Real world outcomes with Ibrutinib monotherapy in chronic lymphocytic leukemia: a single center experience

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Abstract

Introduction. The advent of Bruton's tyrosine kinase (BTK) inhibitors brought about a paradigm shift in the management of chronic lymphocytic leukemia (CLL), by offering a well-tolerated chemotherapy-free approach. Here, we share the experience with ibrutinib of a major Romanian regional cancer center.

Methods. We screened patients treated for CLL in our center over 6 years (2017-2022) and included those who were treated with ibrutinib either in the first line of therapy or in subsequent lines.

Results. We enrolled 61 patients, 40 with treatment-naïve (TN) CLL and 21 with relapsed/refractory (R/R) CLL, with a median age at treatment initiation of 65 years. Concerning the prognostic-predictive workup, IgHV mutational status was available for 78.7% of the patients, TP53 sequencing for 82%, assessment of 17p deletion for 82%, and CD38 marker analysis was performed for 70.5%. With a median follow-up period of 55 months, the overall response rate (ORR) was 90.2%, with a median progression-free survival (PFS) of 33 months and a median overall survival (OS) that has not been reached. In our cohort, albeit non-significant statistically, patients with TP53 mutation had a shorter OS and those with mutated IgHV, a shorter PFS. Rai 3-4 and Binet C stages at diagnosis were associated with a shorter PFS, but not OS. In our cohort, the correlation between survival and high Cumulative Illness Rating Scale (CIRS) index was not statistically significant. Ibrutinib was generally well tolerated in our cohort, as only 14.8% of our patients discontinued treatment due to adverse effects.

Conclusion. Our study suggests that ibrutinib is a valid therapeutic option for TN or R/R CLL patients, with a high ORR and a good safety profile.

Keywords: Chronic Lymphocytic Leukemia, CLL, Ibrutinib

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Introduction

Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative neoplasm, defined by the presence of ≥ 5 x 10^9/l clonal, CD5+, CD23+, CD19+, B lymphocytes in the peripheral blood, which persist for at least 3 months. The clonal cells also proliferate and accumulate in the bone marrow, lymph nodes and spleen [1]. The diagnosis is established in most cases by flow cytometry, according to the Matutes Score, which includes the evaluation of 5 surface markers [2,3]. Small Lymphocytic Lymphoma (SLL) is the term used for the "localized" form of CLL, when the malignant process is limited to the lymph nodes [4].

Among all types of leukemia, CLL accounts for 30% of cases, making it the most prevalent form in the Western world [5-7]. The incidence has been

found to increase exponentially with age, being a disease of the elderly, with a median age at diagnosis of 70 years, which applies to all ethnic groups [8]. US statistics show that around 9.1% of CLL patients are under 45 years of age [1]. CLL is more frequent in male patients [1]. The epidemiological data are similar in both USA and Europe, while in Asian countries and Middle Eastern ancestry, the incidence is lower [9,10].

The standard treatment for fit patients with CLL was chemo-immunotherapy, which combines rituximab, an anti-CD20 monoclonal antibody, with fludarabine and cyclophosphamide (FCR) [11]. Given the median age at diagnosis, many patients were not suitable candidates for this therapy. Moreover, once TP53 mutations, the presence of 17p deletion (del17p) and immunoglobulin heavy chain variation (IgHV) mutational status were identified as predictive markers, it has become evident that FCR is not a suitable treatment option for all fit patients, and it is even less appropriate for those with relapsed/refractory (R/R) disease [12]. Consequently, the demand for gentler therapies to address high-risk CLL, as well as R/R disease cases, has led to the development of targeted therapies in CLL, which have contributed to a reduction in mortality, despite the incidence of the disease remaining stable over the past two decades [1]. Ibrutinib is a Bruton tyrosine kinase inhibitor (BTKi) which initially, in 2014, was approved in relapsed/refractory (R/R) and 17p deletion cases of CLL, and later reimbursed as a first-line treatment for all patients, as a single agent or in combination with other drugs [13,14]. RESONATE-2 phase 3 trial demonstrated that ibrutinib yielded superior outcomes compared to chlorambucil in frail patients, even in the absence of high-risk factors [15]. The phase 3 trials A041202 and E1912 once again demonstrated the superiority of ibrutinib over BR and FCR, irrespective of the patients' genetic and molecular profiles [16,17]. The A041202 study also indicated that adding rituximab to ibrutinib does not provide any additional benefit [17]. The combination of ibrutinib and venetoclax, a BCL-2 inhibitor, demonstrated favorable overall survival (OS) and progression-free survival (PFS), achieving undetectable minimal residual disease (uMRD) in 66% of patients who received 24 cycles of treatment. However, this benefit came with a higher risk of toxicity compared to single-agent therapy with BTK inhibitors, which had not previously validated this endpoint [18].

