A comparative analysis of treatment-emergent cardiovascular events among patients with chronic lymphocytic leukemia treated with Bruton's tyrosine kinase inhibitors –a single-centre real-world analysis

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Introduction: Bruton's tyrosine kinase inhibitors (BTKi) have revolutionized the management of chronic lymphocytic leukemia (CLL), offering effective chemotherapy-free options across different treatment settings[1]. However, first-generation BTKi ibrutinib is associated with increased cardiovascular toxicity, particularly atrial fibrillation and hypertension[1-3]. Second-generation BTKi acalabrutinib and zanubrutinib were developed to enhance selectivity and reduce occurrence of these events, which has been confirmed in both clinical trials and recent real-world analyses[2-4]. Our aim was to compare the incidence of treatment-emergent arterial hypertension and atrial fibrillation among patients with CLL treated with first- versus second-generation BTKi.

Patients and Methods: We retrospectively analyzed 30 adult CLL patients treated with BTKi in our Hematology Department between December 2017 and December 2024. Seventeen patients received ibrutinib and thirteen patients a second-generation BTKi (acalabrutinib or zanubrutinib). Clinical data, including demographics and cardiovascular comorbidities were collected from electronic medical records. Hypertension and atrial fibrillation were defined and graded according to *CTCAE* v5.0. Baseline hypertension was defined as a previously known condition or ongoing therapy; *de novo* cases and worsening events were identified during treatment.

TABLE 1. Baseline characteristics and treatment-emergent cardiovascular events in patients with chronic lymphocytic leukemia treated with first- and second-generation Bruton's tyrosine kinase inhibitors.

Baseline characteristics	All patients (N=30)	First-generation BTKi (ibrutinib) (n=17)	Second-generation BTKi (acalabrutinib / zanubrutinib) (n=13)
Demographics			
Gender M/F	16 (53%) / 14 (47%)	10 (59%) / 7 (41%)	6 (46%) / 7 (54%)
Age (median/range)	73 / 56-88 y	72 / 56-83 y	75 / 59-88 y
Clinical characteristics			
Hypertension at baseline, n (%)	18 (60%)	10 (59%)	8 (62%)
-De novo hypertension during therapy, n (%)	4 (13%)	3 (18%)	1 (8%)
- Worsening hypertension, n (%)	2 (7%)	1 (6%)	1 (8%)
Atrial fibrillation at baseline, n (%)	0 (0%)	0 (0%)	0 (0%)
- De novo atrial fibrillation, n (%)	4 (13%)	3 (18%)	1 (8%)

Values are presented as number (percentage) or median (range), as appropriate. Baseline hypertension and baseline atrial fibrillation denote previously known diagnoses or ongoing therapy at BTKi initiation. De novo hypertension and de novo atrial fibrillation refer to new-onset events occurring during BTKi therapy in patients without these conditions at baseline. Worsening hypertension was defined as an increase of ≥ 1 CTCAE v5.0 grade or the need for intensification of antihypertensive therapy. Abbreviations: BTKi – Bruton's tyrosine kinase inhibitor; AF – atrial fibrillation; CTCAE – Common Terminology Criteria for Adverse Events.

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Results: At treatment initiation, arterial hypertension was present in 59% of patients receiving ibrutinib and in 62% of those treated with second-generation BTKi (**Table 1**). During therapy, de novo hypertension occurred in 18% of ibrutinib-treated patients compared with 8% among those receiving second-generation BTKi, while worsening of pre-existing hypertension was observed in 6% and 8% of patients, respectively. None of the patients had a history of atrial fibrillation at baseline. During treatment, de novo atrial fibrillation developed in 3 patients (18%) on ibrutinib and in 1 patient (8%) receiving second-generation BTKi. Most cardiovascular events were grade 1–2 and managed with standard therapy without permanent discontinuation of BTKi treatment.

Conclusion: In this single-centre real-world analysis, cardiovascular adverse events, particularly hypertension and atrial fibrillation, were more frequent in patients treated with ibrutinib compared to those receiving second-generation BTKi. These findings support previous evidence suggesting a more favorable cardiovascular safety profile of acalabrutinib and zanubrutinib, emphasizing the importance of systematic cardiovascular monitoring and multidisciplinary collaboration between hematologists and cardiologists during BTKi therapy.

LITERATURE

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