Evaluation of the Role of Ibrutinib as Monotherapy Treatment in Elderly Chronic Lymphocytic Leukemia Patients

El- Shafie SA[1], Taha MA[1], Hussein FZ[1], Said WM[1]

[1] Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Received: 20 July 2025
Accepted: 21 August 2025

Abstract:

Background: In the Western world, the leukemia most prevalent form is chronic lymphocytic leukemia (CLL), with an annual frequency of 4.2/100,000, or 30% of all leukemia cases. This work aim was to assess the ibrutinib efficacy (depth, objective response rate, and frequency), survival parameters, and tolerability as a monotherapy TN elderly CLL patients in 1 year.

Methods: This prospective study was conducted on 20 CLL elderly cases at the Clinical Oncology Department at Tanta University. All patients were subjected to baseline evaluation eastern cooperative oncology group (ECOG), performance status (PS) score, routine laboratory investigations as baseline immunoglobulin heavy chain variable region mutation status, complete blood count and differential count, Beta-2 Microglobulin Levels as a Prognostic Biomarker for CLL, staging classifications including RAI (American classification) for CLL and Binet (Europe staging systems) for CLL.

Results: The mean 1-year OS was significantly different among different ECOG PS scores (P=0.011), being significantly elevated in ECOG PS 0 and PS 1 cases. The mean 1-year OS was significantly different between high and very high risk cases regarding to the international prognostic index score (P=0.017).

Conclusions: Single-agent ibrutinib demonstrated remarkable efficacy in treating CLL in elderly patients, achieving a 1-year OS rate of 95% with effective responses and a tolerable side effect profile.

Keywords: Ibrutinib, Monotherapy Treatment, Chronic Lymphocytic Leukemia, Elderly Patients.

Authors Information:

Shahd Alaa El-Dein El- Shafie
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
email: Shahdelshafie4@gmail.com

Marwa Aboalsoud Taha
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
email: marwa.alsoud@med.tanta.edu.eg

Fatma Zakaria Hussein
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
email: fatma.hassan@med.tanta.edu.eg

Wael Mansour Said
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
email: wael.mansour@med.tanta.edu.eg

Corresponding Author:
Shahd Alaa El-Dein El- Shafie
Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt
email: Shahdelshafie4@gmail.com

Introduction:

The leukemia most popular form in the Western world, chronic lymphocytic leukemia (CLL) accounts for 30% of all leukemia cases, with a prevalence of 4.2/100,000/year. Nevertheless, it is rare in the Eastern world. CLL is responsible for approximately 11.3% of all leukemia cases in Upper Egypt. Throught diagnosis, 72 years was the median age. It has been reported that approximately 10% of CLL cases are younger than 55. Families CLL cases with are at a six- to ninefold increased risk of developing CLL due to an inherited genetic susceptibility.[1, 2].

This hematopoietic neoplasm is result from B-lymphocytes (LYM) in the bone marrow, LNs, and peripheral circulation.[2].

Further, the clinical path of CLL can range from months to decades, as it is a genetically heterogeneous illnesses. chromosomal aberrations serve as successful prognostic markers, with an estimated 85% of CLL patients exhibiting them.[2].

A favorable prognosis is associated with deletions in 13q14, which are the most common aberrations (50-60%). Trisomy 12 is the second most prevalent aberration and is usually associated with an intermediate prognosis (12-25%). 17p13 (5-10%) and 11q22.3 (10-20%) deletions are linked to a poor prognosis. These irregularities are considered critical prognostic biomarkers for the treatment decision-making purpose.[2].

It is supposed that the CLL cases 5-year relative survival has been rising over the past few decades, reaching 87.2% in 2021. Over the past three decades, numerous novel medications have been authorized. Ibrutinib, idelalisib, and venetoclax are specific inhibitors that have been approved for the purpose of disrupting critical pathways that are vital for the survival of CLL cells. Chemoimmunotherapy has been progressively supplanted by these inhibitors in first- and second-line indications.[3, 4].

Ibrutinib, a small-molecule compound that is orally active, suggests apoptosis in B-cell lymphomas and CLL cells. Ibrutinib has determined exceptional single-agent activity in CLL with a tolerable toxicity profile.[5]. The therapeutic landscape of CLL was significantly transformed by ibrutinib, which demonstrated effectiveness in treatment-naïve (TN) and relapsed/refractory cases, as those with high-risk cytogenetic mutations, such as 17p deletion or TP53 changes. Ibrutinib demonstrated superior efficacy and tolerability in TN patients when compared to standard-of-care chemotherapy in the pivotal RESONATE-2 phase 3 study.[6].

This work aim was to assess the ibrutinib efficiency (objective response rate (ORR), depth, and frequency), survival (progression-free survival (PFS), tolerability, and overall survival (OS)), as a monotherapy TN elderly CLL patients in 1 year.

Patients and Methods:

This prospective study was conducted at Tanta University Clinical Oncology Department from September 2023 to September 2024 on 20 elderly patients with CLL. The patients provided written consent that was informed. The investigation was conducted with the sanction of the Ethics Committee of the Faculty of Medicine at Tanta University.

(approval code: 36264MS316/9/23).

The cases inclusion criteria were elderly cases aged ≥ 65ys, both sexes, patients with active disease including indications of treatment [7, 8]: (Progressive, symptomatic, or bulky disease (spleen >6 cm below the costal margin, lymph nodes >10 cm), significant disease-related symptoms [fatigue, drenching night sweats, unintentional weight loss (≥10% in the previous 6 months), fever without infection], progressive thrombocytopenia, progressive anemia, or , threat to end-organ function, Progressive lymphocytosis with an increase of >50% over 2 months or a LYM doubling time of <6 months, steroid-refractory autoimmune cytopenias [9]), confirmed diagnosis of patients of CLL with 17p deletion positive (cut off value 20%), ECOG performance status (PS) score of ≤ 2 [10] and unfit for chemotherapy.

