A real-world study to assess the association of cardiovascular adverse events (CVAEs) with ibrutinib as first-line (1L) treatment for patients with Chronic Lymphocytic Leukemia (CLL) in the United States

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INTRODUCTION

- Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in Western countries, with an incidence rate of approximately 4-6 per 100,000.[1] With a median age at diagnosis of 72, senior adults are impacted the most by the disease;[1] among this group of patients, the incidence and prevalence of cardiovascular disease (CVD) are high
- In a recently published population-based study among patients with CLL, it was reported that 145 of 521 patients (28%) with no CVD at the beginning of treatment developed new CVD in 5 years; the same study also reported CVD as the main cause for 19% of the 678 death events observed in the study[2]
- Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, is commonly used as a first-line (1L) or relapsed/refractory treatment for management of CLL
- The cardiotoxicity profile of ibrutinib has been noted in previous trials and real-world studies and poses a major limitation to its use as a treat-to-progression strategy[3-7]
- However, prior real-world analyses have been limited in that none examined a patient's baseline risk factors for ibrutinib-associated cardiovascular adverse events (CVAEs) and therefore only report rates of incidence and discontinuation due to CVAEs
- Since ibrutinib is one of the most prescribed BTK inhibitors for managing CLL, it is important to investigate whether the treatment itself is associated with increased CVAEs while controlling for patient baseline CVD risk profiles
- This current study is the first to use real-world data to simultaneously investigate the role of pre-existing cardiac risk factors and the relative cardiotoxicity of ibrutinib vs other therapies among patients receiving 1L therapy for CLL
- The aim of this analysis was to ascertain whether ibrutinib confers additional CVAE risk over and above the patient's pre-existing baseline CVD risk
- This information may help clinicians optimize treatment decisions to achieve improved outcomes

METHODS

Study design and data source

- This study utilized nationwide retrospective longitudinal cohort data based on the real-world electronic health record-derived de-identified Flatiron Health database
- The Flatiron Health database is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction; during the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care)
- All patient records were retrieved based on the following criteria: age ≥18 years, diagnosed with CLL/small lymphocytic leukemia (SLL) (ICD-9 code: 204.1x; ICD-10 codes: C91.1x, C83.0x), ≥2 clinic encounters, and initiated 1L treatment between 1/1/2016 and 12/31/2019
- Cohorts were defined by the 1L treatment; the cohorts were separated into three groups as shown in **Table 1**:
  - Ibrutinib monotherapy group
  - Intensive therapy (IT) group (primarily bendamustine plus anti-CD20 therapy and fludarabine, cyclophosphamide plus anti-CD20 therapy)
  - Non-intensive therapy (NIT) group (primarily anti-CD20 therapy alone and chlorambucil plus anti-CD20 therapy)
- Cardiac risk factors were abstracted based on presence of a documented cardiac risk factor prior to the start of 1L treatment
- Similarly, CVAEs were abstracted based on documented new occurrence of a CVAE or a worsening of a prior condition

Independent variables and outcome variables

- Patient characteristics were captured using variables retrieved from their medical records
- The baseline variables were age, body mass index (BMI), systolic blood pressure (SBP), smoking status, diabetes status, Rai stage at diagnosis, ECOG at index date, Del17p status, IgHV mutation status, history of acute coronary syndrome (ACS)/myocardial infarction (MI), angina/coronary revascularization, congestive heart failure, atrial fibrillation/atrial flutter (AF), other arrythmias, cerebrovascular disease, peripheral arterial disease, and hypercholesterolemia
- The primary study outcomes were the occurrence of any CVAE, new or worsening hypertension, and new or worsening AF

Analysis

- We performed three main analysis steps as described below:
  - Firstly, to characterize pre-treatment CVD risk, we calculated Framingham cardiovascular (CV) risk score, which included age, gender, BMI, SBP, smoking status, and diabetes status as a continuous variable[8]
    - Other baseline variables not used in the Framingham risk score calculation were treated as independent covariates
  - Descriptive analysis was performed for all variables by treatment cohort
  - For continuous variables, means and standard deviations were reported
  - For categorical variables, frequencies and counts were reported
  - Statistical tests were performed on each variable to check for any significant imbalance across the treatment cohorts
- Secondly, logistic regression with inverse probability treatment weighting (IPTW) was used to investigate the main effects of baseline CV risk based on the Framingham risk score and 1L treatment on CVAE outcomes while controlling for other potential baseline confounders
  - Specifically, the following were included as potential confounders: Rai stage at diagnosis, ECOG at index date, Del17p status, IgHV mutation status, history of ACS/MI, angina/coronary revascularization, congestive heart failure, AF, other arrythmias, cerebrovascular disease, peripheral arterial disease, and hypercholesterolemia
  - Since IPTW allows comparisons between only 2 groups at a time, ibrutinib was compared against IT and NIT separately
- Finally, three types of sensitivity analyses were performed to evaluate the robustness of the findings
  - To check the result stability against IPTW variation, we used stepwise regression to determine the variables used in IPTW
  - To evaluate robustness against treatment grouping, we combined the IT and NIT cohorts and reran the analysis against the ibrutinib cohorts
  - To address confounding between treatment choice and Framingham score, the interaction term for these was added to the model to examine result stability against model specification change

