Real-World Adherence to First-Line Ibrutinib and Acalabrutinib Monotherapy among Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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BACKGROUND

- Ibrutinib (once-daily) and acalabrutinib (twice-daily) are two Bruton's tyrosine kinase inhibitors (BTKi) that are approved for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[1,2]
- Sustained adherence to medication is important to achieve and maintain optimal clinical outcomes in CLL[3]
- While the clinical outcomes, including safety and efficacy, associated with ibrutinib and acalabrutinib have been evaluated in clinical trials for patients with CLL, there is limited data on real-world treatment adherence
- For the treatment of chronic diseases, once-daily regimens have been associated with higher adherence than twice-daily regimens,[4] suggesting that adherence may differ between patients treated with ibrutinib and acalabrutinib

OBJECTIVE

- To describe and compare refill adherence between CLL/SLL patients treated with first-line (1L) ibrutinib or acalabrutinib monotherapy in the United States (US)

METHODS

Data Source

- Data from the Acentrus academic electronic medical record (EMR) database (01/01/2017-11/30/2020) were used
- Acentrus is a health system solution for specialty pharmacy that includes patient records from 6 community and 11 academic sites across 10 US states
- 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
- The index date was the date of initiation of ibrutinib or acalabrutinib monotherapy in 1L
  - Monotherapy was indicated by the absence of other antineoplastic agents within 28 days of initiation of ibrutinib or acalabrutinib
  - A washout period of ≥12 months of continuous insurance eligibility without any use of antineoplastic agents was used to identify 1L therapy
- The baseline period comprised the 12 months 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

Patient selection

- The sample selection criteria are presented in **Figure 1**

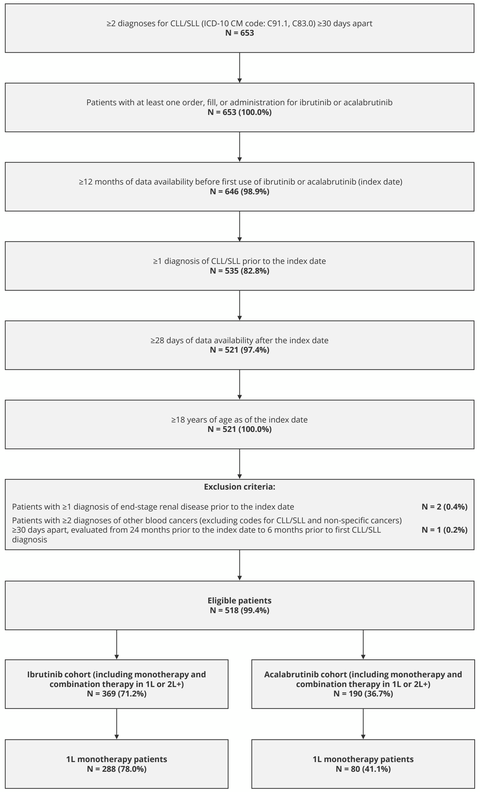
Study Outcomes

- Adherence was measured using the following:
  - Proportion of days covered (PDC): 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 2L initiation, death, or end of data availability)
  - Medication possession ratio (MPR): 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 for the first 3, 6, 9, and 12 months of the line of therapy among patients with a line of therapy duration ≥3, ≥6, ≥9, and ≥12 months, respectively

Statistical Analyses

- 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 the ibrutinib and acalabrutinib cohorts using t-tests for continuous variables and chi-square tests for categorial variables
- Adherence was compared between the ibrutinib and acalabrutinib cohorts using logistic regression models for proportions of patients with PDC and MPR above thresholds (i.e., ≥50%, ≥60%, ≥70%, ≥80%, and ≥90%; with ≥80% considered a standard threshold to consider patients as adherent[5]), and ordinary least squares regression models for mean PDC and MPR
  - Models were adjusted for baseline characteristics (i.e., age, gender, baseline Quan-Charlson Comorbidity Index [Quan-CCI], risk of a cardiovascular [CV] event, and diagnosis of atrial fibrillation)
  - For logistic regressions, odds ratios (ORs), 95% confidence intervals (CIs), and *P*-values were reported; for ordinary least squares regressions, mean differences (MDs), 95% CIs, and *P*-values were reported

Figure 1. Identification of CLL/SLL patients treated with acalabrutinib or ibrutinib monotherapy



1L: first line; 2L+: second line or later; CLL: chronic lymphocytic leukemia; ICD-10 CM: International Classification of Diseases, Tenth Revision, Clinical Modification; SLL: small lymphocytic lymphoma.

