

Scientific Letters**Cardiovascular Risk Reduction and Ibrutinib Dose Optimization in Chronic Lymphocytic Leukemia: A Real-World Experience****Keywords:** Ibrutinib; Chronic lymphocytic leukemia; Real-world clinical practice; Dose reduction; Side effects.**Published:** November 01, 2026**Received:** September 18, 2026**Accepted:** October 22, 2026**Citation:** Laureana R., Niscola P., Morgagni R., Giannarelli D., Postorino M., Pupo L., Del Principe M.I. Cardiovascular risk reduction and ibrutinib dose optimization in chronic lymphocytic leukemia: a real-world experience. *Mediterr J Hematol Infect Dis* 2026, 18(1): e2026090, DOI: <http://dx.doi.org/10.4084/MJHID.2026.090>

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To the Editor.

Bruton tyrosine kinase (BTK) inhibitors have changed the treatment of chronic lymphocytic leukemia (CLL).¹ The first-in-class agent ibrutinib has exhibited promising results in progression-free survival (PFS) and overall survival (OS) in both treatment-naïve (TN) and relapsed/refractory (R/R) settings.^{1,2} Despite pivotal Phase III trial results demonstrating long-lasting response with manageable toxicity,²⁻⁴ real-world evidence suggests higher rates of AEs, DR, and treatment discontinuation, likely due to the older age of the non-selected population and more comorbidities and polypharmacy.⁵⁻⁸ Patients with CLL have a high baseline CV risk. Nearly one-third of them demonstrate the presence of CV comorbidities at diagnosis, and more than a quarter develop a CV event within five years after treatment initiation. This link is mainly explained by a similar systemic pro-inflammatory background, in which inflammatory mediators cause endothelial dysfunction and promote atherosclerosis.⁴ Therapeutic use of BTK inhibitors represents another level of cardiotoxicity, leading to an increased CV risk profile above the age-matched control group.⁴ On the practical level, it manifests itself as increased burden of AEs with prevalence of atrial fibrillation (10-20%) and development of new-onset or progressive hypertension. As a result, optimal BTK inhibition requires a detailed baseline risk assessment, individual drug selection, and coordinated management. In the current clinical setting, managing cardiotoxicity is challenging because treatment interruption is always associated with poor prognosis,^{10,11} but the effect of dose reduction (DR) on disease outcome is unknown. In this regard, pharmacodynamic and pharmacokinetic research showed that BTK occupancy remains > 95% after ibrutinib dose reduction (DR),¹²⁻¹⁴ making it possible to provide individualized therapy without impairing efficacy or increasing the likelihood of AE

development. This observation and retrospective study involving only one center was approved by the Ethics Committee of the institution with approval number 205.24 CET2 PTV. A total of 100 adult patients with CLL were included in the study; all received ibrutinib at the Hematology Unit of Policlinico Tor Vergata, Rome, Italy, from January 2016 to December 2022. We gathered the following data: demographic features, Rai and Binet stage, genetic and molecular markers (IGHV, FISH abnormalities [del(11q), del(13q), del(17p), trisomy 12], TP53 and NOTCH1 mutations), comorbidities, cardiovascular risk, and previous therapies for patients receiving or not receiving ibrutinib DR (**Tables 1 and 2**). Patients were classified according to the dose strategy adopted: the Standard Dose (SD) group, including all patients who continued treatment with the standard ibrutinib dose of 420 mg per day; and the DR group, including patients who experienced a DR to 280 mg or 140 mg daily due to the first incidence of an AE, a label-based indication (e.g., concomitant CYP3A inhibitors, hepatic dysfunction), or a reduced starting dose at the physician's discretion. Responses were evaluated according to the iwCLL guidelines.¹⁴ Complete remission (CR) was defined as the resolution of clinical disease manifestations, normalization of peripheral blood counts, and a negative bone marrow evaluation. The primary endpoint was PFS; the other secondary endpoints were TTNT, OS, and development of new AEs after DR. A time-dependent covariate was applied to eliminate immortal time bias. The study had 64% males and 36% females, with a median age of 64 years (IQR 57-70). Of these patients, 44 used ibrutinib as first-line treatment, while 56 used it in the R/R setting. The median age of ibrutinib initiation was 69 years (46-86). CV risk stratification using SCORE2 and SCORE2-OP, recommended by the ESC guidelines for global cardiovascular risk stratification in primary prevention,

Table 1. Baseline Clinical and Biological Characteristics of Patients.

