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ORIGINAL RESEARCH

Arrhythmogenic Cardiotoxicity Associated With Contemporary Treatments of Lymphoproliferative Disorders

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BACKGROUND: There are limited data on risk of arrhythmias among patients with lymphoproliferative disorders. We designed this study to determine the risk of atrial and ventricular arrhythmia during treatment of lymphoma in a real-world setting.

METHODS AND RESULTS: The study population comprised 2064 patients included in the University of Rochester Medical Center Lymphoma Database from January 2013 to August 2019. Cardiac arrhythmias—atrial fibrillation/flutter, supraventricular tachycardia, ventricular arrhythmia, and bradyarrhythmia—were identified using *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes. Multivariate Cox regression analysis was used to assess the risk of arrhythmic events with treatments categorized as Bruton tyrosine kinase inhibitor (BTKi), mainly ibrutinib/non-BTKi treatment versus no treatment. Median age was 64 (54–72) years, and 42% were women. The overall rate of any arrhythmia at 5 years following the initiation of BTKi was (61%) compared with (18%) without treatment. Atrial fibrillation/flutter was the most common type of arrhythmia accounting for 41%. Multivariate analysis showed that BTKi treatment was associated with a 4.3-fold (P<0.001) increased risk for arrhythmic event (P<0.001) compared with no treatment, whereas non-BTKi treatment was associated with a 2-fold (P<0.001) risk increase. Among subgroups, patients without a history of prior arrhythmia exhibited a pronounced increase in the risk for the development of arrhythmogenic cardiotoxicity (3.2-fold; P<0.001).

CONCLUSIONS: Our study identifies a high burden of arrhythmic events after initiation of treatment, which is most pronounced among patients treated with the BTKi ibrutinib. Patients undergoing treatments for lymphoma may benefit from prospective focused cardiovascular monitoring prior, during, and after treatment regardless of arrhythmia history.

Key Words: arrhythmia ■ Bruton tyrosine kinase inhibitor ■ cardiotoxicity ■ ibrutinib ■ lymphoma

In recent years, progress in the early detection of and success of cancer treatment has led to an impressive reduction in both mortality and morbidity.[1] At the same time, cardiac complications resulting from cancer chemotherapy have been recognized as major contributors to morbidity and, ultimately, mortality in cancer survivors.[2–7] Furthermore, in contrast to initial expectations, the risk of cardiotoxicity may be even more pronounced with novel drugs acting as specific-signaling inhibitors ('targeted therapy'), given off-target effects on the heart.[6] Targeted therapy with ibrutinib, a Bruton tyrosine kinase inhibitor (BTKi), is now a first-line therapy option in patients with indolent lymphoma including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL), resulting in a near normal life expectancy in this population.[8,9] However, BTKi treatment has been associated with both supraventricular and ventricular arrhythmia.[10–12] Unfortunately, proarrhythmia, defined as the provocation

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CLINICAL PERSPECTIVE

What Is New?

- This study provides a comprehensive review of arrythmia risk among patients with lymphoproliferative disorders in a real-world setting with long-term follow-up of 5 years.
- It provides a comparison of arrhythmia risk with newer targeted therapies, mainly ibrutinib, against traditional chemotherapeutic agent.
- It also shows that non-Bruton tyrosine kinase inhibitor treatments are also associated with arrhythmogenic cardiotoxicity and identifies that even patients with lymphoma without arrhythmia history have a pronounced risk for arrhythmogenic cardiotoxicity.

What Are the Clinical Implications?

- Close cardiac monitoring and symptom awareness should be considered in patients with lymphoproliferative disorders undergoing lymphoma treatments even without traditional risk factors for arrhythmia.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation or atrial flutter
BTKi	Bruton tyrosine kinase inhibitor
CLL	chronic lymphocytic leukemia

of a new arrhythmia or the aggravation of a pre-existing one during cancer therapy is still understudied and not well understood.[6] Furthermore, data on the long-term arrhythmic burden associated with BTKi treatment, compared with other treatments for lymphoma, in a real-world setting are limited, and there is a need for patient-specific risk stratification algorithms to identify those who are more likely to develop arrhythmic events during BTKi treatment.

The present study was conducted in a large population of patients with lymphoma who were managed in a tertiary health care system between 2013 and 2019. We aimed to (1) determine the overall risk of arrhythmic events during treatment of lymphoma; (2) compare the risk of arrhythmic events between types of treatment (categorized as BTKi versus non-BTKi); and (3) study the interaction of pre-existing cardiovascular risk factors with the subsequent risk of arrhythmogenic cardiotoxicity during lymphoma treatment of lymphoproliferative disorders.

METHODS

The data that support the findings of our study are available from the corresponding author upon request.

University of Rochester Medical Center Lymphoma Database

Patients were identified from the University of Rochester Medical Center Lymphoma Database. The University of Rochester Medical Center Lymphoma Database maintains a list of patients seen in the Lymphoma Service at the Wilmot Cancer Institute. All patients who were diagnosed with lymphoma and underwent evaluation between January 2013 to August 2019 were included. Patient demographics, clinical/pathological diagnosis, oncologic disease stage, and clinical trial enrollment are captured by careful review of medical records.

Comorbid conditions known to be associated with arrhythmias including hypertension, diabetes, congestive heart failure, coronary artery disease, and history of arrhythmias were identified for each of the study patients using electronic medical record system. The *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes were used to search the electronic medical record for comorbid conditions. Patients received treatments from hematologist using standard of care treatment protocols at our institution. For example, International Workshop on Chronic Lymphocytic Leukemia guidelines are used for management of patients with chronic lymphocytic leukemia.[13] Most patients with lymphoma do undergo treatment at some stage of their disease course. However, in some lymphoma subtypes, patients with early-stage indolent disease can be observed for variable times because they progress to needing treatment. The protocol for this study was approved by University of Rochester Medical Center, Institutional Review Board, and the requirement for informed consent was waived.