In Romania, ibrutinib was first approved in 2017 as a single-agent therapy for R/R CLL, and later, for all CLL cases with therapeutic indication, as a single agent or in combination with other drugs.

In this study, we performed a retrospective analysis of patients diagnosed with CLL and treated with ibrutinib single agent as the first, second or third line of therapy, providing evidence of the efficacy and safety of this treatment in real-world clinical practice.

Methods

We conducted a retrospective analysis of patients diagnosed with CLL who were treated with ibrutinib single-agent as their first, second, or third line of therapy at the 'Ion Chiricuta' Institute of Oncology in Cluj-Napoca, Romania, over five years. Our evaluation included 370 patients diagnosed with CLL, small lymphocytic lymphoma (SLL), and CLL-like disorders between January 1, 2017, and December 31, 2022. However, we excluded the patients whose CLL/SLL diagnosis was not confirmed, and those who did not receive ibrutinib treatment during the follow-up period.

Finally, we enrolled 61 treatment-naïve or R/R CLL/SLL patients, treated with ibrutinib. We collected data regarding their age, gender, date of diagnosis, Cumulative Illness Rating Scale (CIRS) index, Rai/Binet/Ann Arbor stage, biological characteristics at the diagnosis, presence of CD38+ at diagnosis, molecular and genetic characteristics, treatment regimens before and after ibrutinib therapy, response to ibrutinib, survival, date of death or last clinic visit. The analysis was conducted by reviewing medical and digital records, with the data collected in Excel spreadsheets. Statistical correlations and Kaplan-Meier survival curves were generated using GraphPad Prism 9 (GraphPad Software, Inc., La Jolla, CA). Patients were censored as of July 31, 2024, and any patients lost to follow-up were censored at their last clinic visit. A p-value of less than 0.05 was considered statistically significant. This study was carried out in accordance with the Declaration of Helsinki.

Results

Of the 61 patients, 92% were identified with CLL and 8.2% with SLL. Of these, 65.6% were treated with ibrutinib as front-line therapy, while 34.4% were treated for R/R disease. The distribution of patients by the year of diagnosis was relatively consistent, except in 2022, when only four patients qualified for inclusion criteria. Similar to previous reports, our patient cohort also exhibited a male predominance. The median age at diagnosis was 63 years, and the median age at the beginning of treatment was 65. The CIRS index had a median of 5 points.

In terms of CLL staging, 42.6% of participants were classified as Binet A and 47.9 as Binet B and C. Concerning Rai staging, 69% were categorized as Rai 0-2 and 23% as Rai 3-4. Since 5 of our patients were diagnosed with SLL, Rai/Binet stages were not evaluated for them.

The prognostic molecular profile, which includes IgHV mutational status, was obtained for 78.7% of patients. Additionally, del 17p was analyzed for 82% of patients, and TP53 abnormalities were available for 82% of patients. Of the patients included, 21.3% exhibited mutated IgHV, 11.5% had a 17p deletion, and 8.2% showed mutations in the TP53 gene. Moreover, CD38 was evaluated in 70.5% of the patients, resulting in a positivity rate of 11.5%.

Table I. Detailed characteristic features of the study group.

