Cancer Control
Volume 27: 1-3

DOI: 10.1177/1073274820931808
journals.sagepub.com/home/ccx
SAGE

Electrocardiographic Changes Associated With Ibrutinib Exposure

Michael G. Fradley, MD[1], Allan Welter-Frost, MD[1], Matthew Gliksman, BS[1], Josephine Emole, MD[2], Federico Viganego, MD[1], Dae Hyun Lee, MD[1], Bijal Shah, MD[3], Julio C. Chavez, MD[3], Javier Pinilla-Ibarz, MD, PhD[3], and Matthew B. Schabath, PhD[4]

Abstract

Although ibrutinib-associated atrial and ventricular arrhythmias have been well described, there is little information about ibrutinib's effects on other electrocardiographic parameters, particularly the QT interval. Using our database of 137 patients treated with ibrutinib, we retrospectively identified 21 patients in whom an electrocardiogram (ECG) was obtained both prior to and after ibrutinib exposure. All traditional ECG parameters as well as QT dispersion were manually measured by an electrophysiologist. Compared to baseline ECGs, post ibrutinib ECGs demonstrated QT interval shortening from 386 ms to 356 ms ($P = .007$), corrected QT interval shortening using Bazett's formula from 446 ms to 437 ms ($P = .04$), and corrected QT interval shortening using Fridericia's formula from 425 ms to 407 ms ($P = .003$). QT dispersion also increased post ibrutinib exposure compared to baseline (39.8 ms vs 57.3 ms, $P = .002$). There was no significant change in other ECG parameters. In conclusion, both the absolute and corrected QT intervals significantly shortened after ibrutinib exposure, while there was a significant increase in QT dispersion. These findings may point to a common underlying electrophysiologic mechanism of ibrutinib-associated arrhythmias.

Keywords

cardio-oncology, cardiotoxicity, electrocardiogram, ibrutinib, QT interval

Received February 12, 2020. Received revised April 11, 2020. Accepted for publication May 13, 2020.

Ibrutinib is a small molecular inhibitor of Bruton tyrosine kinase (BTK) used to treat multiple B-cell malignancies including chronic lymphocytic leukemia and mantle cell lymphoma. Despite its anticancer efficacy, multiple cardiotoxicities have been identified including both atrial and ventricular arrhythmias.[1-3] Prior studies have shown that ibrutinib is an independent risk factor for the development of atrial arrhythmias with rates of atrial fibrillation in excess of 10% to 15%.[4-6] Aside from the development of frank arrhythmias, little is known about the potential effects of ibrutinib on electrocardiographic (ECG) parameters. Although significant QT prolongation was not identified during clinical trials, other ECG parameters have not been systematically evaluated. We hypothesized that ibrutinib will influence easily measured ECG parameters that may help direct future basic and translational research into its arrhythmic effects.

[1] Cardio-Oncology Program, Division of Cardiovascular Medicine, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida Morsani College of Medicine, Tampa, FL, USA
[2] Department of Medical Oncology, Henry Ford Health System, Detroit MI, USA
[3] Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
[4] Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Corresponding Author:
Michael G. Fradley, Cardio-Oncology Center of Excellence, Department of Medicine, Division of Cardiology, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Blvd., Philadelphia, PA 19104, USA.
Email: michael.fradley@pennmedicine.upenn.edu

Table 1. Baseline Patient Demographics.[a]

Age, mean years (SD)	64 (9.1)
Male sex	16 (76%)
BMI: mean (kg/m^2 [SD])	29.5 (5.9)
Ever smokers	15 (71%)
Baseline cardiovascular disease	
Coronary artery disease	5 (24%)
Valvular disease	4 (19%)
Hypertension	12 (57%)
Diabetes	5 (24%)
Hyperlipidemia	9 (43%)
Cardiomyopathy	0 (0%)
Stroke	0 (0%)
Baseline cardiovascular medications	
Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers	6 (29%)
Beta blockers	7 (33%)
Nondihydropyridine calcium channel blockers	1 (5%)
Digoxin	1 (5%)
Statin	4 (19%)
Aspirin	7 (33%)
Antiarrhythmics	0 (0%)
Malignancy	
Chronic lymphocytic leukemia	12 (57%)
Mantle cell lymphoma	9 (43%)
Waldenstrom macroglobulinemia	0
Ibrutinib dose, mg, mean (SD)	440 (117)

Abbreviation: BMI, body mass index.
[a]N = 21.

