

Efficacy and Safety of Ibrutinib Therapy in Patients with Chronic Lymphocytic Leukemia: Retrospective Analysis of Real-Life Data

Kronik Lenfositik Lösemili Hastalarda Ibrutinib Tedavisinin Etkililiği ve Güvenilirliği: Gerçek Hayat Verilerinin Retrospektif Analizi

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Abstract

Objective: This study aimed to retrospectively evaluate the efficacy, safety, and survival outcome of single-agent ibrutinib therapy in chronic lymphocytic leukemia patients.

Materials and Methods: A total of 136 patients (mean age $\pm$ standard deviation: 64.6 ± 10.3 years, 66.9% males) who had received at least one dose of ibrutinib were included in this retrospective multicenter, noninterventional hospital-registry study conducted at 33 centers across Turkey. Data on patient demographics, baseline characteristics, laboratory findings, and leukemia-cell cytogenetics were retrieved. Treatment response, survival outcome including overall survival (OS) and progression-free survival (PFS), and safety data were analyzed.

Results: Overall, 36.7% of patients were categorized as Eastern Cooperative Oncology Group (ECOG) class 2-3, while 44.9% were in Rai stage 4. Fluorescence in situ hybridization revealed the presence of del(17p) in 39.8% of the patients. Patients received a median of 2.0 (range: 0-7) lines of pre-ibrutinib therapy. Median duration of therapy was 8.8 months (range: 0.4-58.0 months). The 1-year PFS and OS rates were 82.2% and 84.6%, respectively, while median PFS time was 30.0 (standard error, 95% confidence interval: 5.1, 20.0-40.0) months and median OS time was 37.9 (3.2, 31.5-44.2) months. Treatment response (complete or partial response), PFS time, and OS time were better with 0-2 lines versus 3-7 lines of prior therapy ($p < 0.001$, $p = 0.001$, and $p < 0.001$, respectively), with ECOG class 0-1 versus class 2-3 ($p = 0.006$, $p = 0.011$, and $p = 0.001$, respectively), and with Rai stage 0-2 versus 3-4 ($p = 0.002$, $p = 0.001$, and $p = 0.002$, respectively). No significant difference was noted in treatment response rates or survival outcome with respect to the presence of comorbidity, bulky disease, or del(17p). While 176 adverse events (AEs) were reported in 74 (54.4%) patients, 46 of those 176 AEs were grade 3-4, including pneumonia ($n = 12$), neutropenia ($n = 11$), anemia ($n = 5$), thrombocytopenia ($n = 5$), and fever ($n = 5$).

Conclusion: This real-life analysis confirms the favorable efficacy and safety profile of long-term ibrutinib treatment while emphasizing the potential adverse impacts of poorer ECOG performance status, heavy treatment prior to ibrutinib, and advanced Rai stage on patient compliance, treatment response, and survival outcomes.

Keywords: Chronic lymphocytic leukemia, Ibrutinib, Bruton's tyrosine kinase inhibitor

Öz

Amaç: Kronik lenfositik lösemi hastalarında tek ajan ibrutinib tedavisinin etkinliğini, güvenliğini ve sağkalım sonuçlarını geriye dönük olarak değerlendirmek.

Gereç ve Yöntemler: Otuz üç merkezde yapılan bu retrospektif, çok merkezli, girişimsel olmayan hastane kayıt çalışmasına en az bir doz ibrutinib uygulanan 136 hasta (ortalama $\pm$ standart sapma yaş 64,6 10,3, % 66,9'u erkek) dahil edildi. Hastaların demografik verileri, bazal karakteristikleri, laboratuvar bulguları, lösemi hücre sitogenetiği ile ilgili veriler kaydedildi. Tedavi yanıtı, genel sağkalım (OS), progresyonsuz sağkalım (PFS) ve güvenlik verileri analiz edildi.

Bulgular: Hastaların %36,7'sinde ECOG 2-3, % 44,9'u Rai evre 4 idi. FISH ile hastaların %39,8'inde del(17p) varlığını gösterdi. Hastalar medyan 2 (0 ila 7 arasında) sıra pre-ibrutinib tedavisi aldı. Medyan tedavi süresi 8,8 aydı (0,4-58 ay). Bir yıllık PFS ve OS oranları sırasıyla %82,2 ve %84,6, medyan (SE, %95 güven aralığı) PFS süresi 30 (5,1, 20-40) ay ve OS süresi 37,9 (3,2, 31,5-44,2) aydı. Tedavi yanıtı (CR veya PR), PFS ve OS süreleri; ibrutinib öncesi 3-7 basamak tedaviye karşı 0-2 basamak tedavi alanlarda ($p < 0,001$, $p = 0,001$ ve $p < 0,001$, sırayla), ECOG 2-3'e göre ECOG 0-2 olanlarda ($p = 0,006$, $p = 0,011$ ve $p = 0,001$, sırayla), Rai evre 0-2 olanlarda Rai evre 3-4 olanlara göre ($p = 0,002$, $p = 0,001$ and $p = 0,002$, sırayla) daha iyiydi. Komorbidite, hacimli hastalık veya del(17p) varlığına göre tedaviye yanıt oranlarında veya sağkalım sonuçlarında önemli bir fark kaydedilmedi. 74 hastada (%54,4) 176 advers olay (AE) saptandı; 176 AE'nin 46'sı derece 3-4 idi. Bunlar; pnömoni ($n = 12$), nötropeni ($n = 11$), anemi ($n = 5$), trombositopeni ($n = 5$) ve ateş ($n = 5$) idi.

Sonuç: Bu gerçek hayat analizi, uzun vadeli ibrutinib tedavisinin olumlu etkililiğini ve güvenlik profilini doğrularken, kötü ECOG performans durumunun, ibrutinib'den önce ağır şekilde tedavi verilmiş olmasının ve ileri evre hastalığın, hasta uyumu, tedavi yanıtı ve sağkalım üzerindeki potansiyel olumsuz etkilerini ortaya koymuştur.