Exclusion criteria were patients already had a previous history of chemotherapy or chemoimmunotherapy for CLL, in a clinical trial, patients who are actively infected and require systemic antiviral, antibiotic, or antifungal therapy should have their infection controlled before commencing treatment.

patients with active second malignancies and severe comorbidities as cerebrovascular diseases, and pregnant patients.

All patients were subjected to regular CLL evaluation including demographic data collection as age, sex, ECOG PS score, and molecular cytogenetic fluorescence in situ hybridization (FISH), routine laboratory investigations as diagnostic criteria: molecular cytogenetic FISH for del (17p) in peripheral blood LYMs (immunophenotyping of peripheral blood), serum chemistry (sodium level and potassium level), complete blood count and differential count, Characteristic peripheral blood LYM flow cytometric immunophenotype [CD5+/CD23+/CD20 (dim)], infectious disease status (hepatitis , Herpes Zoster, and human immunodeficiency virus (HIV)), chest radiograph, pelviabdominal US, ECG to follow up on the drug side effects, neck, chest, pelvis, and abdomen CT scan if needed, If needed, a positron emission tomography and magnetic resonance image and staging classifications including RAI (American classification) for CLL and Binet (Europe staging systems) for CLL.

Baseline immunoglobulin heavy chain variable region mutation status (IGHV) was tested in only 4 patients. Beta-2 Microglobulin Levels as a Prognostic Biomarker for CLL were evaluated.

Ibrutinib orally administrated 420 mg once daily to all patients in this study was administered until progressive disease (PD) or unacceptable toxicity was observed. Data on the ordering/ recording, treatment start, and stop (discontinuing) were collected. Disease evaluation for all patients was assessed in terms of objective response (partial remission, stationary course, or PD) and minimal residual disease, either detectable or undetectable in bone marrow or blood, estimated at 3 months and 12 months of treatment if possible. All patients in the study were assessed for survival (PFS and OS) with a minimal 6 months follow-up, and the mortality rate. PFS refers to the duration from the ibrutinib initiation until PD or death [11]. OS: measures from diagnosis until death from any cause. It is a definitive measure of treatment efficacy and patient prognosis [12].

ECOG PS score: The ECOG PS scale indicates progressively disability higher levels, with a score of zero showing full activity, 1, restricted in strenuous activity, 2, ambulatory and capable of self-care but restricted in work activity, 3, capable of limited self-care, 4, wholly disabled, and 5, deceased. [13, 14].

Statistical analysis:

With SPSS v28 (IBM©, Armonk, NY, USA) all statistical analyses were implemented. The data distribution's normality was evaluated using Shapiro-

Wilk's test and histograms. Quantitative parametric data were analyzed using the ANOVA (F) test with a post hoc test (Tukey), which were summarized as mean and standard deviation (SD). The Chi-square test was implemented to evaluate qualitative variables, which were described in terms of frequency and percentage (%). To be considered statistically significant, a two-tailed P value was required to be less than 0.05. A Pearson or Spearman correlation was employed to estimate the degree of correlation between two quantitative variables. Kaplan-Meier curves were implemented to illustrate the OS rate.

Results:

Regarding the baseline characteristics, the range age was from 60 to 77 years, and the mean was 68.05±3.55 years. There were 13 (65%) males and 7 (35%) females. The ECOG PS was 0 in 14 (70%) patients, was 1 in 4 (20%) patients, and was 2 in 2 (10%) patients. Thirteen (65%) patients had splenomegaly, 7 (35%) patients with lymphadenopathy, and constitutional symptoms were present in 10 (50%) patients. Four (20%) patients had HBV, 3 (12%) cases had a history of HCV; No patients had HCV, HIV, or CMV. Table 1

In all our patients, Del 17p was positive, but IGHV was unmutated in 1 (5%) patient, mutated in 3 (15%) patients, and not tested in 16 (80%) patients. Rai classification was high risk in 15 (75%) patients, intermediate risk in 4 (20%) patients, but in Binet classification, high risk was in 16 (80%) patients and intermediate risk in 4 (20%) patients. The IPI score was elevated risk in 17 (85%) patients and very high risk in 3 (15%). B2 microglobulin ranged from 1.7 to 8.1 mg/L with a mean value (± SD) of 3.02 ±1.47 mg/L. Serum sodium level ranged from 135 to 144 mEq/l with a mean value (± SD) of 139.2 ± 3.04 mEq/l, and serum potassium level ranged from 3.6 to 5.1 mmol/L with a SD of 4.5 ± 0.47 mmol/L. Table 2

The constitutional symptoms significantly decreased to 7 (35%) at 3 months and 0 (0.00%) at1 year (P=0.002). The laboratory findings were significantly different during the follow-up (P<0.05). significantly elevation observed regarding Hb concentration at 3 months and 1 year in comparison to baseline level (P=0.003, <0.001) and was significantly elevated at 1 year in comparison to the level at 3 months (P<0.001). WBCS and LYMs declined at 3 months and enhanced at 1 year in 35%. However, initial leukocytosis (mainly lymphocytosis) occurred at 3 months and enhanced at 1 year in 65% (P<0.001). WBCs and LYM count were significantly elevated at 3 months compared to baseline (P<0.05), whereas they were substantially decreased at 1 year compared to baseline and at 3 months (P<0.05). Platelets were substantially increased at 1 year in comparison to baseline and 3 months (P=0.001, 0.001), while there was insignificant difference involving baseline and 3 months. Table 3