RESULTS

- A total of 515 patients were included in three treatment groups, with 191 on ibrutinib monotherapy, 195 on IT, and 129 on NIT (**Table 1**)

Table 1. Treatment groups

Treatment group	n
Ibrutinib monotherapy	191
IT	195
Bendamustine, CD20	142
Cyclophosphamide, fludarabine, CD20	42
Cyclophosphamide, vincristine, CD20	5
Fludarabine, CD20	5
Cyclophosphamide, doxorubicin, vincristine, CD20	1
NIT	129
CD20	79
Chlorambucil, CD20	36
Chlorambucil	8
Venetoclax, CD20	5
Cyclophosphamide, CD20	1
All patients	515

1L = first-line; CD20 = anti-CD20 antibody (ofatumumab, rituximab, obinutuzumab); IT = intensive therapy; NIT = non-intensive therapy.

- Baseline variable descriptive statistics and p-values for balance across treatment cohorts are reported in **Table 2**
- Given that >20% (0.2) is considered a high CV risk, most patients had very high CV risk, with a median Framingham score of 0.340, 0.299, and 0.419 for the ibrutinib, IT, and NIT groups, respectively

Table 2. Baseline characteristics

Baseline characteristic	Ibrutinib monotherapy (n = 191)	IT (n = 195)	NIT (n = 129)
Gender, male, n (%)	120 (62.8)	136 (69.7)	68 (52.7)
Age at index date, years, mean (SD)	71.2 (9.9)	66.2 (10.6)*	74.5 (7.9)**
Rai stage at diagnosis, n (%)			
0	59 (30.9)	44 (22.6)	34 (26.4)
I	33 (17.3)	26 (13.3)	13 (10.1)
II	9 (4.7)	14 (7.2)	5 (3.9)
III	16 (8.4)	14 (7.2)	7 (5.4)
IV	15 (7.9)	31 (15.9)	11 (8.5)
Not documented	59 (30.9)	66 (33.8)	59 (45.7)
ECOG at index date, n (%)			
0	55 (28.8)	84 (43.1)§	46 (35.7)
1	51 (26.7)	46 (23.6)	41 (31.8)
2	15 (7.9)	6 (3.1)	8 (6.2)
3	2 (1.1)	1 (0.5)	1 (0.8)
4	1 (0.5)	2 (1.0)	1 (0.8)
Unknown/Not documented	67 (35.1)	56 (28.7)	32 (24.8)
Del(17p) deletion present, n (%)	51 (26.7)	7 (3.6)*	4 (3.1)**
IgHV mutated, n (%)	29 (15.2)	35 (17.9)	26 (20.2)
BMI at baseline, mean (SD)	28.5 (6.5)	29.0 (6.4)	28.5 (6.7)
Framingham risk score, median	0.340	0.299	0.419
Diabetes mellitus, n (%)	107 (56.0)	86 (44.1)*	82 (63.6)
Smoking status, yes, n (%)	48 (25.1)	47 (24.1)	36 (27.9)
ACS/MI, n (%)	15 (7.9)	13 (6.7)	15 (11.6)
Angina/coronary revascularization, n (%)	5 (2.6)	4 (2.1)	11 (8.5)**
Congestive heart failure, n (%)	10 (5.2)	4 (2.1)	10 (7.8)
Pre-existing HTN, n (%)	6 (3.1)	2 (1.0)	7 (5.4)
AF, n (%)	27 (14.1)	23 (11.8)	34 (26.4)**
Other arrhythmias, n (%)	97 (50.8)	107 (54.9)	65 (50.4)
Cerebrovascular disease, n (%)	17 (8.9)	23 (11.8)	26 (20.2)**
Peripheral arterial disease, n (%)	18 (9.4)	9 (4.6)	7 (5.4)
Hypercholesterolemia, n (%)	131 (68.6)	113 (57.9)*	95 (73.6)

Note: If the continuous variable was normally distributed, t-test was applied; otherwise, signed-rank test was used; chi-square test was applied for categorical variables, and Fisher's exact test was applied if at least one cell had an expected frequency less than 5.
ACS/MI = acute coronary syndrome/myocardial infarction; AF = atrial fibrillation/atrial flutter; CV = cardiovascular; ECOG = Eastern Cooperative Oncology Group performance status; HTN = hypertension; IT = intensive therapy; NIT = non-intensive therapy.
§$p < 0.05$, IM vs IT for all levels of ECOG; *$p < 0.05$, IM vs IT; **$p < 0.05$, IM vs NIT.

