INCIDENCE OF ARRHYTHMIA IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED WITH IBRUTINIB: A REAL-WORLD RETROSPECTIVE ANALYSIS FROM TWO ITALIAN CENTERS

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INTRODUCTION

Ibrutinib, the first-in-class BTK inhibitor, has significantly improved the natural history of chronic lymphocytic leukemia (CLL) in both treatment-naïve (TN) and relapsed/refractory (R/R) patients but its beneficial effects on progression-free survival (PFS) and overall survival (OS) may be outweighed by off-target effects.

Ibrutinib is currently in widespread clinical use, which has led to an increase in the frequency of both common and uncommon adverse events (AEs), less frequently observed in early clinical trials.

Up to 29% of patients discontinue ibrutinib treatment because of side effects. In particular, atrial fibrillation (AF) is the most common reason, ranging from 5% to 20% in clinical trials and 8% to 25% in clinical practice. We currently know that predisposing risk factors and cardiac comorbidities seem to be the main elements that define an increased risk of AF.

AIMS

To evaluate:

- the cumulative incidence (CI) of AF over time and its clinical impact on event-free survival (EFS), [event defined as AF, definitive treatment discontinuation (TD), PD, or death from any cause], PFS and OS;
- associations between clinical factors and higher incidence of AF;
- the incidence of cardiovascular events (CE) during treatment and long-term follow-up (FU);
- changes in cardiac medication during treatment; the length of drug exposure; causes of TD.

METHODS

Unselected CLL patients treated with ibrutinib for at least 6 months between 01/2014 and 12/2022 were enrolled in a double-center retrospective cohort study. There were no exclusion criteria.
Data were obtained from medical records. Demographic and treatment data, biological characteristics of disease and concomitant cardiac comorbidities were collected. FU ended on May 01, 2023.
AF and all AEs were described according to CTCAE 5.0.

RESULTS (I)

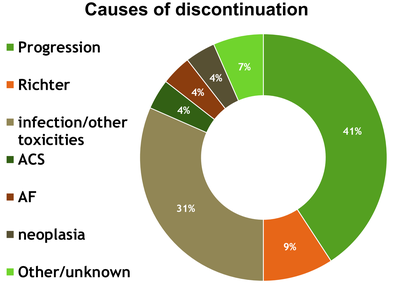
We enrolled 179 patients (M/F: 102/77) (Tab.1). The median age was 70 years (36-83). IGHV unmutated was detected in 85 patients (62.5%) and mutated in 51 (37.5%). *TP53/del17p* disruptions were detected in 63 patients (35%).

Fifty-nine CLL patients received ibrutinib as TN and 120 as R/R, with a median number of lines of therapy of 1 (1-6).

The median FU was 24.2 months (0.3-102.8). The median time to drug discontinuation was 41.4 months with a CI of TD of 32% at 24 months. There was no difference in TD between TN and R/R (p=0.232).

Specifically, the CI of TD was 29% in TN and 33% in R/R at 24 months. Now a day 103 (58%) CLL patients were on treatment, while 76 (42%) had discontinued ibrutinib therapy.

TD was mainly due to progression and Richter's transformation (RT) (21%), followed by toxicity (18%).



Among toxicities, CE led to TD in 6/33 patients (18%) [3 acute coronary syndrome (ACS), 3 AF].

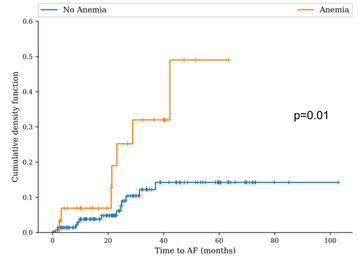
The most common AEs were AF (11%), always defined ≤3 CTCAE; infections (12%); ACS (2%).

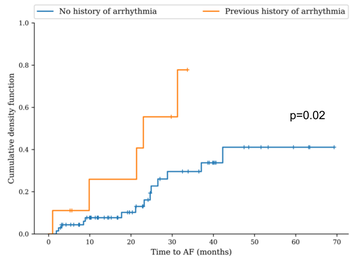
Second malignancies were observed in 10% (n° 18). No major bleeding was recorded. Nineteen of 20 AF patients started DOACs.

