Cumulative Incidence of Grade 3 or Higher Infections in Patients with CLL/SLL Treated with BTKi-Based Regimens

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Context

Bruton tyrosine kinase inhibitors (BTKi) have shifted the treatment approach for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

Objective

To calculate the **incidence of grade 3 or higher infections** among patients with CLL/SLL who are treated with a **BTKi-based regimen.**

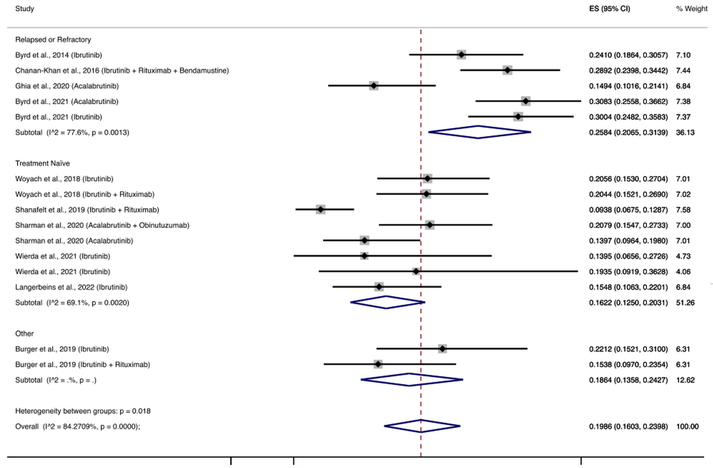
Methods/Design

- We searched the PubMed and EMBASE databases for randomized controlled trials (RCTs) and performed a random-effects meta-analysis to estimate the cumulative incidence of infections among patients receiving BTKi-based treatment **(ibrutinib and acalabrutinib)**.
- Followed the PRISMA statement for systematic reviews and meta-analyses and performed the analysis using the DerSimonian and Laird approach. For this analysis we focused on infections grade 3 or higher.

Results

- **10 studies** which were published between 2014 and 2022 and included **2,672** patients treated with **15 BTKi-based regimens**, fulfilled our criteria (follow-up: 9.1-40.9 months).
- There were 558 patients with ≥grade 3 infections with a pooled cumulative incidence of **19.86%** (95%CI: 16.03-23.98%).
- The most common sources of infection were lower (2.2–10.5%) or upper (0.4-2.9%) respiratory tract and urinary tract (0-4%).

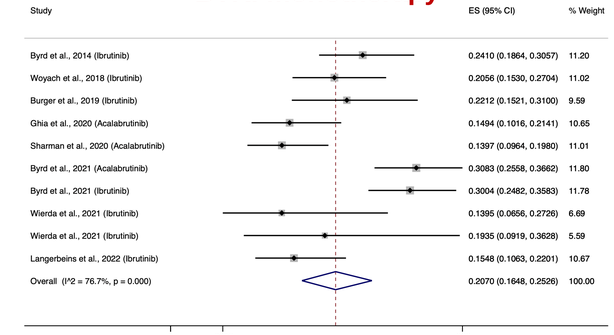
Cumulative incidence of severe infections with BTK inhibitors



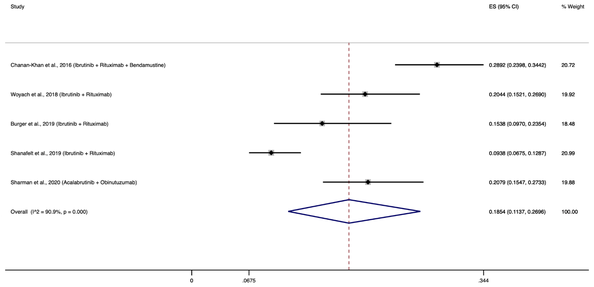
The pooled cumulative incidence of infection when BTKi were used as:

- **Monotherapy** (8 studies, 352 patients) was **20.7%** (95%CI: 16.48-25.26%) while when used as
- part of a **combination regimen** (5 studies, 206 patients) was **18.54%** (95%CI: 11.37-26.96%).

BTKi monotherapy



Combination Treatment



- In a subgroup analysis, the pooled incidence for infections was statistically significant higher in patients with:
  - **relapsed or refractory disease** (**25.84%**, 95%CI: 20.65-31.39%) compared to
  - **treatment-naïve** patients (**16.22%**, 95%CI: 12.5-20.31%)

Conclusions

- Almost **1 out of 5 patients (19.86%)** receiving a BTKi agent for the management of CLL/SLL develops a **high-grade infection**.
- Patients with **relapsed/refractory** disease are **more likely** to develop an infection compared to treatment-naïve.
- Continued surveillance and post-market trials are needed to study these infectious complications, identify high-risk patients and those at risk for multiple severe infections, and develop effective prophylactic strategies.

Key References

1. Hilal T, Gea-Banacloche JC, Leis JF. Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: Linking mechanisms with infections. Blood Rev. 2018;32(5):387-99
2. Tillman BF, Pauff JM, Satyanarayana G, Talbott M, Warner JL. Systematic review of infectious events with the Bruton tyrosine kinase inhibitor ibrutinib in the treatment of hematologic malignancies. Eur J Haematol. 2018;100(4):325-34.
3. Palma M, Mulder TA, Österborg A. BTK Inhibitors in Chronic Lymphocytic Leukemia: Biological Activity and Immune Effects. Frontiers in Immunology. 2021;12