Anahtar Sözcükler: Kronik lenfositik lösemi, Ibrutinib, Bruton tirozin kinaz inhibitörü

Introduction

Owing to novel therapeutics such as combination chemotherapy with fludarabine and cyclophosphamide (FC) and chemoimmunotherapy with rituximab (FCR), the survival outcome and long-term remission rates of chronic lymphocytic leukemia (CLL) patients have improved significantly over the last decade, particularly in younger, low-risk CLL patients [1,2,3,4,5]. However, older patients with higher-risk genetic abnormalities or del(17p) still have inferior survival outcomes, while significant toxicities of chemotherapeutic regimens and poor survival rates with the use of conventional salvage regimens following relapse after FCR are also considered challenging factors in the management of CLL [3,4,6,7,8].

Given the importance of B-cell-receptor signaling in CLL and the central role of Bruton's tyrosine kinase (BTK) in this pathway, targeted therapy with kinase inhibitors has become an alternative to conventional therapy for CLL [9,10,11]. The introduction of ibrutinib, an irreversible inhibitor of BTK, enabled significant improvement in the survival outcomes of CLL patients [10,11]. The results from three phase III trials demonstrated improved progression-free survival (PFS) and overall survival (OS) with ibrutinib compared to FCR or chlorambucil [12,13,14], while data from the RESONATE trial indicated the association of ibrutinib with significantly improved PFS, OS, and overall response rate (ORR) when compared to ofatumumab in previously treated CLL patients with several high-risk prognostic factors [15]. Accordingly, ibrutinib has become the standard of care in

relapsed/refractory patients and is now being recommended for use in front-line treatment of patients regardless of age or del(17p) status [16,17,18,19,20,21].

Given the potential differences in baseline characteristics and treatment responses of patients recruited in clinical trials and those treated outside of clinical trials, there is considerable interest in real-world experience with the use of novel targeted drugs in the management of CLL patients, particularly for drugs such as ibrutinib that are recommended to be used continuously until progression [10,22,23,24,25]. This real-life multicenter study was therefore designed to retrospectively evaluate efficacy and safety along with survival outcomes of single-agent ibrutinib therapy in CLL patients who were treated outside the setting of clinical trials.

Materials and Methods

Study Population

A total of 136 adult patients diagnosed with CLL (≥ 18 years old; mean age $\pm$ standard deviation: 64.6 ± 10.3 years; 66.9% male patients) who had received at least one dose of single-agent ibrutinib therapy after January 2013 were included in this retrospective multicenter, noninterventive hospital-registry study conducted between December 2018 and March 2019 at 33 centers across Turkey. Patients who had sensitivity to an active ingredient or component of the medication or who had ibrutinib treatment before December 2012 were excluded.

The study was conducted in full accordance with local good clinical practice guidelines and current legislations, while permission was obtained from the relevant institutional ethics committee for the use of patient data for publication purposes.

Data Collection

Data on patient demographics (age, gender), baseline characteristics (comorbidity, bulky disease, organomegaly, infection, Eastern Cooperative Oncology Group [ECOG] performance status, Rai stage, previous treatments), and laboratory findings including hemoglobin, platelet count, leukocyte count, lymphocyte count, erythrocyte sedimentation rate, lactate dehydrogenase level, beta-2 microglobulin and IgG levels, Coombs test, and leukemia-cell cytogenetics (metaphase karyotyping, interphase fluorescence in situ hybridization [FISH] analysis) were retrieved from hospital records. Treatment responses including partial response (PR), complete response (CR), stable disease (SD), and progressive disease as well as final treatment response (PR and CR) were evaluated according to the relevant International Workshop Group on CLL response criteria [25]. Assessment of response was performed at least 2 months after achieving "maximum response". The OS (duration, rate), PFS (duration, rate), and

adverse events (AEs) were also analyzed for patients who received single-agent ibrutinib treatment within the study period. PFS was defined as the period from the date of ibrutinib initiation to the first recurrence/death or the last follow-up. OS was defined as the period from the date of diagnosis to death or last follow-up.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics 22.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline characteristics. Pearson's chi-square (χ^2) test was used for the comparison of categorical data. Survival analysis was performed via Kaplan-Meier analysis and comparisons were made via log-rank test. Data were expressed as mean $\pm$ standard deviation, median (minimum-maximum), 95% confidence interval (CI), and/or percentage (%) as appropriate.

Results

Baseline Characteristics

The mean patient age was 64.6 ± 10.3 (range: 39-94) years and 61.9% of patients were male. Diabetes mellitus (25.7%) and hypertension (22.9%) were the most common comorbidities, while hepatosplenomegaly was noted in 33.8% of patients. Overall, 36.7% of patients were categorized as ECOG performance status class 2-3 and 44.9% were in Rai stage 4 (44.9%), while FISH testing revealed the presence of del(17p) in 39.8% of the patients (Table 1).

Prior Lines of Therapy and Related Treatment Responses

Patients received a median of 2.0 (range: 0-7) lines of pre-ibrutinib therapy. CR rates were 27.8%, 32.8%, 10.7%, and 15.4% for patients having received 1, 2, 3, and ≥ 4 lines of prior therapy (Table 2).

Characteristics of Ibrutinib Therapy

For the majority of patients, ibrutinib was administered orally at a daily dose of 420 mg. The treatment indications were B signs and stage 4 disease in 52.2% and 41.2% of patients, respectively (Table 3).

Median duration of ibrutinib therapy was 8.8 months (range: 0.4-58.0 months), while dose reduction, dose delay, treatment discontinuation, and AEs occurred in 16.9%, 26.5%, 24.3%, and 54.4% of patients, respectively (Table 3).

Lymphocyte counts increased within the first month of treatment, followed by a gradual decrease starting from the second month and resolving at the sixth month (Table 3).

