CLL-586

Real-World Dosing Patterns and Outcomes Among Patients With Chronic Lymphocytic Leukemia With or Without a Dose Adjustment of First-Line Ibrutinib

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BACKGROUND

- Ibrutinib is a once-daily Bruton's tyrosine kinase inhibitor (BTKi) that has become a standard of care for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[1]
- Across numerous phase III clinical trials in the first-line (1L), ibrutinib is the only BTKi that has demonstrated improved overall survival relative to chemotherapy and/or chemoimmunotherapy treatments and, most recently, similar overall survival to an age-matched general population in a pooled analysis[2-6]
- Dosing flexibility with ibrutinib allows patients to adjust their daily dose to help prevent recurrence or worsening of adverse events, while maintaining efficacy by allowing patients to stay on treatment and benefit from long-term treatment outcomes[5,6]
- There is a need to better understand outcomes associated with ibrutinib dosing flexibility in a real-world clinical practice setting

OBJECTIVE

- This descriptive real-world study aimed to describe dosing characteristics and outcomes for patients with CLL/SLL treated with 1L ibrutinib with or without a dose adjustment

METHODS

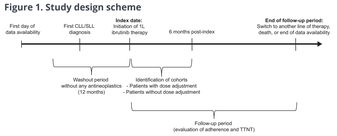
Data source

- Electronic medical records (EMR) from the Acentrus database (01/01/2016 to 04/30/2022) were used
- Acentrus is a health system solution used by 128,000 prescribers, containing inpatient and outpatient data from 27 sites, including 10 National Cancer Institute designated sites, and 6 National Comprehensive Cancer Network members
  - Acentrus pharmacy data draw information from both medication orders and refills
- It includes patient records from 12 non-teaching and 15 academic hospital systems across 15 US states and contains information on demographic characteristics, insurance plan, medications, visits, date of death, diagnoses, laboratory test results, vitals, and medication orders/fills/administrations
- Data are de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA)

Study design

- A retrospective study design was used (**Figure 1**)

Figure 1. Study design scheme



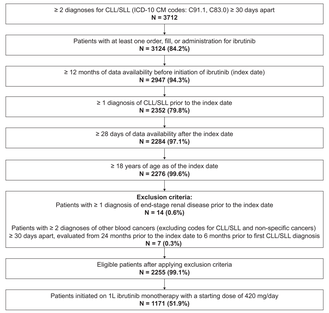
1L: first-line; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; TTNT: time to next treatment.

- The index date was defined as the date of initiation of ibrutinib monotherapy in 1L at a daily dose of 420 mg
  - A washout period of ≥ 12 months of data availability prior to the index date without any use of antineoplastic agents was used to identify 1L therapy
  - A window of 28 days post-index was used to ascertain that no other antineoplastic agents were used in combination with ibrutinib
- The baseline period was defined as the 12-month period prior to the index date
- The follow-up period was defined as the period from the index date to the earliest of initiation of second-line (2L) therapy, death, or end of data availability
- The first 6 months post-index were used to ascertain whether patients had a dose adjustment; a 6-month window was selected as dose adjustment was expected to occur quickly after initiation if related to a clinical event and as the majority of patients had a dose adjustment within the first 6 months, thus minimizing immortal time bias (i.e., patients with a dose adjustment are required to survive on 1L therapy at least until their dose adjustment), while maintaining sufficient sample size
  - Patients who started at initial dose of 420 mg/day, who then received < 420 mg/day within the first 6 months of treatment were considered as having a dose adjustment
  - Patients who remained on a starting dose of 420 mg/day during the first 6 months post-index were considered as not having a dose adjustment

Study population

- The patient selection criteria are presented in **Figure 2**

Figure 2. Study population selection



1L: first-line; CLL: chronic lymphocytic leukemia; ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; SLL: small lymphocytic lymphoma.