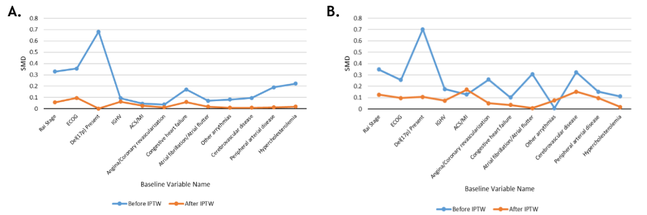
- Univariate logistic regression confirmed that baseline CV risk measured by the Framingham score was significantly associated with any CVAE and new or worsening hypertension within each treatment cohort (**Table 3**)

Table 3. Univariate logistic regressions of CVAE outcomes against Framingham score as an independent variable

Dependent variable	Odds ratio (95% CI)
Any CVAE	1.37 (1.13, 1.66)*
New or worsening hypertension	1.37 (1.07, 1.74)*
New or worsening AF	1.16 (0.85, 1.60)

AF = atrial fibrillation/atrial flutter; CI = confidence interval; CVAE = cardiovascular adverse event.
*$p < 0.05$.

Figure 1. IPTW adjustment for ibrutinib monotherapy vs A) IT and B) NIT



ACS/MI = acute coronary syndrome/myocardial infarction; ECOG = Eastern Cooperative Oncology Group performance status; IPTW = inverse probability treatment weighting; SMD = standard mean difference.

- IPTW adjustment was performed for both ibrutinib vs IT and ibrutinib vs NIT; patient baseline characteristics balance and comparability were significantly improved; the before and after IPTW standard mean differences (SMDs) for all variables are shown in **Figure 1A-B**
- Logistic regression confirmed that both baseline CV risk and ibrutinib were statistically significant independent predictors of CVAEs
- The main-effect analysis showed that compared to IT and NIT, 1L ibrutinib treatment was significantly associated with increased risk of CVAE for all patients at any Framingham CV risk level (**Table 4**)

Table 4. Analysis results from logistic regression with IPTW

Groups	Dependent variable	Independent variable	Odds ratio (95% CI)
Ibrutinib monotherapy vs IT	Any CVAEs	1L Treatment	2.61 (1.86, 3.67)*
		Framingham score	1.48 (1.24, 1.75)*
	New or worsening hypertension	1L Treatment	3.66 (2.30, 5.80)*
		Framingham score	1.27 (1.03, 1.57)*
	New or worsening AF	1L Treatment	3.02 (1.64, 5.56)*
		Framingham score	1.20 (0.91, 1.58)
Ibrutinib monotherapy vs NIT	Any CVAEs	1L Treatment	1.88 (1.32, 2.67)*
		Framingham score	1.39 (1.17, 1.65)*
	New or worsening hypertension	1L Treatment	2.13 (1.37, 3.31)*
		Framingham score	1.36 (1.11, 1.68)*
	New or worsening AF	1L Treatment	2.46 (1.36, 4.44)*
		Framingham score	1.51 (1.16, 1.96)*

1L = first-line; AF = atrial fibrillation/atrial flutter; CI = confidence interval; CVAE = cardiovascular adverse event; IT = intensive therapy; NIT = non-intensive therapy.
*$p < 0.05$.

- Odds ratios of CVAE with ibrutinib vs IT and NIT were 2.61 (95% CI: 1.86, 3.67) and 1.88 (1.32, 2.67), respectively; odds ratios of new or worsening hypertension were 3.66 (2.30, 5.80) and 2.13 (1.37, 3.31); and odds ratios of new or worsening AF were 3.02 (1.64, 5.56) and 2.46 (1.36, 4.44)
- Sensitivity analysis confirmed that the findings were robust against changes in IPTW methodology, treatment grouping changes, and model specification

CONCLUSIONS

- The study confirmed that higher baseline CV risk and treatment with ibrutinib were independently associated with a significantly increased risk of CVAE
- Clinical consideration may be warranted when selecting ibrutinib treatment for CLL patients with higher CV risk to avoid compounding risks of CVAE

REFERENCES

1. Scarfò, L, et al. *Crit Rev Oncol Hematol*. 2016;104:169-82.
2. Larsson, K, et al. *Br J Haematol*. 2020;190(4):e245-8.
3. Leong, DP, et al. *Blood*. 2016;128(1):138-40.
4. Rhodes, JM & Barrientos, JC *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):24-32.
5. Baptiste, F, et al. *Open Heart*. 2019;6(1):e001049.
6. Dickerson, T, et al. *Blood*. 2019;134(22):1919-28.
7. Roeker, LE, et al. *JAMA Netw Open*. 2019;2(12):e1916326.
8. D'Agostino, RB, et al. *Circulation*. 2008;117(6):743-53.

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DISCLOSURES

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