The European Research Journal 2023;9(6):1483-1492 Original Article

DOI: 10.18621/eurj.1359362 *Hematology*

Efficacy and safety outcomes of single-agent ibrutinib therapy in chronic lymphocytic leukemia and relapsed/refractory mantle-cell lymphoma

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ABSTRACT

Objectives: We aimed to evaluate patients using ibrutinib for the treatment of chronic lymphocytic leukemia (CLL) and relapsed/refractory mantle-cell lymphoma (MCL), focusing on high-risk subgroups, predictors of efficacy, response levels, and safety profile.

Methods: This retrospective cohort study included adult patients diagnosed with CLL and relapsed/refractory MCL who were started on ibrutinib as a single-agent between May 2015 and December 2021 in Bursa Uludag University, Department of Hematology.

Results: Of the 45 patients (23 CLL, 22 MCL) started on ibrutinib, the median age was 65 (range: 48-86) years, and 66.7% were male. Del(17p) was present in 47.8% of CLL patients; there was no remarkable difference between del(17p) status and the rates of achieving CR. The median follow-up with ibrutinib treatment in CLL patients was 13.3 (range: 0.3-77.8) months. In univariate analysis, progression-free survival (PFS) and overall survival (OS) were associated with the advanced Eastern Cooperative Oncology Group (ECOG) score ($p = 0.003$ and $p = 0.004$, respectively), and > 2 lines treatment regimens before ibrutinib ($p = 0.016$ and $p = 0.050$, respectively). In multivariate analysis, the ECOG performance status remained significant for OS. The median use of ibrutinib for MCL patients was 6 (range: 1-48) months, and the proportion of patients who achieved CR was 27.3%. In the univariate analysis of MCL patients, the ECOG performance status for PFS and OS was statistically significant ($p = 0.045$ and $p = 0.016$, respectively). Patients' most common non-hematological adverse events were pneumonia and urinary tract infection.

Conclusions: Our investigation of patient outcomes treated outside clinical trials confirms ibrutinib's sufficient efficacy and safety profile in CLL and relapsed/refractory MCL.

Keywords: Ibrutinib, efficiency, safety, chronic lymphocytic leukemia, mantle-cell lymphoma

Ibrutinib is the first oral agent that inhibits Bruton's tyrosine kinase (BTK) and is used in the treatment of chronic lymphocytic leukemia (CLL), Waldenstrom macroglobulinemia and relapsed/refractory mantle-cell lymphoma (MCL) in our country. Although there are randomized controlled studies evaluating treatment selection for these diseases, duration of therapy, and disease outcomes at different treatment stages, there

Received: ***September 12, 2023;*** *Accepted:* ***October 19, 2023;*** *Published Online:* ***October 24, 2023***

How to cite this article: *Pınar İE, Özkocaman V. Efficacy and safety outcomes of single-agent ibrutinib therapy in chronic lymphocytic leukemia and relapsed/refractory mantle-cell lymphoma. Eur Res J 2023;9(6):1483-1492. DOI: 10.18621/eurj.1359362*

e-ISSN: 2149-3189

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is a lack of data in the literature to assess real-life data. Although conventional chemoimmunotherapy has improved clinical outcomes in CLL, subsequent relapse is common, and shorter remissions are related to shorter survival, independent of salvage therapy [1]. In addition, chemotherapeutic regimens are related to typical and notable toxicities in elderly individuals, who comprise the majority of patients and have comorbidities, their use is limited [2-4].

The impact of identifying genomic features on survival results in CLL patients is critical. The presence of an unmutated immunoglobulin heavy-chain variable region (IGHV) gene, 11q deletion, or del(17p)/TP53 mutations has been related to lower progression-free survival (PFS) in cases administered chemoimmunotherapy, including fludarabine, cyclophosphamide, and rituximab [4-9]. Also, 17p deletion was identified as the most significant adverse prognostic marker for PFS and overall survival (OS) [4, 9].

On the other hand, outcomes from the international, open-label, phase 2 study that provided approval for ibrutinib in relapsed/refractory MCL showed a high overall response rate of 68%, with a complete remission (CR) of 21% [10].

We evaluated CLL and MCL patients according to high-risk subgroups, efficacy markers, and response levels. Since it is a continuous oral therapy in the treatment of CLL, we also focused on safety data that expands over time.