Definitions and End Points

Electronic medical records were also searched for the treatment patient received, and they were broadly dichotomized as those receiving BTKi and non-BTKi therapy. BTKi treatment included ibrutinib and acalabrutinib. The non-BTKi treatments included anthracycline based chemotherapy (with or without immune therapy), monoclonal antibody therapy, other immune therapy, and other agents. Indications for BTKi treatment versus non-BTKi were determined by lymphoma subtypes. BTKis are used for treatment of CLL, lymphoplasmacytic lymphoma, marginal zone lymphoma, and mantle cell lymphoma.

Primary outcome of study was any cardiac arrhythmia occurring during study follow-up.

Cardiac arrhythmia was defined using *ICD-10* codes and consisted of atrial fibrillation or atrial flutter (AF), supraventricular tachycardia, ventricular tachyarrhythmias, premature atrial contractions and/ or premature ventricular contractions, atrioventricular block, bradyarrhythmia, and unspecified forms of tachycardia, which included sinus tachycardia.

Random sample of medical records were reviewed for data quality and accuracy among patients with arrhythmias.

Follow-up was measured from 1 day after the date of lymphoma diagnosis or initial patient visit in Wilmot Cancer Institute. For the 2 patients without these data, the therapy start date was used for beginning of follow-up period.

The secondary outcome of the study included the occurrence of any AF and all-cause mortality. All-cause mortality was captured from lymphoma database and cause of death was independently adjudicated by study personnel. Medical records were reviewed for narratives including a description of the circumstances surrounding each patient's death and statements of those present at the terminal event. Mode of death was categorized as cardiac or noncardiac. Cardiac cause of mortality was further categorized as sudden cardiac death with ventricular tachyarrhythmias or pulseless electrical activity subtypes or non-sudden cardiac death. Sudden cardiac death was defined by using the modified Hinkle-Thaler classification, which has been used in prior trials.[14]

Statistical Analysis

Differences in patients' characteristics between those who did or did not receive cancer treatment were compared using Chi-square or Fisher exact tests for categorical variables or Wilcoxon rank-sum test for continuous variables. The Simon and Makuch nonparametric methodology was used to graphically display the time-dependent nature of lymphoma treatment and its relationship with the end point of arrhythmic events.

Multivariable Cox proportional hazards regression models were used to assess the association of time-dependent cancer treatment relative to no treatment with risk of any arrhythmia or AF. In all statistical models for the occurrence of a first arrhythmic event, treatment was assessed as a time-dependent covariate, with follow-up time beginning at the time of lymphoma diagnosis. At each unique follow-up time t_k where an event occurs, patients on treatment were compared with those not receiving treatment at time t_k, with the overall effect summarized in the hazard ratio for time-dependent treatment covariate. Similarly, multivariable Cox proportional hazards regression models were used to assess the risk of arrhythmia among time-dependent BTKi versus no treatment, non-BTKi versus no treatment, and patients treated with BTKi versus non-BTKi. When patients in either treatment group changed or stopped treatment, their follow-up was censored. There was a single Cox proportional hazards regression model estimated for each end point using 3 time-dependent variables, BTKi treatment, non-BTKi treatment, and no treatment. Two of these time-dependent variables were included in the model with the third as a reference group. Clinical variables were selected using stepwise selection approach with selection and remain in model significance levels at $P<0.05$.

Age dichotomized at the median, 64 years, was an excellent predictor and easier to interpret. Further, using age as a linear predictor resulted in little change to the hazard ratio (HR) ratio estimates of treatment. Additionally, to understand the robustness of the treatment effect size we added additional clinically meaningful adjustment variables that were not predictive of end point to the multivariable models.

Arrhythmia risk associated with treatment was estimated in subgroups with the use of interaction terms in the Cox regression models. The main effects of treatment and interaction *P* values for the subgroups of history/no history of arrhythmia, aged < or ≥64 years, women/men, and history/no history of hypertension are reported. All statistical tests were performed 2-sided, and statistical significance was defined by a *P* value <0.05. Statistical software SAS 9.4 (Cary, NC) was used for statistical analyses.

RESULTS

Study Participants

The study population included 2064 patients with a median age of 64 (54–72) years, of whom 42% were women, and 1910 (91%) were of White race. Among study patients 920 (44%) had indolent lymphoma, 504 (24%) had diffuse large B-cell lymphoma, and 228 (11%) had Hodgkin lymphoma. A detailed description of lymphoma histologic subtypes is presented in Table S1.

At the time of lymphoma diagnosis, 575 patients (28%) had history of hypertension, 526 (26%) had hyperlipidemia, 220 (11%) had diabetes, 197 (10%) had coronary artery disease, and 72 (3%) had history of heart failure. A prior history of arrhythmia was present in 227 (11%) patients. During a median follow-up of 22 months, 1112 (54%) patients received lymphoma treatment, whereas 952 (46%) did not receive treatment. Among the 1112 treated patients, 205 (18%) were treated with a BTKi. Ibrutinib, the most common BTKi used, was used in 185 (90%) patients, and acalabrutinib in 20 (10%) patients. There were 907 subjects who received non-BTKi treatment, including an

anthracycline and monoclonal antibody combination with other treatments 515 (57%), monoclonal antibody without anthracycline 287 (32%), and other combinations not using monoclonal antibodies/immune therapy nor anthracyclines 105 (11%).

