Rates and Risk of Atrial Arrhythmias in Patients Treated With Ibrutinib Compared With Cytotoxic Chemotherapy

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There is increasing evidence that rates of atrial arrhythmias (AA), specifically atrial fibrillation and flutter are elevated in patients treated with the tyrosine kinase inhibitor, ibrutinib; however, the exact risk of ibrutinib-associated AA is not definitively established. We conducted a retrospective study of 137 patients diagnosed with B-cell malignancies treated with ibrutinib compared with 106 patients treated with chemotherapy for the same cancers in order to quantify the rates and risk of AA in a "real-world" sample of cancer patients. Fisher's exact test was used to evaluate for any statistically significant differences between groups. Logistic regression was used to generate odds ratios, adjusting for potential confounders. Incidence of AA was 14% (n = 17) in ibrutinib-treated patients compared with 3% (n = 3) in patients treated with chemotherapy (p = 0.009). Ibrutinib-treated patients were significantly older (mean age 67 vs 63 years, p = 0.003); however, there were no other significant differences in baseline characteristics. Ibrutinib use, age, hypertension, and previous use of ACE inhibitors, angiotensin receptor blocker use, β blocker use, and aspirin use were independently associated with incident arrhythmias. In multivariable analysis, patients treated with ibrutinib were associated with a 5-fold increased risk of developing AA (odds ratio = 5.18, 95% confidence interval 1.42 to 18.89). In conclusion, the rates and risk of AA are higher in patients treated with ibrutinib compared with chemotherapy, and this study provides strong evidence that ibrutinib itself is an independent risk factor for the development of incident AA. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;124:539−544)**

Ibrutinib is a first-in-class oral Bruton's tyrosine kinase inhibitor approved for use in chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and Waldenstrom's Macroglobulinemia.[1−4] Since its approval, ibrutinib has rapidly become the standard of care for these disease states, especially for high risk and older patients. Nevertheless, an increased incidence of atrial fibrillation (AF) has been reported with ibrutinib, ranging from 5% to 16%.[1,5−9] Pooled analysis of randomized controlled trials shows that ibrutinib consistently increases the risk of incident AF compared with alternative therapies at a rate of 3.3 per 100 person-years.[10] Despite this association, the mechanism of AF in the setting of ibrutinib is poorly understood, and a causal link between ibrutinib and incident AF is not definitively established as previous studies included patients with a history of arrhythmias in the analysis.[7,11] In our study, we report the incidence of AF and atrial flutter (AFL) in a "real-world" sample of ibrutinib-treated patients compared with standard chemotherapy, whereas excluding patients with a known history of arrhythmia from the analysis to establish ibrutinib as an independent risk factor for the development of atrial arrhythmias.

Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its late amendments or comparable ethical standards. This was a retrospective chart review study. As such, informed consent is not necessary. The study was approved by the University of South Florida Institutional Review Board and the H. Lee Moffitt Cancer Center (MCC) and Research Institute Scientific Review Committee (Pro00022060; MCC #18229).

The patient population was derived from the MCC Malignant Hematology Program. All patients must have received their oncologic care primarily at MCC to be

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included in the study. Patient-related data are maintained in the electronic medical record for all inpatient and outpatient evaluations at MCC. The "case" group consisted of patients diagnosed with B-cell malignancies and initiated on ibrutinib therapy between January 1, 2010 and December 31, 2017, and the "control" were patients diagnosed with the same subset of B-cell malignancies and treated with cytotoxic chemotherapy during the same time frame (bendamustine/rituximab, lenalidomide/rituximab, or fludarabine/cyclophosphamide/rituximab). Patients who received ibrutinib must have completed at least one 28-day cycle of ibrutinib in order to be included the analysis. Patients without appropriate follow up or incomplete clinical documentation were excluded.

Medical records of patients who met inclusion criteria were thoroughly evaluated for baseline characteristics including age, gender, race, body mass index, indication for ibrutinib or chemotherapy use, date of initiation of therapy and therapy termination date if available. Preexisting cardiovascular (CV) risk factors or disease including coronary artery disease, stroke, cardiomyopathy, congestive heart failure, valve disease, hypertension, diabetes mellitus, hyperlipidemia, tobacco use, and family history of CV disease were also recorded. A complete CV medication review including baseline use of β blockers, nondihydropyridine calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, digoxin, antiarrhythmic drugs, and aspirin was completed.