Table 1. Baseline characteristics of patients.		
Patient demographics		
Age (years)	Mean $\pm$ SD	64.6 $\pm$ 10.3
Gender, n (%)	Male	91 (66.9)
	Female	45 (33.1)
Clinical findings		n (%)
Comorbidities¹		70 (51.5)
Diabetes mellitus		18 (25.7)
Hypertension		16 (22.9)
Coronary artery disease		8 (11.4)
Hepatitis B infection		6 (8.6)
Other (each <3%)		22 (30.9)
Bulky disease²		29 (21.3)
Organomegaly²		90 (66.2)
Hepatosplenomegaly		46 (33.8)
Splenomegaly		37 (27.2)
Hepatomegaly		2 (1.5)
Infection³		14 (10.3)
Pneumonia		4 (28.6)
Urinary tract infection		3 (21.4)
ECOG status⁴	1	51 (37.5)
	2	35 (25.7)
	0	23 (16.9)
	3	15 (11.0)
Rai stage⁵	4	61 (44.9)
	3	32 (23.5)
	2	24 (17.6)
	1	4 (2.9)
	0	1 (0.7)
Laboratory findings		
Hemoglobin (n=128), median (min-max)		10.2 (4.7-15.3)
Platelets (n=128), median (min-max)		108000 (5000-494000)
Leukocytes (n=128), median (min-max)		29380 (400-433849)
Lymphocytes (n=127), median (min-max)		20040 (294-355077)
LDH (n=107), median (min-max)		244 (89-3132)
Beta-2 microglobulin (n=54), median (min-max)		5.2 (0.3-16.2)
ESR (n=93), median (min-max)		23 (1.0-247.0)
IgG (n=89), n (%)	>500	59 (43.4)
	<500	30 (22.1)
Coombs test (n=108), n (%)	Negative	101 (74.3)
	Positive	7 (5.1)
Cytogenetic (n=48), n (%)	Normal	41 (85.4)
	Trisomy 12	7 (14.5)
FISH (n=103), n (%)	17p del	41 (39.8)
	11q del	8 (7.7)
	13q del	8 (7.7)

SD: Standard deviation; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; IgG: immunoglobulin G; FISH: fluorescence in situ hybridization; min: minimum; max: maximum.
Missing data for ¹2, ²1, ³82, ⁴12, and ⁵14 patients.

Treatment Response and Survival Outcome with Respect To Prognostic Factors

Final treatment response (CR or PR) was better in patients with 0-2 lines versus 3-7 lines of prior therapy (79.3% vs. 41.5%, $p<0.001$), in patients with ECOG performance status class 0-1 versus class 2-3 (75.0% vs. 50.0%, $p=0.006$), and in patients with Rai stage 0-2 versus 3-4 (88.9% vs. 57.0%, $p=0.002$). No significant difference was noted in final treatment response rates with respect to presence of comorbidity, bulky disease, or del(17p) status (Table 4).

After a median of 69.0 (range: 9.0-296.0) months of follow-up, mortality had occurred for 29 of 136 patients (21.3%), while 107 (81.3%) patients survived. Sepsis (31.0%) was the most common cause of death, followed by cardiac arrest (13.8%), pneumonia (10.3%), and Richter's syndrome (10.3%) (Table 5).

Overall, 1-year PFS and OS rates were 82.2% and 84.6%, respectively (Table 5), while median (standard error [SE], 95% CI) PFS time was 30.0 (5.1, 20.0-40.0) months and median (SE, 95% CI) OS time was 37.9 (3.2, 31.5-44.2) months (Table 6, Figure 1).

Mean PFS time was longer in patients with 0-2 lines versus 3-7 lines of prior therapy (39.2 ± 4.4 vs. 20.5 ± 2.9 months, log-rank $p=0.001$, Figure 2), in patients with ECOG performance

Table 2. Prior lines of therapy and related treatment responses.					
	Median (min-max)				
Number of prior lines of therapy ¹	2.0 (0.0-7.0)				
Time to last treatment response before ibrutinib ²	6.0 (0.0-120.0)				
	Treatment response				
	CR	PD	PR	SD	Total
Last treatment response before ibrutinib ³	19 (14.0)	30 (22.1)	65 (47.8)	17 (12.5)	131 (100.0)
Prior lines of therapy					
None	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	3 (2.4)
1 ⁴	5 (27.8)	3 (16.7)	9 (50.0)	1 (5.6)	18 (14.6)
2 ⁵	20 (32.8)	7 (11.5)	28 (45.9)	6 (9.8)	61 (49.6)
3 ⁶	3 (10.7)	13 (46.4)	7 (25.0)	5 (17.9)	28 (22.8)
>4	2 (15.4)	6 (46.2)	5 (38.5)	0 (0.0)	13 (10.6)
Total	32 (26.0)	29 (23.6)	50 (40.7)	12 (9.8)	123 (100.0)

PR: Partial response; CR: complete response; SD: stable disease; PD: progressive disease; min: minimum; max: maximum.
Missing data for ¹1, ²46, ³2 (also excluding 3 patients with first-line ibrutinib therapy), ⁴10, ⁵27, and ⁶44 patients.

Table 3. Characteristics of ibrutinib therapy.

Dose, n (%)		
420 mg		131 (96.3)
280 mg		3 (2.2)
140 mg		2 (1.5)
Treatment indication, n (%)		
Stage 4 disease		56 (41.2)
Stage 3 disease		29 (21.3)
Rapid doubling time		22 (16.2)
B signs		71 (52.2)
Bulky disease		12 (8.8)
Richter's syndrome		4 (2.9)
Rapidly progressive disease		1 (0.7)
Treatment duration (months)		
Mean $\pm$ SD		12.2 $\pm$ 11.1
Median (min-max)		8.8 (0.4-58.0)
Number of treatment cycles (n=133)		
Mean $\pm$ SD		11.2 $\pm$ 10.5
Median (min-max)		8 (1-58)
Dose reduction, n (%) (n=135)		
23 (16.9)		
Dose delay, n (%) (n=136)		
36 (26.5)		
Discontinuation, n (%) (n=111)		
33 (24.3)		
Adverse events, n (%)		
74 (54.4)		
Lymphocyte levels	n	Median (min-max)
Week 1	97	30000 (350-528000)
Month 1	109	29984 (340-441000)
Month 2	98	12200 (105-337000)
Month 3	75	8400 (400-313000)
Month 6	57	4740 (250-129370)
Month 12	30	3530 (1100-82000)
Month 18	17	2810 (980-73000)
Month 24	4	12275 (4000-171000)

SD: Standard deviation; min: minimum; max: maximum.

status class 0-1 versus class 2-3 (37.0 $\pm$ 4.0 vs. 21.7 $\pm$ 3.3 months, log-rank p=0.011, Figure 3), and in patients with Rai grade 0-2 versus 3-4 (47.5 $\pm$ 5.4 vs. 24.7 $\pm$ 3.0 months, log-rank p=0.001, Figure 4) (Table 6).