Clinical characteristics of patients who did or did not receive treatment during study follow-up are presented in Table 1. Patients who received lymphoma treatment were younger than patients who did not receive treatment, median age 63 versus 64 years (P=0.01). There was no difference in sex distribution (women, 41% versus 43% [P=0.50]) or race categories (White patients, 92% versus 91% [P=0.07]). There was no difference in baseline cardiovascular risk factors including distribution of hypertension, hyperlipidemia, diabetes, coronary artery disease, heart failure, or prior history of arrhythmia (all P>0.10) Table 1. There were 152 (7%) patients on beta-blockers at the time of diagnosis: 139 (12%) patients who received treatment, and 13 (1.3%) patients in the no treatment group.

Table 1. Clinical Characteristics by Treatment Status

Clinical characteristics	Treatment (Yes)	Treatment (No)	*P* value
No. of patients, %	1112	952	
Age, y	63 (53; 72)	64 (55; 74)	0.01
Women, n (%)	459 (41)	407 (43)	0.49
White race, n (%)	1022 (92)	866 (91)	0.07
Medical history, n (%)			
Hypertension	328 (29)	247 (26)	0.07
Hyperlipidemia	302 (27)	224 (24)	0.06
Diabetes	125 (11)	95 (10)	0.35
Coronary artery disease	115 (10)	82 (9)	0.18
Heart failure	41 (4)	31 (3)	0.59
Arrhythmia history	129 (12)	98 (10)	0.34
Lymphoma histology, n (%)			
Diffuse large B-cell lymphoma	359 (32)	145 (15)	
CLL/SLL/MBL	139 (12)	289 (30)	
Follicular lymphoma	143 (13)	145 (15)	
Hodgkin's lymphoma	150 (13)	78 (8)	
Marginal zone lymphoma/ MALT	52 (5)	113 (12)	
Mantle cell lymphoma	72 (6)	30 (3)	
Peripheral T-cell lymphoma NOS	44 (3)	54 (6)	
Lymphoplasmacytic lymphoma	52 (5)	28 (3)	
Lymphoproliferative disorders NOS	15 (1)	17 (2)	
Hairy cell leukemia	18 (2)	11 (1)	
Mediastinal B cell DLBCL	15 (1)	4 (0.4)	
Hairy cell leukemia variant/SDRPL	4 (0.3)	10 (1)	
Other combined	49 (4)	27 (3)	
Treatment, n (%)			
BTKi	205 (18)		
Non-BTKi	917 (82)		

BTKi indicates Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa associated lymphoid tissue lymphoma; MBL, monoclonal B cell lymphocytosis; NOS, not otherwise specified; SDRPL, splenic diffuse red pulp lymphoma; and SLL, small lymphocytic lymphoma.

Frequency and Type of Arrhythmic Events During Treatment of Lymphoma

Arrhythmia diagnosis was identified in 422 (20%) of the study population. The median time to onset of any arrhythmia was 5.8 months.

AF was the most common arrhythmia noted in 174 patients (41%), followed by unspecified tachycardia in 131 (31%), and supraventricular tachycardia in 31 patients (7%). Bradyarrhythmia was noted in 43 patients (10%), atrioventricular block in 18 (4%), premature atrial contractions in 12 (3%), and ventricular tachyarrhythmias in 13 (3%) patients. Frequency distribution of arrythmia subtypes among study population is presented in Figure S1.

The relationship of time-dependent treatment and cumulative rate of any arrhythmias and of AF alone are presented in Figures 1 and 2, respectively. The overall rate of any arrhythmia at 5 years was significantly higher following the initiation of treatment (41%) compared with before or without treatment (19%) Figure 1. Of note, the increase in the rate of arrhythmic events was apparent and most pronounced immediately after the initiation of treatment and was sustained through 5 years of follow-up. Similarly, the rate of AF at 5 years was significantly higher following the initiation of treatment (14%) compared with (9%) patients not receiving treatment (Figure 2).

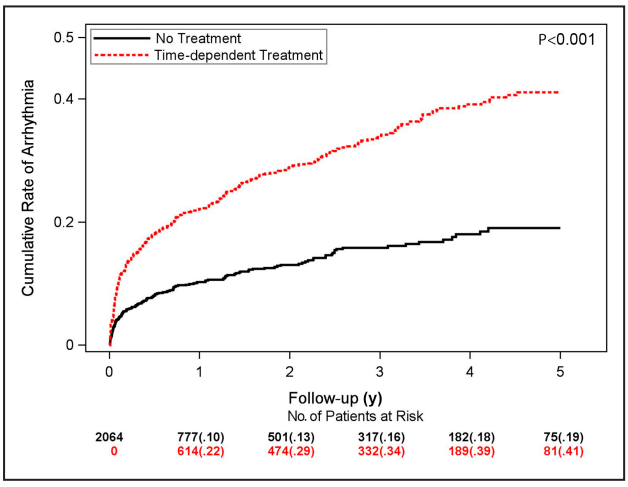

Figure 1. Cumulative rate of any arrhythmic event following initiation of treatment in study population.
At 5 years, the overall of rate of any arrhythmia was 41% following the initiation of treatment compared with the rate of 19% before or without treatment. P<0.001.

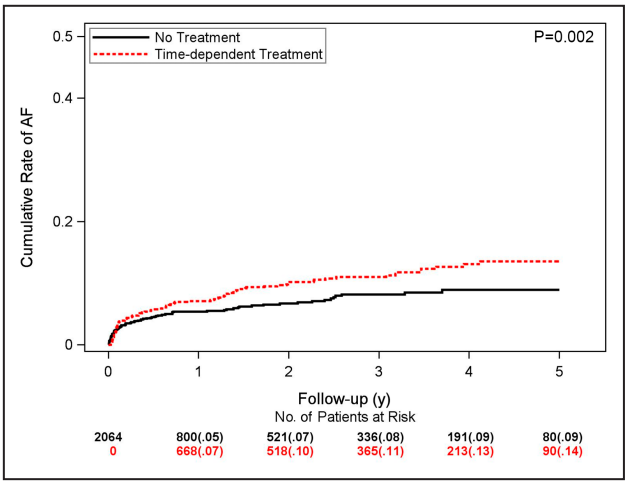

Figure 2. Cumulative rate of atrial fibrillation following initiation of lymphoma treatment.
At 5 years, the rate of atrial fibrillation was 14% following the initiation of treatment compared with the rate of 9% before or without treatment. *P*=0.002.