The primary end point of the study was the development of atrial arrhythmias, particularly AF or AFL. Occurrence and type of cardiac arrhythmias since initiation of ibrutinib or chemotherapy was recorded. Arrhythmias were diagnosed via 12-lead electrocardiogram, telemetry, or cardiac implantable electronic device. The specific arrhythmia diagnosis was adjudicated by the study cardiologist. For cardiac implantable electronic devices, mode switch events were not sufficient to diagnose arrhythmias; direct evaluation of recorded arrhythmia electrograms by the study cardiologist/electrophysiologist were required and performed.

Fisher's exact test was used to test the differences between case and control patients for categorical covariates and Student's *t*-test was used to test differences between the cases and control patients for continuous covariates. Univariable and multivariable logistic regression was used to generate odds ratios (ORs) and 95% confidence intervals as an estimate of the relative risk. A model building approach was employed to reduce the number of covariates and identify the most informative clinical characteristics. First, univariable logistic regression identified covariates significantly ($p < 0.05$) associated with risk. To produce a parsimonious model ("reduced model"), all the significant clinical covariates from univariable analyses were included in a stepwise backward elimination model using a threshold of 0.05 for inclusion. All statistical analyses were 2-sided and performed using Stata/MP 14.2 (Stata Corporation, College Station, Texas).

Results

Baseline demographics and clinical characteristics are summarized in Table 1 for the 137 patients treated with ibrutinib for B-cell malignancies versus 106 patients receiving cytotoxic chemotherapy regimens for B-cell malignancies. Newly diagnosed, incident AF or AFL after initiation of therapy occurred in 14% of the cases (n = 17) compared with 3% of the controls (n = 3; p = 0.015). The majority of patients had a diagnosis of CLL (cases 68%; controls 58%). In the control patients, the most common chemotherapy regimen was bendamustine/rituximab (62%) followed by fludarabine/cyclophosphamide/rituximab and lenalidomide/rituximab. The study populations were predominately white men. Although patients receiving ibrutinib were significant older than the control patients receiving chemotherapy, there were no other significant differences between the groups.

Because we found a significant difference in incident atrial arrhythmias (Table 1), univariable analyses were conducted to assess the association between the patient characteristics and risk of incident atrial arrhythmia with several patient characteristics independently associated with incident atrial arrhythmias including ibrutinib use (Table 2).

In multivariable analysis (Table 3), the "full model" containing all significant covariates from the univariable analyses revealed that only age and previous use of aspirin were significantly associated with incident atrial arrhythmias. Based on the covariates from the full model, a backward elimination approach was applied to identify a parsimonious model containing the most informative covariates. This reduced, parsimonious model revealed ibrutinib use was independently associated with a 5.2-fold increased risk of developing incident AF or AFL. When age was forced into the reduced model, ibrutinib and aspirin remained significantly associated with incident arrhythmias. Of note, patients with preexisting/prevalent AA were excluded from both the univariable and multivariable analyses.

Management of ibrutinib-associated incident AF or AFL varied among the 17 patients who developed this outcome. The mean CHADS-VASc score in this cohort was 2.76 (SD $\pm$ 1.68). Ten patients (59%) received anticoagulation with a direct oral anticoagulant (DOAC) including apixaban, rivaroxaban, or dabigatran. No patients received vitamin K antagonists, and the remainder were on no anticoagulation or were treated with aspirin. Among those treated with a DOAC, 70% of the patients were given apixaban. Ibrutinib was discontinued in 9 of these patients, with the development of AF cited as the primary reason in 5 of these patients (56%). There were no major bleeding complications in any of the patients treated with anticoagulation nor was bleeding cited as a reason for discontinuation of ibrutinib use in the cohort of patients with ibrutinib-associated incident AF. Eleven patients received a rate control strategy (the majority of whom were given β blockers) whereas 6 patients were treated with a rhythm control strategy (3 patients with sotalol, 2 patients with flecainide, and 1 patient with amiodarone). There was no difference in outcomes including ibrutinib discontinuation or bleeding based on the prescribed AF treatment. Moreover, there was no difference in the clinical presentation of AF between groups with respect to ventricular rates or symptomatic heart failure events.