The study started with 20 patients, and one patient died in the 9th month due to chest infection. The response at 1 year was partial remission in 19 (100%) cases with no evidence of disease progression. Regarding the toxicity of the treatment, the most common toxicity was hypertension, occurring in 6 patients, followed by diarrhea in 4 patients, bleeding in 2 patients, and atrial fibrillation in 1 patient, respectively (30%, 20%, 10%, and 5%). The most common toxicity was hypertension, with grade 1 occurring in 4 cases (20%) and grade 2 in 2 cases (10%). This was followed by diarrhea, with grade 1 occurring in 3 patients (15%) and grade 2 in 1 patient (5%). Bleeding toxicity was grade 1 in 2 patients (10%), and atrial fibrillation toxicity was grade 1 in 1 patient (5%), respectively. The dose was not reduced in any of the patients. One patient (5%) died from a chest infection, and the toxicity was grade 4. Table 4

Between IPI score and Rai classification a significant positive correlation was observed (r=0.454, P=0.044), Binet classification (r=0.440, P=0.050), and B2 microglobulin (r=0.803, P< 0.001). Table 1

Between males and females 1-year OS mean was insignificantly different. Figure 1A The mean 1-year OS was significantly different among different ECOG PS scores (P=0.011), being significantly elvated in ECOG PS 0 and PS 1 cases. Figure 1B The mean 1-year OS was insignificantly different between patients without splenomegaly and those with splenomegaly. Figure 1C The mean 1-year OS was insignificantly different between patients with and those without LN affection and constitutional symptoms. Figure 1D,E The mean 1-year OS was insignificantly different between patients with and those without muted IGHV. Figure 1F

The mean 1-year OS was insignificantly different among patients with high, intermediate and low risk according to Rai classification. Figure 2A The mean 1-year OS was insignificantly different among high and intermediate risk cases according to the Binet classification. Figure 2B The mean 1-year OS was significantly different between high and very high risk cases with according to IPI score (P=0.017). Figure 2C The mean 1-year OS was insignificantly different between patients who had toxicity (diarrhea, hypertension, bleeding, and atrial fibrillation) and those with no toxicity. Figure 2D-G

Table 1: Demographic characteristics, clinical symptoms and infectious disease

		Total (n=20)
Age (years)		68.05± 3.55
Sex	**Male**	13 (65%)
	Female	7 (35%)
ECOG PS	**PS 0**	14 (70%)
	PS 1	4 (20%)
	PS 2	2 (10%)
Clinical symptoms	**Splenomegaly**	13 (65%)
	LN affection	7 (35%)
	Constitutional symptoms	10 (50%)
Infectious disease	**HBV**	4 (20%)
	HCV	0 (0%)
	HIV	0 (0%)
	CMV	0 (0%)

Data are presented as mean ± SD or frequency (%). ECOG: Eastern Cooperative Oncology Group, PS: performance status, LN: lymph node, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, CMV: Cytomegalovirus

Table 2: Molecular data, clinical classification, IPI score, laboratory investigations, OS time of the studied patients

		Total (n=20)
Del 17p	**Positive**	20 (100%)
	Negative	0 (0%)
P53	**Tested**	0 (0%)
IGHV	**Un-mutated**	1 (5%)
	Mutated	3 (15%)
	Not tested	16 (80%)
Rai classification	**Low risk**	1 (5%)
	Intermediate risk	4 (20%)
	High risk	15 (75%)
Binet classification	**Low risk**	0 (0%)
	Intermediate risk	4 (20%)
	High risk	16 (80%)
IPI score	**Mild risk**	0 (0%)
	Moderate risk	0 (0%)
	High risk	17 (85%)
	Very high risk	3 (15%)
Laboratory investigations	**B2 microglobulin (mg/L)**	3.02 ± 1.47
	Sodium level (mEq/l)	139.2 ± 3.04
	Potassium level (mmol/L)	4.5 ± 0.47
Overall survival time	**OS time (months)**	11.7± 0.73
	1-year OS rate	95%

Data presents as mean ± SD or frequency (%). IPI: International prognostic index. IGHV: Immunoglobulin heavy-chain variable region gene.

Table 3: Clinical symptoms, laboratory investigations of the studied patients at 3 months and 1 year

	Baseline (n=20)	At 3 months (n=20)	At 1 year (n=19)	P value
Clinical symptoms				
Splenomegaly	13 (65%)	13 (65%)	0 (0.00%)	**<0.001***
Lymph node affection	7 (35.00%)	7 (35.00%)	1 (5.00%)	**0.044***
Constitutional symptoms	10 (50%)	7 (35%)	0 (0%)	**0.002***
Laboratory investigations				
Hb (g/dL)	9.84± 1.62	10.9± 0.69	11.63± 0.42	**<0.001***
		P1=0.003*, P2<0.001*, P3<0.001*		
WBCs (*10^9/L)	68.19± 48.07	90.26± 64.08	17.43± 8.81	**<0.001***
		P1=0.001*, P2<0.001*, P3<0.001*		
Platelets (*10^9/L)	144.05± 59.7	164.85± 36.7	190.16± 44.4	**0.015***
		P1=0.191, **P2=0.001*, P3=0.001***		
Lymphocyte count (*10^9/L)	60.82± 45.88	81.14± 59.59	10.52± 5.34	**<0.001***
		P1=0.001*, P2<0.001*, P3<0.001*		

Data presents as frequency (%). Hb: hemoglobin, WBCs: white blood cells, *: statistically significant as p value <0.05, P1: p value between baseline and at 3 months, P2: p value between baseline and at 1 year, P3: p value between at 3 months and at 1 year.