Consistent with the univariate findings, the multivariate model showed that time-dependent lymphoma treatment was associated with >2-fold (*P*<0.001) higher risk of any arrythmia during follow-up (Table 2: left panel). Similarly, time-dependent lymphoma treatment was independently associated with a 1.5-fold (*P*=0.006) increased risk for the end point of AF development (Table 2: right panel).

In subgroup analysis (Figure 3) the association of lymphoma treatment and the risk of any arrhythmic events was consistent by age and sex (*P* value for interactions >0.10). However, the risk of arrhythmia development during lymphoma treatment was significantly higher among patients who did not have prior history of arrythmia (HR, 3.27 [95% CI, 2.53–4.24; *P*<0.001]) as compared with those with a prior history of arrythmia (HR, 1.22 [95% CI, 0.85–1.74; *P*=0.283]), *P* value for treatment-by-arrhythmia history interaction <0.001 (Figure 3). Similarly, the risk of arrhythmia development during treatment was higher among patients with no history of hypertension (HR, 2.95 [95% CI, 2.21–3.93; *P*<0.001]) as compared with patients with history of hypertension (HR, 1.87 [95% CI, 1.41–2.49; *P*<0.001]); *P* value for lymphoma treatment-by-hypertension interaction=0.021.

In secondary analyses lymphomas were further subcategorized as aggressive and indolent based on histologic subtypes (Table S2). Results of this analysis showed a consistent association of time-dependent treatment with arrhythmic risk. This data are included in Figure S2A and S2B.

Time-dependent treatment remained significantly associated with a higher risk of arrhythmias after adjustment with additional clinically meaningful variables (race, male sex, age, history of coronary artery disease, hyperlipidemia, diabetes, hypertension, heart failure, and history of prior arrhythmias). These results are shown in Table S3.

BTKi and the Risk of Arrhythmic Events

Median duration for BTKi (mainly ibrutinib) was 18.6 months. When evaluating in a time-dependent manner, BTKi treatment was associated with significantly higher risk of any arrhythmia when compared with patients not receiving lymphoma therapy. At 5 years, the overall rate of any arrhythmia event was significantly higher following the initiation of BTKi (61%) compared with those not on lymphoma therapy (18%) (Figure 4). Similarly, the risk associated with BTKi was higher than the risk of arrythmias with non-BTKi treatment. At 5 years the cumulative probability of any arrhythmia was 44% in patients treated with BTKi compared with 30% when compared with non-BTKi (Figure 5).

There were consistent results found in the multivariate model (Table 2). BTKi was associated with a 4-fold higher risk of arrhythmia (HR, 4.37 [95% CI, 3.18–6.00; *P* <0.001]) compared with patients who did not receive treatment. Time-dependent non-BTKi treatments (including anthracycline, monoclonal antibody/immune therapy, and other) were also associated with a 2-fold

Table 2. Cox Model for Any Arrhythmia Episode During Study Follow-Up

	Any arrhythmia		Atrial fibrillation	
End point	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Time-dependent lymphoma treatment				
Overall vs no Rx	2.31 (1.87–2.85)	<0.001	1.58 (1.13–2.20)	0.006
By treatment type				
BTKi vs no treatment	4.37 (3.18–6.00)	<0.001	3.67 (2.26–5.97)	<0.001
Non-BTKi vs no treatment	2.02 (1.62–2.52)	<0.001	1.28 (0.89–1.83)	0.181
BTKi vs non-BTKi	2.17 (1.59–2.95)	<0.001	2.87 (1.74–4.72)	<0.001

Findings were adjusted for male sex, age ≥64 years, hypertension, heart failure, and prior history of arrhythmia.
BTKi indicates Bruton tyrosine kinase inhibitor; and HR, hazard ratio.