Discussion

We conducted a single-center retrospective study of real-world patients that confirms earlier findings of increased rates of AF in the setting of ibrutinib use.[5,7,12]

Table 1
Patient demographics by chemotherapy regimen*

	Patients treated with Ibrutinib Chemotherapy (n = 137)	Patients treated standard-of-care Chemotherapy (n = 106)	p Value
Age at onset of therapy − mean years (standard deviation [SD])	67 (0.86)	63 (1.09)	**0.003**
Female sex	40 (29%)	33 (31%)	0.779
BMI − mean (kg/m^2 [SD])	27.4 (5%)	28.4 (6%)	0.183
Ever smokers	74 (54%)	57 (54%)	0.999
Incident atrial arrhythmia after therapy†	17 (14%)	3 (3%)	**0.009**
Prior history of atrial arrhythmia	14 (10%)	15 (14%)	0.426
Atrial arrhythmia risk factors			
Prior valvular disease	10 (7%)	11 (10%)	0.491
Prior coronary artery disease	19 (14%)	21 (20%)	0.227
Prior cardiomyopathy	7 (5%)	5 (8%)	0.999
Prior hypertension	78 (57%)	53 (50%)	0.301
Prior diabetes mellitus	29 (21%)	18 (17%)	0.513
Prior hyperlipidemia	70 (50%)	47 (44%)	0.304
Prior stroke	3 (2%)	6 (6%)	0.184
Family history of coronary artery disease	38 (28%)	30 (28%)	0.999
Baseline cardiovascular medications			
Prior angiotensin converting enzyme inhibitors/Angiotensin II receptor blockers use	43 (31%)	28 (26%)	0.477
Prior beta-blockers use	46 (34%)	24 (23%)	0.065
Prior nondihydropyridine calcium channel blockers use	5 (4%)	6 (6%)	0.541
Prior digoxin use	4 (3%)	3 (3%)	0.999
Prior antiarrhythmics use	2 (2%)	2 (2%)	0.999
Prior statin use	48 (35%)	39 (37%)	0.789
Prior aspirin use	38 (28%)	33 (31%)	0.573
Malignancy‡			
Chronic lymphocytic leukemia	93 (68%)	61 (58%)	
Mantle cell lymphoma	25 (18%)	44 (42%)	**< 0.001**
Waldenstrom's macroglobulinemia	14 (10%)	1 (1%)	**0.011**
Other	5 (4%)	0 (0.0%)	0.157

Bold p values are statistically significant.
* Overall, 93% of the study population were white and 95% were non-Hispanic. All percentages were rounded up to the nearest whole value.
† Patients with prior history of atrial arrhythmias were excluded; Ibrutinib = 124 and Standard-of-Care Chemotherapy = 91
‡ p values based on comparing distributions of MCL vs. CLL, WM vs. CLL, and Other vs. CLL, respectively.

Analyses were conducted to identify the most informative characteristics associated with risk of incident AF which revealed a 5.2-fold increased risk for ibrutinib use. When age was included in this parsimonious model, the OR for ibrutinib use was somewhat attenuated (OR = 4.15), but remained statistically significant. As such, ibrutinib is confirmed as an independent risk factor for the development of atrial arrhythmias.

AF affects more than 33 million people worldwide and is associated with an increased risk of stroke, heart failure, and all-cause mortality.[13–15] It is especially common in cancer patients with a prevalence of more than 4% to 5% which may be related to either the malignancy itself or as a result of the cancer treatments.[16] For example, in patients with CLL, 6.1% develop incident AF regardless of treatment[17,18] Ibrutinib is a novel tyrosine kinase inhibitor targeting the Bruton's tyrosine kinase and the tec protein tyrosine kinase (TEC), used in the treatment of various B-cell malignancies.[19] It is well documented that ibrutinib use leads to increased rates of AF, as high as 14% to 16%.[5–9] Our data are consistent with these previous studies, with an incidence of 14%.