Mean OS time was also longer in patients with 0-2 lines versus 3-7 lines of prior therapy (45.9 $\pm$ 4.19 vs. 22.1 $\pm$ 3.1 months, log-rank p<0.001, Figure 2), in patients with ECOG performance status class 0-1 versus class 2-3 (43.7 $\pm$ 3.9 vs. 22.1 $\pm$ 3.49 months, log-rank p=0.001, Figure 3), and in patients with Rai stage 0-2 versus 3-4 (52.0 $\pm$ 4.1 vs. 28.6 $\pm$ 3.4 months, log-rank p=0.002, Figure 4) (Table 6).

No significant difference was noted in PFS time and OS time with respect to presence of comorbidity, bulky disease, del(17p) status, or overall FISH findings (Table 6).

Safety Profile

Overall, 176 AEs were reported in 74 (54.4%) patients, and 46 of those 176 AEs were grade 3-4 AEs, including pneumonia (n=12), neutropenia (n=11), anemia (n=5), thrombocytopenia (n=5), and fever (n=5) in most cases. The atrial fibrillation rate was low (n=2) (Table 7).

Discussion

Our findings revealed the favorable efficacy and safety profile of ibrutinib in CLL patients (mean age of 64.6 years, del(17p) mutation in 28.7%, Rai stage 3/4 in 68.4%) with 1-year PFS and OS rates of 82.2% and 84.6% at a median follow-up of 69.0 months, respectively. The final treatment response (CR or PR) was better and survival times (PFS and OS) were longer for patients with fewer than <2 lines of prior therapy, ECOG performance class 0-1, and Rai stage 0-2 while there was no significant impact of comorbidity, bulky disease, or del(17p) status on treatment response or survival outcomes.

Overall study population

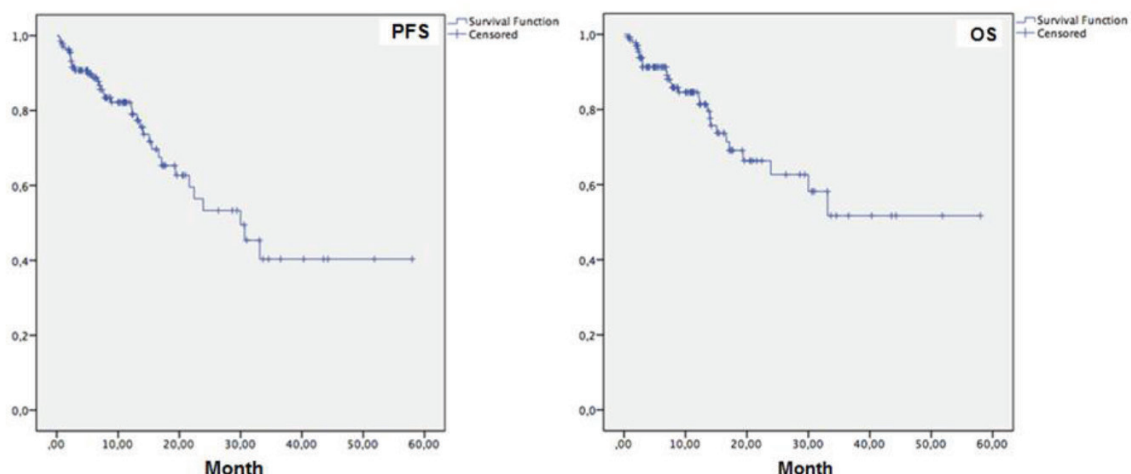


Figure 1. Overall 1-year progression-free survival (PFS) and overall survival (OS) rates.

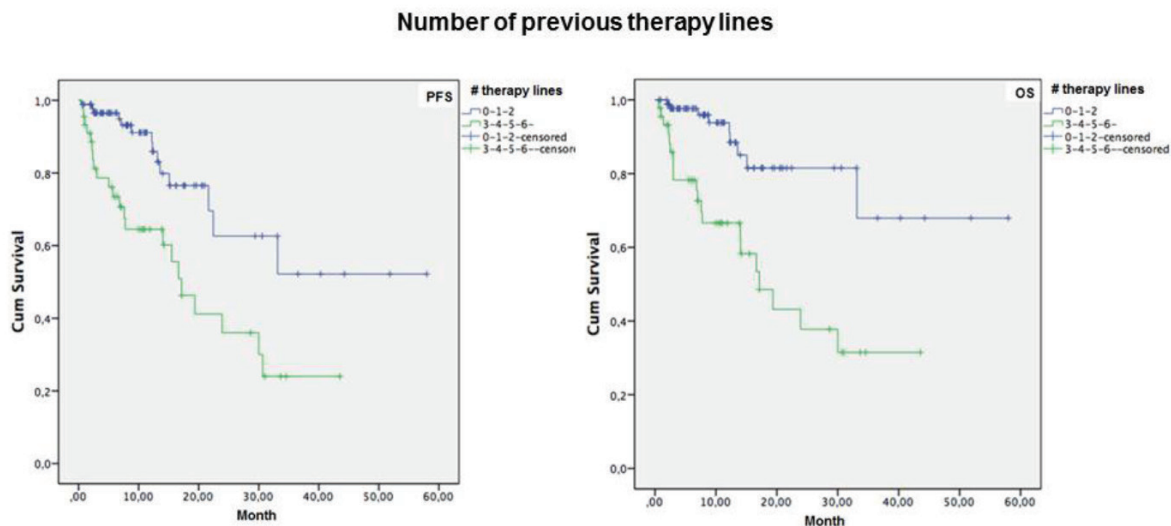


Figure 2. One-year progression-free survival (PFS) and overall survival (OS) rates in patients with 0-2 lines versus 3-7 lines of prior therapy.