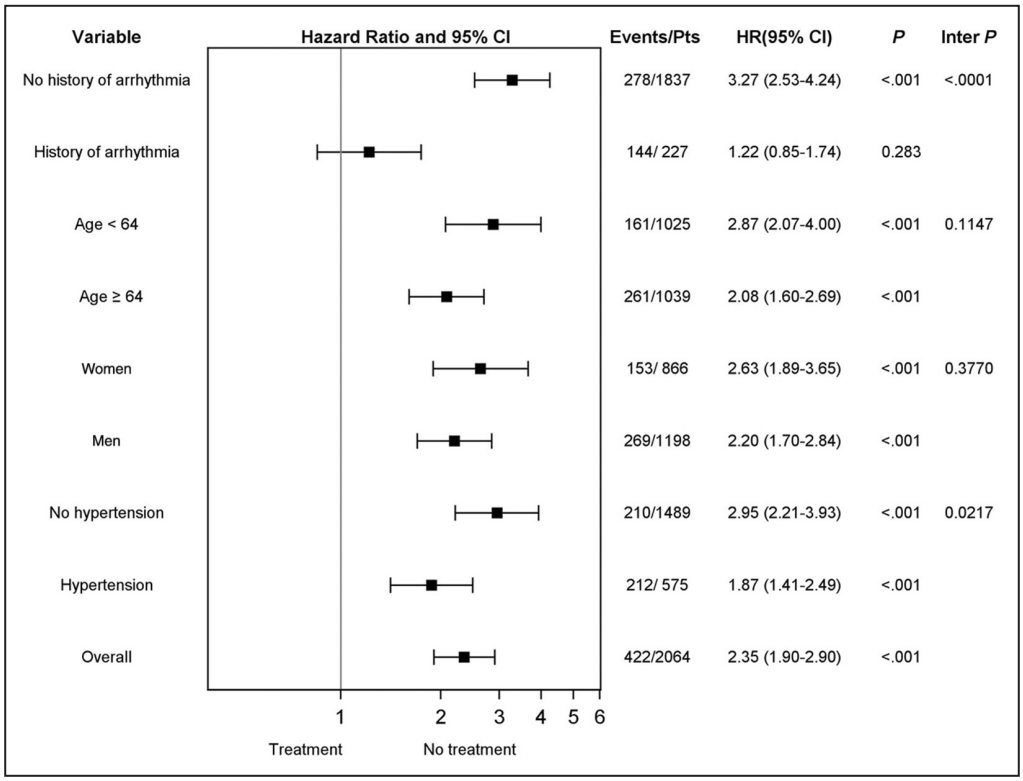

Figure 3. Risk of arrhythmia associated with lymphoma treatment vs no treatment in prespecified subgroups.
The risk of arrhythmia during lymphoma treatment was significantly higher among patients who did not have prior history of arrythmia as compared with those with a prior history of arrythmia. *P* value for treatment-by-arrhythmia history interaction *P*<0.001. HR indicates hazard ratio.

(*P*<0.001) higher risk of arrythmia when compared with patients not treated. However, when compared with non-BTKi treatment, treatment with a BTKi was associated with a significant >2-fold (*P*=0.001) increased risk for development of arrhythmic events.

At 3 years of follow-up, risk of death was 35% versus 10% among BTKi treated versus no treatment. Similarly, cumulative rate of death was 31% versus 11% among patients treated with non-BTKi and those with no treatment.

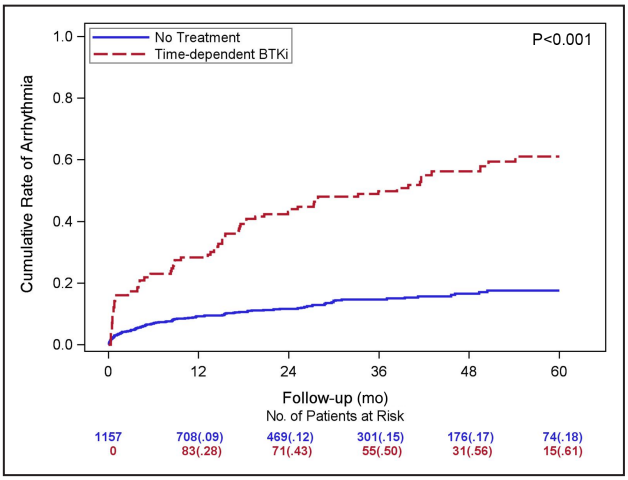

Figure 4. Comparison of time-dependent Bruton tyrosine kinase inhibitor vs no treatment.
At 5 years, the overall rate of any arrhythmia event following the initiation of BTKi (61%) compared with those not on lymphoma therapy (18%). *P*=0.001. BTKi indicates Bruton tyrosine kinase inhibitor.

Cause-Specific Mortality During Treatment of Lymphoma

Three hundred and twenty-six patients died with 216 (19%) deaths among patients who received treatment and 110 (12%) among patients who did not receive treatment. Among the 326 patients who died, cardiovascular mortality was observed in 29 (9%) patients. Of note, the major cause of cardiovascular mortality was sudden cardiac death, noted in 21 of 29 patients.

DISCUSSION

The present study provides several clinically important findings with regards to risk of arrythmia among patients with lymphoproliferative disorders. We have shown that: (1) overall rate of any arrhythmia event

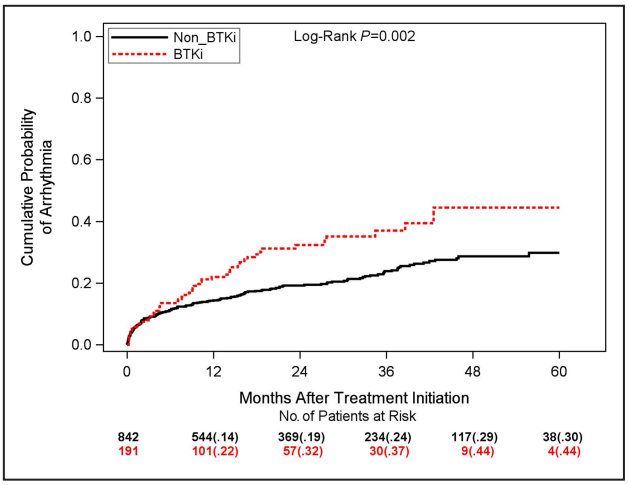

Figure 5. Cumulative probability of any arrhythmia episode by Bruton tyrosine kinase inhibitor vs non-Bruton tyrosine kinase inhibitor treatment.
At 5 years, the cumulative probability of any arrhythmia was 44% in patients treated with BTKi and 30% in patients treated with non-BTKi (central illustration). BTKi indicates Bruton tyrosine kinase inhibitor.

during long-term follow-up (5 years) was significantly higher following the initiation of treatment (41%) compared with patients without treatment (19%), with AF being the predominant arrhythmia induced by lymphoma treatment; (2) BTKi (mainly ibrutinib) were associated with a 4-fold higher arrhythmia risk when compared with non-treated patients and 2-fold higher risk when compared with non-BTKis; (3) the risk of arrhythmia development during lymphoma treatment is even more pronounced among patients without underlying arrhythmia history or hypertension, suggesting a need for close follow-up even among patients considered to be at a lower arrhythmic risk. There were consistent results when analyses were performed in aggressive and indolent lymphoma subtypes.