Parameter		1st line, N=40 (65.6%)	2nd line, N=16 (26.2%)	3rd line, N=5 (8.2%)	Overall, N=61 (100%)
CLL, n (%)		36 (59%)	15 (24.6%)	5 (8.2%)	56 (92%)
SLL, n (%)		4 (6.6%)	1 (1.6%)	0 (0%)	5 (8.2%)
Year of Diagnosis, n (%)	2017	7 (11.5%)	5 (8.2%)	2 (3.3%)	14 (23%)
	2018	6 (9.8%)	4 (6.6%)	2 (3.3%)	12 (19.7%)
	2019	2 (3.3%)	5 (8.2%)	1 (1.6%)	8 (13.1%)
	2020	10 (16.4%)	1 (1.6%)	0 (0%)	11 (18 %)
	2021	10 (16.4%)	1 (1.6%)	0 (0%)	11 (18 %)
	2022	4 (6.6%)	0 (0%)	0 (0%)	4 (6.6%)
TTFT (months)		9 (0-58)	1.5 (0-56)	4 (0-7)	7 (0-58)
Gender, n (%)	Male	22 (36%)	8 (13.1%)	5 (8.2%)	35 (57.4%)
	Female	18 (29.5%)	8 (13.1%)	0 (0%)	26 (42.6%)
Age	Median	61 (41-83)	66.5 (53-82)	70 (34-73)	63 (34-83)
CIRS index	Median	4(4-11)	6 (4-14)	5 (4-7)	5 (4-14)
	NA	13	3	0	16
Rai Stage at Diagnosis, n (%)	0	7 (11.5%)	0 (0%)	0 (0%)	7 (11.5%)
	1	12 (19.7%)	5 (8.2%)	0 (0%)	17(27.9%)
	2	11 (18%)	5 (8.2%)	2 (3.3%)	18 (29.5%)
	3	1 (1.6%)	2 (3.3%)	1 (1.6%)	4 (6.6%)
	4	5 (8.2%)	3 (4.9%)	2 (3.3%)	10 (16.4%)
	NA	4 (6.6%)	1 (1.6%)	0 (0%)	5 (8.2%)
Binet Stage at diagnosis, n (%)	A	22 (36%)	4 (6.6%)	0 (0%)	26 (42.6%)
	B	7 (11.5%)	7 (11.5%)	2 (3.3%)	16 (26.2%)
	C	6 (9.8%)	4 (6.6%)	3 (4.9%)	13 (21.3%)
	NA	4 (6.6%)	1 (1.6%)	0 (0%)	5 (8.2%)
Ann Arbor, n (%)	II A	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
	II B	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
	III A	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
	IV A	1 (1.6%)	0 (0%)	0 (0%)	1 (1.6%)
	IV BX	0 (0%)	1 (1.6%)	0 (0%)	1 (1.6%)
Prognostic factors, n (%)	M- IgHV	12 (19.7%)	1 (1.6%)	0 (0%)	13 (21.3%)
	U- IgHV	23 (37.7%)	9 (14.8%)	3 (4.9%)	35 (57.4%)
	IgHV NA	5 (8.2%)	6 (9.8%)	2 (3.3%)	13 (21.3%)
	del17p	4 (6.6%)	2 (3.3%)	1 (1.6%)	7 (11.5%)
	No del17p	33 (54%)	8 (13.1%)	2 (3.3%)	43 (70.5%)
	del17p NA	3 (4.9%)	6 (9.8%)	2 (3.3%)	11 (18%)
	TP53 -M	4 (6.6%)	0 (0%)	1 (1.6%)	5 (8.2%)
	TP53 -U	33 (54%)	10 (16.4%)	2 (3.3%)	45 (73.8%)
	TP53 NA	3 (4.9%)	6 (9.8%)	2 (3.3%)	11 (18%)
	CD38+	3 (4.9%)	3 (4.9%)	1 (1.6%)	7 (11.5%)
	CD38-	25 (41%)	9 (14.8%)	2 (3.3%)	36 (59%)
	CD38+ NA	12 (19.7%)	4 (6.6%)	2 (3.3%)	18 (29.5%)
Biological parameters	ALC x 10^9/L	42 (2 -326)	26.3 (2.8-394)	102 (0.6-176)	34 (0.6-394)
	AMC x 10^9/L	1 (0.37-216)	0.8 (0.16-10)	1.79 (0.84-25)	1 (0.16-216)
	Hb g/dl	13.7 (4.8 – 16)	11.9 (6-16.7)	10.7 (6.7-14.7)	13 (4.8-16.7)
	MCV fl	87.8 (80.5-107.1)	90 (80.7-112.3)	96.6 (85.6-100)	88 (80.5-112.3)
	Plt x 10^9/L	164 (54 -331)	155 (35-326)	90 (17-253)	161 (17-331)
	LDH UI/L	413 (210-912)	454 (306-1555)	292 (248-430)	419 (210-1555)
	IgG mg/dl	856 (315-3242)	755 (504-1640)	696 (616-875)	794 (315-3242)
	Creatinine mg/dl	1.08 (0.56-1.45)	1.04 (0.3-1.68)	1.08 (0.83-1.19)	1.08(0.3-1.68)
	Uric acid mg/dl	5.6 (3.26- 10.6)	5.4 (2.9-10)	5.7 (4.59-8.51)	5.55(2.98-10.6)

Abbreviations: TTFT-time to first treatment, U-IgHV- unmutated IgHV, M-IgHV-mutated IgHV, TP53-U-unmutated TP53, TP53-M-mutated TP53, NA-not assessed or unknown, CLL- Chronic lymphocytic leukemia, SLL-small lymphocytic lymphoma, ALC-absolute lymphocyte count; AMC-absolute monocyte count; MCV-mean corpuscular volume, Hb- hemoglobin, Plt-platelets.

The median follow-up period since the diagnosis was 55 months (range 18-89 months), with a median time to first treatment (TTFT) of 7 months (range 0-58 months).