Table 4: Response to ibrutinib after 1 year, toxicity of the treatment, mortality and grade of toxicity of the studied patients

					At 1 year (n=19)
Response to ibrutininb	**Partial remission**				19 (100%)
	Stationary course				0 (0%)
	Progressive disease				0 (0%)
Toxicity					
	G0	**G1**	**G2**	**G3**	**G4**
Hypertension	14 (70%)	4 (20%)	2 (10%)	0 (0%)	0 (0%)
Diarrhea	16 (80%)	3 (15%)	1 (5%)	0 (0%)	0 (0%)
Bleeding	18 (90%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)
Atrial fibrillation	19 (95%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
					Total (n=20)
Mortality rate					1 (5%)
Cause of death	**Chest infection and pneumonia**				1 (5%)
Grade of toxicity	**Grade 4**				1 (5%)

Data presents as frequency (%).

Table 5: Correlation of the IPI score and the different parameters

	IPI score	
	r	**P**
Rai classification	0.454	**0.044***
Binet classification	0.440	**0.050***
B2 microglobulin (mg/L)	0.803	**< 0.001***

IPI: International prognostic index, r: correlation coefficient, *: statistically significant as p value <0.05.

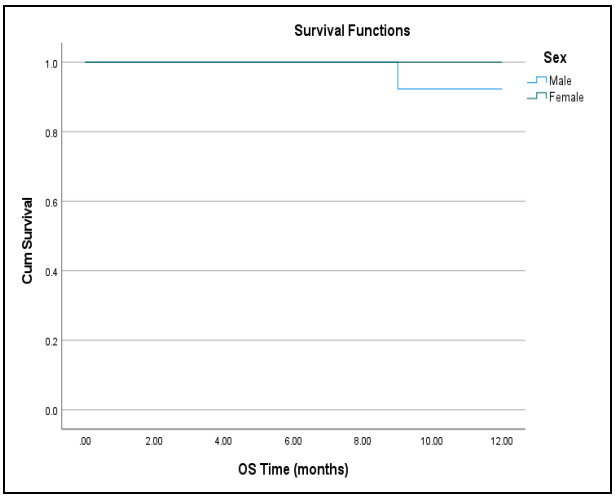

Figure 1: (A): 1-year Overall survival of the studied patients regarding sex

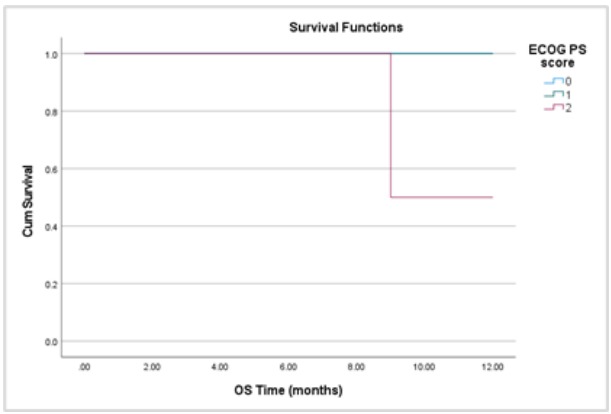

Figure 2: (B): 1-year Overall survival of the studied patients regarding ECOG PS

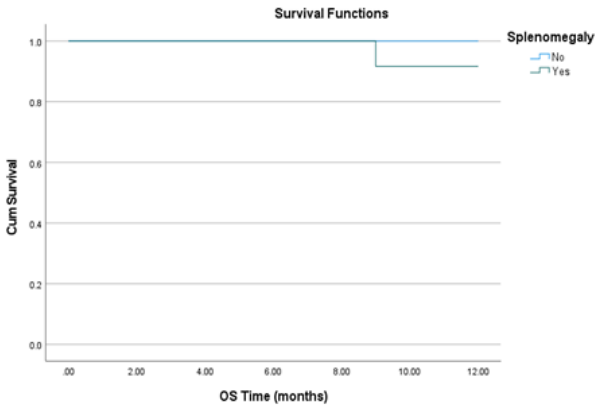

Figure 3: (C): 1-year Overall survival of the studied patients regarding splenomegaly

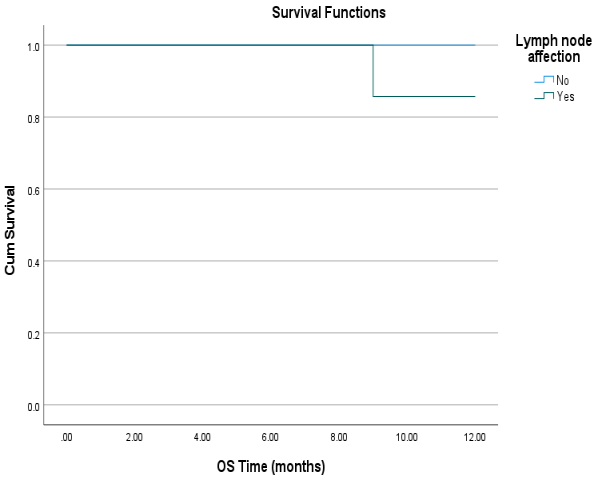

Figure 4: (D): 1-year Overall survival of the studied patients regarding LN affection