Cardiac arrhythmias, particularly AF is a common complication in the management of cancer patients.[6] Prior studies have shown a higher risk of AF in CLL population when compared with general population. According to 1 of the studies, 12% of CLL patients experienced AF at some point during their disease considering both AF present at the time of diagnosis and acquired during follow-up.[15] There is also evidence that an increasing number of chemotherapy drugs can produce electrophysiological changes (QTc prolongation) and a wide spectrum of arrhythmias, including bradyarrhythmias, supraventricular, ventricular arrhythmias, and sudden cardiac death.[6,7,16] Our findings are consistent with recent data suggesting increased risk of AF with treatments for lymphoproliferative diseases. In a multivariate analysis, time-dependent treatment for CLL was associated with a 2-fold higher risk for developing incident AF (HR, 2.1 [95% CI, 1.4–3.0; P=0.0002]).[15] Anthracyclines, a common group of chemotherapeutic agents used in management of lymphoproliferative disorders was associated with AF at a rate of 2% to 10% but rarely with malignant ventricular arrhythmia.[7] Similarly, newer oral targeted agents are also associated with significant cardiovascular toxicity because of either off-target or on-target effects.[17] Recent data suggest an increased risk of AF during treatment with ibrutinib, first approved BTKi. In a recent meta-analysis, it was shown that in patients treated with ibrutinib, the occurrence of AF was distinctly higher than in the non-ibrutinib treated patients and age matched normal subjects.[10,18] The exact mechanism for increased risk of AF in ibrutinib treated patients is not known. However, inhibition of protective phosphoinositide 3-kinase (PI3K)-Akt pathway which plays a significant role in cardiac protection under stress conditions was shown to play a mediating role for this increased risk.[19] Xiao et al reported role of inhibition of CSK (C-terminal Src kinase) as strongest candidate for ibrutinib associated AF.[20] Treatment of mice with ibrutinib for 4 weeks, led to inducible AF, left atrial enlargement, myocardial fibrosis, and inflammation. This was reproduced in mice lacking BTK but not in mice treated with acalabrutinib, a more specific BTKi, demonstrating an off-target side effect. Future studies are needed to better understand underlying mechanisms with analysis of newer generation BTKis compared with ibrutinib.

Furthermore, BTKi were also shown to increase risk of supraventricular arrhythmias, life-threatening ventricular arrhythmias, and sudden cardiac death.[10,11] In contrast to our findings, Nickel et al reported less risk of arrythmia in cancer patients treated with targeted chemotherapy agents when compared with patients treated with anthracyclines. Overall risk of any arrhythmia within 6 months of treatment was 12%. Among patients treated with targeted agents, tyrosine kinase inhibitors (ibrutinib, imatinib, sunitinib, vemurafenib, sorafenib, erlotinib, and lapatinib) and immune checkpoint inhibitors (nivolumab, pembrolizumab, ipilimumab, atezolizumab, and tremelimumab) were associated with a higher incidence of arrhythmias than other monoclonal antibodies targeting cell proliferation (trastuzumab and bevacizumab).[21] In this study, patients were selected based on cancer treatment and therefore included other patients' population beyond lymphoproliferative disorders.

Risk Factors for the Development of Arrhythmia During Lymphoma Treatment

Evidence suggests that a history of prior arrhythmias and heart failure were significant predictors of atrial fibrillation among patients with CLL.[22] Older age,

male sex, hypertension, and a history of congestive heart failure were also associated with a significantly increased risk of cancer treatment associated arrhythmias[21] However, fewer studies have evaluated the interaction of cancer treatments and pre-existing cardiovascular conditions. Cardiovascular risk factors were common among patients in our study as 26% had a history of hypertension, and 11% had a history of arrhythmia at the time of diagnosis. Prior data have shown that ibrutinib use was associated with a substantial increase in the incidence and severity of hypertension which was associated with subsequent increased risk of cardiac adverse events.[23] In another study of ibrutinib treated patients, a history of AF was found to be a risk factor for future AF.[24] Our results suggest that lymphoma treatment confers an even more pronounced arrhythmia risk (>3-fold) among patients with no prior history of arrhythmia. History of arrhythmias relative to no history was indeed associated with a much higher risk of subsequent arrhythmias (HR, 8.5, not reported in Table 2). Because having prior arrhythmias puts these patients at such high risk of subsequent arrhythmias it appears that the use of BTKi in this group did not substantially increase the risk, probably because their risk was already very high. This is seen in Figures 4 and 5 where the risk of arrhythmias associated with treatment is high compared with those without prior arrhythmias (HR, 3.27), yet those with prior arrhythmias do not have an increased risk (HR, 1.22). Because they are already at such a high risk, the drug therapy does not appreciably increase the risk in this subgroup. This mechanism was also observed for hypertension, which overall increases the risk of arrhythmia (HR, 1.7). Therefore, since patients with a history of hypertension already have increased risk of AF, treatment increases the risk of arrhythmias significantly less in the hypertensive patients' group than in those without a history of hypertension, although in contrast to the history of arrhythmias case, the risk associated with treatment is statistically significant in both groups. Cancer treatment may unmask a propensity to develop arrhythmias among those without having prior risk factors such as hypertension or a prior history of arrhythmias. We did not have information on cardiac medication use, particularly calcium channel blockers and anti-arrhythmic medications among patients in our database. It is possible that medications used for treatment of hypertension or prior history of arrhythmia mitigate future risk of arrhythmia. This needs to be further studied in future projects. Similarly, we did not have data on concomitant medications that may have interacted with chemotherapeutic agents and affected the risk of arrhythmias. These findings may possibly be since a patient with a history of arrhythmia and hypertension are more likely to developed AF and arrhythmic events, regardless of lymphoma treatments, whereas patients without such risk factors are more likely to develop new onset AF/arrhythmia after exposure to lymphoma treatment. Importantly, our findings stress the need for close monitoring for arrhythmic events during lymphoma treatment even among those considered at low arrhythmic risk based on conventional risk factor assessment.