METHODS

Adult patients diagnosed with CLL and relapsed/refractory MCL who started ibrutinib treatment as a single agent between May 2015 and December 2021 were included in the study. This retrospective cohort study was conducted in Bursa Uludag University Faculty of Medicine, Department of Hematology.

The following characteristics of the participants in the study were recorded: cytogenetic features, previous treatments and response status, OS (time, rate), PFS (time, rate), and side effects during ibrutinib treatment. Patients who had an allergic reaction to the active substance or component of the drug and whose files had missing data for analysis were excluded from the study. Additionally, patients who were administered ibrutinib treatment with B-cell lymphoma diagnoses other than MCL and who used ibrutinib for graft versus host disease after allogeneic stem cell transplantation were excluded from the study.

If no dose adjustment was required, ibrutinib was administered once daily for CLL and MCL patients, 420 mg and 560 mg, respectively. The presence of the 17p deletion was assessed at local laboratories using interphase fluorescence in situ hybridization (FISH). Quality of response, such as CR, partial response (PR), stable disease, and progressive disease (PD), was assessed by the 2008 International Workshop on CLL response criteria [11]. Side effects during ibrutinib treatment were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 criteria [12]. PFS was defined as the time from the ibrutinib start date to the first relapse or death/last follow-up. OS was defined as the time from diagnosis to death or final follow-up. The Rai staging system for CLL is a prognostic marker using physical examination and complete blood count; It ranges from 0 (low risk), I or II (moderate risk), III or IV (high risk). The Eastern Cooperative Oncology Group (ECOG) score ranges from 0 to 5, with higher scores indicating more severe functional impairment. The MCL International Prognostic Index (MIPI) divides patients into three risk groups (low, intermediate, and high risk) based on survival status, using performance score, age, serum lactate dehydrogenase, and leukocyte count.

The study complied with good clinical practice guidelines and obtained ethics committee approval (Bursa Uludag University, date, 24 November 2021; no, 2021-17/34). The study was conducted by the 1964 Declaration of Helsinki and subsequent revisions.

Statistical Analysis

Descriptive statistics were used to identify essential characteristics. PFS and OS were evaluated according to the Kaplan-Meier method, and comparisons were made with the log-rank test. The chi-square or Fisher's exact tests were used to compare categorical data in clinical parameters. Data were expressed ade-

quately as mean ± standard deviation, median (min-max), or percentage (%). Both univariate and multivariate analyses were performed using Cox regression analysis as proper, including the following potential prognostic parameters: age (≤ 65 vs. > 65), gender, 17p deletion (negative vs. positive), Rai stage at ibrutinib onset (0-2 vs. 3-4), ECOG performance score (0-1 vs. 2-4), treatment regimens before ibrutinib (0-2 vs. > 2), response status (CR vs. Others). Statistical analysis was performed using IBM SPSS Statistics 22.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Ibrutinib therapy was started in 45 cases, 23 of whom were diagnosed with CLL and 22 with MCL, at Bursa Uludag University, Department of Hematology, between May 2015 - December 2021. The median age was 65 (range: 48-86) years, 66.7% of the participants were male, and 71.1% were classified as ECOG performance score 0-1.

Of the cases diagnosed with CLL, 78.3% were Rai stage 0-2, and del(17p) was detected in 47.8% by the

