropenia, anemia, thrombocytopenia, and the incidence of severe infections were more frequent in the FCR group. Hospitalization rate and the use of granulocyte-colony stimulating factor (G-CSF) and erythropoietin were all significantly higher with FCR therapy than that with BR therapy until five months after the end of therapy (Table III).

Additionally, one patient in the FCR group developed a secondary lung tumor. No cases in our study died of external reasons other than treatment side effects or disease progression, nor did we lose contact with any patient. The main cause of death was severe myelosuppression followed by infections in both groups, with a higher incidence in the FCR group.

Survival

26 patients in the entire population died during the two-year period. The median OS and PFS was 19.5 ± 7.4 and 16.3 ± 8.4 months, respectively. Progression-free survival was slightly shorter for FCR compared to BR [median 15.1 months (95% confidence interval {CI} 12.4–17.8) vs. 17.7 months (95% CI 15.4–20.1)] without any statistical significance. In elderly patients (>65 years) median PFS was significantly ($p = 0.046$) longer with the BR treatment [median 19.9 months (95% CI 17.2–22.5)] than with the FCR [median 11.6 months (95% CI 6–17.2)]. PFS did not differ between the two treatment arms in the younger population (≤65 years) (Figure 2). Regarding OS, no significant difference between the two groups was documented (median 19 months for FCR vs. 20 months for BR) (Figure 3). Similarly, OS did not differ between the two age populations. However, OS was higher clinically with the BR therapy in the elderly (median 20.8 months vs. 15.6 months).

Table III. Comparison between adverse events in FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab) groups

Adverse events	FCR (n = 44)	BR (n = 34)	*p* value
Deletion of cycles	21 (47.7%)	9 (26.5%)	**0.050**
Delay of cycles	32 (72.7%)	10 (29.4%)	**<0.001**
Hospitalization	12 (27.3%)	3 (8.8%)	**0.040**
Blood transfusion	7 (15.9%)	1 (2.9%)	0.061
Platelets transfusion	1 (2.3%)	0 (0%)	0.376
G-CSF use	16 (36.4%)	5 (14.7%)	**0.032**
Erythropoietin use	8 (18.2%)	1 (2.9%)	**0.037**

G-CSF — granulocyte-colony stimulating factor

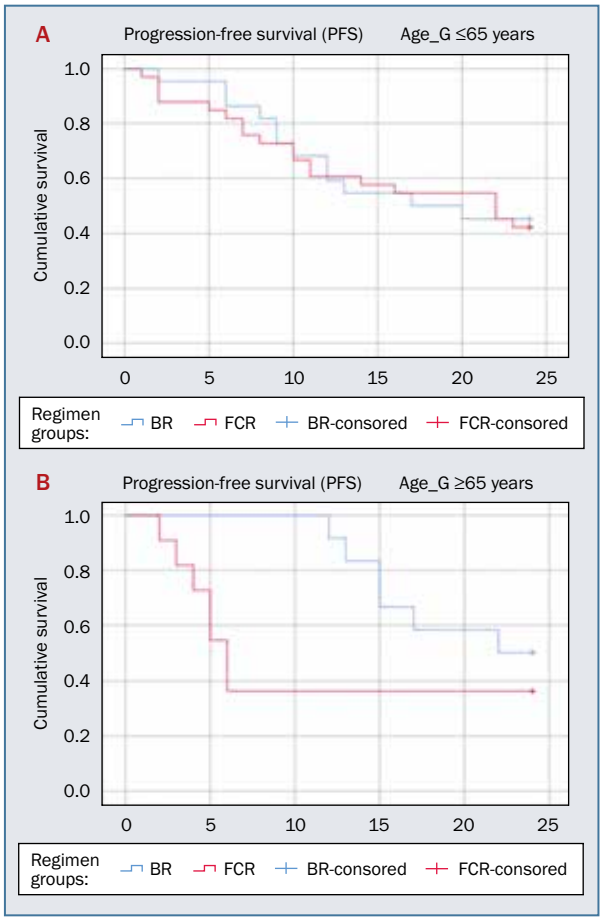

Figure 2. Kaplan-Meier curve demonstrates progression-free survival between the two treatment groups in patients ≤65 years (**A**), and in patients >65 years (**B**); BR — bendamustine, rituximab; FCR — fludarabine, cyclophosphamide, rituximab

Prognostic factors

We evaluated the demographic characteristics, laboratory parameters, radiological findings, staging and immunophenotyping results according to the two prognostic groups of PFS in the entire sample (Table IV). We found that LDH (p <0.001), ZAP-70 (p = 0.05), stage C (p = 0.003), and splenomegaly (p = 0.001) were all indicators of poor prognosis in correlation with PFS.