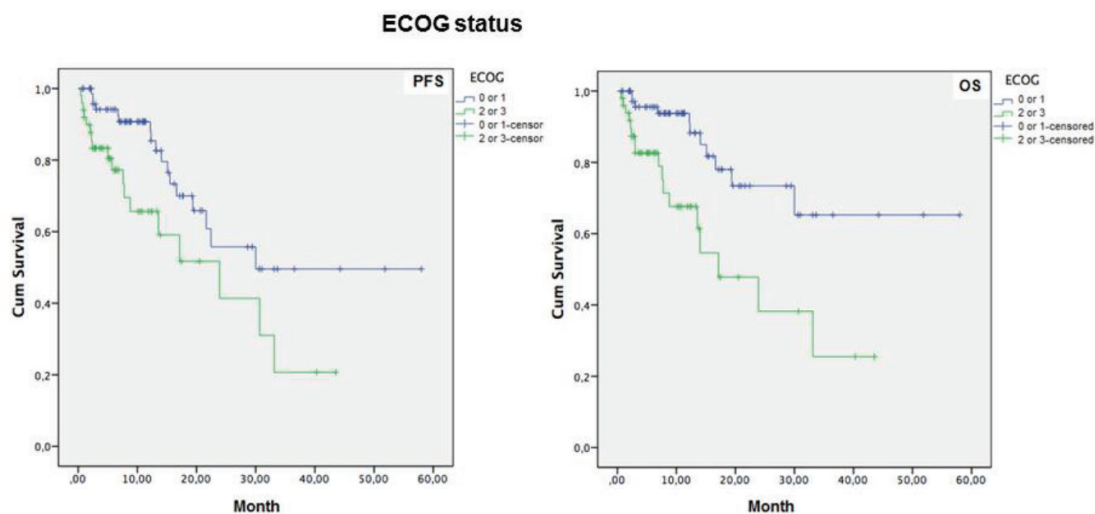


Figure 3. One-year progression-free survival (PFS) and overall survival (OS) rates in patients with Eastern Cooperative Oncology Group (ECOG) performance status class 0-1 versus class 2-3.

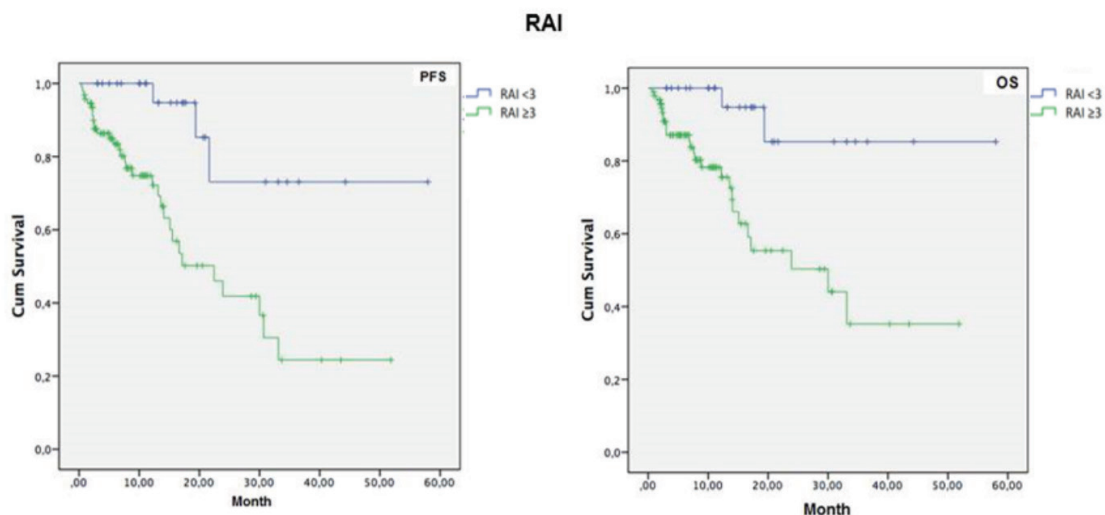


Figure 4. One-year progression-free survival (PFS) and overall survival (OS) rates in patients with Rai grade 0-2 versus 3-4.

Data from a real-life retrospective study including 32 ibrutinib-treated patients (11 had CLL) in Turkey revealed that in patients with CLL, ibrutinib treatment (median: 4 months) was associated with an ORR of 85.6% (28.5% CR and 57.1% PR) and occurrence of diarrhea in 3 (27.3%), pneumonia in 3 (27.3%), and thrombocytopenia and/or neutropenia in 2 (18.2%) patients [26]. The authors considered ibrutinib a good treatment option for CLL and other B-cell lymphomas, with an acceptable side-effect profile and a high and promising CR/PR response rate [26].

Similarly, according to real-life data from the UK CLL Forum obtained from 315 CLL patients with a median of 16 months of follow-up, the authors noted 1-year discontinuation-free survival (DFS) of 73.7% and 1-year OS of 83.8% with no significant difference in DFS and OS rates with respect to del(17p) status, whereas there was an association of better pre-treatment performance status (0/1 vs. 2+) with superior DFS (77.5% vs. 61.3%) and OS (86.3% vs. 76.0%) and an association of 1 prior line of therapy versus 2+ prior lines of therapy with a significant 1-year PFS advantage (94% vs. 82%) [22]. The same authors also noted no significant difference between more or less heavily pre-treated patients in terms of prognostic factors such as performance status and del(17p), while emphasizing the likelihood of older patients and those with del(17p) to have inferior DFS and OS when treated with ibrutinib beyond the second line [22].

In a multicenter Swedish study providing real-life data from 95 CLL patients (median age: 69 years, del(17p)/TP53 mutation in 63%, Rai stage 3/4 in 65%), the authors reported that once-a-day ibrutinib treatment was well tolerated and associated with an ORR of 84%, PFS of 77%, and OS rate of 83% at a median follow-up of 10.2 months [23]. However, in contrast to our findings, the authors indicated that del(17p)/TP53 mutation remained a therapeutic challenge given the significantly shorter PFS and OS in patients with del(17p)/TP53 mutation [23].

In addition, data from a mutation analysis study of 63 patients who were still on ibrutinib after 3 years in an early-access program at 29 French centers revealed detection of *BTK* and *PLCG2* mutations in 57% and 13% of the next-generation sequencing samples (n=30) and the authors reported that after a median follow-up of 8.5 months from sample collection, the presence versus the lack of a BTK mutation was significantly associated with subsequent CLL progression [27]. The same authors emphasized a need for clinical trials to evaluate whether patients with BTK mutation may benefit from an early switch to another treatment [27].