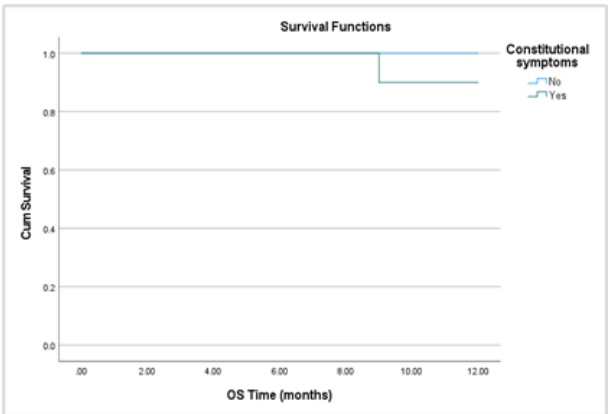

Figure 5: (E): 1-year Overall survival of the studied patients regarding constitutional symptoms

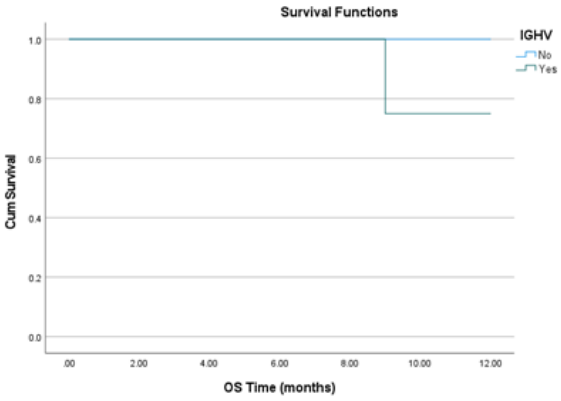

Figure 6: (F): 1-year Overall survival of the studied patients regarding IGHV

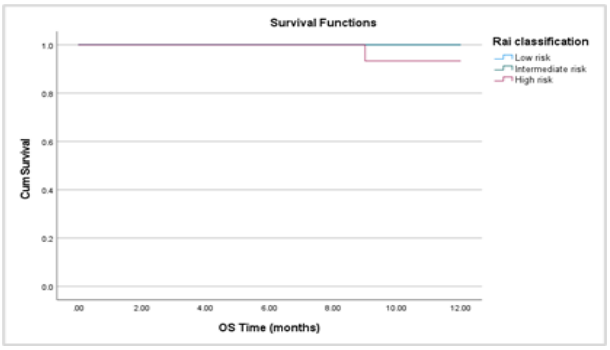

Figure 7: (A):1-year Overall survival of the studied patients regarding Rai classification

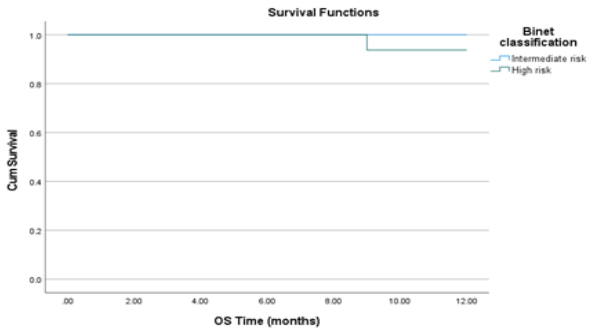

Figure 8: (B):1-year Overall survival of the studied patients regarding Binet classification

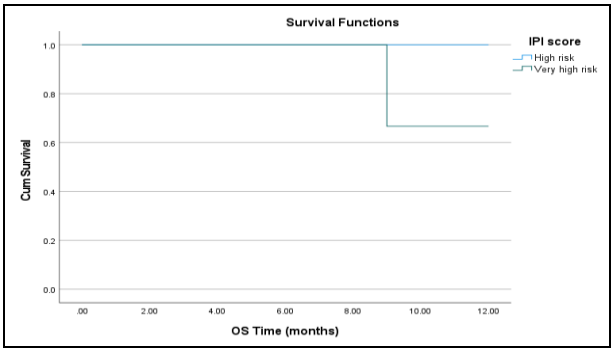

Figure 9: (C):1-year Overall survival of the studied patients regarding IPI score

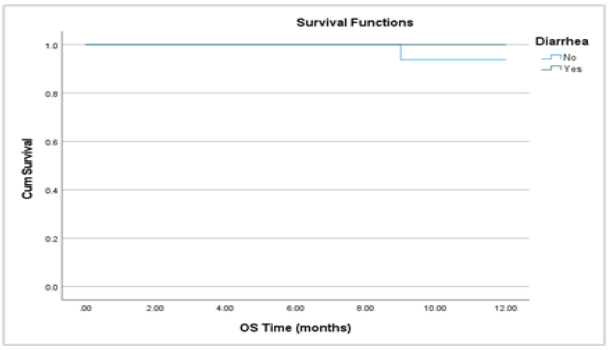

Figure 10: (D):1-year Overall survival of the studied patients regarding diarrhea

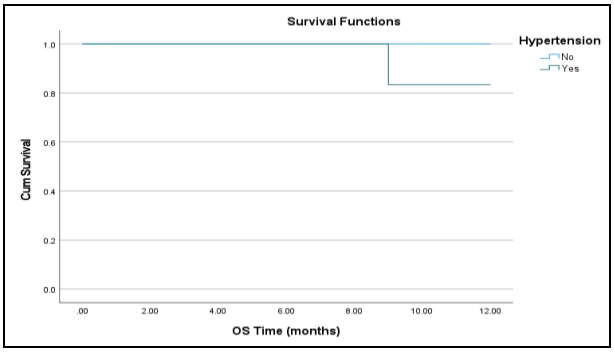

Figure 11: (E):1-year Overall survival of the studied patients regarding hypertension

