A real-world study to assess the association of cardiovascular adverse events with ibrutinib as first-line (1L) treatment for patients with chronic lymphocytic leukemia

Abstract Text

Introduction: Ibrutinib, a Bruton 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 both trials and previous real-world studies and poses a major limitation to its use as a treat-to-progression strategy (NCT02477696; NCT03734016; Leong, 2016; Dickerson, 2019; Ahn 2019; Mato, 2016; Olsweski, 2019; Roeker, 2019). However, prior real-world analyses have been limited in that few examined a patient's baseline risk factors for ibrutinib-associated cardiovascular adverse events (CVAEs) and therefore report only rates of incidence and discontinuation due to CVAEs. This study is the first to use real-world data to simultaneously investigate the role of pre-existing cardiovascular (CV) risk factors and the relative cardiotoxicity of ibrutinib vs other therapies in patients receiving 1L therapy for CLL. The aim of this analysis was to ascertain whether ibrutinib confers additional CVAE risk over and above a patient's pre-existing baseline CV risk.

Methods: Patient records were retrieved from the nationwide, electronic health record-derived, de-identified Flatiron Health database based on the following criteria: age ≥18 years, diagnosed with CLL/small lymphocytic lymphoma, ≥2 clinic encounters, and initiated 1L treatment between 1/1/2016 and 12/31/2019. The study population included patients with CLL treated in the 1L setting in one of three groups: 1) ibrutinib monotherapy, 2) intensive therapy (IT; bendamustine plus anti-CD20 therapy and fludarabine, cyclophosphamide plus anti-CD20 therapy), and 3) non-intensive therapy (NIT; anti-CD20 therapy alone and chlorambucil plus anti-CD20 therapy). The first analysis step was the pretreatment calculation of the Framingham CV risk score (D'Agostino, 2008), which included age, body mass index, systolic blood pressure, smoking status, and diabetes status, as a continuous variable. The primary study outcomes were the occurrence of any CVAE, new or worsening hypertension, and new or worsening atrial fibrillation/atrial flutter (AF). 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, del(17p) status, IgHV mutation status, history of acute coronary syndrome/myocardial infarction, angina/coronary revascularization, congestive heart failure, AF, other arrythmias, cerebrovascular disease, peripheral arterial disease, and hypercholesterolemia. Sensitivity analyses were performed to evaluate the robustness of the findings with variations to IPTW methods, treatment grouping, and model specification.

Results: A total of 515 patients were included in three treatment groups, with 191 on ibrutinib monotherapy, 195 on IT, and 129 on NIT. Considering that a Framingham score of >0.20 is considered a high CV risk, most

of the patients had very high CV risk, with median Framingham scores of 0.34, 0.30, and 0.42 for the ibrutinib, IT, and NIT groups, respectively. Univariate logistic regression confirmed that baseline CV risk measured by the Framingham score was significantly associated with any CVAE and hypertension (Table 1; $p<0.05$). Patient baseline characteristics were balanced and comparable after IPTW adjustment. Logistic regression confirmed that both baseline CV risk and 1L ibrutinib treatment were statistically significant independent predictors of CVAEs. The main effect of ibrutinib indicated that 1L ibrutinib treatment was significantly associated with increased risk of CVAEs compared to IT and NIT for all patients at any Framingham CV risk level (Table 2). Comparing ibrutinib vs IT, odds ratios (ORs) for the occurrence of any CVAE, hypertension, and AF were 2.61 (95% CI: 1.86, 3.67), 3.66 (95% CI: 2.30, 5.80), and 3.02 (95% CI: 1.64, 5.56), respectively, while comparing ibrutinib vs NIT, the ORs were 1.88 (95% CI: 1.32, 2.67), 2.13 (95% CI: 1.37, 3.31), and 2.46 (95% CI: 1.36, 4.44), respectively. All ORs were significantly different at $p<0.05$. Sensitivity analysis confirmed that the findings were robust to changes in IPTW methodology, treatment grouping changes, and model specification.

Conclusion: This study demonstrated that both high baseline CV risk and 1L ibrutinib treatment were significantly associated with increased risk of CVAEs. Clinical consideration may be warranted when selecting ibrutinib for CLL patients with high CV risk to avoid compounding risks of CVAEs.

Table 1: Univariate logistic regressions of CVAE outcomes against Framingham score

Dependent Variable	Independent Variable	Odds Ratio (95% CI)	p-value
Any CVAEs	Framingham score	1.37 (1.13, 1.66)	0.0014
New or worsening hypertension	Framingham score	1.37 (1.07, 1.74)	0.0112
New or worsening AF	Framingham score	1.16 (0.85, 1.60)	0.3529

AF, atrial fibrillation/atrial flutter; CVAE, cardiovascular adverse event.

Table 2: Logistic regression with IPTW to assess the impact of Framingham score and 1L treatment on CVAE outcomes

1L Treatment Groups	Dependent Variable	Independent Variable	Odds Ratio (95% CI)	p-value
Ibrutinib vs IT	Any CVAEs	1L treatment	2.61 (1.86,3.67)	<0.0001
		Framingham score	1.48 (1.24,1.75)	<0.0001
	New or worsening hypertension	1L treatment	3.66 (2.30,5.80)	<0.0001
		Framingham score	1.27 (1.03,1.57)	0.0243
	New or worsening AF	1L treatment	3.02 (1.64,5.56)	0.0004
		Framingham score	1.20 (0.91,1.58)	0.2012
Ibrutinib vs NIT	Any CVAEs	1L treatment	1.88 (1.32,2.67)	0.0004
		Framingham score	1.39 (1.17,1.65)	0.0002
	New or worsening hypertension	1L treatment	2.13 (1.37,3.31)	0.0008
		Framingham score	1.36 (1.11,1.68)	0.0033
	New or worsening AF	1L treatment	2.46 (1.36,4.44)	0.0029
		Framingham score	1.51 (1.16,1.96)	0.0025

1L, first-line; AF, atrial fibrillation/atrial flutter; CVAE, cardiovascular adverse event; IT, intensive therapy; NIT, non-intensive therapy.