In a real-life study on the efficacy of ibrutinib as a single agent in 180 patients with CLL recruited from three independent cohorts from Italy, 73 patients were reported to have discontinued

Table 4. Treatment response with respect to prognostic factors.

Ibrutinib-treated patients (n=136) ^a		Final treatment response (CR or PR)		Total	p
		No	Yes		
Pre-ibrutinib lines of therapy	0-2	17 (20.7)	65 (79.3)	82	<0.001
	3-7	24 (58.5)	17 (41.5)	41	
	Total	41	82	123	
17p deletion	Present	13 (35.1)	24 (64.9)	37	0.409
	Absent	27 (43.5)	35 (56.5)	62	
	Total	40	59	99	
ECOG	0 or 1	18 (25.0)	54 (75.0)	72	0.006
	2 or 3	22 (50.0)	22 (50.0)	44	
	Total	40	76	116	
Rai	0-2	3 (11.1)	24 (88.9)	27	0.002
	3-4	37 (43.0)	49 (57.0)	86	
	Total	40	73	113	
Comorbidity	Present	24 (38.1)	39 (61.9)	63	0.197
	Absent	16 (27.1)	43 (72.9)	59	
	Total	40	82	122	
Bulky disease	Present	9 (36.0)	16 (64.0)	25	0.751
	Absent	32 (32.7)	66 (67.3)	98	
	Total	41	82	123	

ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence in situ hybridization; PR: partial response; CR: complete response.

^aMissing data for 13 patients.

Pearson chi-square.

ibrutinib for progression or for AEs, while *NOTCH1*-mutated patients were reported to have less redistribution lymphocytosis at 3 months on ibrutinib, to show inferior nodal response at 6 months, and to have significantly shorter PFS and OS [28]. The same authors noted that *NOTCH1* M plus lower BAX/BCL-2 ratio identified a CLL subset showing the worst PFS and OS, emphasizing the likelihood of either new small-molecule combination approaches or antibodies targeting *NOTCH1* being more appropriate therapeutic options for *NOTCH1*-mutated patients [28].

Notably, based on data from a study conducted in Poland on the potential significance of the mutational status of 30 selected genes for disease outcome in a real-life cohort of 45 heavily pretreated patients with CLL, the authors reported that despite the accumulation of several poor prognostic factors such as *TP53* (40.0%), *NOTCH1* (28.8%), *SF3B1* (24.4%), *ATM* (15.6%), *MED12* (13.3%), *CHD2* (11.1%), *XPO1* (11.1%), *NFKBIE* (11.1%), *BIRC3* (8.9%), *SPEN* (8.9%), *POT1* (8.9%), *EGR2* (6.7%), and *RPS15* (6.7%) in their cohort, ibrutinib treatment showed long-term clinical benefits in terms of 36-month PFS (64.0%) and OS (68.2%) rates and the ORR (51.1%) [29].

Higher treatment response and better PFS and OS outcomes in patients previously treated with 0-2 lines of therapy versus more heavily treated patients in the current study seem to be consistent with data from other real-life studies [22]. Fewer lines of prior therapy were also reported to be associated with significantly improved PFS and OS outcomes and higher CR rates

and 5-year PFS and OS rates in treatment-naïve (TN) patients compared to relapsed/refractory (R/R) patients, emphasizing the deepening of responses with continued ibrutinib therapy and the likelihood of superior efficacy of initiating ibrutinib in earlier lines of therapy [16].

Dose reduction (16.9%), dose delay (26.5%), and treatment discontinuation (24.3%) rates in the current study also seem to be consistent with previous real-life data on ibrutinib discontinuation rates (10.5% to 17.5%), dose reductions (26.0%), and temporary treatment breaks (>14 days, 13.0%) or permanent treatment discontinuation (17.5% to 41%) [22,23,30,31]. Notably, neither the dose reductions nor the temporary treatment breaks were reported to be associated with survival outcome, whereas permanent cessation of ibrutinib was associated with reduced 1-year OS survival [22]. Similar to our findings, poorer 1-year DFS (16.2%) and OS (9.3%) in patients with poorer pre-treatment performance status (PS 2+) were reported while also noting a higher likelihood of treatment breaks within the first year of therapy in the PS 2+ group [22].

In a recent FILO Group study on the OS benefits of symptom monitoring in real-world CLL patients treated with ibrutinib, the authors reported that drug intolerance and toxicities (26.3%) rather than progressive disease accounted for most drug withdrawals [27] and they indicated the higher likelihood of stopping ibrutinib due to toxicities in the real-life setting when compared to ibrutinib discontinuation rates due to toxicity (10%) and CLL progression (13.5%) as reported in RESONATE and RESONATE-2 pooled analysis [32]. The potential role of certain factors in this discrepancy has been suggested, such as the clinical experience of physicians in managing toxicity, the availability of alternative therapy, and the characteristics of real-life populations in terms of performance status and comorbidities [31].

In a recent French study on patterns of use and safety of ibrutinib in real-life practice in 102 patients, half of whom were CLL patients, the authors reported that 42.1% of patients permanently discontinued ibrutinib in the first year, mostly for progression (51.2%) or adverse drug reactions (ADRs) (32.6%), while 47.1% of patients experienced at least one ibrutinib-associated serious ADR (SADR; hematological, infectious, and vascular disorders in particular) [33]. These authors also reported the probability of developing an ibrutinib-associated SADR to be 35.1% (95% CI: 26.3-45.7) at 3 months, 44.8% (95% CI: 35.2-55.8) at 6 months, and 54.3% (95% CI: 44.0-65.2) at 12 months, further indicating a significant association of age of ≥ 80 years (hazard ratio [HR]: 2.03; 95% CI: 1.02-4.05) and being treated for CLL (HR: 1.81; 95% CI: 1.01-3.25) with a higher risk of SADR occurrence [33].

Table 5. Survival outcome with respect to prognostic factors.