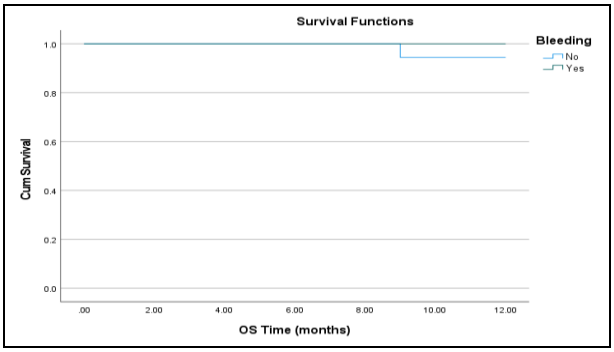

Figure 12: (F):1-year Overall survival of the studied patients regarding bleeding

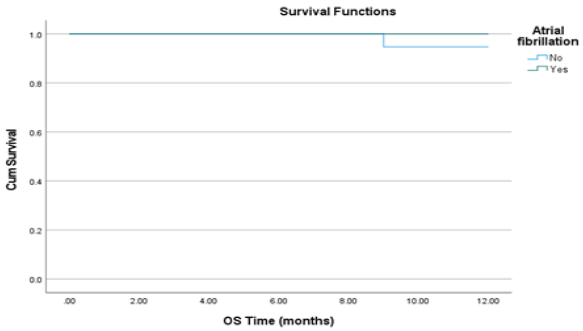

Figure 13: (G):1-year Overall survival of the studied patients regarding atrial fibrillation

Discussion:

Among leukemias, CLL is the most prevalent in Western world and is growing in prevalence. A prolonged survival rate has been achieved as a consequence of the introduction of innovative combinations and targeted treatments, including ibrutinib..[15]. The management of this predominantly elderly population is a topic of controversy due to the frequent comorbidities that frequently preclude aggressive therapy, with a median age at diagnosis of 71 years.[16].

In our results, 4 (20%) patients had HBV, 3(12%) patients had previously had HCV, and no patients had HIV or CMV. T

hese results are supported by Minuk et al., [17] who found that both HBV and HCV have been implicated in the CLL pathogenesis.

In all our patients, Del 17p was positive. The presence of del 17p correlates with poor response to chemotherapy and unfavorable outcome, but IGHV was unmutated in 1 (5%) patient, mutated in 3 (15%) patients, and not tested in 16 (80%) patients.

These findings are consistent with Bronstein et al. [18], who examined 254 patients diagnosed with CLL between 1991 and 2020 at the Tel-Aviv Sourasky Medical Center. The IGHV mutational status has been ascertained through cDNA Sanger or next-generation sequencing. Of the 132 individuals, 52.0% possessed an unmutated IGHV gene, while 122 individuals (48.0%) were mutated (M-IGHV).

According to the response to treatment, the number of patients with splenomegaly, lymphadenopathy remained the same at three months but decreased to 0 (0.00%) and 1 (5.00%) at one year (P<0.001, 0.044). The constitutional symptoms significantly decreased to 7 (35%) at 3 months and 0 (0.00%) at 1 year (P=0.002).

Following our results, Ryan et al., [19] observed that evaluable lymphadenopathy cases experienced significant reductions in LN size, with an aggregate median reduction of 88.6%. As determined this cohort had an ORR of 87.5% (14 of 16 cases. For progressive disease, none of the investigator-assessed greatest responses were observed. Two patients achieved a complete response, ten patients underwent a partial response, and two patients underwent a partial response with lymphocytosis.

Further, Ahn et al., [20] reported that Enrollment of 86 patients was reported; 51 cases met the criteria to TP53 aberration (TP53 cohort) and 35 patients were eligible as age of 65 or older. The majority of patients, 53 (61.6%), had TN-CLL, 58 (67.4%) had enhanced Rai stage (III/IV), and 57 (66.3%) had unmutated IGHV. 4.8 years was the median duration on study, with a range of 4.0-6.0 years, and 57.0 percent of patients remained in the study. A partial response was obtained by one patient at 2 months, and they progressed (in comparison to the 2-month nadir) at 6 months. Two patients did not respond. After receiving ibrutinib, the disease burden decreased gradually in all anatomic compartments over time. At the three-year mark, the median decrease in absolute LYM count was 97%, bone marrow reduction was 94%, sum of the product of target LN was 89%, and splenic volume reduction was 89%.

Based on the results, Hb concentration at 3 months and 1 year was significantly elevated compared to the baseline level (P=0.003, <0.001). WBCS and LYMs declined at 3 months and get better at 1 year in 35%. However, initial leukocytosis (mainly lymphocytosis) occurred at 3 months and progressed at 1 year in 65% (P<0.001). Also, at 3 months WBCs and LYM count were significantly raised compared to baseline (P<0.05), while they were significantly decreased at 1 year compared to baseline and at 3 months (P<0.05). Platelets were significantly increased at 1 year compared to baseline and 3 months (P=0.001, 0.001), with no significant difference between baseline and 3 months.

Following our study, Vitale et al. [21] reported that treatment with ibrutinib significantly causes an increase in Hb level in CLL cases . Furthermore, Mayerhoefer et al. [22] revealed that Bruton's tyrosine kinase inhibitor ibrutinib effectively treats CLL. Nevertheless, individuals frequently experience a rise in their CLL blood cell count following the initiation of ibrutinib treatment. The number of CXCR4high (tissue-resident) CLL cells increased, as did eukocytosis. The Volume of the LN and Spleen was Decreased. Leukocytosis decreased as a result of prolonged ibrutinib treatment, which was followed by a decrease in [68Ga] Uptake of pentixafor in the spleen. the pre-existing clinical hypothesis of a "compartment shift" of CLL cells from the lymph node to the peripheral circulation is substantiated by these findings. Furthermore, they enhance the mechanistic model by documenting the bone marrow early clearanceand the CLL cells re-distribution to the orthotopic splenic cavernous system responding to ibrutinib treatment..