Discussion

In this study, we demonstrated the characteristics of a population of previously untreated fit patients in a major oncology center in Latakia, Syria. Then, we compared treatment outcomes in two groups, the FCR group and the BR group. The median age at diagnosis was 60.2 years. All patients were diagnosed with stages B and C because there are no routine tests in our country and visits to clinics are generally limited.

Our study found that a bendamustine and rituximab regimen could be considered non-inferior to the standard front-line therapy of fludarabine, cyclophosphamide, and rituximab for previously untreated, fit patients with chronic lymphocytic leukemia. On the contrary, the CLL10 trial [15], a major study conducted by the German CLL Study Group (GCLLSG), concluded that FCR had superior PFS compared to BR for young patients (median 55.2 months vs. 41.7 months, p = 0.0003). However, both studies agreed that BR is the safer choice in elderly patients (>65 years). The German study showed that there was no significant difference in PFS in elderly (>65 years) patients in the FCR group compared to the BR group, while our data showed that PFS was significantly longer with the BR treatment (median 19.9 months) than with the FCR (median 11.6 months) (p = 0.046). The difference in PFS between the German study and our study could be explained by the small size of the sample, poor management of CIT adverse effects, and the short follow-up period in our study. Furthermore, no difference in OS was observed between treatment groups in either study. However, this might change with a longer observation time, and it might also be affected by those patients who received second-line treatment regimens.

Similarly to the CLL10 trial, we found that elderly patients treated with bendamustine and rituximab had a longer PFS than younger patients treated with the same

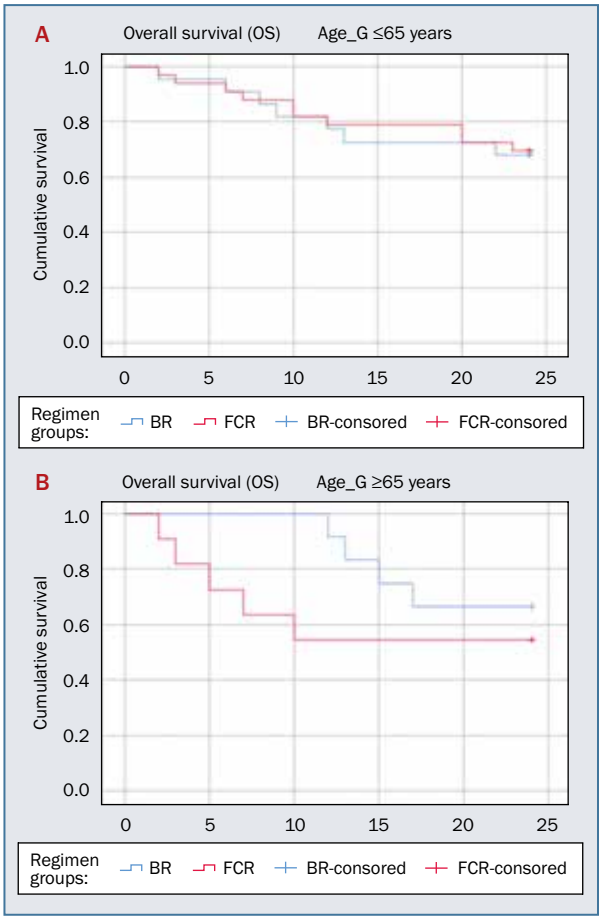

Figure 3. Kaplan-Meier curve demonstrates overall survival between the two treatment groups in patients ≤65 years (**A**), and in patients >65 years (**B**); BR — bendamustine, rituximab; FCR — fludarabine, cyclophosphamide, rituximab

regimen. However, no differences in pharmacokinetics of bendamustine in different age groups have been observed in previous studies [16].

Regarding response to treatment, we found that CD22 was associated with a higher complete response rate in the BR group. This has not appeared before in the literature. Therefore, it needs further investigation in the future.