Duration of follow-up, median (min-max)	69.0 (9.0-296.0)
Survivor, n (%)	107 (78.7)
Non-survivor, n (%)	29 (21.3)
Cause of death, n (%)	
Sepsis	9 (31.0)
Cardiac arrest	4 (13.8)
Pneumonia	3 (10.3)
Richter's syndrome	3 (10.3)
Sudden death	1 (3.4)
Cerebral hemorrhage	1 (3.4)
Fungal sinusitis and pneumonia	1 (3.4)
Mucor infection	1 (3.4)
Cerebral aspergillosis	1 (3.4)
Respiratory arrest	1 (3.4)
Stroke	1 (3.4)
Total	26
Missing	3
One-year survival rate (%)	
PFS	82.2
OS	84.6
PFS: Progression-free survival; OS: overall survival; min: minimum; max: maximum.	

Based on data from a Greek single-center retrospective real-world study including 58 CLL patients (11 first-line, 47 R/R) treated with ibrutinib monotherapy (for a median of 6.6 and 16.3 months, respectively), treatment discontinuation was reported to be associated with AEs (due to atrial fibrillation in 3.5% of patients) in 9% of the first-line and 10.6% of the R/R patients, while it was due to disease progression in 13 (24.5%) patients [34]. These authors concluded that CLL patients had outcomes similar to those of clinical trials if treated homogeneously according to standard guidelines, resulting in fewer unneeded discontinuations and shrinkage of the treatment armamentarium [34]. The superior efficacy of ibrutinib with significantly improved ORR, PFS, and OS compared to ofatumumab in R/R patients or compared to chlorambucil as frontline therapy in TN patients was established in the RESONATE trials, which included extended follow-up analyses [9,13,15,24,35,36,37,38].

Accordingly, our findings support favorable treatment responses and survival outcomes with the use of off-trial ibrutinib, similar to data from multicenter prospective pivotal trials

on ibrutinib, despite the fact that patients included in the pivotal clinical trials were often younger, had better ECOG classifications, and presented with milder lymphadenopathy [22,23]. Nonetheless, our findings support the potential roles of poorer ECOG performance status and having been heavily treated before ibrutinib in the likelihood of observing higher treatment discontinuation rates and inferior survival outcome in real-world settings, given the more stringent rules for dose modifications or interruptions and thus higher levels of drug compliance in clinical trials [22].

While del(17p) status had no significant impact on survival outcome in the current study, poorer survival outcome was reported for patients with del(17p) in the 3-year follow-up of a phase 1b-2 multicenter study [37] and in the RESONATE-17 study [39], as well as in a real-life study [23]. However, subgroup analysis of the RESONATE study also showed that the presence of del(17p) was not associated with inferior PFS outcomes with similar ORRs (89% and 91%, respectively) and 18-month PFS rates (71% and 79%, respectively) in patients with del(17p)

Table 6. Further analysis of survival outcome with respect to prognostic factors.

	Progression-free survival time (months)								Overall survival time (months)							
	Mean	SD	95% CI		Median	SE	95% CI		Mean	SD	95% CI		Median	SE	95% CI	
			LB	UB			LB	UB			LB	UB			LB	UB
Overall	33.3	3.1	27.2	39.5	30.0	5.1	20.0	40.0	37.9	3.2	31.5	44.2	-	-	-	-
Lines of pre-ibrutinib therapy																
0-1-2	39.2	4.4	30.5	47.9	-	-	-	-	45.9	4.1	37.9	53.9	-	-	-	-
3-4-5-6-7	20.5	2.9	14.9	26.2	17.1	2.6	12.1	22.1	22.1	3.1	16.0	28.1	17.1	3.4	10.5	23.7
p ¹	0.001								<0.001							
17p deletion																
Present	20.05	2.9	14.3	25.7	14.1	4.4	5.4	22.7	22.1	3.2	15.7	28.4	19.4	4.3	10.9	27.8
Absent	33.8	4.2	25.7	42.0	30.7	7.6	15.8	45.5	40.0	4.0	32.1	47.8	.	.	.	.
p ¹	0.224								0.123							
ECOG status																
0 or 1	37.0	4.0	29.1	44.8	30.0	-	-	-	43.7	3.9	36.1	51.3	-.	-	-	-.
2 or 3	21.7	3.3	15.3	28.1	23.9	7.4	9.3	38.5	22.1	3.49	15.4	28.8	17.1	5.0	7.3	27.0
p ¹	0.011								0.001							
Rai																
0, 1, 2	47.5	5.4	36.9	58.19	.	.	.	.	52.0	4.1	43.9	59.9	.	.	.	.
3, 4	24.7	3.0	18.9	30.6	22.4	4.7	13.3	31.5-6	28.6	3.4	22.1	35.2	30.0	11.1	8.5	51.7
p ¹	0.001								0.002							
Comorbidities																
Present	26.6	3.3	20.1	33.0	22.4	4.0	14.6	30.3	29.4	3.6	22.4	36.4	23.9	8.0	8.2	39.6
Absent	39.5	4.9	29.8	49.1	.	.	.	.	45.5	4.5	36.8	54.2	.	.	.	.
p ¹	0.203								0.074							
Bulky disease																
Present	26.6	3.0	20.7	32.5	30.0	4.7	20.8	39.2	26.2	3.0	20.3	32.2	30.0	4.7	20.7	39.3
Absent	32.3	3.5	25.5	39.1	22.4	7.5	7.8	37.1	38.3	3.6	31.3	45.38	.	.	.	.
p ¹	0.543								0.918							
SD: Standard deviation; CI: confidence interval; LB: lower bound; UB: upper bound; ECOG: Eastern Cooperative Oncology Group.																

SD: Standard deviation; CI: confidence interval; LB: lower bound; UB: upper bound; ECOG: Eastern Cooperative Oncology Group.

and those without del(17p) [35]. Likewise, 3-year PFS in ibrutinib-treated CLL patients was reported to be 53% for patients with del(17p), 66% for those with del(11q), and 58% for patients without these abnormalities [40]. In a phase 1b-2 multicenter study of 85 CLL patients, the authors reported ibrutinib to promote durable responses irrespective of the dose, with similar ORRs (71%) in the 420-mg and 840-mg cohorts along with 26-month PFS and OS rates of 75% and 83%, respectively [11]. The authors also noted no significant impact of traditional high-risk prognostic features, including del(17p), on the treatment response rates [11].

