RESEARCH LETTER

blood advances

TO THE EDITOR:

Ibrutinib in patients over 80 years old with CLL: a multicenter Italian cohort

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Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in Western countries, with an incidence increasing to 30/100 000 per years at an age of >80 years. According to recent International Workshop on Chronic Lymphocytic Leukemia guidelines, symptomatic/active disease requires therapeutic interventions aiming to improve overall survival (OS).[1] Ibrutinib is a first-in-class Bruton tyrosine kinase inhibitor (BTKi) that has changed the treatment paradigm of both treatment-naïve (TN) and relapsed/refractory (R/R) patients.[2] This therapeutic option has high rates of responses but also a not neglectable toxicity in the published clinical trials with accurately selected candidate patients.[3-5] Few real-world studies regarding patients treated with ibrutinib are available, integrating the information reported by trials, although not focused on patients that are over 80.[6-10] We aimed to retrospectively evaluate ibrutinib in a cohort of older patients with TN or R/R CLL to retrieve real-world information for safety and effectiveness of the drug.

We performed a multicenter, national study enrolling 60 consecutive patients diagnosed with TN or R/R CLL who were ≥80 years old, with a median age of 81 years (range, 80-87 years) at ibrutinib start. Patients starting ibrutinib in label from January 2014 to March 2021 were enrolled from 6 Italian sites (Table 1). Second-generation BTKis were not available as compassionate use or in clinical trials. The median observation period was 27 months, with a maximum of 87.7 months. The study was approved by the Istituto di Ricerca e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico and was conducted according to the Declaration of Helsinki.

A total of 13 patients (21.7%) achieved nodal complete response (CR; bone marrow evaluation not performed), 40 (66.7%) achieved partial response (PR; 88.3% overall response rate), and 7 (11.6%) achieved stable disease (SD). Discontinuation because of progressive disease (PD) occurred mostly in R/R patients and in 1 TN patient, whereas discontinuation because of toxicity occurred in 8 R/R patients and 6 TN patients. Median progression-free survival (PFS) was 51.8 months (95% confidence interval [CI]: 47.4-56.2), and median OS was 53.2 months (95% CI: 43.3-63.0), as most patients died after PD. Patients achieving a response during ibrutinib experienced a prolonged PFS compared with patients achieving SD ($P < .0001$).

A median PFS of 69.7 months (95% CI: 46.1-93.2) was achieved in patients not experiencing temporary drug withholding (7-30 days), whereas patients who had drug interruptions had a median PFS of 49.7 months (95% CI: 35.4-63.9; $P = .079$); a total of 10 patients (28.6%) among the 35 patients who did not temporarily suspended ibrutinib then permanently discontinued the drug, and among the 25 patients experiencing drug withholdings, 19 patients (76%) discontinued treatment (Figure 1).

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The full-text version of this article contains a data supplement.

Table 1. Patients' and CLL characteristics

Patients' and CLL characteristics	Patients (n = 60)
Median age, y (range)	81 (80-87)
Male, n (%)	33 (55)
Female, n (%)	27 (45)
Total CIRS score > 6, n (%)	46 (76.6)
Preexistent cardiovascular risk factors, n (%)	
Hypertension	38 (63.3)
Diabetes	8 (13.3)
Dyslipidemia	6 (10)
Obesity	6 (10)
Arteriopathy	3 (5)
No known CV risk factors	14 (23.3)
≥2 CV risk factors	14 (23.3)
Concomitant cardioactive therapies, n (%)	
At least 1 cardioactive drug	44 (73.3)
>2 cardioactive drugs	18 (10.8)
Antihypertensive drugs	38 (63.3)
Anticoagulants	3 (5)
Lipid-lowering drugs	10 (16.7)
Antiplatelets drugs	21 (35)
Prior cardiovascular events, n (%)	
Atrial fibrillation	3 (5)
NSTEMI	3 (5)
STEMI	2 (3.3)
Cerebrovascular events	5 (8.3)
Echocardiographic baseline evaluation	
Left ventricular ejection fraction, %	41 (±6.7)
Left atrial diameter, mm	47 (±11.6)
IGHV mutational status, n (%)	
Mutated	24 (40)
Unmutated	32 (53.3)
Not determined	2 (3.3)
Not performed	2 (3.3)
Cytogenetic subgroup, n (%)	
Deletion in 17p	20 (33.3)
Deletion in 11q	12 (20)
Deletion in 13q alone	6 (10)
Trisomy 12	5 (8.3)
No abnormalities	10 (16.7)
Not performed	7 (11.6)
TP53 mutational status, n (%)	
Mutated	19 (31.7)
Unmutated	34 (56.7)
Not performed	7 (11.6)
Anti-infective prophylaxis and vaccinations	
Trimethoprim-sulfamethoxazole	35 (58)
Acyclovir	39 (65)
Vaccination for SARS-CoV-2	40 (66.7)
Seasonal influenza vaccine	38 (63.3)
Pneumococcal vaccine	17 (28.3)
Baseline immunoglobulin mean values	
IgA	1.93 g/L
IgM	1.09 g/L
IgG	11.7 g/L
Precedent therapies	
Treatment naïve patients	20 (33.3)
Relapsed/refractory patients	40 (66.6)
Medium number of previous lines	1 (range, 0-8)
Chlorambucil+rituximab	22 (36.6)
Bendamustine+rituximab	20 (33.3)
Fludarabine-cyclophosphamide+rituximab	6 (10)
Ofatumumab	2 (3.3)
Alemtuzumab	1 (1.6)

