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LETTER TO THE EDITOR

Left atrial abnormality (LAA) as a predictor of ibrutinib-associated atrial fibrillation in patients with chronic lymphocytic leukemia

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ABSTRACT

Results from several recent studies in chronic lymphocytic leukemia (CLL) have demonstrated an association between ibrutinib exposure and the development of atrial fibrillation, estimated incidence of 11% with long-term follow up. This is a common cause of ibrutinib discontinuation. Risk factors for atrial fibrillation include advanced age, hypertension (HTN), mitral valve disease (MVD), left atrial remodeling, coronary artery disease (CAD) and risk factors for cardiovascular dysfunction We conducted a retrospective case control study using the presence of left atrial abnormality identified on pre-ibrutinib EKGs, defined as either (1) Lead II-bifed p wave, with 40 mcsec between peaks for $\geq$ 2.5 mm wide $\geq$ 100 msec in duration, (2) Lead V1-biphasic P wave with terminal portion $\geq$ 40 msec in duration or terminal portion $\geq$ 1 mm deep or (3) PR interval $\geq$ 200 msec (intra-atrial conduction delay) as a predictor for development of atrial fibrillation. 183 consecutively CLL patients treated with ibrutinib were identified. 44 patients met inclusion criteria (20 cases, 24 controls). 20 (11.3%) of patients developed atrial fibrillation. Left atrial enlargement was identified as a significant predictor of development of atrial fibrillation (OR 9.1, 95% CI 2.2–37.3, p=0.02). Age, baseline HTN, CAD, diabetes, age and sex were not significant predictors. Area under the ROC curve for the model was estimated to be 75%. LAA identified by EKG is a moderately specific and sensitive finding that can identify patients at increased risk for this toxicity.

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Introduction

Randomized data from three large clinical trials have demonstrated an association between ibrutinib treatment and the development of atrial fibrillation (AFIB) in chronic lymphocytic leukemia (CLL) patients with an incidence of 11% in long-term follow-up.[1–4] Notably, AFIB is the most common cause of ibrutinib discontinuation in clinical practice, underscoring the need to decrease the risk of AFIB and premature, unnecessary ibrutinib discontinuation.[5] Advanced age, hypertension (HTN), mitral valve disease (MVD), coronary artery disease (CAD), and left atrial remodeling (fibrosis, microscopic myocyte hypertrophy, and enlargement) are known cardiovascular (CV) risk factors for developing AFIB in the general population; whether these factors affect development of AFIB in ibrutinib-treated CLL patients has been suggested[6] but currently not proven.[7]

Our goal was to develop a simple, real-world model to predict patients at the highest risk for new AFIB after ibrutinib initiation. We evaluated known CV risk factors and the presence of electrocardiogram (ECG) determined left atrial abnormality (LAA) to identify these patients.

Methods

We conducted a retrospective case-control study of CLL patients treated with ibrutinib at 2 centers. Patients were excluded if they had a preexisting AFIB diagnosis, did not have a pre-ibrutinib ECG (within 3 months) or were treated with doses of ibrutinib < 420 mg per day, which is the FDA-recommended dose.

The primary endpoint was the development of AFIB while on ibrutinib therapy. AFIB was defined as lack of discrete P waves, "F" waves at a rate between 350 with a random ventricular response that is irregularly irregular. The primary exposure was pre-ibrutinib LAA on ECG. LAA was defined as presence of one of the following: (1) Lead II-bifed P wave ("p mitrale") with 40 msec between peaks or > 2.5 mm wide or > 100 msec in duration, (2) Lead V1-biphasic P wave with terminal portion > 40 msec in duration or terminal portion > 1 mm deep or (3) PR interval $\geq$ 200 msec (intra-atrial conduction delay). All ECGs were interpreted by two cardio-oncologists who were blinded to the primary study outcome.

Logistic regression was used to test the association between CV risk factors and AFIB. We also used descriptive methods and receiver operator characteristic (ROC) analysis (non-parametric) to define LAA test characteristics.

Results

183 consecutive CLL patients treated with ibrutinib were identified. Baseline (median) CLL characteristics for the entire cohort

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Table 1. Cardiovascular characteristics associated with ibrutinib-associated atrial fibrillation.

Variable	OR (95% CI)	P value
LAA	6.6 (1.5–29.2)	.01
Baseline HTN	1.6 (0.3–8.2)	.59
Baseline CAD	1.7 (0.2–14.2)	.61
Age	1.0 (0.94–1.1)	.63

Table 2. ECG as a predictor of ibrutinib-associated atrial fibrillation.

Characteristic	Value	95 % CI
Sensitivity	79%	54–94%
Specificity	71%	49–87%
Positive likelihood ratio	2.7	1.4–5.3
Negative likelihood ratio	0.30	0.1–0.74
Positive predictive value	68%	45–86%
Negative predictive value	81%	58–95%

included: age at ibrutinib start 70 years, 2 prior therapies, 87% relapsed-refractory, 27% del(17p) and follow up 17 months. Baseline CV characteristics included: HTN 42%, CAD 12%, AFIB 8% and MVD 5%. 44 patients (20 cases and 24 controls) were selected who met study entry criteria for LAA analysis.

20 patients (11.3%) developed AFIB at a median time of 7 months from ibrutinib initiation. In univariate analyses (covariates LAA, baseline HTN, CAD, diabetes, age, sex) pre-ibrutinib, LAA was the only variable significantly associated with the development of AFIB (OR 9.1, 95%CI 2.2–37.3, p = .02). LAA remained significantly associated (OR 6.6, 95%CI 1.5–29.2, p-.01) with AFIB when controlling for baseline HTN, CAD and age in multivariate analysis (Table 1). Test characteristics for LAA as a predictor of ibrutinib-associated AFIB are described in Table 2. Area under the ROC curve for the model was estimated to be 75%.

Discussion

AFIB is an ibrutinib-associated CV event occurring in approximately 10% of ibrutinib-treated patients. We found that a LAA, identified by ECG (a universally available, simple to interpret and inexpensive test) is a moderately specific and sensitive finding that independently identifies patients at an increased risk for this toxicity. A pre-treatment ECG may provide useful stratification for aggressive pre and in-treatment cardiovascular risk factor management; this alone has an independent primary benefit. We recognize that there are limitations to reliance on LAA. Even though all patients with LAA will not develop AFIB, there is still benefit with minimal downside to select those with LAA for optimal cardiac risk factor management and avoids unnecessary over-treatment and follow-up in "low" risk patients. We also do not endorse withholding the appropriate initiation of ibrutinib in patients with screening LAA. The presence of LAA provides context and guidance for the initiation and follow-up for treatment with ibrutinib.

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