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Original Research

Determinants of Atrial Fibrillation Development among Patients undergoing Ibrutinib Therapy

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Objective: Within the last decade, the use of ibrutinib, a first-generation, non-selective, irreversible Burton's tyrosine kinase inhibitor for the treatment of hematological malignancies has proven highly effective in improving patient outcomes.

Background: Ibrutinib has been associated with an increase in atrial fibrillation (AF). The predisposing factors are thought to be pre-existing cardiovascular risk factors, but these have not been directly evaluated.

Methods: We conducted a nested case-control study, recruiting consecutive ibrutinib treated subjects to evaluate cardiovascular risk factors associated with the development of AF in patients diagnosed with hematological B-cell malignancies.

Results: Of the 189 patients treated with ibrutinib and without AF at baseline, 54 (29%) developed AF. Cardiovascular risk factors associated with AF development were, older age, prior hypertension (HTN), history of heart failure (HF) and congenital heart disease. A patient with HF at baseline had a 1, 2, 6, and 12 month cumulative hazard of AF of 40%, 48%, 64%, and 71%, respectively. Patients with prior HTN without HF at baseline had a 1, 2, 6, and 12 month cumulative hazard of AF of 5%, 10%, 23%, and 31%, respectively while on ibrutinib therapy.

Conclusions: The relationship between ibrutinib, cardiovascular comorbidities, and AF is through pre-existing cardiovascular disease. An individualized, multidisciplinary approach involving cardiologists should be considered when initiating ibrutinib, particularly when there is a history of HTN, HF or congenital heart disease. In such patients, there should be close cardiovascular monitoring and prompt intervention when AF develops to improve patient outcomes.

Keywords: Ibrutinib; Atrial fibrillation; B-cell malignancies; Hematological malignancies; Risk factors; Bruton's tyrosine kinase

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Ibrutinib is a novel oral bioavailable irreversible inhibitor of first-class Bruton's tyrosine kinase (BTK), a pathway that plays a crucial role in B-cell malignancies.[1,2] Ibrutinib was first approved by the U.S. Food and Drug Administration (FDA) in 2013 as monotherapy or in combination with other chemo-immunotherapeutic agents.[2] Ibrutinib is effective in treating chronic graft-versus-host disease (cGVHD) and B-cell malignancies like chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), some non-Hodgkin's lymphomas and Waldenström macroglobulinemia.[3,4] It is also highly effective against refractory or relapsing disease, prolonging progression-free survival.[3,4]

While BTK is the primary target for ibrutinib, it has been shown to interact with other BTK-like kinases such as TEC, RLK, ITK, Erb4, and BMK with resultant off-target manifestations.[5] Despite ibrutinib's clinical success, its non-specificity has resulted in clinically recognized adverse events and toxicities.[6-8] Ibrutinib has been reported to affect the heart, neutrophils, platelets, red blood cells, skin, the immune system, and many other organ systems. Inhibition of BTK also expressed on cardiac tissue results in the inhibition of the cardio-protective PI3K–AKT signaling process, a process that is fundamental in protecting cardiac tissue during stress.[6,911]

Despite ibrutinib's initial promising results and clinical successes, subsequent studies have revealed an association with the development of atrial fibrillation (AF). A common cardiovascular complication, AF has the risk being maximal in the initial months of ibrutinib therapy, with a median time to development occurring within 6-14 months, and an increasing incidence over time with continued ibrutinib therapy.[9] The risk factors known to predispose to AF in the general population include older age, hypertension (HTN), obstructive sleep apnea, coronary artery disease, and a previous history of AF, which are now considered as possible risk factors in ibrutinib-related AF.[11-13] With the increasing knowledge of the etiology and pathophysiology of AF, it is becoming clear that AF almost never presents as a lone diagnosis; rather, it presents on the backdrop of undetected cardiovascular disease and some modifiable risk factors. Identification of these modifiable risk factors associated with incident AF are necessary for early institution of measures to prevent, initiate early treatment, or at the very least delay AF development.[11-13]

No general consensus exists regarding the risk factors implicated in the development of ibrutinib-related AF, and their nature and relationship to ibrutinib-related AF remains poorly characterized.[6-14] We, therefore, undertook this study to determine the cardiovascular predictors of AF development in patients on ibrutinib.