Limitations

There are several limitations to our study. This was a single-center observational study, and diagnosis are based on *ICD-10* codes. We did not have control of monitoring or follow-up of patients. Overall morbidity burden is not known, and because of retrospective design, it is likely the arrhythmic burden reported might still be an underestimate. Our data suggest that both the risks of mortality and arrhythmia are higher among patients with lymphoma who received treatments (BTKi or non-BTKi) when compared with patients who did not receive treatment. Therefore, increased mortality in the treatment group did not attenuate the arrhythmic risk associated with lymphoma treatment. However, possible bias may exist in selection of treatments because of comorbidities or disease progression. We did not have data on ejection fraction or incidence of cardiomyopathy during treatment. We also did not have information on development of post-cancer treatment hypertension. We also did not have information regarding significant electrolyte abnormalities or other metabolic derangements during follow-up that could have predisposed to arrhythmias. We describe the risk of a wide range of arrhythmias in a heterogenous real-world population of patients during treatment of lymphoproliferative disorders. We also provide a comparison of arrhythmia risk with newer targeted therapies against traditional chemotherapeutic agents. Ibrutinib was the most frequently used BTKi. Future projects are needed to compare the newer-generation BTKi and ibrutinib. Our study highlights the fact that providers should be aware that an increasing number of chemotherapeutic agents are associated with proarrhythmic effects, especially among patients without traditional risk factors for arrhythmic risk. Future studies are needed to study treatment algorithms that can help reduce risk of arrhythmia events in patients with lymphoproliferative disorders who need chemotherapeutic agents, traditional chemotherapy, or novel oncologic therapies.

Conclusions

Our data show that time-dependent treatment was associated with increased risk of arrhythmia in a population of patients with lymphoproliferative disorders, and this risk is most pronounced among patients treated with a BTKi, mainly ibrutinib, in our study. Patients with lymphoproliferative disorders that undergo treatments

are at higher risk of cardiac arrhythmias. Atrial fibrillation is one of the most common types of arrythmias in this population. Close cardiac monitoring and symptom awareness should be considered in patients with lymphoproliferative disorders undergoing lymphoma treatments.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Histologic types of lymphoma in order of frequency

Histologic Type of Lymphoma	N= 2064
Diffuse large B cell lymphoma	504
Chronic lymphocytic leukemia/Small cell lymphocytic lymphoma/ Monoclonal B cell lymphocytosis (MBL)	413/15
Follicular lymphoma	288
Hodgkin Lymphoma	228
Marginal zone lymphoma/MALT	139/26
Mantle cell lymphoma	102
Peripheral T-cell lymphoma NOS	98
Waldenstrom's Macroglobulinemia	80
Lymphoproliferative disorders not otherwise specified	32
Hairy cell leukemia	30
Mediastinal large B cell lymphoma	19
Hairy cell leukemia variant /Splenic diffuse red pulp lymphoma (SDRPL)	10/14
Burkitt's lymphoma	13
Cutaneous T cell lymphoma	12
Anaplastic large cell	11
T-cell large granular lymphocytic leukemia	10
Prolymphocytic Leukemia	9
Mycosis Fungoides	7
Angioimmunoblastic T-cell lymphoma	5
Lymphomatoid Papulosis (LyP)	4
Plasmablastic lymphoma	3
B acute lymphoblastic leukemia/lymphoma	2

Table S2. Histologic Subtypes by Indolent and Aggressive Categories

Histologic Type of Lymphoma	
Indolent Lymphoma	
Chronic lymphocytic leukemia/Small cell lymphocytic lymphoma/ Monoclonal B cell lymphocytosis (MBL)	413/15
Follicular lymphoma	288
Marginal zone lymphoma/MALT	139/26
Waldenstrom's Macroglobulinemia	80
Hairy cell leukemia	30
Hairy cell leukemia variant /Splenic diffuse red pulp lymphoma (SDRPL)	10/14
Cutaneous T cell lymphoma	12
T-cell large granular lymphocytic leukemia	10
Mycosis Fungoides	7
Aggressive Lymphoma	
Diffuse large B cell lymphoma	504
Mantle cell lymphoma	102
Peripheral T-cell lymphoma NOS	98
Mediastinal large B cell lymphoma	19
Burkitt's lymphoma	13
Anaplastic large cell	11
Prolymphocytic Leukemia	9
Angioimmunoblastic T-cell lymphoma	5
Lymphomatoid Papulosis (LyP)	4
Plasmablastic lymphoma	3

Table S3. Cox Model for Time dependent treatment and Risk of Arrhythmia

	HR	95% CI	P value
Time dependent Treatment overall vs. no treatment	2.08	1.62-2.68	<0.001
Race	1.11	0.68-1.79	0.666
Male	1.68	1.29-2.17	<0.001
Age	1.04	1.03-1.05	<0.001
CAD	0.81	0.58-1.12	0.216
Hyperlipidemia	1.21	0.89-1.64	0.205
Diabetes Mellitus	0.99	0.71-1.38	0.994
Hypertension	1.31	0.94-1.82	0.099
Heart Failure	1.89	1.24-2.87	0.002