Numerous risk factors for ibrutinib-associated AF have been identified including previous history of AF, hypertension, and an enlarged left atrial diameter and age over 65 years.[5,7] In our study, 6 variables were shown in univariate analysis to be associated with incident atrial arrhythmias including ibrutinib use, age, hypertension, ACE/angiotensin receptor blockers use, β blocker use, and aspirin use. Our study of "real-world" patients demonstrates that ibrutinib remains an independent predictor of incident atrial arrhythmias with an OR of 5.18 in a parsimonious model. Previous studies have not rigorously controlled for prevalent AF; therefore, these data are significant because our study population (and subsequent analyses) excluded patients with a previous history of arrhythmias. As such, it is increasingly clear that ibrutinib itself increases the likelihood of developing AF and other atrial arrhythmias. Moreover, in our cohort, AF was the primary reason for discontinuation of ibrutinib therapy in 56% of patients. Identifying the mechanism of ibrutinib-associated AF will hopefully lead to better risk mitigation and prevention strategies to avoid unnecessary cancer treatment disruption.

AF is associated with several CV sequelae, the most concerning of which is stroke and thromboembolism. AF confers a 5-fold higher risk of stroke compared with the general population.[20] Systemic anticoagulation with vitamin K antagonists or DOACs can reduce the risk of stroke

Table 2
Odds ratios for the association between patient characteristics and incident atrial arrhythmia

Covariate	OR (95% CI)
Ibrutinib use	
No	1.00 (referent)
Yes	**4.66 (1.32 − 16.42)**
Age, continuous	**1.09 (1.04 − 1.15)**
Gender	
Male	1.00 (referent)
Female	0.38 (0.11 − 1.34)
Tobacco use	
Never smoker	1.00 (referent)
Ever smoker	0.98 (0.39 − 2.48)
Body mass index, categorical	
<25	1.00 (referent)
>=25 and <30	0.62 (0.20 − 1.95)
>=30	1.07 (0.35 − 3.26)
Body mass index, continuous	0.99 (0.92 − 1.08)
Prior coronary artery disease	
No	1.00 (referent)
Yes	2.38 (0.79 − 7.12)
Prior cardiomyopathy	
No	1.00 (referent)
Yes	2.59 (0.51 − 13.17)
Prior hypertension	
No	1.00 (referent)
Yes	**3.22 (1.12 − 9.21)**
Prior diabetes mellitus	
No	1.00 (referent)
Yes	1.25 (0.43 − 3.64)
Prior stroke	
No	1.00 (referent)
Yes	1.23 (0.15 − 10.37)
Used of any of the following prior to therapy: Beta blocker, Nondihydropyridine calcium channel blocker	
No	1.00 (referent)
Yes	2.22 (0.84 − 5.86)
Prior ACE/ARB use	
No	1.00 (referent)
Yes	**2.75 (1.08 − 6.99)**
Prior beta blocker use	
No	1.00 (referent)
Yes	**2.89 (1.12 − 7.43)**
Prior nondihydropyridine calcium channel Blocker use	
No	1.00 (referent)
Yes	1.49 (0.18 − 12.81)
Prior digoxin use	
No	1.00 (referent)
Yes	10.21 (0.61 − 169.86)
Prior statin use	
No	1.00 (referent)
Yes	2.09 (0.83 − 5.29)
Prior aspirin use	
No	1.00 (referent)
Yes	**6.02 (2.27 − 15.97)**

Bold point estimates are statistically significant.

Patients with prior history of atrial arrhythmia were excluded from these analyses.