- A subgroup of patients with high cardiovascular (CV) risk was also analysed, and was defined as patients with pre-existing CV comorbidities or at high risk for a CV event
  - Pre-existing CV comorbidities included hypertension, diabetes, acute coronary syndrome, cardiac arrhythmia/dysrhythmia, obesity, atrial fibrillation, sleep apnea, hypercholesterolemia, cardiac failure, valvular disease, congestive heart failure, cerebrovascular disease, ischemic stroke, atrial flutter, transient ischemic attack, or ventricular arrhythmias
  - Patients at high risk for a CV event were defined as being in the 'high risk' category for ≥ 1 of the following scales: congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled) (CHA$_2$DS$_2$), CHA$_2$DS$_2$-vascular disease, age 65 to 74 and sex category (female) (CHA$_2$DS$_2$-VASc), Mayo, atherosclerotic cardiovascular disease (ASCVD), cohorts for heart and aging research in genomic epidemiology atrial fibrillation (CHARGE-AF), or Framingham Heart Study AF

Study outcomes

- Adherence to ibrutinib during 1L therapy was measured using the proportion of days covered (PDC) and medication possession ratio (MPR)
  - PDC was defined as the sum of non-overlapping days of supply (DOS), where prescriptions with overlapping DOS were shifted forward, divided by the line of therapy duration (i.e., number of days between index date and earliest of switch to another line of therapy, death, or end of data availability)
  - MPR was defined as the number of days of medication supplied during the line of therapy, divided by the line of therapy duration; MPR was capped at 100%
  - PDC and MPR were also evaluated at fixed periods of time, ie, for the first 3, 6, 9, and 12 months of the line of therapy, among patients with ≥ 3, ≥ 6, ≥ 9, and ≥ 12 months line of therapy duration
  - Patients were considered adherent to ibrutinib treatment if they had ≥ PDC/MPR ≥ 80%
- Time to next treatment (TTNT) was defined as the time from the index date to the date of initiation of a next regimen
  - Patients who did not initiate a subsequent regimen were censored at the date of death or the end of data availability
  - Patients with an observed within-class BTKi switch at any time or with a venetoclax or anti-CD20 add-on within 180 days of initiation of 1L ibrutinib were censored at the date of switch/add-on
  - Patients who switched to agents for non-hematologic cancers were censored at the date of switch

Statistical analyses

- Dose adjustment characteristics, baseline characteristics, and adherence were reported using means, standard deviations (SDs), and medians for continuous variables, and frequencies and proportions for categorical variables
  - Baseline characteristics were compared between patients with or without a dose adjustment using t-tests for continuous variables, and chi-squared tests for categorical variables
- TTNT was reported using Kaplan-Meier (KM) survival curves; KM rates were reported along with 95% confidence intervals and log-rank *P*-values

RESULTS

Study population and dosing patterns

- A total of 1171 patients initiated 1L ibrutinib with a 420 mg/day starting dose; among them, 724 had a high risk of CV disease (**Table 1**)
- Overall, 229 patients (19.6%) had a dose adjustment at any time during 1L, with a mean time to first dose adjustment of 9.0 months (median, 5.5 months)
- Among patients in the high-risk CV subgroup, 154 patients (21.3%) had a dose adjustment at any time during 1L, with a mean time to first dose adjustment of 8.5 months (median, 5.4 months)
- Within the first 6 months of 1L initiation, 126 patients (10.8%) overall and 88 (12.2%) in the high-risk CV subgroup had a dose adjustment
- Subsequent analyses focused on patients with and without dose adjustment in the first 6 months of 1L ibrutinib initiation

TABLE 1: Ibrutinib dosing patterns

	Overall study population N = 1171	CV subgroup N = 724
Patients with a dose adjustment at any time during 1L, n (%)	**229 (19.6%)**	**154 (21.3%)**
Time to first dose adjustment, months, mean ± SD [median]	9.0 ± 9.2 [5.5]	8.5 ± 8.7 [5.4]
Time from first dose adjustment to end of 1L, months, mean ± SD [median]	22.1 ± 14.0 [22.1]	22.6 ± 14.4 [23.3]
Patients staying on reduced dose for the remainder of 1L, n (%)	138 (60.3%)	93 (60.4%)
Patients returning to 420 mg/day, n (%)	25 (10.9%)	14 (9.1%)
Patients further reducing their dose following initial dose adjustment, n (%)	22 (9.6%)	17 (11.0%)
Patients with other dosing patterns following dose adjustment, n (%)	44 (19.2%)	30 (19.5%)
Patient cohorts for baseline and outcome analyses, n (%)		
Dose adjustment within first 6 months	126 (10.8%)	88 (12.2%)
No dose adjustment during first 6 months	1038 (88.6%)	634 (87.6%)

1L: first-line; CV: cardiovascular; SD: standard deviation.