FCR was associated with more toxic effects than was BR. Multiple studies have compared dose-reduced fludarabine, cyclophosphamide, and rituximab in elderly CLL patients. In these studies, PFS was shorter compared to a full-dose regimen. This could be due to early treatment cessation or lower efficacy [17–19].

A bendamustine and rituximab regimen has been reported to be efficient and well-tolerable as a front-line therapy for elderly CLL patients [20, 21]. Additionally, severe cytopenias have also been described before with FCR therapy [22], predisposing a higher infection rate. Our study detected only one case of a second malignancy after FCR because of the short follow-up. Yet retrospective studies have found that the lifetime risk of secondary malignancies after FCR therapy actually ranges between 4% and 10% [23].

Several factors should be considered with young, fit patients with CLL, such as molecular status, CIT eligibility, patient preference, quality of life, duration of treatment, sequencing, short-term and long-term safety implications, insurance availability, and transplant eligibility.

Results with targeted therapies, such as ibrutinib and venetoclax, are very superior to those achieved with CIT regimens [24, 25] in first-line untreated CLL patients especially with del17 and defective P53, while CIT is only preserved as first-line treatment for patients with mutated *IGHV* and without del17 [26]. Despite this, CIT is still widely used instead of target therapies in first-line treatment for untreated fit CLL patients in low-income countries such as Syria. The reasons for this fact include the huge increases in treatment costs, and the lack of transparency and free-market competition, especially in countries with significant healthcare budget constraints [13, 27, 28].

In addition, some patients in developed countries still prefer CIT rather than Bruton kinase (BTK) inhibitors like ibrutinib and acalabrutinib. This is because of the disturbing side effects of ibrutinib (mainly cardiovascular ones), the high cost of these drugs, and the need for long-term administration until progression or unacceptable toxicity [28].

Cytogenetics are the main limitation to our study. They are becoming an essential part of the treatment approach, but most patients in low-income countries such as Syria cannot afford them. Thus, we needed to investigate further clinical and laboratory parameters to assess the prognosis and survival of CLL patients.

Similarly to the CLL10 study, our study demonstrated that splenomegaly, the elevation of LDH, Binet C, and the positive expression of ZAP-70 were all correlated with a poor prognosis. This association has been well established in several previous studies [29–31]. However, those studies reported other important indicators like lymphocytosis and positive expression of CD38 and CD23, which are highly prognostic of a poor disease course, but could not be proved in our study. This could be explained by the small sample size and the heterogeneous nature of the tests, given that they were carried out in different laboratories.

Furthermore, when analyzing different variables between the two treatment groups, PFS did not differ between the two prognostic groups regarding age category. This could be justified by the selection of very fit elderly patients. Thus, we can conclude that therapy decisions should rely on an assessment of fitness, rather than on chronological age.

Conclusions

Our study found that a BR regimen had comparable efficacy to the standard front-line therapy of FCR for previously untreated, fit patients with CLL. BR is the safer choice in

Table VI. Evaluation of demographic characteristics, laboratory parameters, radiological findings, staging and immunophenotyping results according to the two prognostic groups of progression-free survival (PFS)

Variable		PFS ≥24 months (n = 34)	PFS <24 months (n = 44)	*p* value
Sex	Male	21 (61.8%)	31 (70.5%)	0.419
	Female	13 (38.2%)	13 (29.5%)	
Age		60.3 ± 8.7	60.1 ± 10.1	0.928
	≤65	24 (70.6%)	31 (70.5%)	0.990
	>65	10 (29.4%)	13 (29.5%)	
Laboratory results	WBC	58.2 ± 69.2	75.3 ± 73.6	0.302
	LYM	45.3 ± 55.6	60.7 ± 64.4	0.270
	Hb	11.7 ± 1.9	10.7 ± 2.7	0.074
	PLT	159.5 ± 67.8	150.5 ± 98.6	0.649
	LDH	343.4 ± 153.5	486.1 ± 174.4	**<0.001**
CDs expression	CD22	19 (73.1%)	24 (68.6%)	0.703
	CD23	21 (72.4%)	29 (78.4%)	0.575
	CD38	11 (39.3%)	21 (55.3%)	0.199
	ZAP-70	6 (21.4%)	17 (44.7%)	**0.050**
Binet staging	Stage B	24 (70.6%)	16 (36.4%)	**0.003**
	Stage C	10 (29.4%)	28 (63.6%)	
Radiological findings	Splenomegaly	17 (50%)	37 (84.1%)	**0.001**

WBC — white blood cells; LYM — lymphocytes; Hb — hemoglobin; PLT — platelets; LDH — lactate dehydrogenase

elderly patients (>65 years). While striving for better diagnostic and therapeutic availability and reduced costs, there is a need to use the limited available investigations and drugs at our disposal to better treat CLL patients.