Table 1. Essential characteristics of the study cohort

		CLL		MCL		Total	
		n or median (min - max)	%	n or median (min - max)	%	n or median (min - max)	%
Age (years)		68 (48-82)		65 (49-86)		65 (48-86)	
Gender	**Male**	13	56.5	17	77.3	30	66.7
	Female	10	43.5	5	22.7	15	33.3
Bulky disease	**No**	20	87.0	18	81.8	38	84.4
	Yes	3	13.0	4	18.2	7	15.6
ECOG performance score	**0**	10	43.5	11	50.0	21	46.7
	1	7	30.4	4	18.2	11	24.4
	2	3	13.0	3	13.6	6	13.3
	3	3	13.0	4	18.2	7	15.6
	4	0	0.0	0	0.0	0	0.0
Rai classification	**Stage 0**	4	17.4				
	Stage 1	10	43.5				
	Stage 2	4	17.4				
	Stage 3	2	8.7				
	Stage 4	3	13.0				
WBC ($\times10^9$/L)		39.3 (1.54-342)		6.85 (1.93-37.22)		7.43 (1.54-342)	
Neutrophil ($\times10^9$/L)		2.81 (0.36-10.6)		3.38 (0.82-11.1)		3.33 (0.36-11.1)	
Lymphocyte ($\times10^9$/L)		33.37 (0.62-316)		1.75 (0.79-34.54)		3.41 (0.62-316)	
Hemoglobin (g/dL)		9,5 (6.5-15.3)		13.2 (8.3-16.4)		11.2 (6.5-16.4)	
Platelet ($\times10^9$/L)		103 (8.5-406)		151.4 (34.9-297.6)		127 (8.5-406)	
LDH (U/L)		228 (129-928)		217 (158-507)		220 (129-928)	
Creatine (mg/dL)		0.9 (0.6-1.2)		0.8 (0.6-2.5)		0.8 (0.6-2.5)	
17p deletion	**Negative**	12	52.2				
	Positive	11	47.8				

CLL = Chronic lymphocytic leukemia, MCL = Mantle-cell lymphoma, ECOG = Eastern Cooperative Oncology Group, WBC = White blood cell count, LDH = Lactate dehydrogenase

Table 2. Cox regression analysis outcomes for CLL patients

Variables	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age								
≤ 65 years	Reference		Reference		Reference			
> 65 years	9.9 (1.2-79.1)	**0.030**	5.7 (0.6-57.5)	0.138	4.8 (0.6-38)	0.138		
ECOG performance score								
0-1	Reference		Reference		Reference		Reference	
2-3-4	7.1 (2-25.7)	**0.003**	2.4 (0.6-10.5)	0.244	6.4 (1.8-23.1)	**0.004**	4.9 (1.2-20.2)	**0.030**
Pre-ibrutinib treatment lines								
≤ 2	Reference		Reference		Reference		Reference	
> 2	5.1 (1.4-18.7)	**0.016**	3.5 (0.7-16.7)	0.115	3.6 (1-13)	**0.050**	1.9 (0.4-7.7)	0.398
Rai stage								
0-1-2	Reference				Reference			
3-4	0.8 (0.2-3.7)	0.763			1 (0.2-4.8)	0.989		
17p deletion								
Negative	Reference				Reference			
Positive	0.8 (0.2-2.9)	0.740			1 (0.3-3.6)	0.983		
Bulky disease								
No	Reference				Reference			
Yes	2.3 (0.5-11.2)	0.284			4.1 (0.8-21.5)	0.094		

CLL = Chronic lymphocytic leukemia, PFS = Progression-free survival, OS = Overall survival, HR = Hazard ratio, CI = Confidence interval, ECOG = Eastern Cooperative Oncology Group

FISH test. Of the participants diagnosed with MCL, 45.5% were at high risk according to the MIPI, 22.6% received >2 lines of treatment regimen before ibrutinib, and 27.3% had refractory disease. Particular essential characteristics of the patients are presented in Table 1.

Outcomes of Cases Diagnosed with CLL

Patients diagnosed with CLL administrated a median of 2 (range: 0-5) treatment regimens before ibrutinib. The median follow-up with ibrutinib treatment was 13.3 (range. 0.3-77.8) months. While CR rates were 28.6% in patients who received 1 or 2 lines of treatment before ibrutinib therapy, CR could not be obtained in patients who received 3 or more treatment regimens. There was no remarkable difference in the rate of achieving CR according to prognostic markers such as age, ECOG performance score, number of treatment lines before ibrutinib therapy, presence of bulky disease, del(17p) status, and Rai stage (p > 0.05).

During ibrutinib therapy, lymphocytosis was observed in 21.7% of CLL cases. In patients with lymphocytosis, the median maximum lymphocyte count was 195 (range: 94.7-688) × 109/L. The median development of lymphocytosis with ibrutinib treatment was 17 (range: 3-97) days. Lymphocytosis returned to baseline, median 86 (range: 9-272) days. Symptomatic lymphocytosis was observed in only one patient during ibrutinib treatment.

