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P632 COMPARISON OF TREATMENT-EMERGENT ADVERSE EVENTS OF ACALABRUTINIB AND ZANUBRUTINIB IN CLINICAL TRIALS IN B-CELL MALIGNANCIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Topic: 6. Chronic lymphocytic leukemia and related disorders - Clinical

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Background:

Second-generation BTK inhibitors (BTKi) acalabrutinib and zanubrutinib are more selective than ibrutinib, a first-in-class BTKi. However, randomized controlled trial data on their adverse events (AE) are limited. In addition, whether acalabrutinib and zanubrutinib have different AE profiles is unknown.

Aims:

To comprehensively analyze and compare treatment-emergent AE of ibrutinib, acalabrutinib, and zanubrutinib reported in clinical trials.

Methods:

PubMed and hematology conference abstracts were searched (last query on January 11, 2023) for trials of BTKi in B-cell malignancies. AE of clinical interest or AE reported by ≥10% of the included trials were analyzed. A novel Bayesian hierarchical model was developed to jointly estimate the incidence probabilities of different grades of AE and the relative risks (RR) between treatments. The proposed model synthesized evidence from both randomized and single-armed studies to enhance the robustness of estimation of AE incidences. It treated ibrutinib as the benchmark and allowed for indirect quantification of the comparison between acalabrutinib and zanubrutinib based on multiple trials. Between-study heterogeneity and partial information contained in the censored data were accounted for.

Results:

A total of 61 trials were included, involving 6959 patients and 68 treatment arms: ibrutinib (n=31; 46%), ibrutinib plus anti-CD20 mAb (n=15; 22%), acalabrutinib (n=11; 16%), and zanubrutinib (n=11; 16%). Most trials were in CLL/SLL (n=36), MCL (n=9), or WM (n=8). Three trials involved randomized comparison between ibrutinib and either acalabrutinib (ELEVATE-RR) or zanubrutinib (ASPEN, ALPINE).

A total of 84 AE were analyzed. Compared with ibrutinib, the average incidence of all grade AE was lower with acalabrutinib (RR=0.74, 95% credible interval [CrI]=0.62-0.85) and zanubrutinib (RR=0.83, 95% CrI=0.71-0.93). In addition, the average incidence of grade ≥3 AE was also lower with acalabrutinib (RR=0.87, 95% CrI=0.63-0.99) and zanubrutinib (RR=0.78, 95% CrI=0.47-1.02) compared to ibrutinib.

Zanubrutinib and acalabrutinib had similar average incidences of all grade (RR=1.12, 95% CrI=0.91-1.37) and grade ≥3 AE (RR=0.90, 95% CrI=0.54-1.37) (Figure). All grade AE that occurred more frequently with

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zanubrutinib relative to acalabrutinib included neutropenia (RR=1.77), leukopenia (RR=4.92), thrombocytopenia (RR=1.29), hypertension (RR=1.43), hematuria (RR=2.54), and cellulitis (RR=8.2). Grade ≥3 AE that occurred more frequently with zanubrutinib included neutropenia (RR=1.43), cellulitis (RR=6.6), and upper respiratory tract infection (RR=2.09). In contrast, all grade AE that occurred more frequently with acalabrutinib relative to zanubrutinib included atrial fibrillation (RR=0.51), infections (RR=0.53), pyrexia (RR=0.59), cough (RR=0.71), fatigue (RR=0.61), nausea (RR=0.63), vomiting (RR=0.71), diarrhea (RR=0.52), myalgias (RR=0.49), headaches (RR=0.32), and dizziness (RR=0.63). Grade ≥3 AE that occurred more frequently with acalabrutinib included anemia (RR=0.58), infections (RR=0.76), and rash (RR=0.03).

Summary/Conclusion:

Overall, results from this meta-analysis show an improved AE profile with acalabrutinib and zanubrutinib compared to ibrutinib. In addition, these data – for the first time – provide a comprehensive comparison of AE between zanubrutinib and acalabrutinib, which will inform clinicians' choice between these highly effective second-generation BTKi treatments for patients with B-cell malignancies.