B-CELL MALIGNANCIES

RESULTS

- Among 288 and 80 patients treated with ibrutinib and acalabrutinib, mean age was 70.9 and 73.2 years, respectively, and 35.8% and 45.0% were female (**Table 1**)

Table 1. Baseline demographic and clinical characteristics evaluated in the 12-month baseline period

	Ibrutinib N = 288	Acalabrutinib N = 80
Age at index date, mean ± SD [median]	70.9 ± 10.3 [71.0]	73.2 ± 11.2 [75.0]
Female, n (%)	103 (35.8)	36 (45.0)
Race, n (%)		
White	179 (62.2)	32 (40.0)
Black	21 (7.3)	1 (1.3)
Asian	9 (3.1)	3 (3.8)
Other	79 (27.4)	44 (55.0)
Quan-CCI, mean ± SD [median]	3.2 ± 1.8 [2.0]	2.8 ± 1.4 [2.0]
Patients with CLL/SLL-related comorbidities, n (%)		
Enlarged lymph nodes (lymphadenopathy)	73 (25.3)	10 (12.5)
Thrombocytopenia	65 (22.6)	17 (21.3)
Fatigue/weakness	47 (16.3)	13 (16.3)
Anemia	47 (16.3)	11 (13.8)
Splenomegaly	37 (12.8)	2 (2.5)
Elixhauser comorbidities, n (%)		
Deficiency anemias	87 (30.4)	20 (25.6)
Coagulation deficiency	67 (23.4)	17 (21.8)
Lymphoma	62 (21.7)	15 (19.2)
Chronic pulmonary disease	34 (11.9)	11 (14.1)
Hypothyroidism	33 (11.5)	9 (11.5)

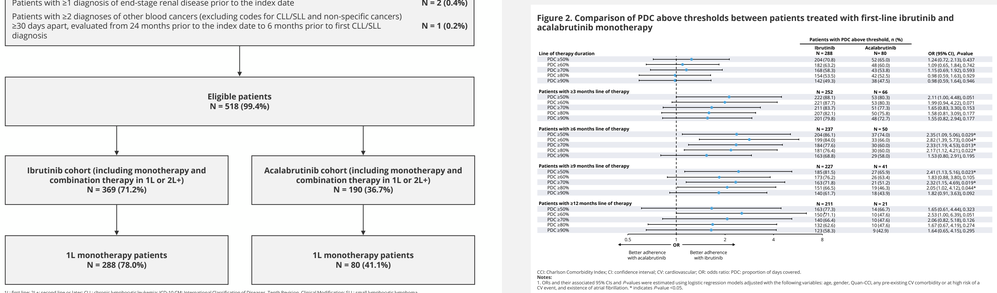
CCI: Charlson Comorbidity Index; CLL: chronic lymphocytic leukemia; CV: cardiovascular; SD: standard deviation; SLL: small lymphocytic lymphoma.
Notes:
1. Patients were considered at high risk of a CV event if they had any pre-existing CV comorbidities or if they had a score indicating high risk. Pre-existing CV comorbidities included hypertension, diabetes, cardiac arrhythmias/dysrhythmias, acute coronary syndrome, atrial fibrillation, cardiac failure, valvular disease, hypercholesterolemia, sleep apnea, congestive heart failure, obesity, cerebrovascular disease, ischemic heart disease, peripheral vascular disease, and pre-existing autoimmune conditions. Risk scores included ASCVD, CHA$_2$DS$_2$-VASc, CHARGE-AF, Framingham Heart Study-AF, Mayo, and CHA$_2$DS$_2$.
2. Presence of acid-related symptoms were used as a proxy to identify use of antacids.