Of the patients included, 65.6% were treated with ibrutinib as their first-line therapy and 34.4% had undergone at least one treatment regimen before initiating ibrutinib; 24.3% of the patients required another line of therapy after ibrutinib. Table II describes the therapies administered before and after ibrutinib.

Table II. Therapies administered before and after ibrutinib.

Regimen	1st line	2nd line	3rd line
Ibrutinib	40 (65.6%)	16 (26.2%)	5 (8.2%)
R-FC	2 (3.3%)	1 (1.6%)	-
R-CVP	7 (11.5%)	1 (1.6%)	-
CVP	1 (1.6%)	1 (1.6%)	-
R-Clb	4 (6.6%)	2 (3.3%)	-
O-Clb	3 (4.9%)	-	-
O	3 (4.9%)	-	-
Clb	1 (1.6%)	-	-
Acala	-	5 (8.2%)	1 (1.6%)
R-Ven	-	4 (6.6%)	1 (1.6%)
O-Ven	-	-	1 (1.6%)
Ven	-	-	1 (1.6%)

Abbreviations: R-FC- rituximab, fludarabine and cyclophosphamide; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; CVP cyclophosphamide, vincristine, and prednisone; R-Clb, rituximab and chlorambucil; O-Clb, obinutuzumab and chlorambucil; O- Obinutuzumab single agent; Clb-chlorambucil single agent; Acala-acalabrutinib; R-Ven – rituximab and venetoclax,; O-Ven -obinutuzumab and venetoclax; Ven-venetoclax single agent.

The evaluation of treatment response was conducted following the guidelines established by the International Working Group on Chronic Lymphocytic Leukemia (iwCLL) [1].

The median follow-up period since the beginning of treatment was 35.5 months (range 2–74), with a median time to next treatment (TTNT) of 33 months (range 5-74). Based on the IwCLL response criteria, the overall response rate (ORR) for both groups, which includes complete responses (CR), complete responses with incomplete marrow recovery (CRi), and partial responses (PR), was 90.2%. In patients receiving ibrutinib as a frontline therapy, the ORR reached 92%, while it was 85.7% for those with R/R disease. A detailed summary of the response assessments according to the treatment line can be found in table III.

Two patients, one from the TN group and one from the R/R group were lost to follow-up and the treatment responses were not evaluated. It is important to note that no bone marrow examination was conducted for the response evaluation.

At the time of censoring, 52 patients (85.2%) were alive and 9 (14.8%) had died. 29.5% (N=18) of patients had stopped ibrutinib treatment, comprising 11 (18%) individuals from the TN group and 7 (11.5%) from the (R/R) group.

Among those who were TN, 3 patients experienced PD, one had uncontrolled hypertension, 2 had developed an arrhythmia, 1 experienced recurrent infection, 1 had cutaneous toxicity and one was diagnosed with Richter's transformation. Additionally, the physician opted to change therapy for 2 patients.

In the R/R group, among those who stopped the treatment, four had PD, one was diagnosed with Richter's transformation, one experienced recurrent infection, and in one case, the treatment was halted at the physician's option. Figure 1 outlines the reasons for discontinuing ibrutinib in our patient cohort.

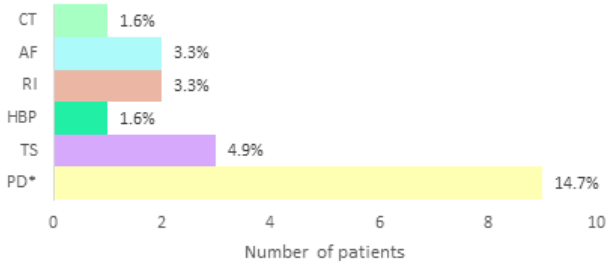

Figure 1. Ibrutinib discontinuation.
Abbreviations: CT-cutaneous toxicity, AF-atrial fibrillation, RI-recurrent infections, HBP-high blood pressure, TS-therapeutic switch, PD-progressive disease.
*3.3% (N=2) patients experienced Richter's disease.

Table III. Response assessments according to treatment line.

Response to treatment	1st line, n (%)	2nd line, n (%)	3rd line, n (%)	Overall response, n (%)
CR (no MO)	22 (55 %)	9 (56.3 %)	3 (60 %)	34 (55.7%)
CRi (no MO)	3 (7.5%)	0 (0%)	0 (0%)	3 (4.9%)
PR	12 (30%)	4 (25 %)	2 (40%)	18 (29.5%)
SD	2 (5 %)	0 (0%)	0 (0%)	2 (3.3%)
PD	0 (0%)	2 (12.5 %)	0 (0%)	2 (3.3%)
NA	1 (2.5%)	1 (6.25%)	0 (0%)	2 (3.3%)

Abbreviations: CR (no MO): complete response (no marrow evaluation); CRi (no MO) CR with incomplete marrow recovery (no marrow evaluation); PR: partial response; SD: stable disease; PD: progressive disease; NA (not assessed) – due to limited treatment period or loss to follow-up.