Figure S1. Distribution of Arrhythmia Types

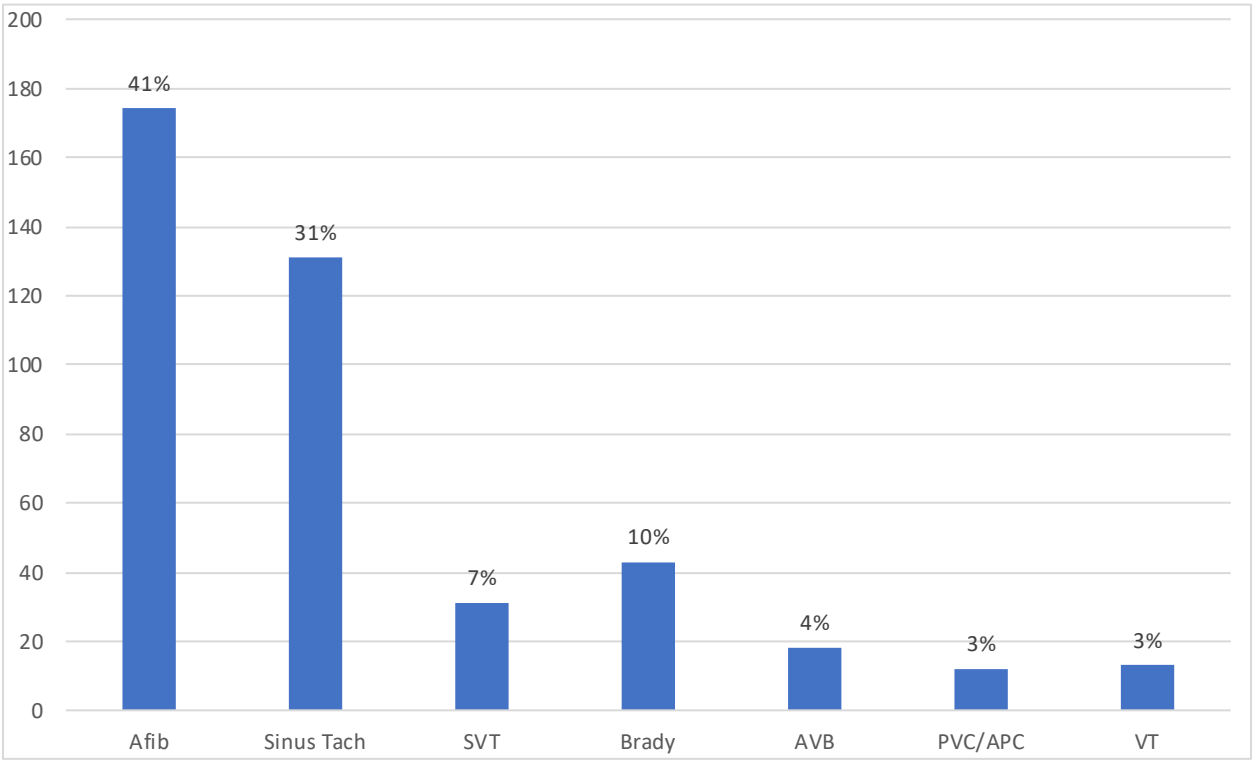

Figure S2A. Time dependent treatment and Cumulative rate of any arrhythmia among patients with aggressive lymphomas

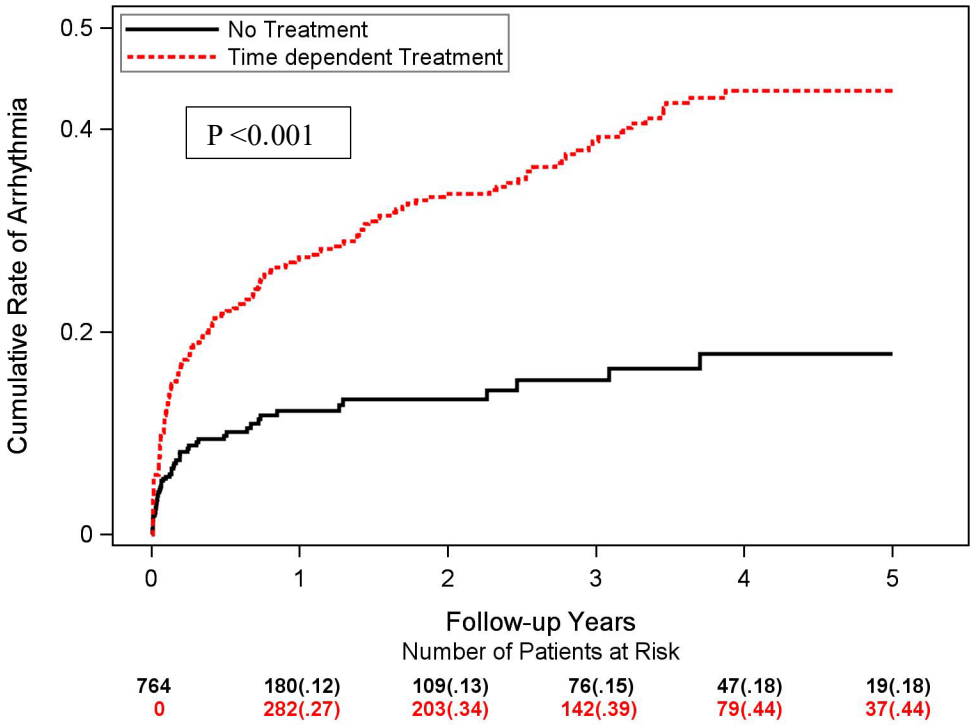

Figure S2B. Time dependent treatment and Cumulative rate of any arrhythmia among patients with Indolent lymphomas