Methods

Study Design and Participants

A nested case-control design was used—"nested" implying that all subjects in the source population (of cases) were included. This source population consisted of individuals aged 18 years and above, diagnosed with B-cell malignancies between March 2013 and February 2019, treated with ibrutinib, free of AF at the start of ibrutinib, and managed at the Marshfield Clinic Health System (MCHS). The Marshfield Health System's research data warehouse, tumor registry, MedsManager, and Security Health Plan (SPH) Claims databases were searched for eligible patients for the study.

Ibrutinib use was determined by the Pharmacy Electronic Prescribing System, which identifies prescriptions dispensed to patients with malignancies. Hospital admissions data were extracted from the Electronic Health Records (EHR) and demographic information from the MCHS data warehouse. Trained health information professionals abstracted diagnoses from patients' charts using ICD 9 and ICD 10 tumor registry diagnosis and procedure codes. Date of cancer diagnosis, date of AF onset, and date of start and end of ibrutinib therapy were extracted from the EHR. For each patient, we identified a period of continuous use of ibrutinib, beginning with the first prescription after diagnosis of cancer until discontinuation or onset of AF. Onset of AF was defined as ICD 9 code 427.3, and ICD 10 code I48 within the EHR via prescription period or shortly thereafter. The study was approved by the Marshfield Clinic Health System Institutional Review Board with waiver of informed consent.

Statistical Methods

Descriptive analyses were conducted to report baseline characteristics of the participants. The date of first prescription of ibrutinib was considered as the index date of entry to being at risk of AF. Cases were those that developed AF whose date of exit from risk was recorded as date of onset of AF. Controls were those that had not developed AF by exit from risk defined as the date when ibrutinib was discontinued or date of study follow-up ended. An indicator for date of exit was created to distinguish exit through AF onset (cases = 1) from exit through drug discontinuation or end to recorded follow-up (controls = 0). All survival estimates, therefore, refer to survival free of AF. Survival estimates at fixed time points were calculated using the Kaplan–Meier method.

Multivariable Cox regression models were used to evaluate the prognostic utility of several risk factor variables. Since this is a prognostic study, by adding other predictors (not confounders) into the multivariable regression model that are known to be associated with the outcome (time to AF), we were able to ascertain if these variables were independent predictors.

These variables, commonly regarded as risk factors for AF, were identified through the literature and included male gender, age above a threshold in years, diabetes mellitus, high blood pressure, coronary artery disease, prior myocardial infarction, heart failure, and structural heart disease. Exact *P* values were reported throughout, and Stata version 15

(StataCorp, College Station, TX, USA) was used for all statistical analyses and for graphical assessment of goodness of fit based on visual inspection of Arjas-like plots produced using stcoxgof as well as to test the link specifications using linktest.

Results

A total of 189 patients met the inclusion critera and were included in the study. The mean age of the participants was 71.7 years (SD ± 11.2), and the majority (66%) were between 60 to 80 years-of-age. Two-thirds (n = 123) of the participants were males, and the majority (91%) were of non-Hispanic white ethnicity. More than half of the participants (57.1%) had a history of HTN: 26.5% had a history of coronary artery disease; 21.2% had a history of chronic kidney disease; 18.5% had diabetes; and 13.2% had heart failure (HF). All baseline characteristics of the patients are summarized in Table 1.

In all, 54 patients (29%) developed new-onset AF, with a median time at risk of 8.8 months (range 0.13 to 63.3 months). Stepwise Cox regression models (Table 2) were employed to identify the independent predictors of AF. The first multivariable regression model (*Model 1*) indicated that increasing age (60 - 80 years [hazard ratio (HR) 4.5; 95% CI 1.1 - 18.9]; >80 years [HR 12.6; 95% CI 2.9 – 55.0]), history of AF prior to ibrutinib (HR 11.7; 95% CI 6.5 - 21.2), and congenital heart disease (HR 11.8; 95% CI 2.6 - 52.6) were independent predictors of AF development. However, prior AF seems to be a proxy for other risk factors, and when excluded from the analysis in *Model 2*, the independent predictors were, congenital heart disease (HR 5.9; 95%CI 1.4 – 25.4), HF (HR 5.5; 95% CI 2.9 - 10.4), and HTN (HR 2.9; 95% CI 1.5 – 5.6) (Table 2).