Summary of patients' characteristics			
AGE	64 (57-70) (41-85)	FISH	
Men	64 (64.0)	Normal	22 (22.0)
Female	36 (36.0)	Del11	15 (15.0)
BINET A	5 (5.0)	Del13	39 (39.0)
BINET B	66 (66.0)	Del17	19 (19.0)
BINETC	29 (29.0)	Tris12	21 (21.0)
IGHVM	22 (22.0)	TP53 no mutation	80 (80.0)
IGHVUM	78(78.0)	TP 53 mutation	20 (20.0)

Abbreviations: FISH: Fluorescence In Situ Hybridization; IGHVM: Immunoglobulin Heavy Chain Variable region Mutated; IGHVUM: Immunoglobulin Heavy Chain Variable region Unmutated; TP53: Tumor Protein p53.

Table 2. Patient Comorbidity Profile.

Summary of patients' comorbidity	
Smoke	38 (38.0)
Diabetes	34 (34.0)
Hypercholesterolemia	28 (28.0)
Previous AMI/ACS	2 (2.0)
PAD	17 (17.0)
CKD	9 (9.0)
Previous AF	3 (3.0)
Hypertension	45(45)

Abbreviations: ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation; AMI: Acute Myocardial Infarction; CKD: Chronic Kidney Disease; PAD: Peripheral Arterial Disease.

predicts 10-year fatal and non-fatal cardiovascular outcomes in European populations. SCORE2-OP is a validated risk tool specific to those older than 70 years. These algorithms enable clinicians to move beyond mortality-only estimates and make better-informed, evidence-based therapeutic decisions across all adult patient populations. In our study population, these models identified 44% of patients as low risk, 13% as moderate risk, 14% as high risk, and 29% as very high risk. Twenty-three percent of patients were on anticoagulant or antiplatelet therapy. We started 85 patients on ibrutinib 420 mg, and 15 on reduced doses (280 mg in 13; 140 mg in 2). The overall response rate was 99% (71% CR, 28% partial response), with one patient showing progressive disease as the best response. The median duration of best response was 10.6 months. DR occurred in 43% (n=43) patients, with a median duration of 10 months (range 3.1-32.9). The main reasons for DR included dose reduction from 420 mg to 280 mg in 36 cases and to 140 mg in 7 patients. The main reasons for DR included atrial fibrillation, neutropenia, recurrent infections, and bleeding. After DR, 60% achieved CR, and 40% achieved PR. A second DR was required in 25.5% of cases, with a median

interval of 9.7 months between the first and second DR. TTI was observed in 29% of cases, with a median period of 61 days (IQR 19-178). This was due to infection (SARS-CoV-2), atrial fibrillation, hemorrhage, surgical procedure, and secondary cancer. Twenty-four patients remained on a lower dose. Five-year progression-free survival (PFS) was 73.3% and 88.8% in the SD and DR groups, respectively (log-rank $p=0.98$). Five-year TTNT was 73.4% versus 88.1% ($p=0.055$), and five-year OS was 92.8% versus 88.1% ($p=0.84$) (**Table 3**). Biological characteristics, disease stage, and performance status did not differ markedly between groups and did not influence PFS, TTNT, or OS. Among those who required DR due to AEs, 25.5% needed another DR, and 31% did so because of recurrence of the same AE. Given the median time to first DR was approximately 10 months, a landmark analysis at 12 months was performed. The 5-year PFS was 66.6% in the early DR group (<12 months) and 63.8% in the other group ($p=0.45$). The 5-year TTNT was 66.7% versus 83.3% ($p=0.22$). Nonetheless, OS was lower in the early DR group and the lower starting-dose groups (62.5% vs. 82.8%, $p=0.41$). This highlights the importance of addressing early toxicity. In the first year of treatment, tumor burden is high, and the lymph node microenvironment supports CLL cell survival and proliferation. Mechanistically, ibrutinib inhibits BCR signaling and chemokine pathways (such as CXCR4/CXCL12), disrupting integrin-based adhesion between CLL cells and the lymph node microenvironment and stromal matrix. This results in CLL cell egress into the peripheral blood. Keeping the full ibrutinib dose (420 mg/day) for the first 12 months is necessary for kinase inhibition because early DR leads to poor lymph node clearance, making it hard to achieve high cytokinesis due to the survival of CLL clones in the protective sites. After the first 12 months, low-dose ibrutinib can maintain >95% BTK occupancy. As such, reducing the incidence of DRs in the first 12 months requires an initial risk assessment of CV, bleeding, and infection risk factors. These results align with prior real-world evidence showing no loss of disease control with clinically guided DR. In contrast to treatment interruptions, which are associated with negative outcomes, DR is a safer toxicity-management strategy that enables continuous BTK inhibition.¹⁶⁻¹⁹ Mechanistically, near-complete BTK occupancy at low doses supports this biological concept. Clinical flexibility of dosing may be especially important in elderly and comorbid patients, including most of the real-world CLL population, who usually develop CV complications, cytopenias, and drug-drug interactions requiring dose adaptations. This study includes an 84-month follow-up period, longer than the control trial⁴ and other observational studies.¹⁶ Time-dependent analysis has been used to solve the problem of immortal

Table 3. Survival Outcomes by Dose Group.