At the time of censoring, of the 61 patients included in the study, 2 patients were lost to follow-up, 9 (14.8%) had died, while 50 (83.6%) were still alive. The median overall survival (OS) had not been reached at the median follow-up period of 55 months (Figure 2).

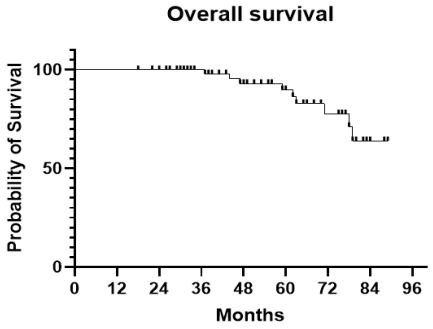

Figure 2. The median overall survival (OS) was not reached by the end of the median follow-up period of 55 months.

At the median follow-up, out of 59 patients, 39 were given ibrutinib as their initial treatment, while 20 received it in subsequent lines of therapy. Among the patients treated with ibrutinib as a first-line therapy, 5 had passed away, while 4 patients with R/R disease also died, with a median follow-up duration of 55 months (Figure 3).

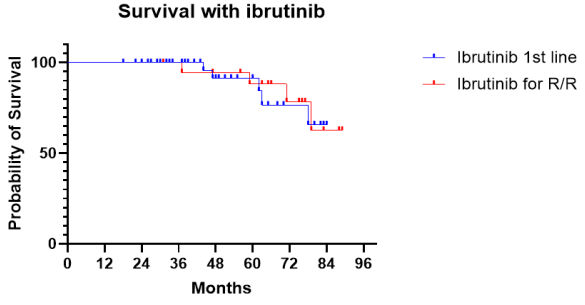

Figure 3. The median overall survival was not reached for either the patient group receiving ibrutinib as a first-line treatment or for those with R/R disease receiving ibrutinib, during the median follow-up of 55 months.

The subgroup analysis found no statistically significant association between a CIRS index of ≥6 and OS or PFS (p>0.05) (Figure 4). Additionally, there was no connection between Binet C/Rai stages 3-4 at diagnosis and OS (p>0.05). However, a correlation was found between advanced Binet/Rai stages at diagnosis and PFS (p<0.05) (Figure 5). Age ≥ 65 did not show any statistically significant correlation with PFS, nor was there an association with a shorter OS (Figure 6). However, regarding negative prognostic factors—specifically del17p, and CD38—our results indicated that these markers did not influence OS or PFS (Figure 7 and Figure 8). Conversely, patients in our cohort with mutated IgHV have a shorter PFS (p<0.05) and those who tested positive for mutated TP53 appear to have poorer OS (p<0.05) (Figure 7 and Figure 8).

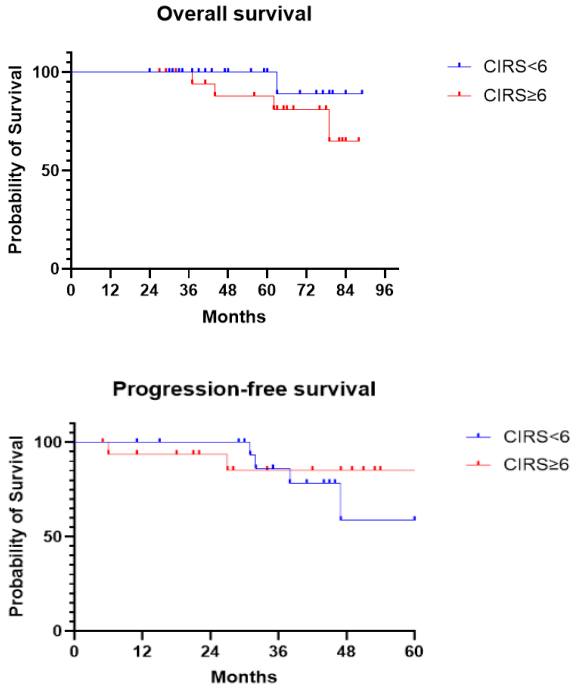

Figure 4. OS and PFS according to CIRS index (p>0.05).

