Poster # CML-619

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Adverse Events (AEs) among Patients with Chronic Myeloid Leukemia (CML) Receiving Tyrosine Kinase Inhibitors and Subsequent Treatment Adjustment: A Large US Commercial Claims Database Analysis

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KEY FINDINGS & CONCLUSIONS

- This is a large retrospective real-world evidence study on the unmet needs of TKIs for CML, focusing on associated AEs and treatment adjustments.
- AEs and treatment adjustments were common among patients with CML receiving 1G and 2G TKIs. AEs often preceded treatment discontinuation, interruption, and dose reduction.
- The high AE burden and high rates of treatment adjustments with 1G and 2G TKIs highlight the need for more tolerable CML treatment regimens that require fewer dose adjustments and less AE management, with the goal of reducing discontinuations while maintaining sustained and optimal efficacy benefits.
- Future studies using data containing the reasons for treatment modifications are warranted to better understand how AEs impact treatment decisions.

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BACKGROUND

- The standard of care for chronic myeloid leukemia (CML) has been tyrosine kinase inhibitors (TKIs), including the first-generation (1G) (imatinib) and the second-generation (2G) TKIs (dasatinib, nilotinib and bosutinib)
- Despite the therapeutic benefit of 1G and 2G TKIs, approximately one-quarter of patients with CML discontinue these treatments, and intolerance is the main reason for discontinuation[1]
- Asciminib demonstrated superior efficacy and favorable safety and tolerability compared with investigator-selected TKIs and with imatinib in patients with newly diagnosed CML.[2] In May 2024, it was granted Food and Drug Administration (FDA) Priority Review for the treatment of adults with newly diagnosed CML
- The current study aims to assess the rates of adverse events (AEs) associated with 1G and 2G TKIs using real-world data
- This study will establish a reference point for tolerability prior to the widespread use of asciminib as an early treatment option in CML

OBJECTIVES

- To describe treatment adjustments and the proportions of patients experiencing AEs for 1G and 2G TKIs among patients with CML

METHODS

Data source

- IQVIA PharMetrics® Plus Commercial claims database (study period: 01/01/2016 – 09/30/2023)
- This longitudinal database is comprised of commercial health plan information from managed care plans throughout the US, with adjudicated medical and pharmacy claims of more than 150 million unique enrollees since 2006
- Key data elements include demographics, healthcare visits and admissions, medications dispensed, diagnostic codes, laboratory results, and dates of services

Study design

- A retrospective cohort study of patients with CML who received 1G (imatinib) or 2G TKIs (dasatinib, nilotinib, bosutinib), regardless of number of previous TKIs received
- The index dates for the 1G and 2G TKI cohorts were defined as the date of first initiation of 1G and 2G TKIs during the cohort identification period, respectively. The TKI initiated on the index date was defined as the index treatment
  - The cohort identification period was from 07/01/2016 to 03/31/2023 as patients were required to have continuous enrollment of medical and pharmacy coverage for at least 6 months before and after the index date
  - The 1G and 2G TKI cohorts are not mutually exclusive. Patients who initiated both 1G and 2G TKIs during the cohort identification period could be included in both cohorts
  - For patients who received two or more 2G TKIs during the cohort identification period, only the first 2G TKI will be defined as the index treatment
- The baseline period was defined as the 6 months before the index date for the 1G and 2G TKI cohorts, respectively
- The follow-up period was defined as the time from the index date to the earliest date of end of data availability, end of health plan coverage, or death
- The proportions of patients experiencing AEs of interest were assessed during the treatment period
  - The treatment period was defined as the time from the index date to the earliest date of (1) discontinuation of the index treatment; (2) one day before switching to another CML treatment including another TKI, omacetaxine mepesuccinate, CML-related chemotherapy, or hematopoietic stem cell transplantation (HSCT); or (3) end of follow-up period
  - A total of 22 AEs of interest (**Figure 2**) were included based on the review of the National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2024) and clinical inputs. The occurrence of AEs was identified via International Classification of Diseases, Tenth Revision (ICD-10) codes in any position of diagnoses in claims across care settings
- The proportions of patients having treatment adjustments were assessed during the follow-up period
  - Treatment interruption was defined as a gap in treatment of ≥ 14 days followed by treatment reinitiation. The interruption date was defined as the last day of supply before the 14-day gap
  - Dose reduction was defined as a change to a dosing level that is lower than the initial dosage
  - Treatment switch was defined as switching from the index treatment to another CML treatment including alternative TKIs, CML-related chemotherapy or transplant
  - Treatment discontinuation was defined as the earliest of the following events: 1) treatment switch, or 2) gap in the index treatment of ≥ 90 days without re-initiation of the index treatment post the gap
- The proportions of patients experiencing AEs within 30 days before treatment adjustments were assessed