by more than 60%.[21] The CHADS-VASc score incorporates baseline risk factors that may increase the likelihood of stroke, and it is utilized to guide the decision to initiate anticoagulation especially if the score is ≥2.[21,22] In our cohort, the mean CHADS-VASc was elevated at 2.76; however, previous published data have reported that the CHADS-VASc score does not adequately predict thromboembolism risk in cancer patients.[16,23] Given the high rates of AF, particularly with ibrutinib use, it will be essential develop appropriate treatment algorithms to minimize the risk of stroke in this population.[24] Nevertheless, ibrutinib is also associated with an increased risk of bleeding with 1 study reporting a major bleeding rate of 14% in patients treated with ibrutinib who developed AF.[11] As such, the concomitant use of anticoagulants and antiplatelets may further enhance these bleeding complications. Although it is generally recommended to avoid the use of vitamin K antagonists with ibrutinib due to increased rates of subdural hematomas reported in a mantle cell lymphoma study,[25] prospective data regarding the risk of bleeding with DOACs are lacking. Nevertheless, it is recognized that DOACs and ibrutinib share similar metabolic pathways which may lead to elevated drug levels and bleeding risk.[26] In our study, the majority of patients with ibrutinib associated AF who received anticoagulation were treated with the DOAC apixaban, and there were no significant bleeding complications. Therefore, studies to determine the safest and most effective anticoagulant in the setting of ibrutinib associated AF are essential.

We acknowledge that our study has some minor limitations. First, this was a retrospective study design at a single cancer center. It is possible that prospective studies specifically evaluating the cardiotoxicity of ibrutinib may yield different results. The relatively low rate of arrhythmia events in the 2 groups could affect the validity of our findings. Moreover, the majority of these patients were primarily evaluated by oncologists and given the challenges in diagnosing AF, particularly in asymptomatic patients, the reported incidence may be underestimated. Regardless, our reported rates are similar to those reported in other studies. It is possible something other than ibrutinib led to the development of arrhythmias in our population; however, our meticulous review of patient characteristics and medications makes this less likely. In addition, our sample size is not as large as some previously reported studies; however, our 2 groups are representative of a real-world sample of patients being treated with these regimens and our strict inclusion of only true incident arrhythmic events in the analysis strengthens the findings and substantially adds to the field. The study was not designed to accurately address appropriate management of arrhythmias or systematically evaluate for adverse CV or hematologic events.

Our study demonstrates that rates and risk of atrial arrhythmias, specifically AF and AFL are higher in “real-world” patients treated with ibrutinib compared with chemotherapy. By eliminating previous history of arrhythmia from our analysis, we determined an accurate incidence of AF or AFL in patients treated with this drug. Moreover, we identified several other risk factors for the development of AF in our population of patients with B-cell malignancies. Large, prospective studies to accurately assess arrhythmia burden in patients treated with ibrutinib would be beneficial and further studies are needed to determine the optimal management strategies for those patients that develop

Table 3
Multivariable odds ratios for the association between Ibrutinib use and incident atrial arrhythmia

Covariate	Full model OR (95% CI)*	Reduced model OR (95% CI)†	Reduced model with age OR (95% CI)‡
Ibrutinib use	3.84 (0.99 − 14.8)	**5.18 (1.42 − 18.89)**	**4.15 (1.11 − 15.47)**
Age, continuous	**1.06 (1.00 − 1.14)**	−	1.06 (0.99 − 1.12)
Prior Hypertension	2.09 (051 − 8.59)	−	
Prior angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers use	1.11 (0.33 − 3.72)	−	
Prior beta blocker use	1.30 (0.41 − 4.11)	−	
Prior aspirin use	**3.82 (1.26 − 11.68)**	**6.51 (2.39 − 17.74)**	**4.48 (1.55 − 12.93)**

Bold odds ratios are statistically significant.
Patients with previous history of atrial arrhythmia were excluded from these analyses.
* The full model includes all statistically significant univariable covariates from Table 2.
† The reduced model was generated from a backwards elimination model based on the full model.
‡ Age was forced into the reduced model.

arrhythmias in the setting of ibrutinib. Nevertheless, this study provides strong evidence that ibrutinib itself is an independent risk factor for the development of AA and thereby increases our knowledge and understanding of this serious cardiotoxicity.

Disclosures

MGF: consultant/advisor for Novartis.; HM: stock and other ownership interest in Cancer Genetics Inc., and Interpares Biomedicine; honoraria from Genentech/Roche; consultant/advisor for Cancer Genetics Inc., Admera Health and NIH/NHGRI.; JPI: investigator for Novartis and Ariad; consultant/advisor for Novartis, Bristol-Myers Squibb, and Ariad; consulting/speakers bureau fees from Janssen and Pharmacyclics. The remaining authors report no other COI.

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