EFFICACY AND SAFETY OF IBRUTINIB COMBINED WITH VENETOCLAX IN THE TREATMENT OF RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction

Chronic lymphocytic leukemia (CLL) is a malignant B-cell disorder with poor prognosis in relapsed or refractory (R/R) cases.

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, and Venetoclax, a BCL-2 inhibitor, have shown individual efficacy in CLL. However, their combined therapeutic potential in R/R CLL remains underexplored.

Aim

This meta-analysis aimed to assess the efficacy and safety of ibrutinib and Venetoclax combination therapy in treating R/R CLL.

Historically, both these agents have been reported to have efficacy individually, but their combination has surfaced in recent years as a promising regimen. Our study examined the safety and efficacy of these agents when combined.

Objectives

To determine the efficacy of the combination in terms of progression-free survival rate, clinical remission rate, and undetectable minimal residual disease.

Safety in terms of the development of complications like HTN, diarrhoea, neutropenia, and atrial fibrillation.

Methods

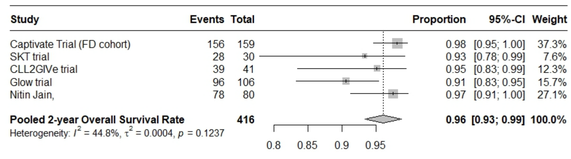
We searched PubMed, Embase, Scopus, and Cochrane databases until April 2025 systematically for relevant studies.

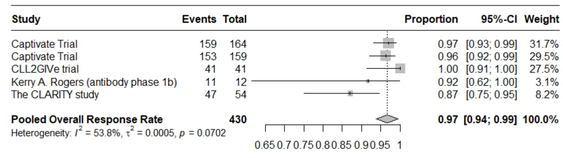
Pooled estimates were calculated using a random-effects model with double arcsine transformation, and heterogeneity was assessed using the I² statistic.

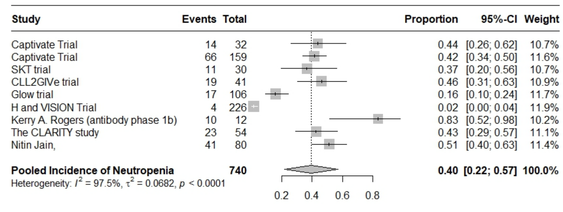
Statistical analyses were performed in R Studio 4.4 using the "meta" package. The quality of the studies was assessed using the MINORS tool.

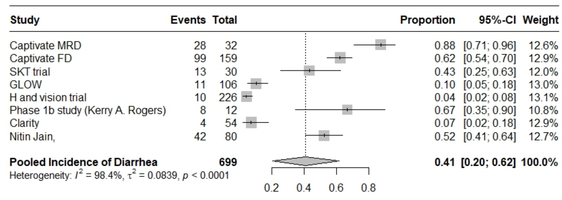
Results

- A total of 9 studies, comprising 872 patients, were included in the meta-analysis.
- The combination of ibrutinib and Venetoclax demonstrated a high pooled 2-year overall survival rate of 96% and a pooled 2-year progression-free survival rate of 92% across the studies.
- The pooled rate for undetectable minimal residual disease (uMRD) in peripheral blood was 67% (95% CI: 52%-82%) and in bone marrow was 61% (95% CI: 47%-74%).
- Regarding safety, neutropenia was observed in 40% (95% CI: 22%-57%) of patients, while hypertension, diarrhea, and atrial fibrillation were seen in 23% (95% CI: 13%-33%), 41% (95% CI: 20%-62%), and 4% (95% CI: 2%-7%), respectively.









Summary & Conclusion

Ibrutinib plus Venetoclax shows high efficacy in relapsed/refractory CLL, with excellent survival and response rates, along with notable undetectable minimal residual disease (uMRD) achievement.

Adverse events such as neutropenia, hypertension, and diarrhea were manageable. These findings support its potential as an effective therapeutic option, though further studies are needed to confirm long-term outcomes.

Discussion

This meta-analysis shows that the combination of ibrutinib and venetoclax is highly effective for relapsed/refractory CLL, with high overall survival (96%), progression-free survival (92%), and response rates (97%). The treatment also achieves significant undetectable minimal residual disease (uMRD) in both blood (67%) and bone marrow (61%).While adverse events like neutropenia, hypertension, and diarrhea were common, they were generally manageable. However, the study's small sample size and heterogeneity limit conclusions, and long-term data are needed to confirm durability and safety. Further trials are necessary to solidify its role in CLL therapy.

Keywords: Ibrutinib, Venetoclax, Chronic Lymphocytic Leukemia