Baseline characteristics

- In the overall study population, patients with a dose adjustment were significantly older than patients without a dose adjustment (mean age: 72.2 vs. 70.2 years; $P = 0.039$) and were more likely to be female (42.9% vs. 33.6%, $P = 0.040$) (**Table 2**)
- Patients in the high-risk CV subgroup were older (mean age: 76.1 years for patients with dose adjustment and 74.8 years for patients without dose adjustment) and had a higher comorbidity burden than the overall study population
  - Overall, similar differences were observed between patients with versus without a dose adjustment in this subgroup, but results didn't reach statistical significance due to small sample size

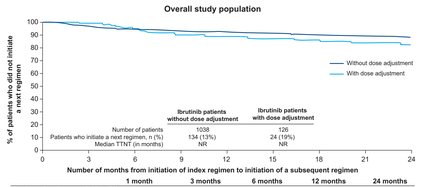
Treatment adherence

- Mean (median) duration of 1L therapy was 775.9 (801.5) days among patients with a dose adjustment and 751.7 (741.0) days among patients without a dose adjustment
- In the overall study population, based on a PDC/MPR ≥ 80% over the entire duration of the line of therapy, a numerically higher proportion of patients with a dose adjustment were adherent to treatment (PDC, 68.3%; MPR, 75.4%) relative those without a dose adjustment (PDC, 52.0%; MPR, 58.6%) (**Table 3**)
- Similarly, mean PDC and MPR were numerically higher over the entire duration of the line of therapy among patients with a dose adjustment (PDC, 0.81; MPR, 0.84) relative to those without (PDC, 0.70; MPR, 0.73)
- Comparable results were observed among the high-risk CV subgroup, and these results were consistent during the first 3, 6, 9, and 12 months of the line of therapy

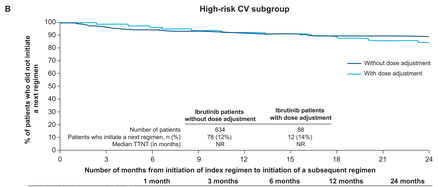
Time to next treatment

- In the overall study population, 12-month KM rates were similar for patients with a dose adjustment (89.1%) relative to patients without a dose adjustment (92.5%; $P = 0.254$); median TTNT was not reached for both cohorts (**Figure 3A**)
- Similar results were observed among the high-risk CV subgroup, where 12-month KM rates were 92.7% and 92.0% among patients with and without a dose adjustment, respectively ($P = 0.774$); median TTNT was not reached for both cohorts (**Figure 3B**)

FIGURE 3: TTNT among patients with or without a dose adjustment



Number of patients at risk[1], n (%)	1 month	3 months	6 months	12 months	24 months
Without dose adjustment	1037 (99.9%)	952 (91.7%)	879 (84.7%)	784 (75.5%)	532 (51.3%)
With dose adjustment	126 (100.0%)	123 (97.6%)	115 (91.3%)	97 (77.0%)	68 (54.0%)
Kaplan-Meier rates (95% CI)					
Without dose adjustment	99.7% (99.1, 99.9)	96.4% (95.1, 97.4)	94.6% (93.0, 95.8)	92.5% (90.6, 94.0)	88.2% (85.9, 90.2)
With dose adjustment	100.0% (100.0, 100.0)	99.2% (94.5, 99.9)	95.1% (89.4, 97.8)	89.1% (81.9, 93.5)	82.7% (74.0, 88.7)
Log-rank test	0.546	0.102	0.753	0.254	0.126



Number of patients at risk[1], n (%)	1 month	3 months	6 months	12 months	24 months
Without dose adjustment	633 (99.8%)	588 (92.7%)	535 (84.4%)	468 (73.8%)	315 (49.7%)
With dose adjustment	88 (100.0%)	85 (96.6%)	81 (92.1%)	68 (77.3%)	47 (53.4%)
Kaplan-Meier rates (95% CI)					
Without dose adjustment	99.7% (98.7, 99.9)	96.6% (94.9, 97.8)	94.4% (92.3, 96.0)	92.0% (89.5, 94.0)	89.2% (86.2, 91.5)
With dose adjustment	100.0% (100.0, 100.0)	98.9% (92.1, 99.8)	96.5% (89.4, 98.8)	92.7% (84.4, 96.6)	84.5% (73.5, 91.2)
Log-rank test	0.598	0.261	0.412	0.774	0.461

CI: confidence interval; CV: cardiovascular; NR: not reached; TTNT: time to next treatment. Note: 1. Refers to the population at risk of having the event at that point in time (i.e., patients who did not have the event and were not lost to follow-up).