Median PFS was not reached. The mean PFS was 41.1 (95% CI: 24.8 to 57.5) months. In univariate Cox regression analysis, factors associated with shortened PFS included old age (p = 0.030), advanced ECOG score (p = 0.003), and 3 or more treatment series before ibrutinib therapy (p = 0.016). Rai stage of disease (p = 0.763), presence of 17p deletion (p = 0.740), and bulky disease status (p = 0.284) were not associated with PFS (Table 2).

Median OS was 120.4 (95% CI: 81.1-159.8) months. Based on the survival analysis, the ECOG performance score and pre-ibrutinib treatment series significantly affected both PFS and OS (Fig. 1). PD and infections were the most common reasons for

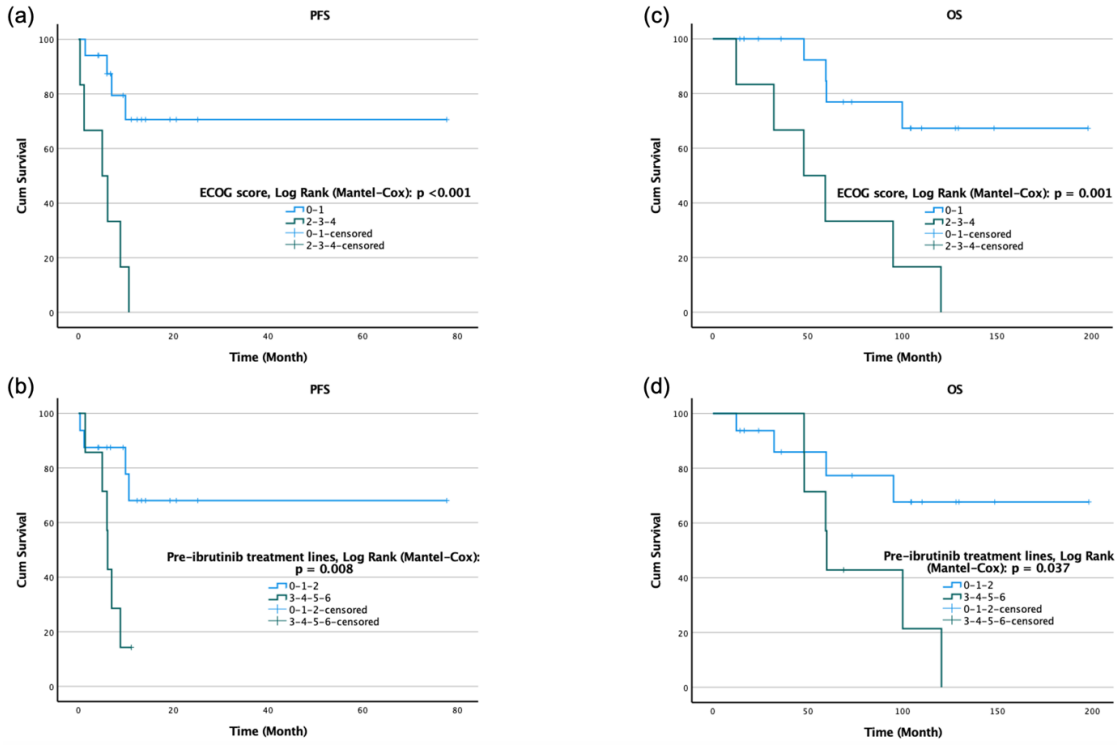

Fig. 1. PFS and OS curves for CLL patients. (a) PFS curves for ECOG performance score, (b) PFS curves for pre-ibrutinib treatment line, (c) OS curves for ECOG performance score, and (d) OS curves for pre-ibrutinib treatment line. CLL = Chronic lymphocytic leukemia, PFS = Progression-free survival, OS = Overall survival, ECOG = Eastern Cooperative Oncology Group