Table 1: Demographic and clinical characteristics of the participants included in the study.

Demographic characteristics	N	%
Study participants	**189**	
Age (years) ±SD	71.7 ± 11.2	
Mean (IQR)	(66 - 79)	
Gender		
Male	123	65.1
Ethnicity		
Other	17.0	8.5
Non-Hispanic or Latino White	173	91.5
Clinical characteristics		
History of cardiac surgery	21	11.1
Family history of atrial fibrillation (AF)	17	9.0
History of Arrhythmias		
Arrhythmias - diagnosed as atrial arrhythmia	14	7.4
Arrhythmias – diagnosed ventricular arrhythmia	9	4.8
Arrhythmias – unspecified arrhythmia	15	7.9
History of cardiomyopathy	7	3.7
History of chronic kidney disease	40	21.2
History of congenital heart disease	3	1.6
History of heart failure (HF)	25	13.2
History of Chronic Obstructive Pulmonary Disease	18	9.5
History of Coronary Artery Disease	50	26.5
History of Diabetes Mellitus	35	18.5
History of Hypertension (HTN)	108	57.1
History of Obstructive Sleep Apnea	17	9.0
History of Thyroid Disease	42	22.2
History of Valvular Heart Disease	33	17.5
History of Venous Thromboembolism	21	11.1
Smoking	22	11.6
Alcohol consumption	8	4.2

Three participants had congenital heart disease (one patient had patent foramen ovale, and two patients had congenital coronary artery anomalies). Of these three, all had HTN, and one had HF; two of the three developed AF. Given the low numbers of participants with congenital heart disease, this was excluded from the final risk models. Cumulative survival free of AF by model is presented in Figure 1 and Figure 2. Table S1 and Figure 1 depict three categories of risk defined by *Model 1*, while Table S2 and Figure 2 depict three categories of risk defined by *Model 2*.

Model 1

Lower risk patients (ie, patients < 80 years old and no prior history of AF) had a 12-month AF cumulative hazard while on ibrutinib of 13%; this increased to 45% in the moderate risk group (ie, patients >80 years-old and no prior history of AF), and 81% in the highest risk group (ie, patients with prior history of AF) as depicted in Table S1 and Figure 1. Median time to AF was 33 months in those aged 80 years and above with no prior AF, while it was only 1.6 months in those with a prior history of AF.

Model 2

A similar risk distribution was observed in lower risk patients (ie, patients with no prior HTN or HF), who had a 12-month AF cumulative hazard while on ibrutinib of

Table 2: Univariable and multivariable analyses exploring the association between different baseline cardiovascular risk factors and the development of atrial fibrillation (AF).

Baseline variables	Univariable analysis Hazard ratio (95% CI)	Multivariable analysis model 1 (forward stepwise selection) Hazard ratio (95% CI)	Multivariable analysis model 2 (forward stepwise selection) Hazard ratio (95% CI)
Age group			
<60	1	1	
60-80	4.97 (1.18-20.90)	4.47 (1.06 – 18.94)	
>80	14.14 (3.27-61.15)	12.61 (2.89 – 55.00)	
Female	1.28 (0.74-2.20)		
Family history of AF	2.57 (1.29-5.12)		
AF prior to Ibrutinib	11.98 (6.69 - 21.44)	11.71 (6.46 – 21.22)	
Heart failure	6.99 (3.75- 13.04)		5.50 (2.90 – 10.42)
Cardiac surgery	2.83 (1.49-5.38)		
Congenital heart disease	6.37 (1.52- 26.80)	11.78 (2.64 – 52.57)	5.87 (1.36 – 25.38)
Coronary artery disease	2.10 (1.20- 3.65)		
Hypertension	3.75 (1.97- 7.16)		2.87 (1.47 – 5.61)
Valvular disease	3.68 (2.11- 6.41)		

9%; this increased to 31% in the moderate risk group (ie, patients with history of HTN but no HF), and 71% in the highest risk group (ie, prior HF), as depicted in Table S2 and Figure 2. Median time to AF was 44 months in those with prior HTN, while it was only 2 months in those with prior HF.