- The mean length of follow-up was 23.9 months for the ibrutinib cohort and 11.0 months for the acalabrutinib cohort
- The mean line of therapy duration was 19.3 months in the ibrutinib cohort and 10.1 months in the acalabrutinib cohort

Treatment adherence based on PDC

- At all time points (i.e., the first 3, 6, 9, and 12 months of the line of therapy), patients treated with ibrutinib were consistently more adherent to treatment relative to those treated with acalabrutinib based on the proportion of patients with PDC ≥80% (**Figure 2**)
- Results reached statistical significance at 6 months (76.4% for ibrutinib vs 60.0% for acalabrutinib; OR [95% CI] = 2.17 [1.12-4.21]; *P*=0.022) and 9 months (66.5% vs 46.3%; 2.05 [1.02-4.12]; *P*=0.044)

Figure 2. Comparison of PDC above thresholds between patients treated with first-line ibrutinib and acalabrutinib monotherapy



CCI: Charlson Comorbidity Index; CI: confidence interval; CV: cardiovascular; OR: odds ratio; PDC: proportion of days covered.
Notes:
1. ORs and their associated 95% CIs and *P*-values were estimated using logistic regression models adjusted with the following variables: age, gender, Quan-CCI, any pre-existing CV comorbidity or at high risk of a CV event, and existence of atrial fibrillation. * indicates *P*-value <0.05.

- Furthermore, statistical significance was reached for the mean PDC at 6 months (0.84 for ibrutinib vs 0.74 for acalabrutinib; MD [95% CI] = 0.11 [0.02-0.19]; *P*=0.017) and 9 months (0.80 for ibrutinib vs 0.67 for acalabrutinib; MD [95% CI] = 0.12 [0.01-0.22]; *P*=0.026) (**Table 2**)

Table 1. Baseline Characteristics of Patients in the 1L and 2L+ Cohorts

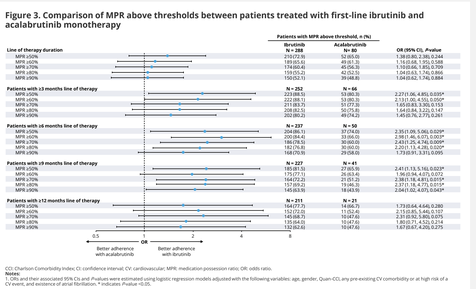
Mean ± SD [median]	Ibrutinib N = 288	Acalabrutinib N = 80	MDs (95% CI); *P*-value[1]
Line of therapy duration, months	19.3 ± 17.4 [12.3]	10.1 ± 7.7 [9.2]	
PDC	0.71 ± 0.34 [0.89]	0.68 ± 0.35 [0.85]	0.02 (-0.07, 0.10); 0.670
MPR	0.72 ± 0.34 [0.94]	0.69 ± 0.36 [0.85]	0.03 (-0.06, 0.11); 0.548
Patients with line of therapy duration ≥3 months	N = 252	N = 66	
PDC	0.90 ± 0.22 [1.00]	0.85 ± 0.27 [1.00]	0.06 (-0.01, 0.12); 0.073
MPR	0.90 ± 0.22 [1.00]	0.85 ± 0.27 [1.00]	0.06 (-0.01, 0.12); 0.074
Patients with line of therapy duration ≥6 months	N = 237	N = 50	
PDC	0.84 ± 0.27 [1.00]	0.74 ± 0.34 [1.00]	0.11 (0.02, 0.19); 0.017*
MPR	0.85 ± 0.27 [1.00]	0.74 ± 0.34 [1.00]	0.11 (0.03, 0.20); 0.010*
Patients line of therapy duration ≥9 months	N = 227	N = 41	
PDC	0.80 ± 0.30 [1.00]	0.67 ± 0.35 [0.78]	0.12 (0.01, 0.22); 0.026*
MPR	0.81 ± 0.30 [1.00]	0.67 ± 0.35 [0.78]	0.13 (0.02, 0.23); 0.016*
Patients with line of therapy duration ≥12 months	N = 211	N = 21	
PDC	0.76 ± 0.33 [0.99]	0.61 ± 0.38 [0.59]	0.13 (-0.01, 0.28); 0.078
MPR	0.77 ± 0.33 [1.00]	0.61 ± 0.38 [0.60]	0.14 (-0.00, 0.29); 0.055