	Total N=179	No AF N = 159	AF N = 20	p-Value
Gender, N pts (%)				
M	102/179 (57%)	89/159 (56%)	13/20 (65%)	0.483
F	77/179 (43%)	70/159 (44%)	7/20 (35%)	
Age at start IBR, All pts Mean ± SD, yrs	68.98 ± 8.82 Range:36.42-83.47	68.91 ± 9.05 Range: 36.42-83.47	69.46 ± 6.93 Range: 55.24-80.92	0.945
Treatment before IBR, All pts Mean ± SD	1.12 ± 1.12 Range: 0-6	1,11 ± 1,09 Range: 0-6	1.25 ± 1.37 Range: 0-5	0.906
IGHV, N pts (%)				
Mutated	51/136 (37.5%)	44/121 (36%)	7/15 (47%)	0.573
Unmutated	85/136 (63.5%)	77/121 (64%)	8/15 (53%)	
***TP53* disruptions, N pts (%)**				
Yes	63/179 (35%)	55/159 (35%)	8/20 (40%)	0.628
No	116/179 (65%)	104/159 (6%)	12/20 (60%)	
RAI STAGE, N pts (%)				
0	23/166 (14%)	23/147 (16%)	0/19 (0%)	0.111
I	21/166 (13%)	18/147 (12%)	3/19 (16%)	
II	65/166 (39%)	58/147 (40%)	7/19 (37%)	
III	31/166 (19%)	24/147 (16%)	7/19 (37%)	
IV	26/166 (16%)	24/147 (16%)	2/19 (10%)	
ECOG, N pts (%)				
0	42/76 (55%)	30/56 (54%)	12/20 (60%)	0.79
1-3	34/76 (45%)	26/56 (46%)	8/20 (40%)	
CIRS SCORE, N pts Mean ± SD	N=79 4.35 ± 2.76 Range: 0 -11	N = 59 4.25 ± 2.93 Range: 0-11	N = 20 4.65 ± 2.25 Range: 0- 9	0.45
Prior Hystory Arrythmia, N pts (%)				
Yes	9/79 (11%)	4/59 (7%)	5/20 (25%)	0.041
No	70/79 (89%)	55/59 (93%)	15/20 (75%)	
Valvular Disease, N pts (%)				
Yes	12/77 (16%)	9/57 (16%)	3/20 (15%)	>0.999
No	65/77 (84%)	48/57 (84%)	17/20 (85%)	
Hypertension, N pts (%)				
Yes	36/77 (47%)	26/57 (46%)	10/20 (50%)	0.798
No	41/77 (53%)	31/57 (54%)	10/20 (50%)	
Hemorrhage, N pts (%)				
Yes	17/79 (22%)	12/59 (20%)	5/20 (25%)	0.755
No	62/79 (78%)	47/59 (80%)	15/20 (75%)	
Infections, N pts (%)				
Yes	22/179 (12%)	18/159 (11%)	4/20 (20%)	0.278
No	157/179 (88%)	141/159 (89%)	16/20 (80%)	
Definitive IBR discontinuation, N pts (%)				
Yes	76/179 (42.46%)	65/159 (40.88%)	11/20 (55.0%)	0.241
No	103/179 (57.54%)	94/159 (59.12%)	9/20 (45.0%)	
Secondary malignancies, N pts (%)				
Yes	18/ 78 (23%)	15/58 (26%)	3/20 (15%)	0.376
No	60/ 78 (77%)	43/58 (74%)	17/20 (85%)	

AF: atrial fibrillation IBR: Ibrutinib; N: number; pts: patients

RESULTS (II)





The CI of AF was 4% and 9% at 12 and 24 months, respectively. We found a statistical difference (p=0.01) between patients with or without anemia (7% vs 4% at 12 months; 25% vs 6% at 24 months). In addition, previous arrhythmias negatively impacted on CI of AF (p=0.02).
PFS was 77% at 24 months (median PFS: 53.4 months). EFS was 59% at 24 months (median EFS: 31.3 months).
OS was 86% at 24 months, with not reached at 5 years. AF had no significant impact on OS; however, TD for any cause negatively impacted on OS (75% vs 96% in the no-discontinuation group at 24 months, p<0.0001).
Finally, only discontinuation due to progression had a worse outcome, while discontinuation due to toxicity had a similar outcome to the continued-therapy group. Main causes of death were progression (n°10), RT (n°9), infection (n°9), and COVID-19 (n°6).

CONCLUSIONS

Our real-world data show that CLL patients treated with ibrutinib have outcomes similar to those seen in clinical trials when consistently treated according to guidelines, resulting in fewer unnecessary treatment discontinuations with minimal impact on treatment armamentarium.
The risk of AF, reaching its maximum effect during long-term FU, is likely a class effect of BTKi, but AF does not per se affect the outcome of patients treated with ibrutinib.

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