Cardiovascular and Infectious Toxicities Associated with Targeted Therapies in Chronic Lymphocytic Leukemia: A Systematic Review and Meta-Analysis

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1 Context

Targeted therapies have transformed the management of chronic lymphocytic leukemia (CLL); however, cardiovascular and infectious toxicities remain key determinants of treatment adherence and long-term outcomes. Comprehensive pooled estimates of these adverse events across therapeutic classes are limited, making it difficult for clinicians to counsel patients on comparative safety. As BTK and BCL-2-directed therapies increasingly replace chemoimmunotherapy as first-line treatment, characterizing their toxicity burden has become essential for informed treatment selection.

2 Objective

To quantify the incidence of major cardiovascular and infectious toxicities associated with Bruton's tyrosine kinase (BTK) and BCL-2-directed therapies in CLL, and to compare toxicity burden between these two therapeutic classes to inform individualized treatment selection.

3 Design

A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed, Embase, Web of Science, and Cochrane Library databases were searched from 2014 through March 2026. Random-effects models pooled incidence proportions (95% CIs) for atrial fibrillation, hypertension, bleeding, infection, and infection-related mortality, with heterogeneity assessed using I^2 statistics and subgroup analyses comparing BTK and BCL-2-directed therapies.

4 Setting

Multicenter phase II–III trials and real-world cohorts evaluating targeted agents in CLL, capturing both controlled trial populations and routine clinical practice.

5 Participants

Thirty studies including 12,486 patients who received BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib) or BCL-2 inhibitor regimens (venetoclax ± anti-CD20 antibody), spanning both treatment-naive and relapsed/refractory CLL populations.

6 Interventions

Targeted monotherapy or combination regimens delivered continuously or for fixed duration, reflecting the range of dosing strategies used in contemporary CLL management.

7 Main Outcome Measures

Incidence of cardiovascular and infectious adverse events, including atrial fibrillation, hypertension, major bleeding, infection, grade ≥3 infection, and infection-related mortality.

Results

BTK or BCL-2 Inhibitor Therapy → Cardiovascular & Infection Monitoring → Adverse Event Pooling → **Class-Specific Toxicity Profile**

45.8%
overall infection incidence across targeted CLL therapies (95% CI 40–51)

9.2%
pooled incidence of atrial fibrillation (95% CI 7.7–10.9; I^2=48)

17.9%
grade ≥3 infections across included studies (95% CI 14–21)

- Across 30 studies including 12,486 patients, atrial fibrillation occurred in 9.2% and hypertension in 17.3% of patients receiving targeted CLL therapy.
- Major bleeding occurred in 4.5% of patients, while infections occurred in 45.8%, with grade ≥3 infections in 17.9%.
- Infection-related mortality was 2.1%, underscoring the clinical significance of infectious complications.
- Infections were significantly more frequent with BTK inhibitors than BCL-2-directed therapies (p = 0.03).
- Sensitivity analyses confirmed the robustness of these findings, with no evidence of publication bias.
- These findings suggest that toxicity profile, not just efficacy, should guide the choice between BTK and BCL-2-directed therapy.

Conclusions

Cardiovascular and infectious toxicities are common in CLL patients receiving targeted therapy, particularly BTK inhibitors. The higher adverse event burden with BTK inhibitors likely reflects off-target kinase inhibition, platelet and PI3K pathway effects, and associated immune dysregulation predisposing to atrial arrhythmias and infection.

These findings underscore the need for vigilant cardiovascular monitoring, infection prophylaxis, and tailored therapy selection to optimize long-term tolerability.

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References: 1. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. 2. Individual study references included in this meta-analysis are available upon request from the corresponding author.