Authors' contributions

LH — data collection and manuscript writing. FH, SA — supervising the work and making final adjustments.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

References

1. Parikh SA, Rabe KG, Kay NE, et al. Chronic lymphocytic leukemia in young (≤ 55 years) patients: a comprehensive analysis of prognostic factors and outcomes. Haematologica. 2014; 99(1): 140–147, doi: 10.3324/haematol.2013.086066, indexed in Pubmed: 23911703.
2. Rai KR, Jain P. Chronic lymphocytic leukemia (CLL) — then and now. Am J Hematol. 2016; 91(3): 330–340, doi: 10.1002/ajh.24282, indexed in Pubmed: 26690614.
3. Hallek M. Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2017; 92(9): 946–965, doi: 10.1002/ajh.24826, indexed in Pubmed: 28782884.
4. Müller-Hermelink HK, Montserrat E, Catovsky D. et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma. In: Swerdlow SH, Campo E, Harris NL. et al. ed. World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Iarc, Lyon 2008: 180–182.
5. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018; 131(25): 2745–2760, doi: 10.1182/blood-2017-09-806398, indexed in Pubmed: 29540348.
6. Andres M, Feller A, Arndt V, et al. Trends of incidence, mortality and survival for chronic lymphocytic leukaemia/small lymphocytic lymphoma in Switzerland between 1997 and 2016: a population-based study. Swiss Med Wkly. 2021; 151: w20463, doi: 10.4414/smw.2021.20463, indexed in Pubmed: 33793959.
7. da Cunha-Bang C, Simonsen J, Rostgaard K, et al. Improved survival for patients diagnosed with chronic lymphocytic leukemia in the era of chemo-immunotherapy: a Danish population-based study of 10455 patients. Blood Cancer J. 2016; 6(11): e499, doi: 10.1038/bcj.2016.105, indexed in Pubmed: 27834937.
8. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981; 48(1): 198–206, doi: 10.1002/1097-0142(19810701)48:1<198::aid-cncr2820480131>3.0.co;2-v, indexed in Pubmed: 7237385.