Discussion

This study reports an extensive single-center experience in adult patients diagnosed with B-cell malignancies exhibiting cardiovascular risk factors for AF in patients treated with ibrutinib. We identified a 9% – 13% cumulative incidence of AF in the lowest risk group and a 71% – 81% cumulative incidence in the highest risk group after a median ibrutinib use of 12 months. Most studies have reported a similar incidence rate of 6.1% – 8.9%,[11,18,19] which increases over time. A study of 2,292 CLL patients at Mayo Clinic demonstrates AF incidence rates ranging from 4% to 33% depending on risk score (0-1 = 4%, 2-3 = 9%, 4 = 17% and ≥5 = 33%) used to stratify patients into four groups, and also suggested a risk model that includes older age, male gender, valvular heart disease, and HTN as independent factors associated with AF.[20]

In our study, we found a median time to AF development of 1.6 to 2 months in the highest risk group, supporting previously reported median times of 2.2 months in patients

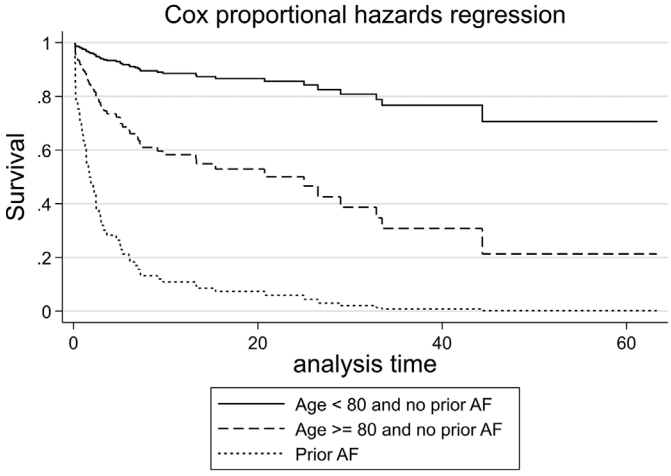

Figure 1. Cumulative atrial fibrillation event-free survival of patients on ibrutinib by model 1 risk stratification.

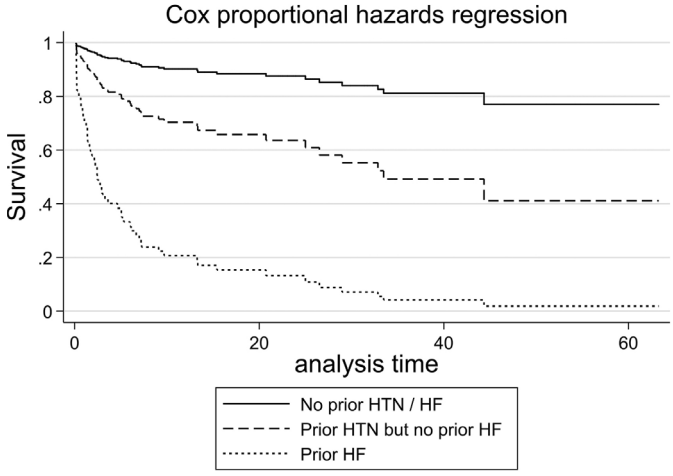

Figure 2. Cumulative atrial fibrillation event-free survival of patients on ibrutinib by model 2 risk stratification.

Supplementary Material

Table S1. *Model 1* – Hazard function of 3 groups (Age & AF) at 1, 2, 6 and 12 months.

Time (months)	Beginning Total	Fail	Survivor Function	95% CI	
Age ≤ 80 No prior AF					
1	127	1	0.99	0.95	1.00
2	118	3	0.97	0.92	0.99
6	96	5	0.92	0.86	0.96
12	69	5	**0.87**	0.79	0.92
Age >80 No prior AF					
1	28	2	0.93	0.75	0.98
2	25	2	0.86	0.68	0.95
6	14	5	0.66	0.44	0.81
12	10	2	**0.55**	0.32	0.73
Prior AF					
1	15	11	0.56	0.35	0.72
2	11	3	0.43	0.23	0.61
6	6	4	0.24	0.09	0.43
12	4	1	**0.19**	0.06	0.38

Note: Survivor function is calculated over full data and evaluated at indicated times; It is not calculated from aggregates shown at left.

