Hematologic Toxicity and Treatment Discontinuation With Venetoclax-Based Regimens in Chronic Lymphocytic Leukemia: A Systematic Review and Meta-Analysis of Randomized Trials

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INTRODUCTION

- Venetoclax-based regimens have become a standard treatment option for patients with chronic lymphocytic leukemia (CLL) in both frontline and relapsed/refractory settings, providing durable disease control with fixed-duration therapy.
- Although venetoclax has demonstrated substantial clinical benefit, concerns remain regarding treatment-related hematologic toxicity and overall tolerability.
- Individual randomized trials have reported variable rates of severe adverse events and treatment discontinuation, making it difficult to define the overall safety profile of venetoclax-based therapy.
- To date, these safety outcomes have not been comprehensively synthesized across randomized clinical trials.
- **Objective:** To systematically evaluate hematologic toxicity and treatment discontinuation associated with venetoclax-based regimens in patients with CLL.

AIM

To systematically evaluate hematologic toxicity and treatment discontinuation associated with venetoclax-based regimens compared with non-venetoclax control regimens in patients with chronic lymphocytic leukemia using evidence from randomized clinical trials.

METHOD

- A systematic literature search was conducted using PubMed, Embase, Cochrane CENTRAL, and major hematology conference proceedings (ASH, EHA, and SOHO) to identify randomized clinical trials evaluating venetoclax-based regimens in patients with chronic lymphocytic leukemia (CLL).
- Eligible studies compared venetoclax-containing regimens with non-venetoclax control regimens in either frontline or relapsed/refractory CLL.
- The primary outcome was treatment discontinuation due to adverse events (AEs). Secondary outcomes included grade ≥3 adverse events, grade ≥3 neutropenia, and grade ≥3 infections.
- Study selection, data extraction, and quality assessment were performed independently by two reviewers according to PRISMA 2020 guidelines.
- Random-effects meta-analyses were performed using pooled odds ratios (ORs) with 95% confidence intervals (CIs) in R (meta package). Statistical heterogeneity was assessed using the I^2 statistic.

CONCLUSIONS

- Venetoclax-based regimens were associated with a significantly higher risk of grade ≥3 adverse events and grade ≥3 neutropenia compared with non-venetoclax control regimens.
- Despite increased hematologic toxicity, venetoclax-based therapy did not significantly increase treatment discontinuation due to adverse events or the risk of grade ≥3 infections.
- These findings support the overall tolerability of venetoclax-based regimens while highlighting the importance of proactive hematologic monitoring and supportive care.
- Additional studies with longer follow-up are warranted to further define the long-term safety profile of venetoclax-based treatment strategies in CLL.

RESULTS

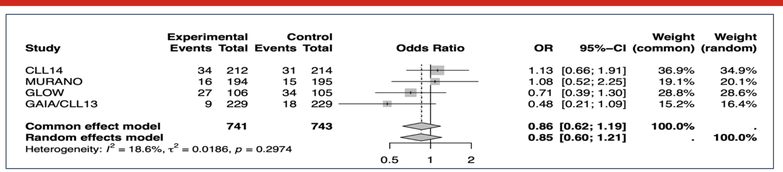


Figure 1. Random-effects meta-analysis of treatment discontinuation due to adverse events. Venetoclax-based regimens were not associated with a significant increase in treatment discontinuation compared with control regimens.

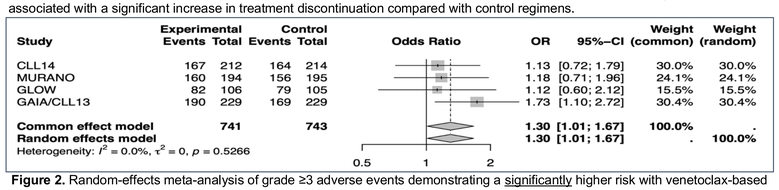


Figure 2. Random-effects meta-analysis of grade ≥3 adverse events demonstrating a significantly higher risk with venetoclax-based regimens.