IGHV, immunoglobulin heavy chain.

At least 1 adverse event (AE) occurred in 41 patients (68.3%), the most common grade ≥3 AEs being respiratory tract infections (23%) and neutropenia (6%). Nineteen patients (31.6%) experienced a cardiovascular event: 9 patients (15%) had atrial fibrillation (AF), 6 (10%) had hypertension (HTN), 1 (1.6%) had heart failure, and 3 (5%) had acute coronary syndromes. Cumulative incidence of AF and HTN was 9% and 6%, respectively, at 6 months, 13% and 10% at 12 months, and 16% for both at 24 months, with a median time to AF of 6.6 months and to HTN of 6.7 months. AF and HTN were grade 2 in all patients. All patients with AF received anticoagulation, and no thrombotic strokes occurred. Hemorrhagic diathesis (grade ≤ 2) occurred in 4 patients, with no major bleedings. OS did not differ between patients experiencing or not experiencing AF during treatment ($P = .39$).

Five patients developing HTN had a worsening of previous diagnosed HTN. No increased incidence of cardiovascular events was found among patients with previous cardiovascular events ($P = .86$) and with preexisting cardiovascular risk factors ($P = .76$).

Mean left atrial (LA) diameter at baseline was 45.1 ± 10.9 mm in patients who did not develop AF and 55.0 ± 12.1 mm in patients developing AF, showing that a higher basal LA diameter could predict AF occurrence with a suggestive P value ($P = .09$).

A total of 20 patients (33.3%) developed infections, with a total of 23 events (9 grade 2 events, other events grade ≥ 3). Thirteen events involved the respiratory tract. Fifteen patients transiently suspended ibrutinib (7-30 days), 3 patients permanently discontinued ibrutinib because of pulmonary infectious events, and 2 of these died after ≥6 months of treatment.

Infections mostly occurred during the first 12 months of therapy (13 events, 56.5%) and were not statistically increased in patients with baseline immunoglobulin A (IgA) values <70 mg/dL ($P = .39$). On ibrutinib, IgA levels significantly increased, both from T0 to T12 ($P = .02$) and from T0 to T36 ($P = .03$). Regarding infectious risk,

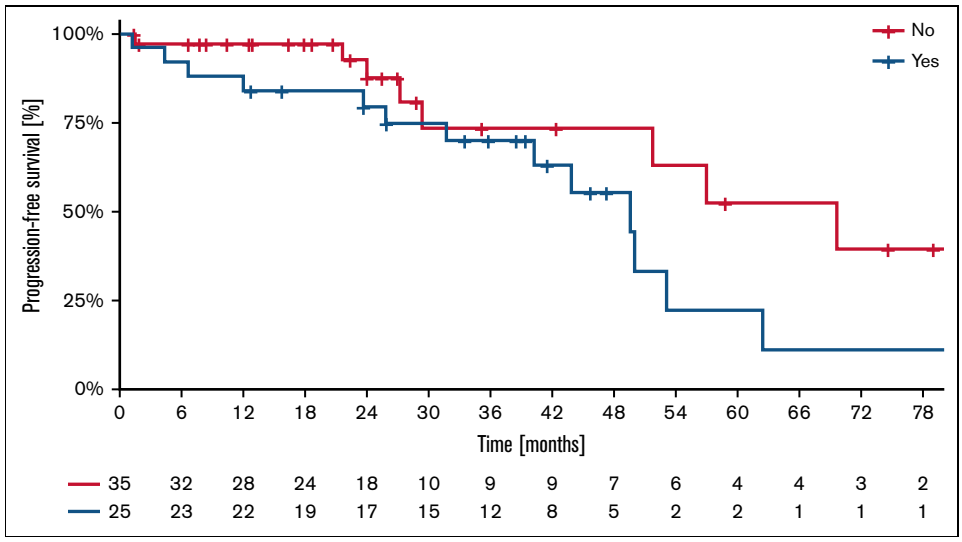

Figure 1. PFS according to ibrutinib temporary withdrawal (yes, more than 7 consecutive days and less than 30 days; no, no drug suspension). $P = .079$.