Table S2. *Model 2* – Hazard function of 3 groups (prior HTN, HF) at 1, 2, 6 and 12 months.

Time (months)	Beginning Total	Fail	Survivor Function	95% CI	
No prior HTN/HF					
1	77	0	1.00	—	—
2	71	2	0.97	0.90	0.99
6	61	2	0.95	0.86	0.98
12	48	2	**0.91**	0.81	0.96
Prior HTN but no prior HF					
1	77	4	0.95	0.88	0.98
2	69	4	0.90	0.81	0.95
6	49	9	0.77	0.66	0.85
12	33	5	**0.69**	0.56	0.78
Prior HF					
1	16	10	0.60	0.38	0.76
2	14	2	0.52	0.31	0.69
6	6	3	0.36	0.16	0.56
12	2	1	**0.29**	0.11	0.50

Note: Survivor function is calculated over full data and evaluated at indicated times; It is not calculated from aggregates shown at left.

with a prior history of AF, which supports the observation that the risk of AF is highest within the first few months of commencing therapy when major risk factors are present.[9,11,14,21] The higher incidence rate and early development of AF in our study population was within the elderly population (age > 80) and with prior AF or HF. The significance of the higher AF incidence and a shorter time to AF development emphasizes the need for preemptive screening prior to ibrutinib initiation, monitoring during ibrutinib therapy, and management of incident AF. It is also necessary to consider the possibility that the actual incidence of AF could be higher, because of missed opportunities in diagnosing cardiovascular disease if the initial manifestation is asymptomatic or silent AF.[11,22]

When prior history of AF was removed, HF and to a lesser degree HTN, were implicated as independent predictors. This suggests that prior AF is a proxy for the risk factors in *Model 2*. Our study validates the premise that the development of AF is significantly higher in patients with cardiovascular risk factors like a prior history of HF, older age, and HTN being the most significant. Several known risk factors for AF have been suggested previously including older age (> 60 years), HTN, ischemic and valvular heart diseases, HF, and infection.[6,14,21,22] Several studies have approximated the median age of patients receiving ibrutinib therapy as 70 years,[1,3,14,18,20,22,23] and these are the age groups most likely to have these cardiovascular risk factors.

Our study further supports previously identified factors like age, HTN, and other structural and functional disorders of the cardiovascular system, as they exert varying degrees of influence in predisposition to AF; however, we did not find an association (in multivariable analyses) between valuvular heart disease and AF, even though valvular heart disease is a condition prone to AF in this cohort, and despite 33 patients

having valvular heart disease. In contrast, there were only three cases of congenital heart disease (one patient had patent foramen ovale, and two patients had congenital coronary artery anomalies); yet, this was a predictor of subsequent AF, and the most likely explanation is that valvular heart disease does not lead to AF unless patients already have some underlying cardiac dysfunction that is proxied by either HTN or HF. So only severe valvular heart disease that results in cardiac dysfuction may end up with a high risk status for AF. This was observed in our study, with all three having HTN and one having HF.

The limitations of the study include a retrospective study design, a low to moderate sample size, unknown prior cancer treatments, and a shortage of cardiovascular imaging data. The high AF incidence could be subject to selection bias and small sample size. Not all previously identified risk factors for AF were replicated in this study, due to sample size, follow-up duration, and undetected cases of AF. Future endeavors should consist of a prospective multi-site survey to ensure a larger sample size, follow-up, explore all possible potential risk factors, and evaluation of the prognosticative value of cardiovascular imaging in the management of ibrutinib related AF.