Details of this study population have been previously described.[4] In brief, patients diagnosed with B-cell malignancies were derived from the Moffitt Cancer Center (MCC) Malignant Hematology Program and those who completed at least one 28-day cycle of ibrutinib between January 1, 2010, and December 31, 2017, were selected. In this analysis, only patients with an ECG completed prior to and during ibrutinib therapy were included. Baseline demographics and cardiovascular risk factors were abstracted from medical records, and ECG parameters including rate, rhythm, QRS axis, PR interval, QRS duration, QT interval, Bazett and Fridericia corrected QT interval, and QT dispersion (QT maximum − QT minimum) were manually calculated by the study electrophysiologist (M.G.F.). Given that there was no discrepancy of >20 ms between the automated and manual measurements, only 1 electrophysiologist adjudicated the results. Electrocardiographs were performed on General Electric (GE) Mac 5500 machines with standard recording algorithms including paper speed (25 mm/s) and scale (10 mm/mV). Descriptive statistics was used to characterize the baseline demographics and Student *t* test were used to test for statistically significant changes in the ECG variables.

Characteristics of the entire study population are previously published including a 13.7% incidence of atrial arrhythmias.[4] From the original study population, 21 patients met the inclusion criteria for the current analysis. Baseline characteristics of these patients are presented in Table 1. The mean age was 64 years and 76% were male. The majority of patients were treated for chronic lymphocytic leukemia (57%). The median time from baseline ECG to ibrutinib initiation was 352 days, and median time from drug initiation to follow-up ECG acquisition was 105 days. All patients in this analysis completed more than 1 cycle of ibrutinib therapy. Compared to pretreatment baseline ECGs, postibrutinib ECGs demonstrated QT interval shortening from 386 ms to 356 ms ($P = .007$) corrected QT interval shortening using Bazett formula from 446 ms to 437 ms ($P = .04$) and using the Fridericia formula from 425 ms to 407 ms ($P = .003$). QT dispersion also increased postibrutinib exposure compared to baseline (39.8 ms vs 57.3 ms, $P = .002$). There were no significant changes for other common ECG parameters (Table 2). Of note, ECG parameters were normally distributed based on the Shapiro-Wilk test for normality.

Table 2. Changes in ECG Parameters Associated With Ibrutinib Exposure.

ECG changes	Before ibrutinib (SD)	After ibrutinib (SD)	*P* value[a]
Rate (beats per minute)	82 (14)	94 (25)	.06
PR interval (ms)	157 (14)	151 (24)	.60
QRS duration (ms)	101 (15)	106 (22)	.12
QRS axis (degrees)	2.3 (37)	8.1 (41)	.14
QT interval (ms)	386 (26)	356 (39)	**.007**
QTc Bazett (ms)	446 (33)	437 (30)	**.04**
QTc Fridericia (ms)	425 (24)	407 (26)	**.003**
QT dispersion (ms)	38.8 (18)	55.7 (24)	**.005**

Abbreviation: ECG, electrocardiography.
[a]Bold values are statistically significant.

This is the largest study to systematically evaluate ECG changes in the setting of ibrutinib use. The main finding was a significant shortening of the QT interval with an increase in QT dispersion. de Jong and colleagues published data from a prospective "thorough QT study," demonstrating a nonsignificant shortening of the QT interval.[7] Nevertheless, fewer patients were evaluated and only received 1 dose of ibrutinib with the final ECG checked 72 hours after administration. In our "real-world" sample, patients received daily ibrutinib use, and the median time to ECG evaluation was 105 days, which likely explains the statistical significance reported in our study. QT interval changes can be associated with both short- and long-term potential cardiovascular complications including atrial and ventricular arrhythmias as well as sudden cardiac death.