PFS	3 years	5 years
Standard Dose	83.2 (71.6-94.8)	73.3 (58.6-88.0)
Reduced Dose	98.1 (94.4-100)	88.8 (75.9-100)
TTNT	3 years	5 years
Standard Dose	83.3 (71.9-94.7)	73.4 (58.7-88.1)
Reduced Dose	98.1 (94.4-100)	88.1 (74.4-100)
OS	3 years	5 years
Standard Dose	95.7 (89.8-100)	92.8 (84.8-100)
Reduced Dose	98.1 (94.4-100)	88.1 (74.4-100)

Abbreviations: OS: Overall Survival; PFS: Progression-Free Survival; TTNT: Time to Next Treatment

time bias. However, this study has weaknesses, including its retrospective design, single-center setting, small sample size, and potential confounders. Doses and treatment interruptions were more frequent than in clinical trials. Nevertheless, toxicity-based ibrutinib dose modifications did not adversely affect PFS, TTNT, or OS, supporting the safety of dose modification. A distinguishing feature of this study is applying the recently introduced SCORE2/SCORE2-OP risk stratification criteria to identify latent cardiovascular complications in CLL patients receiving BTK inhibitors.^{4,15} Notably, high-risk patients had an adverse-event rate comparable to the overall population. Dose adjustment successfully lowers the risk of cardiotoxicity and bleeding. Using SCORE2/SCORE2-OP risk assessment at baseline enables cardio-oncology care to be proactively provided to every patient. Following all current cardiology guidelines, a comprehensive baseline cardio-oncological evaluation enables effective cardiovascular risk reduction. Specifically, early optimization of a high cardiovascular risk profile through strict blood pressure control, lipid management, glycemic control, weight control, and habit changes might help to prevent ibrutinib-induced cardiotoxicity. Consultation with cardio-oncologists should be considered initially in high- and very high-risk patients, in patients with prior cardiovascular history or uncontrolled hypertension, and in patients on anticoagulation. The oncology and CV AE results were similar in the group at risk of CV problems and in the overall group, supporting the efficacy of the dose-optimization strategy for cardiotoxicity and bleeding

prevention. A prompt medical evaluation is recommended during treatment in case of new grade 3 or higher arrhythmia, hypertension, or heart failure. Combining a cardio-oncological perspective and toxicity-driven adjustments of the drug dose allows us to implement a multidisciplinary approach and provide continuous treatment without jeopardizing the cancer treatment. Unlike other real-world studies, the current research provides a thorough analysis of factors associated with secondary dose changes and treatment cessation. One key aspect of this analysis is evaluating the need for additional dose changes. Among patients initially requiring dose adjustments, 25.5% needed a secondary dose change, with a median time of 9.7 months and about one-third of cases representing recurrence of the initial AE. This result proves the existence of recurrent, non-dose-dependent cumulative cardiotoxicity from ibrutinib in some patients owing to drug hypersensitivity. Stepwise dose reduction to 140 mg/day instead of complete drug discontinuation allows the management of recurrent toxicities while keeping BTK occupancy (>95%) and disease control in sensitive patients. Targeted secondary dose reductions do not require other interventions, including those related to other diseases, even in patients with severe CV comorbidities.¹⁷ NCCN guidelines recommend dosing to overcome intolerance and to guarantee efficacy (20). Such an approach assists in overcoming drug intolerance and preserving consistent treatment. However, although BTK inhibitors play an important role in treating CLL/SLL, dose adjustments are often necessary because of age-related comorbidities and poly-pharmacotherapies. In this single-center experience, dose modifications for toxicity were noted in 43% of the cohort, with no effect on efficacy or survival. A very good response rate was seen among patients (99% ORR, 71% CR), with no difference between the five-year PFS rates of standard dose (73.3%) and dose reduction (88.8%; $p = 0.98$), despite their high genomic risk and higher cardiovascular risk by SCORE2/SCORE2-OP. These pharmacodynamic data support optimizing ibrutinib dosing to avoid adverse effects without compromising therapy. Conclusion. Given the long-term real-world data, optimizing ibrutinib dosing in patients with chronic lymphocytic leukemia is a safe and effective precision medicine strategy. Although the first dose is crucial in disease management, dose optimization helps avoid toxicity.

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