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Efficacy and Safety of Venetoclax + Rituximab in the Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia: Results of Bayesian Network Meta-Analysis

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INTRODUCTION

BACKGROUND

- Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in Western countries, with an incidence rate of 3.9 per 100,000 in 2020 in the US[1]
- CLL primarily affects elderly patients, with a median age at diagnosis of 70 years[1]
- The clinical course of the disease varies from mild and not requiring treatment to aggressive, leading to death within three years of diagnosis[2]
- Relapse and refractoriness are one of the main adverse prognostic factors for a patient's survival[2]
- Venetoclax+rituximab (VEN+RTX) is a potent anti-leukemic therapy for relapsed/refractory CLL, superior to bendamustine+rituximab (BEND+RTX) based on the MURANO trial[3]
- Efficacy and safety of VEN+RTX compared to other than BEND+RTX therapies remain unknown

OBJECTIVE

- The study aimed to compare the efficacy and safety of VEN+RTX with other therapies for relapsed/refractory CLL
- Other therapies included:
  - Chemotherapy:
    e.g., bendamustine (BEND), chlorambucil (CLB)
  - Immunotherapy:
    e.g., ofatumumab (OFA), rituximab (RTX), ublituximab (UBL)
  - B-cell receptor inhibitors:
    e.g., acalabrutinib (ACA), duvelisib (DUV), ibrutinib (IBR), idelalisib (IDE), zanubrutinib (ZAN)

  which were used as monotherapy or in combination with other agents

METHODS

SYSTEMATIC LITERATURE REVIEW

- We performed a systematic search for randomized clinical trials conducted in patients with relapsed/refractory disease who previously received at least one treatment line
- Searched sources included medical databases (MEDLINE, EMBASE, CENTRAL), clinical trials registries (e.g., ClinicalTrials.gov), conference proceedings of hematological and oncological societies (e.g., American Society of Hematology), websites of medicines regulatory authorities (e.g., European Medicines Agency) and health-technology assessment agencies (e.g., National Institute for Health and Care Excellence)
- The last systematic search was performed on August 22, 2022
- The systematic review (CRD42022304330) was performed in agreement with PRISMA guidelines and their extension for network meta-analyses (NMA)[4,5]

NETWORK META-ANALYSIS

- We performed Bayesian NMAs to synthesize direct and indirect evidence for relapsed/refractory CLL
- Data for the longest follow-up from the identified by systematic search studies were used to compare progression-free survival (PFS), overall survival (OS), and serious adverse event (SAE) rate
- All analyses were performed using a fixed model and GeMTC package for R software
- The results of NMA were presented as hazard ratios (HR) or risk ratios (RR) with 95% credible intervals (CrI)

RESULTS

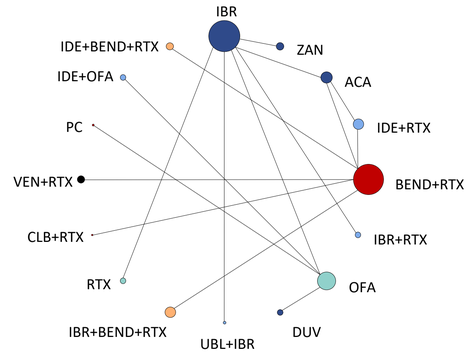

Figure 1. Network plot for trials in relapsed/refractory CLL

SEARCH RESULTS

- The systematic search identified 15 randomized clinical trials for relapsed/refractory CLL, including 4,805 patients (ALPINE[6], ASCEND[7-11], Burger 2019[12], DUO[13,14], ELEVATE-RR[15], GENUINE[16], HELIOS[17-20], Huang 2018[21], MaBLE[22], MURANO[3,23-27], OMB114242[28,29], RESONATE[30-34], Study116[35-38], Study119[39], TUGELA[40]) (Fig. 1)

EFFICACY

- VEN+RTX significantly prolonged PFS compared with:
  - chemoimmunotherapy:
    RTX, OFA, CLB+RTX, and physician's choice
  - regimens based on PI3K inhibitors:
    IDE+OFA, IDE+RTX IDE+BEND+RTX, DUV
- No significant differences were found in PFS for comparisons with BTK inhibitors (AKA, IBR, ZAN) (Fig. 2A)
- Overall survival was similar between VEN+RTX and other therapies except for immunotherapy (RTX, OFA), BEND+RTX, and the physician's choice (Fig. 2B)

SAFETY

- Rates of SAE were markedly decreased in patients treated with VEN+RTX compared with therapies based on PI3K inhibitors (DUV, IDE+RTX, IDE+OFA, IDE+BEND+RTX) (Fig. 2C)

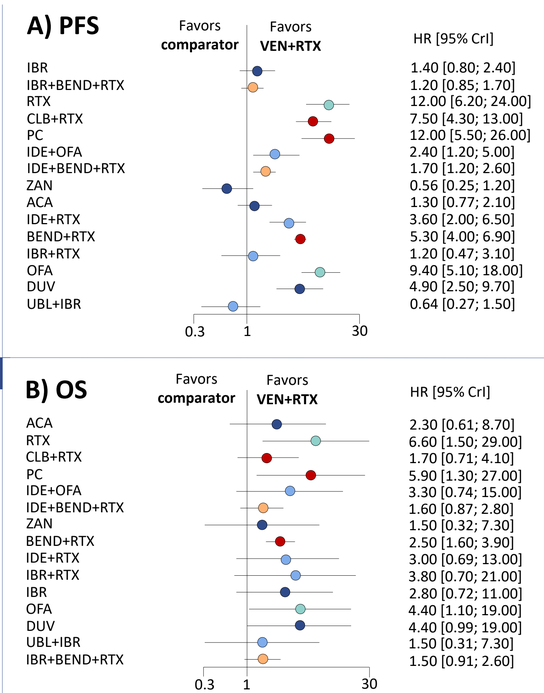

Figure 2. NMA effect estimates for A) PFS, B) OS, and C) SAE rates

CONCLUSIONS

- The results of NMA suggest that VEN+RTX in relapsed/refractory CLL is superior to all chemoimmunotherapy and PI3K regimens in terms of progression-free survival and has similar efficacy to BTK inhibitors.
- The use of VEN+RTX may also result in less frequent serious adverse events than PI3K-based regimes

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FIGURE LEGEND

- Venetoclax+rituximab
- Chemoimmunotherapy
- Immunotherapy (anti-CD20)
- BCR inhibitor
- BCR inhibitor + chemoimmunotherapy
- BCR inhibitor + immunotherapy

ABBREVIATIONS

ACA – acalabrutinib; BEND – bendamustine; CLB – chlorambucil; CLL – chronic lymphocytic leukemia; CrI – credible interval; DUV – duvelisib; HR – hazard ratio; IBR – ibrutinib; IDE – idelalisib; NMA – network meta-analysis; OFA – ofatumumab; OS – overall survival; PC – physician's choice; PFS – progression-free survival; RTX – rituximab; RR – risk ratio; SAE – serious adverse event; UBL – ublituximab; VEN – venetoclax; ZAN – zanubrutinib

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