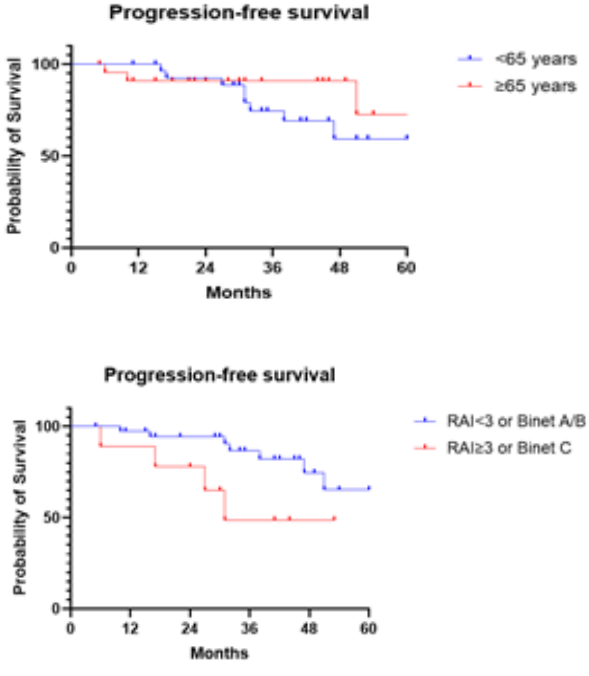

Figure 5. OS was not influenced by the Rai/Binet Staging (p>0.05). PFS was correlated with Rai/Binet stage (p<0.05).

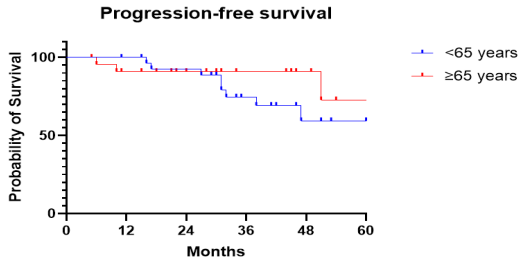

Figure 6. PFS depending on age (p>0.05).

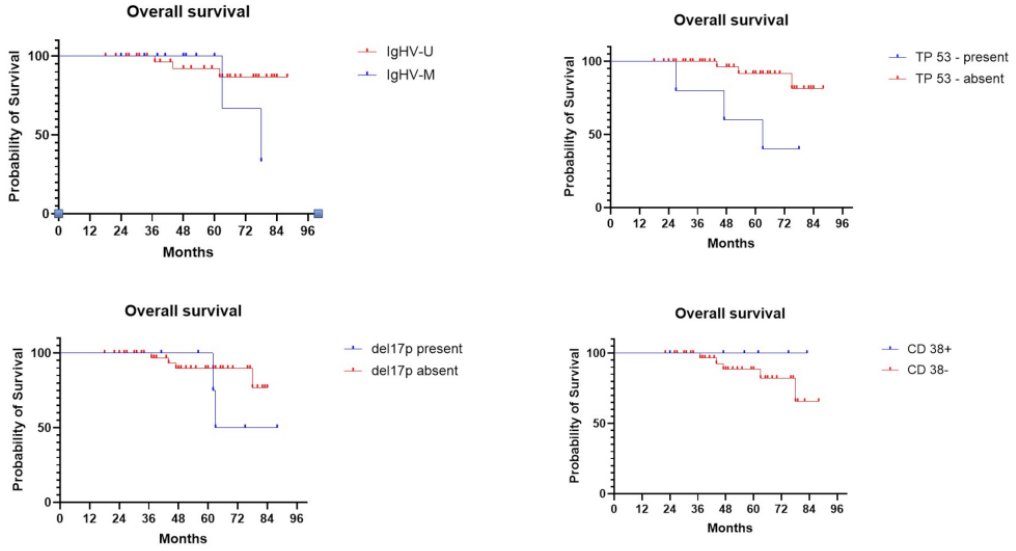

Figure 7. OS is not influenced by IgHV mutational status, del17p or CD38 (p>0.05). Mutated TP53 was correlated with a shorter PFS (p<0.05).