Notably, del(17p) has been suggested to be a poor prognostic factor in patients who receive frontline ibrutinib with no negative impact of del(17p) on OS in the R/R setting, while R/R disease, age, performance status, and comorbidities were reported as determinants of poor OS in ibrutinib-treated patients with CLL [41]. Moreover, the frequency of high-risk genomic abnormalities including del(17p) has been suggested to dramatically increase with increasing lines of chemotherapy, and treatment with single-agent ibrutinib earlier in the disease course before the development of these abnormalities has therefore been considered to improve patient outcomes [16].

Table 7. Safety profile.

	# of AEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Tiredness	29	24	5	-	-	-
Anemia	19	6	8	4	1	-
Pneumonia	19	1	6	11	1	-
Neutropenia	18	3	4	6	5	-
Diarrhea	17	11	6	-	-	-
Thrombocytopenia	10	1	4	4	1	-
Rash	7	5	2	-	-	-
Decreased appetite	6	5	1	-	-	-
Fever	6	1	-	5	-	-
Arthralgia	6	1	5	-	-	-
Nausea	6	5	1	-	-	-
ALT/AST elevation	4	4	-	-	-	-
Gastrointestinal complaints	3	1	2	-	-	-
Stomatitis	2	1	1	-	-	-
Itching	2	1	-	1	-	-
Lymphopenia	2	1	1	-	-	-
Neutropenic fever	2	-	-	2	-	-
Arrhythmia	2	-	2	-	-	-
Eye complaints	2	2	-	-	-	-
Atrial fibrillation	2	-	2	-	-	-
Hypothyroidism	1	1	-	-	-	-
Elevated creatinine	1	1	-	-	-	-
Intracranial hemorrhage	1	-	-	-	-	1
Deep vein thrombosis	1	-	-	3	-	-
Muscle cramps	1	-	2	-	-	-
Ataxia	1	1	-	-	-	-
Confusion	1	1	-	-	-	-
Dyspnea	1	1	-	-	-	-
Cough	1	-	-	1	-	-
Fungal infection	1	-	-	1	-	-
Cellulitis	1	-	2	-	-	-
Hyperpigmentation	1	1	-	-	-	-
Zona	1	1	-	-	-	-

AEs: Adverse events; ALT: aspartate transaminase; AST: alanine transaminase.

Indeed, targeted therapies such as ibrutinib are considered to challenge the value of classic prognostic factors defined in the original CLL International Prognostic Index, emphasizing the need for new risk models applicable to CLL patients treated with all currently approved targeted therapies [41,42,43,44].

In the current study, lymphocyte counts increased within the first month of treatment, followed by a gradual decrease starting from the second month. This is consistent with the transient increase in absolute lymphocyte count expected within the first few weeks of ibrutinib therapy, which may persist for several weeks of treatment and does not signify disease progression [24,45]. Nonetheless, some authors reported the association of prolonged treatment-related lymphocytosis with higher likelihood of ibrutinib responders to carry favorable prognostic markers (i.e., del13q and mutated *IGHV*) and a trend toward improved PFS [35,45], while more rapid and more frequent normalization of lymphocyte counts was also reported in patients with unmutated immunoglobulin genes [11].

The safety profile of ibrutinib-treated patients in the current study seems consistent with previous reports, with most AEs being mild to moderate in severity and neutropenia, hypertension, pneumonia, and anemia being the most commonly reported grade 3-4 events [11,15,37,39]. Overall, 176 AEs were reported for 74 (54.4%) of the patients in the current study, with 46 of those 176 AEs being grade 3-4 AEs including pneumonia (n=12), neutropenia (n=11), anemia (n=5), thrombocytopenia (n=5), and fever (n=5) in most cases. The results from the RESONATE trial with up to 5 years of follow-up also showed that the safety profile of ibrutinib over time remains acceptable and manageable and that extended treatment with ibrutinib is tolerable with no long-term safety signals and a reduction in the majority of grade >3 AEs over time, while effective management of AEs during the first year of treatment is considered critical given the highest discontinuation rates within this period [16,24,40].

Consistent with previous real-life data obtained from ibrutinib-treated CLL patients that identified infection as the main cause of death and the common reason for permanent discontinuation of ibrutinib [22,23], our findings revealed sepsis as the leading cause of death among ibrutinib-treated CLL patients. Nonetheless, it should be noted that in a systematic review and meta-analysis of phase III trials with 1227 patients (617 in the ibrutinib arm and 610 in the control arm), the authors concluded that there was no significant increase in the risk of infection associated with ibrutinib in patients with CLL [46].

Study Limitations

Although the occurrence of atrial fibrillation is generally between 7% and 15% in this age group in real-world analyses,

our finding of atrial fibrillation occurrence of only 2% may be explained by the retrospective design of the current study. While the cardiac arrest (14%) and sudden death (3%) rates in our study population indicate a high rate of cardiac death (17%), none of these deaths were related to ibrutinib treatment and they were associated with the high proportion of elderly patients with comorbidities in the study cohort.

Conclusion

This real-life analysis of CLL patients confirms the favorable efficacy and safety profile of long-term ibrutinib treatment as reported by prospective clinical trials, while emphasizing the potential adverse impact of poorer ECOG performance status, having been heavily treated prior to ibrutinib initiation, and advanced Rai stages but not comorbidity, bulky disease, or del(17p) status on patient compliance, treatment responses, and survival outcomes.

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Ethics

Ethics Committee Approval: The study was conducted in full accordance with local good clinical practice guidelines and current legislations, while permission was obtained from the relevant institutional ethics committee for the use of patient data for publication purposes.

Authorship Contributions

Surgical and Medical Practices: A.T.; Concept: A.T.; Design: A.T.; Data Collection or Processing: A.T., F.P.T., S.S.D., H.D.D., E.K., E.G.Ü., İ.Y., Ö.M., B.D., M.A.Ö., H.T., M.O., N.S., M.Y., V.O., A.K., Ö.Ö., G.Ç., S.D., İ.A., G.S., E.A.D., G.İ., M.A.U., G.Ö., S.A., B.T., İ.B., E.K., M.S., D.S.B., R.Y., V.Ö., A.K.G., B.S., Ş.E., O.M.A., A.B., M.H.D., A.A., A.Ü., A.S., E.G., D.Ç., B.F.; Analysis or Interpretation: A.T.; Literature Search: A.T.; Writing: A.T.

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