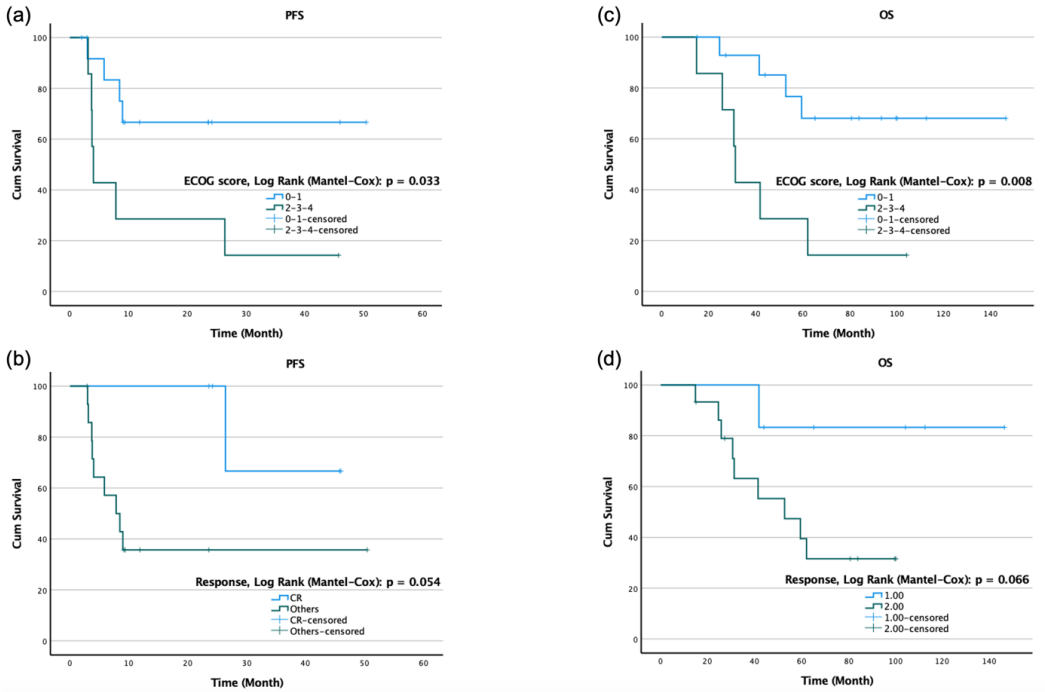

Fig. 2. PFS and OS curves for MCL patients. (a) PFS curves by ECOG performance score, (b) PFS curves by treatment response status, (c) OS curves by ECOG performance score, and (d) OS curves by treatment response status. MCL = Mantle-cell lymphoma, PFS = Progression-free survival, OS = Overall survival, ECOG = Eastern Cooperative Oncology Group

death. According to univariate Cox regression analysis, patients with high ECOG performance scores (p = 0.004) and patients who received three or more treatment lines before ibrutinib (p = 0.05) significantly reduced OS. OS results were comparable with the Rai stage (p = 0.989), age (p = 0.138), bulky disease (p = 0.094), and presence of del(17p) (p = 0.983). In multivariate analysis, the ECOG performance status remained significant for OS (Table 2).

Outcomes of Cases Diagnosed with MCL

For all MCL patients, the median duration of ibrutinib use was 6 months (1 - 48), and the proportion of patients achieving CR was 27.3%. The median OS was not reached for patients with CR, while the mean estimated OS was 129 months (95% CI: 97.8-160.2). At a median follow-up of 93.5 months for all cases diagnosed with MCL, the median PFS was 26.4 months (95% CI: 0-53.6%); the median OS was not reached, while the mean estimated OS was 92.1 months (95% CI: 68-116.3). Based on the survival analysis, the ECOG performance score significantly affected both PFS and OS. Participants with CR showed a trend for more prolonged survival for PFS and OS, although not statistically significant (Fig. 2). According to Kaplan-Meier, 12-month PFS was 52.6%, and 5-year OS was 54.7%.

In Cox regression analysis, no remarkable difference was found in PFS and OS according to age, tumor volume, and the number of treatment regimens before ibrutinib therapy. In the univariate Cox analysis, the ECOG performance score for both PFS and OS was statistically significant (p = 0.045 for PFS, p = 0.016 for OS) (Table 3). In univariate Cox analysis, patients achieving CR showed a trend for more prolonged survival was observed for both PFS and OS, although not statistically significant (p = 0.085 for PFS, 95% CI: 0.8-54.8, for OS p = 0.102, 95% CI: 0.7-44.6) (Table 3).

Safety and Adverse Event Profile in the Study Cohort

Patients' most common non-hematological side effects were pneumonia and urinary tract infection. Neutropenia was reported as the most common grade ≥ 3 hematological side effect. No hematological events led to the discontinuation of ibrutinib. The most common hematological and non-hematological side effects are listed in Table 4.

