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Et Tu, Bruton? Head-to-Head Comparison of the Mortality Rates and Side Effects of 3 Bruton Tyrosine Kinase Inhibitors in Treatment of Chronic Lymphocytic Leukemia

Umer Rizwan, MD[1], **Reece Fletcher**[2*], Ryan Meng[2*] and Michael Cheshire[3*]

[1]Camden Clark Medical Center/WVU Hospitals/Internal Medicine, Hospital, Parkersburg, WV; [2]West Virginia School of Osteopathic Medicine, Parkersburg; [3]800 Garfield Avenue, Camden Clark Medical Center, Parkersburg, WV

Background

Bruton tyrosine kinase inhibitors (BTKi's), first FDA approved in 2013, specifically target Bruton tyrosine kinase, allowing treatment of B-cell cancers, such as chronic lymphocytic leukemia (CLL). Side effects of BTKis vary due to each drug's affinity for Burton tyrosine kinase and other kinases. This study uses an aggregate of data to compare efficacies and side effect profiles of three first-line BTKi's in treating of CLL: acalabrutinib, ibrutinib, and zanubrutinib.

Methods

Data on patients with CLL treated with acalabrutinib, ibrutinib and zanubrutinib was collected from a large federated multi-national network database and compared with a focus on mortality rate and side effect profile. All cohorts used were matched by age, sex assigned at birth and comorbidities including hypertension, heart failure, and diabetes mellitus.

Results

In a cohort of 3,410 patients with CLL where 1705 were treated with acalabrutinib and 1705 were treated with ibrutinib, there were 181 deaths (10.616%) with acalabrutinib compared to 174 deaths (10.205%) with ibrutinib. The risk ratio was 1.04 (95% CI: 0.854,1.267) with a hazard ratio of 1.146 (95% CI:0.93, 1.411, $p<0.2925$). Acalabrutinib had a statistically significant increased risk of diarrhea (3.695%, $p<0.0004$) and headache (2.698%, $p<0.0009$) in headache compared to ibrutinib.

In a cohort of 1,622 patients with CLL where 811 were treated with ibrutinib and 811 were treated with zanubrutinib, there were 74 deaths (9.125%) with ibrutinib compared to 56 deaths (6.905%) with Zanubrutinib. The risk ratio was 1.321 (95%CI = 0.947,1.844) with a hazard ratio of 0.943 (95%CI = 0.662,1.342, p<0.8162). Ibrutinib had a statistically significant decreased risk of neutropenia (-2.959%, p<0.0116) and thrombocytopenia (-4.562%, p>0.0275), and an increased risk of joint pain (3.699%, p>0.0290).

In a cohort of 1,502 patients with CLL where 751 were treated with acalabrutinib and 751 were treated with zanubrutinib, there were 84 deaths (11.185%) with acalabrutinib compared to 52 deaths (6.924%) with zanubrutinib. The risk ratio was 1.615 (95%CI=1.16, 2.249) with a hazard ratio of 1.248 (95%CI=0.88,1.77, p<0.7093). Acalabrutinib had a statistically significant increased risk of diarrhea (6.125%, p<0.0001), joint pain (7.19%, p<0.0001) and headache (2.663%, p<0.0247) compared to zanubrutinib.

Conclusion

No statistically significant difference in mortality risk was found between the three BTKi's. However, Acalabrutinib is associated with higher risks of diarrhea, joint pain, and headache compared to both Zanubrutinib and Ibrutinib. Ibrutinib is associated with lower risks of neutropenia and thrombocytopenia compared to Zanubrutinib, but higher risk of joint pain compared to Zanubrutinib. These statistically significant differences in side effects warrant clinical judgment in selecting appropriate treatment for patients with CLL.

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First Corresponding

Corresponding Corresponding
Umer Rizwan, MD
Hospital
120 Ninth St
Apartment B
Camden Clark Medical Center/WVU Hospitals/Internal Medicine
Parkersburg, WV 26101
Email: ur0001@hsc.wvu.edu -- Will not be published

In the past 24 months, have you had any financial relationships with an ineligible company as defined above? No

Signed on 07/31/2024 by *Umer Rizwan, MD*

Second Presenter

Presenter
Reece Fletcher
West Virginia School of Osteopathic Medicine
Parkersburg,
Email: rfletcher@osteo.wvsom.edu -- Will not be published

In the past 24 months, have you had any financial relationships with an ineligible company as defined above? No

Signed on 07/31/2024 by *Reece Fletcher*

Third Author

Ryan Meng
West Virginia School of Osteopathic Medicine

Parkersburg,
Email: rmeng@osteo.wvsom.edu -- Will not be published

In the past 24 months, have you had any financial relationships with an ineligible company as defined above? No

Signed on 07/31/2024 by *Ryan Meng*

Fourth Author

Michael Cheshire
Camden Clark Medical Center
Room G1
800 Garfield Avenue
Parkersburg, WV 26100
Email: michael.cheshire@wvumedicine.org -- Will not be published

In the past 24 months, have you had any financial relationships with an ineligible company as defined above? No

Signed on 07/31/2024 by *Michael Cheshire*