Our study started with 20 patients, and one patient died in the 9th month due to a chest infection. The response at 1 year was partial remission in 19 (100%) patients.

Regarding the toxicity of the treatment, the most common toxicity was hypertension, occurring in 6 patients, followed by diarrhea in 4 cases, bleeding in 2 cases, and atrial fibrillation in 1 patient, respectively (30%, 20%, 10%, and 5%). The most common toxicity was hypertension, with grade 1 occurring in 4 patients (20%) and grade 2 in 2 patients (10%). This was followed by diarrhea, with grade 1 occurring in 3 patients (15%) and grade 2 in 1 patient (5%). Bleeding toxicity was grade 1 in 2 patients (10%), and atrial fibrillation toxicity was grade 1 in 1 patient (5%), respectively.

One patient (5%) died from a chest infection, and the toxicity was grade 4. The dose was not reduced in any of the patients.

These findings are consistent with Mayerhoefer et al., [22] who declared grade 3 hypertension was informed in 14% of patients receiving ibrutinib.

Additionally, Zhou et al., [23] Ibrutinib was not observed to be significantly correlated to an anemia increased risk (CI: 0.67–1.21, RR: 0.90, 95% ; P=.49),

thrombocytopenia (RR: 0.61, 95% CI: 0.32–1.14; P=.12), neutropenia (RR: 0.50, 95% CI: 0.25–1.00; P=.05), and febrile neutropenia (RR: 0.89, 95% CI: 0.32–2.49; P=.83). Similarly, the risk of respiratory tract infection was observed (RR: 1.01, 95% CI: 0.78–1.30; P=.96). Compared the control group the risk of abdominal manifestations was markedly elevated with ibrutinib (RR: 1.62, 95% CI: 1.32–2.00; P=.00001). There was also a significant increase in the probability of gastroenteritis in the Ibrutinib group (RR: 2.14, 95% CI: 1.44–3.17; P=.0002).

In our study, there was a significant positive correlation between IPI score and Rai classification (r=0.454, P=0.044), Binet classification (r=0.440, P=0.050), and B2 microglobulin (r=0.803, P< 0.001).

Also, Rotbain et al., [24] clarified that the IPI score positively correlated with the Binet classification in CLL patients. As well, Bohn et al., [25] CLL patients had a positive correlation between IPI score and B2 microglobulin. In another study by Bohn et al., [26] high beta-2-microglobulin (B2M) plasma levels commonly suggest a higher CLL-IPI risk category for short OS.

Concerning our results, the OS time of the studied patients ranged from 9 to 12 months, with a mean value (± SD) of 11.7±0.73 months, with a one-year OS rate of 95%.

Our results are consistent with study by Aarup et al., [27] 86.3% and 88.8%, respectively, were the 12-month PFS and OS rates of 205 CLL patients who were treated with ibrutinib.

In our study, the mean 1-year OS was significantly different among different ECOG PS scores (P=0.011), significantly incresed in ECOG PS 0 and PS 1 cases.

Following our results, Tombak et al., [28] the final treatment response (CR or PR) and survival times (PFS and OS) were better in CLL treated with ibrutinib.

Our study shows that the mean OS after 1 year was insignificantly different between patients with and those without splenomegaly, LN affection, constitutional symptoms, muted IGHV, and high, intermediate, and low risk according to Rai classification.

On the other hand, Pektaş et al., [29] had different results as they found throughout the follow-up period, 40.8% of the cases took treatment, 49.3% experiencing partial remission, with 42.5% achieving complete remission, , and 8.2% indicating no response to the theraby. The findings indicated that higher mortality rates were linked to an advanced Binet stage, splenomegaly, a positive direct Coombs test, a 17p deletion, thrombocytopenia, and elevated creatinine, leukocyte, and LYM counts. 17p deletion, reduced hemoglobin levels, and elevated Binet and Rai stages were identified as statistically significant factors. This discrepancy may be attributable to the limited sample size of our investigation.

The study limitations the were short duration of follow-up and lack of comparing monotherapy of ibrutinib to combination modalities, relatively small sample size inevitably lowered the statistical power of the analysis, single-center study, making the results less generalizable,

Conclusion:

Single-agent ibrutinib demonstrated remarkable efficacy in treating CLL in elderly patients, achieving a 1-year OS rate of 95% with effective responses and a tolerable side effect profile.

Therefore, further investigations with larger and stratified sample, multi-center study size are recommended for more accurate results, future studies with a longer duration of follow-up and further studies comparing ibrutinib as monotherapy to combination therapies for CLL in older cases.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculty of Medicine, Tanta University, with approval code: 36264MS316/9/23. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki (1975). The study started in September 2023 and ended in September 2024.

Consent for publication: Not applicable.

Availability of data and material: Data and materials are available upon reasonable request from the corresponding author.

Competing interests: The authors declare no conflict of interest.

Funding: Nil.

Authors' contributions: Shahd Alaa El-Dein El-Shafie conceived and supervised the study; Marwa Aboalsoud Taha and Wael Mansour Said were responsible for data collection. Shahd Alaa El-Dein El-Shafie and Fatma Zakaria Hussein analyzed and interpreted the data. All authors contributed to the manuscript at various stages of development and approved the final version.

Acknowledgements: We are grateful to all patients who participated in this study and contributed to its success.

