Evaluation of Bruton's Tyrosine Kinase Inhibitors in Chronic Lymphocytic Leukemia Patients at a Community Teaching Hospital

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Purpose: Ibrutinib, acalabrutinib, and zanubrutinib are the current FDA-approved Bruton's Tyrosine Kinase (BTK) inhibitors used in chronic lymphocytic leukemia (CLL). All pose risks for hypertension, bleeding, atrial fibrillation, and opportunistic infections, such as pneumonia. BTK inhibitors have been studied in comparison to one another, though the more recent developments of acalabrutinib and zanubrutinib limit long-term outcomes regarding class safety and drug-drug interactions. This study was to serve as a real-world example of documenting safety outcomes for each therapy.

Methods: This study was performed as a retrospective chart review at Mercy Hospital in St. Louis, Missouri. Adult patients who received a BTK inhibitor (acalabrutinib, ibrutinib, or zanubrutinib) for the treatment of CLL through Mercy Oncology in the St. Louis area within the last 2 years were eligible for this study. The primary objective was to describe the incidence of treatment-related adverse effects in patients receiving BTK inhibitors for the treatment of CLL. Secondary objectives were to identify the incidence of treatment-related adverse effects in patients with documented comorbidities that may escalate the risk for these outcomes, prevalence of known drug-drug interactions among patients receiving BTK inhibitor therapy reported from patient chart information, and patient bleed risk via HAS-BLED scoring to compare to the incidence reported in the primary objective. This was a descriptive study and did not include a power analysis. Descriptive statistics, such as mean and median, were used to address the study endpoints.

Results: 52 patients were eligible for this study: 34 ibrutinib, 13 acalabrutinib, and 5 zanubrutinib. In the ibrutinib group, 6/34 (17.6%) patients were diagnosed with an arrhythmia post-therapy initiation. Acalabrutinib and zanubrutinib groups did not yield post-initiation arrhythmia diagnoses. 1/13 (7.7%) patients in the acalabrutinib group experienced bleeding, specifically hematuria. 4/34 (11.8%) patients in the ibrutinib group experienced bleeding post-initiation, with 2 subarachnoid hemorrhages, 1 rectal bleed, and 1 hematuria. No patients experienced bleeding in the zanubrutinib group. In the ibrutinib

group, 5/34 (14.7%) patients had to have concurrent antihypertensive regimens modified post-initiation. The zanubrutinib group yielded one patient who was diagnosed with hypertension post-initiation (20%). No modifications were conducted in the acalabrutinib group. Regarding incidence of infections, upper respiratory infections (URI) and COVID-19 were the most common occurrences between acalabrutinib (15.4%) and ibrutinib (47.1%) groups. No infections were documented for patients with zanubrutinib. The most severe infection, however, was a non-fatal case of mucormycosis in one patient taking ibrutinib. The mean HAS-BLED scores at therapy initiation for acalabrutinib, ibrutinib, and zanubrutinib were 1.15, 1.67, and 2. The mean HAS-BLED score at arrhythmia diagnosis was 2. These scores at baseline and at arrhythmia diagnosis indicated moderate risk for major bleeding.

Conclusion: Of the approved BTK inhibitors, ibrutinib yielded the greatest reports of adverse events both in literature and with the enrolled patients. Patients taking ibrutinib in this study were the only group to develop arrhythmias post-initiation as well as yield the greatest incidence of bleeding, antihypertensive regimen modifications, and opportunistic infections. Patients taking acalabrutinib had moderate incidence for these effects, excluding hypertensive modifications, while zanubrutinib did not report bleeding or infections. Though patients taking acalabrutinib and zanubruitinib had a smaller enrollment period than ibrutinib, we believe these outcomes should reflect what risks may exist for patients, particularly those with predisposing comorbidities.