In conclusion, our results suggest that in the elderly, many of whom have cardiovascular co-morbidities (ie, history of prior AF, HTN, and HF); ibrutinib significantly increases the risk of AF. We recommend that individuals commencing ibrutinib be screened for HTN and HF in addition to prior AF. If any of these are present, this should alert the attending physician to develop a patient-centered individualized approach, with strict clinical surveillance and follow-up to mitigate the cardiovascular consequences of ibrutinib therapy. These findings support the recommendations and suggestions of recently published expert review articles that advocate early screening and prompt treatment.[6,11,21] Therefore, the early onset of the development of AF observed in this study emphasizes the significance of introducing timely systematic cardio-oncology assessment, monitoring, and follow-up for patients on ibrutinib without waiting for symptoms to appear. Monitoring while on ibrutinib will aid early detection of asymptomatic or 'silent' AF by new technologies (eg, smartphone applications) will improve patient outcomes tremendously.[23,24]

References

1. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213-223.
2. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia [published correction appears in N Engl J Med. 2014 Feb 20;370(8):786]. N Engl J Med. 2013;369(1):32-42.
3. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015;372(15):1430-1440.
4. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015;126(6):739-745.
5. Berglöf A, Hamasy A, Meinke S, et al. Targets for Ibrutinib Beyond B Cell Malignancies. Scand J Immunol. 2015;82(3):208-217.
6. Tang CPS, McMullen J, Tam C. Cardiac side effects of bruton tyrosine kinase (BTK) inhibitors. Leuk Lymphoma. 2018;59(7):1554-1564.
7. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-Associated Atrial Fibrillation. JACC Clin Electrophysiol. 2018;4(12):1491-1500.
8. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies [published correction appears in Mol Cancer. 2019 Apr 3;18(1):79]. Mol Cancer. 2018;17(1):57. Published 2018 Feb 19.
9. López-Fernández T, Canales M, Farmakis D. Ibrutinib-associated atrial fibrillation: a practical approach. Ann Hematol Oncol. 2018;5(4):1203.
10. Kapelios CJ, Bonou MS, Diamantopoulos P, et al. Ibrutinib-related atrial fibrillation: Therapeutic challenges. J Oncol Pharm Pract. 2019;25(5):1258-1260.
11. Lentz R, Feinglass J, Ma S, Akhter N. Risk factors for the development of atrial fibrillation on ibrutinib treatment. Leuk Lymphoma. 2019;60(6):1447-1453.
12. Joung B. Risk Factor Management for Atrial Fibrillation. Korean Circulation Journal. 2019;49(9):794-807.
13. Brandes A, Smit MD, Nguyen BO, Rienstra M, Van Gelder IC. Risk Factor Management in Atrial Fibrillation. Arrhythm Electrophysiol Rev. 2018;7(2):118-127.
14. Thompson PA, Lévy V, Tam CS, et al. Atrial fibrillation in CLL patients treated with ibrutinib. An international retrospective study. Br J Haematol. 2016;175(3):462-466.
15. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124(25):3829-3830.
16. Yang T, Moslehi JJ, Roden DM. Proarrhythmic effects of ibrutinib, a clinically approved inhibitor of Bruton's tyrosine kinase (BTK) used in cancer therapy. Circulation. 2015;132(suppl_3):A14587.
17. Solti F, Vecsey T, Kékesi V, Juhász-Nagy A. The effect of atrial dilatation on the genesis of atrial arrhythmias. Cardiovasc Res. 1989;23(10):882-886.

18. Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv. 2017;1(20):1739-1748.
19. Boriani G, Corradini P, Cuneo A, et al. Practical management of ibrutinib in the real life: Focus on atrial fibrillation and bleeding. Hematol Oncol. 2018;36(4):624-632.
20. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017;58(7):1630-1639.
21. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: Systematic review and meta-analysis. PLoS One. 2019;14(2):e0211228.
22. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373(25):2425-2437.
23. Baptiste F, Cautela J, Ancedy Y, et al. High incidence of atrial fibrillation in patients treated with ibrutinib. Open Heart. 2019;6(1):e001049.
24. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102(10):1796-1805.

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Author Contributions

Study design: TOP, NI, SK, SARD, AAO; Data collection: TOP, NI, LFK, SK, SARD, AAO; Data analysis: NI, LFK, SARD; Drafting manuscript: TOP, NI. All authors had full access to the data and approve the final manuscript.