Statistical analyses

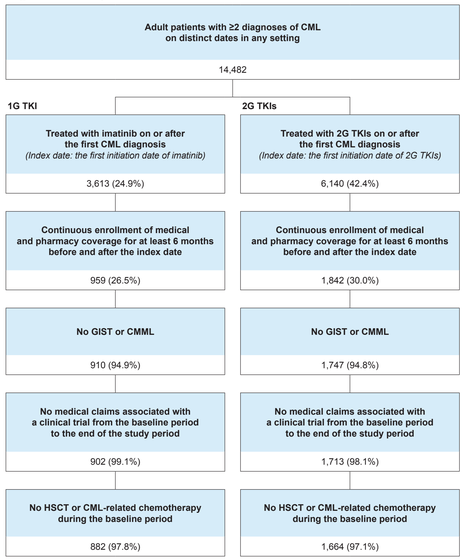
- Counts and proportions were used to describe patients with AEs during the treatment period and within 30 days before treatment adjustments, and Kaplan-Meier (KM) method was used to describe time to treatment adjustments
- All analyses were separately performed for the 1G and 2G TKI cohorts

RESULTS

Sample selection

- A total of 882 (34.6%) patients receiving 1G TKI (imatinib) and 1,664 (65.4%) receiving 2G TKIs (68.8% dasatinib, 22.7% nilotinib, 8.5% bosutinib) were included (**Figure 1**)

Figure 1. Sample selection



Abbreviations: 1G: first generation; 2G: second generation; CML: chronic myeloid leukemia; CMML: chronic myelomonocytic leukemia; GIST: gastrointestinal stromal tumor; HSCT: hematopoietic stem cell transplantation; TKI: tyrosine kinase inhibitor.

Baseline patient characteristics

- Among the 1G/2G TKI cohorts, median ages were 55.0/52.0 years, respectively, with 43.3%/44.1% being female (**Table 1**)
- During the baseline period, 42.0%/41.3% of the 1G/2G TKI cohorts had mild, 40.1%/40.7% had moderate and 17.9%/18.0% had severe Darkow disease complexity
- One-fifth of the 1G TKI cohort and 22.8% of the 2G TKI cohort were previously treated with TKIs during the baseline period

Table 1. Baseline patient characteristics

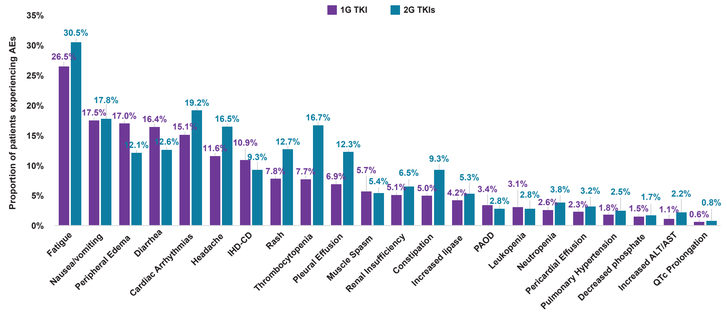
	1G TKI N = 882	2G TKIs N = 1,664
Age (years), median (range)	55.0 (18.0-86.0)	52.0 (18.0-85.0)
Female, N (%)	382 (43.3%)	733 (44.1%)
Darkow disease complexity index, N (%)		
Mild	370 (42.0%)	687 (41.3%)
Moderate	354 (40.1%)	678 (40.7%)
Severe	158 (17.9%)	299 (18.0%)
Prior TKI treatment *(not mutually exclusive)*, N (%)	176 (20.0%)	379 (22.8%)
Imatinib	0 (0.0%)	374 (22.5%)
Dasatinib	129 (14.6%)	0 (0.0%)
Nilotinib	42 (4.8%)	0 (0.0%)
Bosutinib	24 (2.7%)	0 (0.0%)
Ponatinib	1 (0.1%)	5 (0.3%)

Abbreviations: 1G: first generation; 2G: second generation; TKI: tyrosine kinase inhibitor.