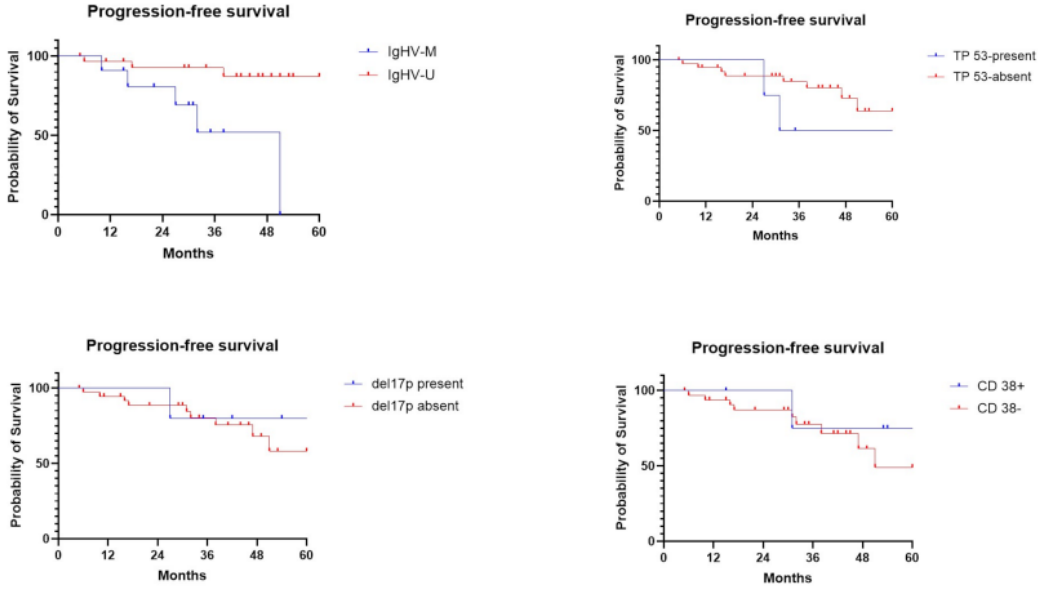

Figure 8. PFS was not influenced by TP53 mutational status, del17p, CD38 status (p>0.05). Patients with mutated IgHV have a shorter PFS (p<0.05).

Discussion

Both in clinical trials and real-world data, ibrutinib has shown an increase in OS and PFS compared to conventional chemo-immunotherapy [19,20]. Furthermore, these data were validated regardless of negative prognostic factors, such as unmutated IgHV, TP53 gene mutations, or 17p deletions [21,22].

Despite the small number of patients included in our study, we aim to evaluate real-world data regarding the response to ibrutinib as a single agent in TN and R/R CLL patients. Patients were monitored from the beginning of treatment, for a median duration of 38 months. The median PFS on ibrutinib was 31 months, and OS was not reached in either patient group. The ORR, which included CR, CRi and PR was 90.2%, while the OS rate was 83.6%. Our findings are consistent with data from clinical trials and other retrospective real-world studies [23-25].

We evaluated the statistical significance of the correlation between and age PFS. Our patients were categorized into two groups: those aged 65 years and older, and those younger than 65. No significant correlation was found. Consistent with previous research, age alone did not have an independent impact on PFS [24,26]. However, real-world data revealed that age-related conditions, such as comorbidities or performance status were associated with shorter OS and PFS while on ibrutinib [27,28].

In the era of targeted therapies classical prognostic indexes, such as Rai/Binet seem to lose their objective, thus the IwCLL proposes International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) as a new prognostic scoring system [29-32]. Nonetheless, because of the poorly standardized protocol, beta 2 microglobulin is not a parameter consistently evaluated in our clinic, hence CLL-IPI could not be calculated for a satisfactory number of patients. Thus, we focused only on Rai, Binet, and CIRS index. We were unable to assess ECOG due to the limited information available in the patient's medical records.

Rai and Binet staging systems were evaluated at the time of diagnosis for all our patients, except for those diagnosed with SLL. Rai 3-4 and Binet C were not correlated with a poorer OS, regardless of whether ibrutinib was given as first-line or in R/R disease. However, we did find that patients with advanced Rai/Binet stages at diagnosis have a shorter PFS. Real-world data are quite contradictory regarding this matter. We did find that in some studies, our results were confirmed [28], but mostly, PFS with ibrutinib treatment is independent of Rai/Binet stages at diagnosis [24,33,34]. Nonetheless, the small population included could represent a bias factor to our correlation.

Gordon et al analyzed 145 patients diagnosed with CLL and treated with ibrutinib for R/R disease. CIRS≥7 was correlated with inferior median event-free survival and 2-year OS [35]. Another real-world Swedish study found a significant statistical correlation between OS and CIRS [34]. The CIRS was assessed for 73.8% of our patients, despite its complexity, which requires evaluating 14 different systems. We investigated whether a CIRS score of 6 points or higher in our patient cohort is associated with poorer OS or a shorter PFS. No statistically significant correlations applied to our group. Nevertheless, in the literature, we also found data that align with the results from our group analysis [24].

