Incidence of cardiac-related deaths among patients aged ≥65 years with B-cell malignancies treated with ibrutinib

Authors

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ABSTRACT

Background

Ibrutinib (ibr) is associated with an increased risk of fatal and serious cardiac failure in clinical trials, likely due to off-target kinase inhibition. However, data on real-world ibr cardiovascular safety are limited. This study reviews real-world incidence of cardiac-related death (CRD) reported among Medicare beneficiaries with B-cell malignancies (BCM) receiving ibr.

Methods

This was a retrospective longitudinal study using the de-identified Medicare Fee-for-Service (FFS) database. Patients (pts) were included if they initiated ibr 01/01/2017-12/31/2021 (National Death Index [NDI] data cutoff), had ≥2 non-drug claims ≥1 day apart of the same qualifying BCM (chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL], follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, or Waldenström macroglobulinemia) and had ≥12 months of continuous Medicare enrollment (Parts A, B, and D) prior to index date (baseline period). Index date was defined as date of ibr initiation in Medicare FFS, and pts were followed until the earliest of ibr discontinuation (days' supply +60 days gap), death, end of Medicare enrollment, or study end. Baseline demographic characteristics were summarized using descriptive statistics in the overall cohort and by BCM. BCM groups were defined based on the closest diagnosis date prior to index date, and mutually exclusive as CLL/SLL, single non-CLL BCM, or multiple BCMs. The primary outcome of interest was CRD, defined as an ICD-10 diagnosis code for cardiac arrest/sudden cardiac death, atrial fibrillation or flutter, heart failure (HF), myocardial infarction (MI), ventricular fibrillation or flutter, or ventricular tachycardia listed as the primary cause of death in NDI. Number and proportion of events were summarized. Incidence rate as a function of time on therapy was estimated as number of events per 100,000 person-years (pys) during ibr treatment. All analyses were performed for the overall cohort and by BCM group.

Results

A total of 13,201 pts were included: 9129 with CLL/SLL, 3710 other non-CLL BCM, and 362 multiple BCMs. Median age at index was 77.2 yrs (interquartile range [IQR]: 72.1-82.8), with 17% of pts aged ≥85. The majority of pts were male (57.7%) and self-reported as non-Hispanic White (90.7%). Only 4.6% were Black/African American, and <1% were Asian/Pacific Islander or Hispanic. Most pts started ibr between 2017 and 2019 (22.7%-22.9% each year) and fewer pts starting in 2020 (18.6%) or 2021 (13.0%). More pts resided in the Southern (35.7%) and Midwest regions of the US (25.4%), and 8.8% of pts had dual Medicare and Medicaid eligibility. Baseline characteristics were similar across BCMs.

A total of 82 (0.6%) CRDs were identified in the overall cohort; most reported HF (n=41; 50%) or MI (n=32; 39%) as the primary cause of death. The overall incidence rate was 509.8 per 100,000 pys (95% CI 405.5-632.8). The median ibr treatment duration was 268 days (IQR: 119-659) for all pts. Among pts with events, the median time-to-event was 141.5 days (IQR: 68-339). Similar results were observed for subgroups. Among pts with CLL/SLL, with a median follow-up of 307 days (IQR: 123-731), a total of 60 (0.7%) CRDs were identified, with 28 (46.7%) HF events and 26 (43.3%) MI events. Incidence of CRD was 497.0 per 100,000 pys (95% CI 379.3-639.7) among CLL/SLL pts, and median time-to-event was 140.5 days (IQR: 75.5-357) among pts with CRDs. Of pts with non-CLL BCM, with median follow-up of 206 days (IQR: 103-479), the incidence of CRD was 533.6 per 100,000 pys (95% CI 321.2-833.2), and the median time-to-event was 182 days (IQR: 57-329) among pts with CRD. Deaths from other causes occurred in 16.1% of the overall population, with a slightly higher proportion in non-CLL BCM (18.5%) than CLL (15.1%) and multiple BCMs (16.6%).

Conclusion

In this large real-world setting among pts aged ≥65 yrs who initiated ibr for BCM, 82 CRDs were identified and a higher incidence rate of CRD (510 per 100,000 pys) was seen than previously reported rates for 65-yr-olds in the general population (200-400 per 100,000 pys; Chugh *J Am Coll Cardiol* 2004). These results were consistent with previous smaller studies with ibr (Lampson *Blood* 2017; Guha *J Am Coll Cardiol* 2020). Additional assessment of secondary causes of death and diagnosis near death are needed to verify study results, as well as extending to other Bruton tyrosine kinase inhibitors.