AEs during treatment with 1G and 2G TKIs

- Median duration of treatment was 14.1/16.1 months for the 1G/2G TKI cohorts, respectively.
- Common AEs (≥10% in either 1G or 2G TKI cohorts) of any grade included fatigue, nausea/vomiting, peripheral edema, diarrhea, cardiac arrhythmias, headache, ischemic heart disease - coronary diseases, rash, thrombocytopenia and pleural effusion (**Figure 2**)

Figure 2. Proportions of patients experiencing AEs of interest during treatment with 1G and 2G TKIs

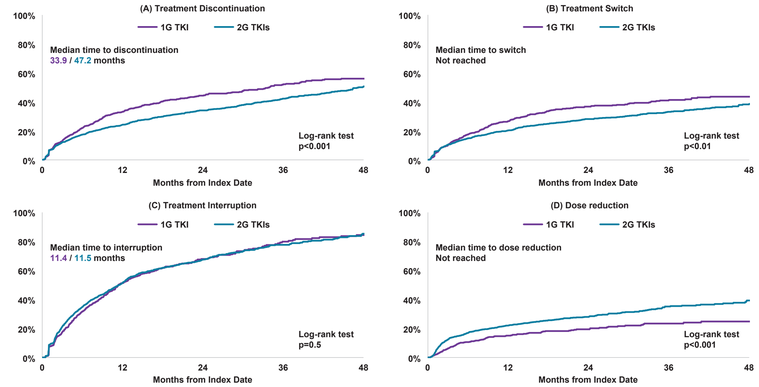


Abbreviations: 1G: first generation; 2G: second generation; IHD-CD: ischemic heart disease - coronary disease; PAOD: peripheral arterial occlusive disease; TKI: tyrosine kinase inhibitor.

Treatment adjustments

- Median duration of the follow-up period was 26.9/24.0 months for the 1G/2G TKI cohorts, respectively
- Median time to treatment discontinuation was 33.9/47.2 months for the 1G/2G TKI cohorts, respectively, with discontinuation rates of 52.5%/42.5% at 3 years. (**Figure 3**)
- Median time to treatment switch was not reached for either cohort, with switch rates of 41.4%/33.4% at 3 years for the 1G/2G TKI cohort, respectively
- Median time to treatment interruption was 11.4/11.5 months for the 1G/2G TKI cohorts, respectively, with interruption rates of 79.8%/77.6% at 3 years
- Median time to dose reduction was not reached for either cohort, with dose reduction rates of 23.4%/35.4% at 3 years for the 1G/2G TKI cohort, respectively
- 1G TKI had a higher rate of treatment discontinuation and switch, while 2G TKIs had a higher rate of dose reduction

Figure 3. Kaplan-Meier rates of treatment adjustments

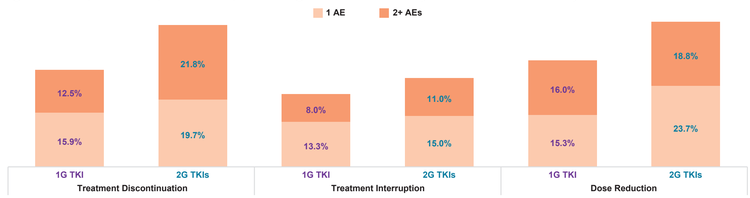


Abbreviations: 1G: first generation; 2G: second generation; TKI: tyrosine kinase inhibitor.

AEs within 30 days before treatment adjustments

- For the 1G/2G TKI cohorts, 28.4%/41.6% experienced at least one AE within 30 days before treatment discontinuation, 21.3%/26.0% before treatment interruption, and 31.3%/42.5% before dose reduction, respectively. (**Figure 4**)
- For the 1G/2G TKI cohorts, 12.5%/21.8% had two or more distinct AEs within 30 days before treatment discontinuation, 8.0%/11.0% before treatment interruption, and 16.0%/18.8% before dose reduction, respectively

Figure 4. Proportion of patients experiencing AEs within 30 days before treatment adjustments



Abbreviations: 1G: first generation; 2G: second generation; AEs: adverse events; TKI: tyrosine kinase inhibitor.

Limitations

- AEs were identified using diagnosis codes in claims data, which may miss low-grade AEs that do not require medical attention, leading to potential underreporting. Additionally, the severity of AEs was not examined
- Causal relationships between AEs and treatment adjustments cannot be established; only temporal sequences were assessed in this study

Acknowledgements

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- Poster presented at the SOHO 2024 Annual Meeting, September 4 - September 7, 2024.

References

1. Rashid N, et al. *J Oncol Pharm Pract.* 2018 Jun;24(4):253-263. PMID: 29284347.
2. Hochhaus A, et al. *N Engl J Med.* 2024 May 31. PMID: 38820078.