TABLE 2: Baseline demographic and clinical characteristics

	Patients without dose adjustment N = 1038	Patients with dose adjustment N = 126	*P*-value
Age at index date, mean ± SD [median]	70.2 ± 9.9 [71.0]	72.2 ± 9.7 [73.5]	0.039*
Female, n (%)	349 (33.6)	54 (42.9)	0.040*
Insurance coverage, n (%)			
Medicare	244 (23.5)	34 (27.0)	0.387
Managed Care	93 (9.0)	7 (5.6)	0.198
Medicaid	14 (1.3)	3 (2.4)	0.362
Other	356 (34.3)	55 (43.7)	0.038*
Unknown	331 (31.9)	27 (21.4)	0.016*
US region, n (%)			
West	363 (35.0)	26 (20.6)	0.001*
South	292 (28.1)	31 (24.6)	0.404
Midwest	258 (24.9)	45 (35.7)	0.009*
Northeast	30 (2.9)	6 (4.8)	0.252
Unknown	95 (9.2)	18 (14.3)	0.066
Race, n (%)			
White	456 (43.9)	49 (38.9)	0.281
Black	48 (4.6)	5 (4.0)	0.739
Asian	31 (3.0)	3 (2.4)	0.703
Other	503 (48.5)	69 (54.8)	0.181
Year of index date, n (%)			
2017	76 (7.3)	6 (4.8)	0.289
2018	242 (23.3)	41 (32.5)	0.023*
2019	316 (30.4)	40 (31.7)	0.764
2020	247 (23.8)	26 (20.6)	0.429
2021	124 (11.9)	12 (9.5)	0.424
2022	33 (3.2)	1 (0.8)	0.133
Quan-CCI, mean ± SD [median]	3.1 ± 1.7 [2.0]	3.0 ± 1.4 [2.0]	0.375
Patients with any pre-existing CV comorbidities or at high risk of a CV event, n (%)	634 (61.1)	88 (69.8)	0.056
CV comorbidities, n (%)			
Hypertension	395 (38.1)	53 (42.1)	0.382
Atrial fibrillation	74 (7.1)	11 (8.7)	0.514
Valvular disease	47 (4.6)	11 (8.7)	0.047*
Renal impairment, n (%)	37 (3.6)	10 (7.9)	0.019*

CV: cardiovascular; Quan-CCI: Quan-Charlson Comorbidity Index; SD: standard deviation. *P-value < 0.05