Table 3. Cox regression analysis outcomes for MCL patients

Variables	PFS Univariate Analysis		OS Univariate Analysis	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age				
≤ 65 years	Reference		Reference	
> 65 years	1.5 (0.4-5.5)	0.521	1.4 (0.4-4.8)	0.638
ECOG performance score				
0-1	Reference		Reference	
2-3-4	3.8 (1-13.9)	**0.045**	4.8 (1.3-17.3)	**0.016**
Pre-ibrutinib treatment lines				
≤ 2	Reference		Reference	
> 2	0.2 (0-1.9)	0.174	0.2 (0-1.9)	0.177
Bulky disease				
No	Reference		Reference	
Yes	1.8 (0-7.2)	0.377	3.2 (0.8-12.4)	0.098
Treatment response				
CR	Reference		Reference	
Others	6.5 (0.8-54.8)	0.085	5.6 (0.7-44.6)	0.102

MCL = Mantle-cell lymphoma, PFS = Progression-free survival, OS = Overall survival, HR = Hazard ratio, CI = Confidence interval, ECOG = Eastern Cooperative Oncology Group

During the study period, 60% of patients were complicated by infections; 30.4% had grade ≥ 3 conditions. Pneumonia was the most frequently reported infectious complication, followed by urinary tract infection and cellulitis. The most commonly reported grade ≥ 3 infection was pneumonia. Due to life-threatening diseases, sepsis was observed in 1 patient and septic shock in 5 patients.

Grade 5 adverse event was seen in only one patient who died due to intracranial hemorrhage. Upper gastrointestinal bleeding was detected in one patient. These results indicate that the incidence of grade ≥ 3 hemorrhagic events is low with continuous ibrutinib treatment.

Atrial fibrillation (AF) was a rare condition seen in 3 patients. AF occurred at a median of 4 months of ibrutinib treatment. Beta-blockers were used as rate-limiting drugs in the treatment of these patients; low molecular weight heparin or new-generation oral anticoagulants were preferred for anticoagulation prophylaxis. AF was transient in one of the patients. While ibrutinib treatment was discontinued in one of the participants with sustained AF, the ibrutinib dose was reduced in the other.

Ibrutinib treatment was discontinued for any reason in 22.2% of the study group. PD was the most common reason for discontinuing therapy.

DISCUSSION

Ibrutinib, the first oral agent to inhibit BTK, is indicated for the treatment of CLL and is used for many B-cell lymphomas, primarily MCL. Although previous studies focused mainly on a single disease, this research included all participants with diagnoses of CLL and MCL who were prescribed ibrutinib. Our investigation of patient outcomes treated outside clinical trials confirms ibrutinib's sufficient effectiveness and safety profile in CLL and relapsed/refractory MCL.

The one-year OS rate in our study does not significantly deviate from the outcomes of the RESONATE research (90%) [13]. However, the 10-month OS in Sweden's compassionate use program reported is

Table 4. Safety and side-effect profile during ibrutinib treatment

	Total (n)	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Grade 5 (n)
Hematological Side effects						
Neutropenia	3	1		2		
Thrombocytopenia	1			1		
Anemia	1		1			
Non-Hematological side effects						
Pneumonia	9	1	2	2	4	
Urinary tract infection	4	2	1		1	
Cellulite	3	1	2			
Upper respiratory tract infection	2	2				
Urticaria	3	2		1		
Headache	1	1				
Atrial fibrillation	3	3				
Heart failure	2	2				
Nausea	1			1		
Diarrhea	2	1	1			
Upper gastrointestinal bleeding	1			1		
Intracranial hemorrhage	1					1

lower (83%) than the RESONATE study [14]. The difference in prognosis may partly be explained by the fact that cases with poor performance status, who comprise a substantial proportion of patients, were exclusion criteria for the RESONATE study. In parallel, our analysis found a higher ECOG performance score as an independent risk factor of shorter PFS and OS. In this respect, our research is similar to the Polish Adult Leukemia Group results [15]. However, our results differ from the Swedish CLL cohort data, which found no worse outcomes in patients with ECOG performance scores > 1 [14].