CCI: Charlson Comorbidity Index; CI: confidence interval; CV: cardiovascular; MD: mean difference; MPR: medication possession ratio; PDC: proportion of days covered; SD: standard deviation.
Notes:
1. MDs and *P*-values were estimated using ordinary least squares regression models adjusted with the following variables: age, gender, Quan-CCI, any pre-existing CV comorbidity or at high risk of a CV event, and existence of atrial fibrillation. * indicates *P*-value <0.05.

Treatment adherence based on MPR

- At all time points (i.e., the first 3, 6, 9, and 12 months of the line of therapy), patients treated with ibrutinib were consistently more adherent to treatment relative to those treated with acalabrutinib based on the proportion of patients with MPR ≥80% (**Figure 3**)
- Results reached statistical significance at 6 months (76.8% for ibrutinib vs 60.0% for acalabrutinib; OR [95% CI] = 2.20 [1.13-4.28]; *P*=0.020), and 9 months (69.2% vs 46.3%; 2.37 [1.18-4.77]; *P*=0.015)
- In addition, statistical significance was reached for the mean MPR at 6 months (0.85 for ibrutinib vs 0.74 for acalabrutinib; MD [95% CI] = 0.11 [0.03-0.20]; *P*=0.010) and 9 months (0.81 for ibrutinib vs 0.67 for acalabrutinib; MD [95% CI] = 0.13 [0.02-0.23]; *P*=0.016) (**Table 2**)

Figure 3. Comparison of MPR above thresholds between patients treated with first-line ibrutinib and acalabrutinib monotherapy



CCI: Charlson Comorbidity Index; CI: confidence interval; CV: cardiovascular; MPR: medication possession ratio; OR: odds ratio.
Notes:
1. ORs and their associated 95% CIs and *P*-values were estimated using logistic regression models adjusted with the following variables: age, gender, Quan-CCI, any pre-existing CV comorbidity or at high risk of a CV event, and existence of atrial fibrillation. * indicates *P*-value <0.05.

LIMITATIONS

- EMR data may contain omissions and inaccuracies, but this is expected to equally affect all patients, and, thus, should have no impact on overarching conclusions
- Prescriptions were assumed to indicate their use; however, patients may not adhere to the treatment regimen as prescribed
- Results of this study may not be generalizable to all CLL/SLL patients treated with 1L ibrutinib or 1L acalabrutinib, since most patients studied were treated in an academic setting
- Although regression models were adjusted for baseline confounders, residual confounding due to unobserved confounders may remain. In addition, given the use of multivariable regression models, results of this study should be interpreted as the association between the use of ibrutinib or acalabrutinib and outcomes, rather than a measure of the impact of ibrutinib or acalabrutinib on outcomes
- Given the small sample size, only a few variables could be adjusted for in the models; comparisons among patients with ≥12 months line of therapy lacked sufficient power to detect statistically significant differences
- Acentrus is a provider-based data source in which records are available to the extent that the visits are part of the network of academic centers included in the Acentrus data; therefore, the database did not capture the services patients received from providers outside of the network

CONCLUSIONS

- Among patients with CLL/SLL, those treated with 1L once-daily ibrutinib monotherapy had higher adherence than those treated with 1L twice-daily acalabrutinib monotherapy across all fixed periods of time (i.e., first 3, 6, 9, and 12 months of the line of therapy)
- Given the importance of medication adherence for attaining optimal clinical outcomes in CLL/SLL, characterization of BTKi adherence rates may inform treatment effectiveness in real-world clinical practice

ACKNOWLEDGMENTS

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