TABLE 3: Treatment adherence among patients with or without a dose adjustment

	Overall study population		High-risk CV subgroup	
	Patients without dose adjustment N = 1038	Patients with dose adjustment N = 126	Patients without dose adjustment N = 634	Patients with dose adjustment N = 88
Line of therapy duration, days, mean ± SD (median)	751.7 ± 461.4 [741.0]	775.9 ± 443.7 [801.5]	727.2 ± 451.3 [716.5]	781.9 ± 448.9 [839.5]
PDC, mean ± SD [median]	0.70 ± 0.34 [0.84]	0.81 ± 0.28 [1.00]	0.69 ± 0.34 [0.87]	0.78 ± 0.30 [0.98]
PDC ≥ 80%, n (%)	540 (52.0)	86 (68.3)	332 (52.4)	55 (62.5)
MPR, mean ± SD [median]	0.73 ± 0.34 [0.98]	0.84 ± 0.28 [1.00]	0.72 ± 0.34 [0.97]	0.81 ± 0.29 [1.00]
MPR ≥ 80%, n (%)	608 (58.6)	95 (75.4)	371 (58.5)	62 (70.5)
Patients with ≥ 3 months line of therapy	N = 1009	N = 124	N = 620	N = 86
PDC, mean ± SD [median]	0.90 ± 0.22 [1.00]	0.96 ± 0.16 [1.00]	0.91 ± 0.21 [1.00]	0.95 ± 0.16 [1.00]
PDC ≥ 80%, n (%)	796 (83.5)	114 (93.4)	491 (83.4)	78 (92.9)
MPR, mean ± SD [median]	0.91 ± 0.21 [1.00]	0.96 ± 0.16 [1.00]	0.91 ± 0.21 [1.00]	0.96 ± 0.16 [1.00]
MPR ≥ 80%, n (%)	801 (84.1)	115 (93.5)	495 (84.0)	79 (92.9)
Patients with ≥ 6 months line of therapy	N = 879	N = 115	N = 535	N = 81
PDC, mean ± SD [median]	0.84 ± 0.28 [1.00]	0.93 ± 0.18 [1.00]	0.84 ± 0.27 [1.00]	0.92 ± 0.19 [1.00]
PDC ≥ 80%, n (%)	658 (74.9)	102 (88.7)	396 (74.0)	71 (87.7)
MPR, mean ± SD [median]	0.85 ± 0.27 [1.00]	0.94 ± 0.18 [1.00]	0.85 ± 0.27 [1.00]	0.93 ± 0.18 [1.00]
MPR ≥ 80%, n (%)	671 (76.3)	103 (89.6)	405 (75.6)	72 (88.9)
Patients with ≥ 9 months line of therapy	N = 836	N = 102	N = 510	N = 73
PDC, mean ± SD [median]	0.80 ± 0.30 [1.00]	0.92 ± 0.19 [1.00]	0.80 ± 0.30 [1.00]	0.91 ± 0.20 [1.00]
PDC ≥ 80%, n (%)	551 (65.9)	90 (88.2)	334 (65.5)	63 (86.3)
MPR, mean ± SD [median]	0.81 ± 0.30 [1.00]	0.93 ± 0.18 [1.00]	0.81 ± 0.30 [1.00]	0.92 ± 0.20 [1.00]
MPR ≥ 80%, n (%)	576 (68.8)	92 (90.2)	352 (68.9)	65 (89.0)
Patients with ≥ 12 months line of therapy	N = 784	N = 96	N = 468	N = 67
PDC, mean ± SD [median]	0.77 ± 0.31 [0.99]	0.90 ± 0.22 [1.00]	0.77 ± 0.31 [0.99]	0.87 ± 0.24 [1.00]
PDC ≥ 80%, n (%)	502 (64.0)	77 (80.2)	300 (64.1)	50 (74.6)
MPR, mean ± SD [median]	0.79 ± 0.31 [1.00]	0.91 ± 0.21 [1.00]	0.79 ± 0.31 [1.00]	0.89 ± 0.23 [1.00]
MPR ≥ 80%, n (%)	529 (67.4)	82 (84.5)	318 (67.8)	55 (80.9)

CV: cardiovascular; MPR: medication possession ratio; PDC: proportion of days covered; SD: standard deviation.

LIMITATIONS

- EMR data may contain omissions and inaccuracies, but this is expected to apply to all patients, and, thus, should have minimal impact on overarching conclusions
- Acentrus is a provider-based data source, meaning that records are only available to the extent that visits are part of the network of academic and non-teaching hospital systems included in the data
- A 12-month washout period was used to identify the use of ibrutinib in 1L, a definition which has been used extensively in real-world studies, but could have included patients in longer remission who had received a previous line of therapy
- Patients were assumed to be using their medication based on prescription fills, but may not always adhere to their treatment regimen as prescribed
  - This limitation is typical of real-world data, but Acentrus database overcomes it by drawing information from both medication orders and refills
- Reasons for dose adjustment were not available in Acentrus, which is a limitation inherent to all claims data-based studies
- Results may not be generalizable to all patients treated with ibrutinib in 1L, but may be generalizable to patients treated at academic/non-teaching hospital systems in the United States

CONCLUSIONS

- Among patients with CLL/SLL treated with 1L ibrutinib and among patients in the high-risk CV subgroup, a small percentage of patients (19.6% and 21.3% respectively) had a dose adjustment, indicating that ibrutinib is well tolerated in the real world
- This descriptive analysis of patients with CLL/SLL treated with 1L ibrutinib showed that patients with a dose adjustment had higher adherence while maintaining similar TTNT relative to those who remained on a 420 mg/day starting dose
- Similar results were observed among the subgroup of patients at high CV risk, both in terms of outcomes and median time to dose adjustment
- These real-world findings, along with previous clinical trial data,[8] suggest that dosing flexibility with ibrutinib may be an effective treatment approach in allowing patients, including those at high CV risk, to achieve optimal outcomes while remaining on long-term continuous treatment in the 1L setting

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B-CELL MALIGNANCIES