In our study and other supportive studies,[16] the presence of 17p deletion in CLL patients using ibrutinib did not demonstrate a significant difference in PFS and OS. A study parallel to our outcomes stated that, high-risk prognostic factors such as 17p deletion did not substantially affect treatment response rates [17]. In contrast, the Swedish study demonstrated substantially shorter PFS and OS in cases with the del(17p)/TP53 mutation, noting that these mutations remain a therapeutic challenge [14].

In our study, the superior PFS and OS results in cases who received ≤ 2 treatment lines before ibrutinib therapy appear consistent with other outcomes from real-life data [16]. In addition, another study highlights the possibility of deepening responses with continued ibrutinib treatment and better efficacy with earlier initiation of ibrutinib therapy [18].

Bortezomib and lenalidomide have been used to treat cases with relapsed/refractory MCL, and response rates were 33% with bortezomib and 28% with lenalidomide. The effectiveness and safety profile of ibrutinib in our study can be compared favorably with these approved agents. In addition, our study's rate of discontinuation of treatment for any reason was 22.2%. The discontinuation rate due to side effects was similar to the pivotal studies with bortezomib and lenalidomide (26% and 19%, respectively) [19, 20]. According to the final analysis from RESONATE, the discontinuation rate of ibrutinib treatment due to side effects was 16.4%. In parallel with our study, the main reason for therapy discontinuation at extended follow-up was PD rather than drug-related toxicity [21].

Although the risk of bleeding increases with ibrutinib treatment, it should be remembered that, the use of anticoagulants and antiplatelet drugs is not contraindicated with ibrutinib treatment. On the other hand, an appropriate risk-benefit assessment should be made when evaluating ibrutinib therapy for the patient group who needs these agents [22]. Our study observed that the incidence of hemorrhagic events was lower compared with other studies. This is most likely due to patients' or treating physicians' underreporting of minor bleeding events.

In our study, AF led to the discontinuation of ibrutinib therapy in only one patient, while appropriate anti-arrhythmic therapy allowed long-term treatment with ibrutinib therapy in other patients. Therefore, careful bleeding risk assessment and proper medical management may ensure that most patients who develop AF to continue ibrutinib therapy.

The frequency of infection is increased in non-Hodgkin lymphoma because chemotherapy suppresses the immune system, and the disease also leads to an immunocompromised state. The most frequently reported infections in this study included pneumonia and urinary tract infections; most were handled in an outpatient setting and were self-limited.

Ibrutinib may be a promising treatment option for CLL and various B-cell lymphomas with a tolerable adverse events profile and a high and favorable response rate [23].

Another essential issue is drug-drug interaction. In a pharmacokinetic study of 18 healthy volunteers, the pharmacokinetics of ibrutinib were compared with the pharmacokinetics of ibrutinib combined with ketoconazole, the potent CYP3A4 inhibitor. Dose-normalized ibrutinib maximum serum concentration and area under the curve increased 29-fold and 24-fold, respectively, when co-administered with ketoconazole [24]. In a case report, a patient with steroid-refractory graft vs. host disease was successfully treated with reduced doses of ibrutinib and itraconazole to minimize the ibrutinib dose and costs by 75% [25]. Given all these results, if the treatment of a patient using ibrutinib requires the administration of potent or moderate CYP3A inhibitors, ibrutinib therapy may need to be discontinued or the dose modified.

Limitations

The most important limitations of our study are the relatively small participant size, the retrospective design of the research, and the short follow-up period with ibrutinib therapy to evaluate the extended time-dependent effectiveness and side effects profile.

CONCLUSION

Consequently, the analysis of real-life data from CLL and MCL patients parallels the outcomes of many other studies of ibrutinib therapy. Ibrutinib is a good treatment option for patients with CLL and relapsed/refractory MCL because of its encouraging response rates and acceptable toxicity. Early treatment with ibrutinib therapy may reduce the toxicity of conventional chemoimmunotherapy and thus improve patients' quality of life.

Authors' Contribution

Study Conception: İEP, VÖ; Study Design: İEP, VÖ; Supervision: VÖ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: İEP; Statistical Analysis and/or Data Interpretation: İEP; Literature Review: İEP, VÖ; Manuscript Preparation: İEP and Critical Review: VÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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