9. Rawstron AC, Villamor N, Ritgen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia. 2007; 21(5): 956–964, doi: 10.1038/sj.leu.2404584, indexed in Pubmed: 17361231.
10. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016; 127(2): 208–215, doi: 10.1182/blood-2015-06-651125, indexed in Pubmed: 26486789.
11. Wei G, Ding L, Wang J, et al. Advances of CD19-directed chimeric antigen receptor-modified T cells in refractory/relapsed acute lymphoblastic leukemia. Exp Hematol Oncol. 2017; 6: 10, doi: 10.1186/s40164-017-0070-9, indexed in Pubmed: 28413717.
12. Zhang LN, Song Y, Liu D. CD19 CAR-T cell therapy for relapsed/refractory acute lymphoblastic leukemia: factors affecting toxicities and long-term efficacies. J Hematol Oncol. 2018; 11(1): 41, doi: 10.1186/s13045-018-0593-5, indexed in Pubmed: 29544528.
13. Smolej L, Vodárek P, Écsiová D, et al. Chemoimmunotherapy in the first-line treatment of chronic lymphocytic leukaemia: dead yet, or alive and kicking? Cancers (Basel). 2021; 13(13), doi: 10.3390/cancers13133134, indexed in Pubmed: 34201565.
14. Hallek M, Cheson BD, Catovsky D, et al. International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008; 111(12): 5446–5456, doi: 10.1182/blood-2007-06-093906, indexed in Pubmed: 18216293.
15. Eichhorst B, Fink AM, Bahlo J, et al. international group of investigators, German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016; 17(7): 928–942, doi: 10.1016/S1470-2045(16)30051-1, indexed in Pubmed: 27216274.
16. Owen JS, Melhem M, Passarell JA, et al. Bendamustine pharmacokinetic profile and exposure-response relationships in patients with indolent non-Hodgkin's lymphoma. Cancer Chemother Pharmacol. 2010; 66(6): 1039–1049, doi: 10.1007/s00280-010-1254-8, indexed in Pubmed: 20140617.
17. Foon KA, Mehta D, Lentzsch S, et al. Long-term results of chemoimmunotherapy with low-dose fludarabine, cyclophosphamide and high-dose rituximab as initial treatment for patients with chronic lymphocytic leukemia. Blood. 2012; 119(13): 3184–3185, doi: 10.1182/blood-2012-01-408047, indexed in Pubmed: 22461474.
18. Dartigeas C, Van Den Neste E, Berthou C, et al. Evaluating abbreviated induction with fludarabine, cyclophosphamide, and dose-dense rituximab in elderly patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2016; 57(2): 328–334, doi: 10.3109/10428194.2015.1063139, indexed in Pubmed: 26140301.
19. Smolej L, Brychtova Y, Doubek M, et al. Low-dose FCR is a safe and effective treatment option for elderly/comorbid patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Updated results of project Q-lite by Czech CLL Study Group. Blood. 2014; 124(21): 4670–4670, doi: 10.1182/blood.v124.21.4670.4670.
20. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012; 30(26): 3209–3216, doi: 10.1200/JCO.2011.39.2688, indexed in Pubmed: 22869884.
21. Laurenti L, Innocenti I, Autore F, et al. Bendamustine in combination with rituximab for elderly patients with previously untreated B-cell chronic lymphocytic leukemia: A retrospective analysis of real-life practice in Italian hematology departments. Leuk Res. 2015; 39(10): 1066–1070, doi: 10.1016/j.leukres.2015.07.009, indexed in Pubmed: 26307523.
22. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016; 127(2): 208–215, doi: 10.1182/blood-2015-06-651125, indexed in Pubmed: 26486789.
23. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood. 2008; 112(4): 975–980, doi: 10.1182/blood-2008-02-140582, indexed in Pubmed: 18411418.
24. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016; 17(10): 1409–1418, doi: 10.1016/S1470-2045(16)30212-1, indexed in Pubmed: 27637985.
25. Stilgenbauer S, Morschhauser F, Wendtner CM, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016; 17(6): 768–778, doi: 10.1016/S1470-2045(16)30019-5, indexed in Pubmed: 27178240.
26. Brown JR, Kay NE. Chemoimmunotherapy is not dead yet in chronic lymphocytic leukemia. J Clin Oncol. 2017; 35(26): 2989–2992, doi: 10.1200/JCO.2017.72.6810, indexed in Pubmed: 28742455.
27. Hilal T, Betcher JA, Leis JF. Economic impact of oral therapies for chronic lymphocytic leukemia — the burden of novelty. Curr Hematol Malig Rep. 2018; 13(4): 237–243, doi: 10.1007/s11899-018-0461-y, indexed in Pubmed: 29982866.
28. Mansfield C, Masaquel A, Sutphin J, et al. Patients' priorities in selecting chronic lymphocytic leukemia treatments. Blood Adv. 2017; 1(24): 2176–2185, doi: 10.1182/bloodadvances.2017007294, indexed in Pubmed: 29296865.
29. Yun X, Zhang Ya, Wang X. Recent progress of prognostic biomarkers and risk scoring systems in chronic lymphocytic leukemia. Biomark Res. 2020; 8: 40, doi: 10.1186/s40364-020-00222-3, indexed in Pubmed: 32939265.
30. Gowda A, Byrd JC. Use of prognostic factors in risk stratification at diagnosis and time of treatment of patients with chronic lymphocytic leukemia. Curr Opin Hematol. 2006; 13(4): 266–272, doi: 10.1097/01.moh.0000231425.46148.b0, indexed in Pubmed: 16755224.
31. Eichhorst B, Hallek M. Prognostication of chronic lymphocytic leukemia in the era of new agents. Hematology Am Soc Hematol Educ Program. 2016; 2016(1): 149–155, doi: 10.1182/asheducation-2016.1.149, indexed in Pubmed: 27913474.