no correlation emerged with Rai staging ($P = .49$), immunoglobulin heavy chain status ($P = .57$), or number of previous therapies ($P = .38$); fluorescence in situ hybridization positivity for del(17p) was associated with a higher infectious rate ($P = .05$).

Hematologic toxicity grade 3 to 4 was reported in 6 patients: 4 nonfebrile neutropenia, 1 anemia, and 2 patients with both. Drug was suspended (<30 days) in 2 patients with grade 4 neutropenia.

Bleeding occurred in 22 patients (36.6%): grade 2 in 15 patients, grade 1 in 6, and grade 3 in 1. Ibrutinib was temporarily withheld in 5 patients and permanently discontinued in 2 patients. Median time to hemorrhagic events was 24 months, with a cumulative incidence of 20% at 6 months, 27% at 12 months, and 33% at 24 months. Ten patients were chronically taking antiplatelet therapy, 5 patients were anticoagulated, and 2 patients were taking both antiplatelet agents and anticoagulants. A not significantly higher hemorrhagic diathesis emerged among patients chronically assuming anticoagulants (45%) or antiplatelet drugs (43%) compared with patients not assuming anticoagulants (35%) or antiplatelet therapy (36%).

Second malignancies were reported after CLL diagnosis in 5 patients (bladder cancer, breast cancer, lung adenocarcinoma, 2 skin squamocellular carcinoma).

Temporary drug withdrawal (7-30 days) occurred in 25 patients (41.6%), predominantly for infections and cardiovascular events (15 and 5 patients), 3 (5%) for hemorrhagic diathesis, and 3 and 2 (3.3%) for hematologic toxicity. Two patients (3.3%) had to reduce ibrutinib dosage within the first year of therapy because of neutropenia and hemorrhagic events. Ibrutinib was permanently discontinued in 24 patients (40%): 10 patients for PD, 2 for hemorrhagic diathesis, 4 for infections, 3 for cardiac failure, 2 for sudden cardiac death, and 3 for second malignancy.

This study is, to our knowledge, the largest real-world study investigating outcomes of older patients with CLL. The achievement of response was the only factor affecting PFS; no difference in PFS emerged regarding TP53 dysfunction either because of the shortness of follow-up or the unselected population (TN vs R/R).

The safety profile remains consistent with previous literature data, and no unexpected AEs were noted in this older cohort.[11-13] The main reason for treatment discontinuation was PD rather than drug-related toxicity, indicating that knowledge of potential AEs and expert clinical management could aid in reducing the chances of discontinuation for toxicities to other effective therapeutic chances. Handling AEs to keep patients on treatment is of crucial importance as therapy interruptions could negatively impact on PFS.[14]

Incidence of cardiovascular events in our cohort is substantially similar to literature data regarding younger patients, perhaps reflecting both the inclusion of a more comorbid population and the high number of patients treated with antiarrhitmic and antihypertensive medications.[15,16]

No relationship emerged between concomitant cardiovascular risk factors or previous events and the development of HTN or AF, probably because of the higher prevalence of cardiovascular risk factors in these patients. Concern remains that risk of severe cardiotoxicity and cardiovascular deaths could be higher in patients with significant cardiac disease, as ibrutinib is an arrhythmogenic molecule.[16-18]

Echocardiographic LA measurement could serve as a widespread and low-cost procedure to identify patients at higher risk of developing AF.[19-21] The incidence of major hemorrhage was low, although frequency of low-grade bleedings was high, including numerous patients on antiplatelets and/or anticoagulation. The infection rate was similar to clinical trials and decreased over time, possibly because of a partial reconstitution of the immune system.[22-25]

Ibrutinib represents an attractive therapeutic choice in patients with advanced age and comorbidities; identification of prognostic markers to predict the risk of AEs could reduce frequency and severity of iatrogenic toxicities.

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