List of Abbreviations:

CLL	Chronic lymphocytic leukemia
ECOG	Eastern cooperative oncology group
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IGHV	Immunoglobulin heavy chain variable region mutation status
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
WBCs	White blood cells

References:

1. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:23-33.
2. Eid OM, Abdel Kader RMA, Fathalla LA, et al. Evaluation of MLPA as a comprehensive molecular cytogenetic tool to detect cytogenetic markers of chronic lymphocytic leukemia in Egyptian patients. J Genet Eng Biotechnol. 2021;19:98-9.
3. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021;96:1679-705.
4. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. Am J Hematol. 2019;94:66-87.
5. Martino EA, Mauro FR, Reda G, et al. Ibrutinib as first line therapy in chronic lymphocytic leukemia patients over 80 years old: A retrospective real-life multicenter Italian cohort. Hematol Oncol. 2024;42:32-49.
6. Khelifi RS, Huang SJ, Savage KJ, et al. Population-level impact of ibrutinib for chronic lymphocytic leukemia in British Columbia, Canada. Leuk Lymphoma. 2023;64:1129-38.
7. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. J Am Soc Hematol. 2018;131:45-60.
8. Shadman M. Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Review. JAMA. 2023;329:918-32.
9. Andersen MA, Grand MK, Brieghel C, et al. Pre-diagnostic trajectories of lymphocytosis predict time to treatment and death in patients with chronic lymphocytic leukemia. Commun Med (Lond). 2022;2:50-60.
10. Hess LM, Smith D, Cui ZL, et al. The relationship between Eastern Cooperative Oncology Group performance status and healthcare resource utilization among patients with advanced or metastatic colorectal, lung or gastric cancer. J Drug Assess. 2020;10:10-7.
11. Winqvist M, Andersson PO, Asklid A, et al. Long-term real-world results of ibrutinib therapy in patients with relapsed or refractory chronic lymphocytic leukemia: 30-month follow up of the Swedish compassionate use cohort. Haematologica. 2019;104:208-10.
12. Robak T, Doubek M, Ferrant E, et al. Overall survival of patients with CLL treated with ibrutinib in the first line compared to second-line ibrutinib after chemotherapy/chemoimmunotherapy. Curr Med Res Opin. 2024;40:1369-78.
13. Passaro A, Spitaleri G, Gyawali B, et al. Immunotherapy in non–small-cell lung cancer patients with performance status 2: clinical decision making with scant evidence. Clin Oncol. 2019;37:1863-7.
14. Sehgal K, Gill RR, Widick P, et al. Association of Performance Status With Survival in Patients With Advanced Non-Small Cell Lung Cancer Treated With Pembrolizumab Monotherapy. JAMA Netw Open. 2021;4:71-9.
15. Wainman LM, Khan WA, Kaur P. Chronic Lymphocytic Leukemia: Current Knowledge and Future Advances in Cytogenomic Testing. Exon Publications. 2023;18:93-9.
16. Barr PM, Robak T, Owen C, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica. 2018;103:15-32.
17. Minuk GY, Lerner B, Gibson SB, et al. Hepatitis B and hepatitis C viral infections in patients with chronic lymphocytic leukemia. Can J Gastroenterol Hepatol. 2014;28:31-4.
18. Bronstein Y, Levi S, Herishanu Y. Improved outcomes in patients with chronic lymphocytic leukaemia infected during the omicron BA.5 subvariant surge. Br J Haematol. 2023;201:1125-8.
19. Ryan CE, Sahaf B, Logan AC, et al. Ibrutinib efficacy and tolerability in patients with relapsed chronic lymphocytic leukemia following allogeneic HCT. Blood. 2016;128:2899-908.
20. Ahn IE, Farooqui MZH, Tian X, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood. 2018;131:2357-66.
21. Vitale C, Ahn IE, Sivina M, et al. Autoimmune cytopenias in patients with chronic lymphocytic leukemia treated with ibrutinib. Haematologica. 2016;101:e254-8.
22. Mayerhoefer ME, Haug A, Jäger U, et al. In Human Visualization of Ibrutinib-Induced CLL Compartment Shift. Cancer Immunol Res. 2020;8:984-9.
23. Zhou Y, Lu H, Yang M, et al. Adverse drug events associated with ibrutinib for the treatment of elderly patients with chronic lymphocytic leukemia: A systematic review and meta-analysis of randomized trials. Medicine (Baltimore). 2019;98:46-79.
24. Rotbain EC, da Cunha-Bang C, Brieghel C, et al. CLL-IPI applied in Binet A CLL: a nationwide cohort study. Blood Adv. 2022;6:5698-701.
25. Bohn J-P, Stolzlechner V, Göbel G, et al. Reduced prognostic value of beta-2-microglobulin for time to first treatment in CLL patients with compromised kidney function. Leuk Lymphoma. 2024;65:2108-15.
26. Bohn J-P, Stolzlechner V, Göbel G, et al. Beta-2-Microglobulin Maintains Overall Survival Prediction in Binet A Stage Chronic Lymphocytic Leukemia Patients with Compromised Kidney Function in Both Treatment Eras of Chemoimmunotherapy and Targeted Agents. Cancers. 2024;16:37-44.
27. Aarup K, Rotbain EC, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. Eur J Haematol. 2020;105:646-54.
28. Tombak A, Pepedil Tanrıkulu F, et al. Efficacy and Safety of Ibrutinib Therapy in Patients with Chronic Lymphocytic Leukemia: Retrospective Analysis of Real-Life Data. Turk J Haematol. 2021;38:273-85.
29. Pektaş G, Gönül E, Öncü Ş, et al. Chronic Lymphocytic Leukemia: Investigation of Survival and Prognostic Factors with Drug-Related Remission. Diagnostics. 2025;15:72-88.