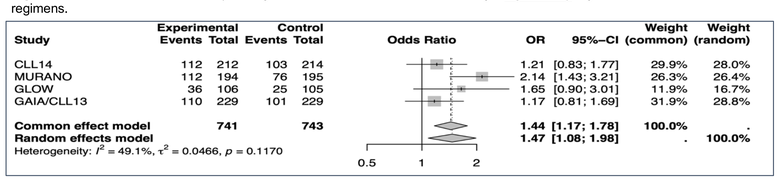


Figure 3. Random-effects meta-analysis of grade ≥3 neutropenia. Venetoclax-based regimens were associated with a significantly

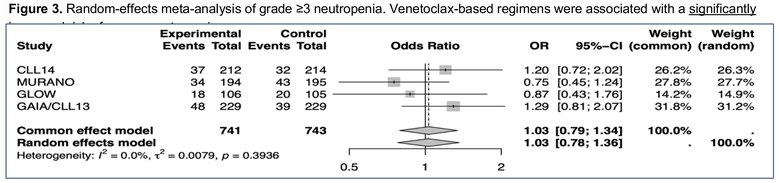


Figure 4. Random-effects meta-analysis of grade ≥3 infections showing no significant difference between venetoclax-based and comparator regimens.

Trial	Setting	Experimental Arm	Comparator	N
CLL14	Frontline	Venetoclax + Obinutuzumab	Chlorambucil + Obinutuzumab	426
MURANO	Relapsed/Refractory	Venetoclax + Rituximab	Bendamustine + Rituximab	389
GLOW	Frontline	Ibrutinib + Venetoclax	Chlorambucil + Obinutuzumab	211
GAIA/CLL13	Frontline	Venetoclax + Obinutuzumab	Chemoimmunotherapy	458

Table 1. Characteristics of Randomized Clinical Trials Included in the Meta-Analysis

Abbreviations: CLL, chronic lymphocytic leukemia; Ven, venetoclax; Obi, obinutuzumab; BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; Clb, chlorambucil.

KEY FINDINGS

✓ **1,484 patients** from **4 randomized phase III trials** were included.

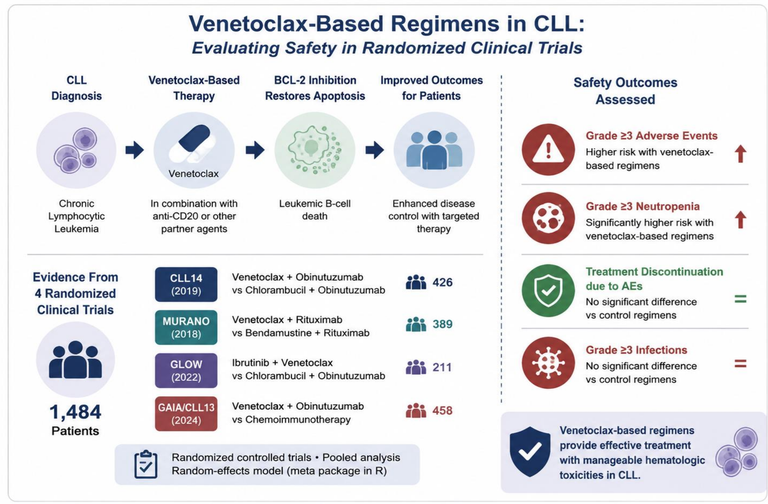
✓ Venetoclax-based regimens significantly increased:

- Grade ≥3 adverse events (OR 1.30, 95% CI 1.01–1.67)
- Grade ≥3 neutropenia (OR 1.47, 95% CI 1.08–1.98)

✓ No significant differences were observed for:

- Treatment discontinuation due to adverse events (OR 0.85, 95% CI 0.60–1.21)
- Grade ≥3 infections (OR 1.03, 95% CI 0.78–1.36)

✓ Low-to-moderate heterogeneity across analyses supported the consistency of pooled findings.



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