Among the patients involved in the study, IgHV mutational status was determined for 78.7% of them, TP53 status for 82%, the assessment of 17p deletion for 82%, and CD38 marker for 70.5%, which indicates a satisfactory rate of evaluating genetic alterations in CLL, according to current guidelines. However, our findings were quite contradictory, as it is widely recognized that mutated IgHV typically correlates with a favorable prognosis. In our patient cohort, mutated IgHV was linked to a shorter PFS, a finding not supported by real-world or clinical trial data [25,27,33,36-38]. Notably, 7 of the 13 patients with mutated IgHV were in the TN group. We investigated to which extent these patients had IgHV3-21 serotype, known to be associated with an unfavorable prognosis, but none of them was found in this category [39]. Considering that in our cohort of patients, advanced Rai/Binet stages were correlated with a shorter PFS, we evaluated how many patients with mutated IgHV, had advanced disease stages at diagnosis. We identified two such patients. We further investigated if IgHV mutated patients presented traits that have been described to impact PFS and OS in other real-world clinical trials, such as age and high CIRS index [27,28,34]. Only one patient had a CIRS index ≥ 6 points, while five of them were older than 65. Due to the limited size of the IgHV mutated population, it is not feasible to assess any statistical correlations concerning the impact of CIRS≥6 points, age ≥ 65, or advanced Rai/Binet stages on this group.

An explanation for this correlation could reside in the small population included, and also in the absence of a laboratory that employs a standardized protocol, potentially resulting in erroneous results of IgHV testing. To standardize the IGHV mutational status analysis outcomes, The European Research Initiative on CLL (ERIC) is continuously working on guidelines for its processing and interpretation [40]. We believe that carrying out all genetic assessments in ERIC-accredited laboratories may help reduce bias.

When examining the relationship between TP53 mutations and OS and PFS, we observed that mutated TP53 was linked to a shorter OS, but did not show a statistically significant correlation with PFS. Our findings were supported by other real-world data [34,41,42].

For the del17p and CD38 markers, no statistically significant associations were found between these prognostic factors and PFS or OS in patients treated with ibrutinib, regardless of their line of treatment. This finding is consistent with observations from both clinical trials and

real-world studies [25,27,33,36-38,43,44].

In terms of the safety profile, our patient cohort generally tolerated ibrutinib well, similar to findings in other real-world clinical trials [24,33,42,43,45-47].

At the time of data cutoff, 29.5% of patients had permanently discontinued ibrutinib treatment, with 18% (N=11) from the TN group and 11.5% (N=7) from the R/R group. Among those who discontinued treatment, 11.5% did so due to disease progression, including 3.3% (N=2) who were diagnosed with Richter's transformation. In our cohort 14.8% (N=9) of patients stopped ibrutinib because of adverse events (AEs). Specifically, 2 patients developed atrial fibrillation, 1 experienced uncontrolled high blood pressure, 2 had recurrent infections, 1 suffered from cutaneous toxicity, and a therapeutic switch was decided for 3 patients, but the reason for treatment ceasing was not mentioned. The discontinuation rate observed in our cohort of patients is quite similar to other real-world clinical trials, including a study conducted in Canada that involved 106 patients from various ethnic groups [24,34,48].

At the time of censoring, 9 patients (14.8%) had died. One patient died from a pulmonary infection, and two because of Richter's transformation. However, the causes of death for the remaining six patients were not documented in the medical records and it would be impossible to state whether ibrutinib treatment had any impact on this aspect or not. The proportion of patients who died compared to the total number of patients in each group indicates a lower frequency of deaths in the TN group, a finding that is supported by the existing literature [37,49,50].

Our findings should be understood in light of the median age at diagnosis of 63 years and a low median CIRS index, which could help explain the favorable tolerance of ibrutinib observed in our study.

While our study results are consistent with findings from clinical trials and real-world studies, it is important to note that our research was conducted at a single center, resulting in a small patient cohort. Additionally, the data we collected were not originally gathered for a clinical trial, and our clinic currently lacks a clearly standardized protocol for all clinical and biological data relevant to CLL patients. However, our study limitations could be improved by including patients with CLL treated with ibrutinib from various centers across Romania, by applying standardized diagnosis, follow-up, and data collection protocols. Furthermore, cytogenetic and molecular biology evaluations should be done in specially equipped laboratories, employing a consistent detection protocol, such as the one ERIC proposes.

Conclusions

Our study has found that the TP53 mutation is linked to poorer OS, while advanced Rai/Binet stages at diagnosis are associated with shorter PFS during ibrutinib treatment. Our data confirm that ibrutinib is a safe treatment option characterized by a favorable safety profile, ORR, OS, and PFS, with a lower incidence of fatalities in TN patients compared to those with R/R disease, which aligns with expectations. However, our study revealed that mutated IgHV was associated with shorter PFS, a result not corroborated by real-world or clinical trial data. Our data resulted from a small number of patients, and the collected information originated from medical records that were not specifically designed for research purposes. Therefore, it does not allow for statistically significant inferences. However, it can contribute to a better understanding of ibrutinib tolerance and outcomes in real-world patients with chronic lymphocytic leukemia.

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