Multiple studies have reported that ibrutinib use is associated with increased rates of both atrial and ventricular arrhythmias; however, the underlying mechanism of this drug's arrhythmogenicity remains unclear. Although ibrutinib has been shown to impact the PI3K-AKT signaling pathway, which has been implicated in the development of AF,[8] this may not be sufficient to explain the mechanism of ibrutinib-induced AF. Calcium ions play a significant role in the electrophysiology of both atrial and ventricular myocytes and may help to explain

ibrutinib's arrhythmogenesis. Using a murine model, Jiang and colleagues identified potential mechanisms for ibrutinib-associated AF including dysregulated calcium handling, enhanced delayed afterdepolarization, and increased activity of CaMKII.[9] In a rabbit model of long QT syndrome, the administration of an inhibitor of sarcoplasmic reticulum calcium cycling led to prolongation of the action potential duration (APD) with enhancement of the calcium transient amplitude.[10] Interestingly, this is the opposite effect seen in atrial myocytes when exposed to ibrutinib. Extrapolating on this finding, a similar effect may occur with ventricular myocytes that would translate to QT interval shortening. It should be recognized that both the QT interval and QT dispersion have significant limitations in predicting arrhythmic events however.[11]

We recognize several limitations with this analysis. First, this was a retrospective study at a single cancer center with the associated inherent biases. We acknowledge the sample size is a small percentage of our original cohort which could introduce selection bias; however, baseline ECGs are not routinely obtained in this patient population. There are no recommendations for ECG monitoring in patients treated with ibrutinib, and therefore, we had to rely on those ECGs obtained for other clinical reasons. As such, the lack of standard intervals for baseline and follow-up ECGs in this study can lead to the introduction of significant bias. It is also recognized that the QT interval varies with activity and the circadian cycle; however, all ECGs were obtained during waking hours, and the use of standardized heart rate correction formulae should minimize these potential biases. Finally, we cannot comment on the association of these ECG abnormalities and the development of arrhythmias as ECGs were commonly checked in individuals with signs or symptoms of abnormal heart rhythms.

In summary, our study is the first to report ECG changes associated with ibrutinib exposure. Ibrutinib leads to significant QT/QTc shortening and an increase in QT dispersion. These findings provide a foundation for the development of future basic and translational studies to identify the mechanism of ibrutinib-induced arrhythmogenesis.

Authors' Note

J.P.-I. and M.B.S. are cosenior authors. M.G.F. designed, performed research, analyzed data, and wrote/edited paper. A.W.F., M.G., J.E., F.V., and D.L. performed research and analyzed data and wrote/edited paper. B.S. and JCC analyzed data and edited paper. J.P. designed study and edited paper. M.S. analyzed data and wrote/edited paper.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.G.F. is a consultant/advisor for Novartis. J.P.I. is an investigator for Novartis and Ariad; consultant/advisor for Novartis, Bristol-Myers Squibb, and Ariad; consulting/speakers bureau fees from Janssen and Pharmacyclics.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Michael G. Fradley, MD https://orcid.org/0000-0001-8352-8975
Dae Hyun Lee, MD https://orcid.org/0000-0001-8141-0404
Matthew B. Schabath, PhD https://orcid.org/0000-0003-3241-3216

References

1. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol*. 2019; 74(3):1667-1678.
2. Guha A, Derbala MH, Zhao Q, et al. Ventricular arrhythmias following ibrutinib initiation for lymphoid malignancies. *J Am Coll Cardiol*. 2018;72(7):697-698.
3. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica*. 2018;103(5):874-879.
4. Fradley MG, Gliksman M, Emole J, et al. Rates and risk of atrial arrhythmias in patients treated with ibrutinib compared with cytotoxic chemotherapy. *Am J Cardiol*. 2019;124(3):539-544.
5. Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. *Blood*. 2016;128(6):138-140.
6. 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(4):1739-1748.
7. de Jong J, Hellemans P, Jiao JJ, et al. Ibrutinib does not prolong the corrected QT interval in healthy subjects: results from a thorough QT study. *Cancer Chemother Pharmacol*. 2017;80(3): 1227-1237.
8. 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(4):3829-3830.
9. Jiang L, Li L, Ruan Y, et al. Ibrutinib promotes atrial fibrillation by inducing structural remodeling and calcium dysregulation in the atrium. *Heart Rhythm*. 2019;16(9):1374-1382.
10. Chang PC, Wo HT, Lee HL, et al. Role of sarcoplasmic reticulum calcium in development of secondary calcium rise and early afterdepolarizations in long QT syndrome rabbit model. *PLoS One*. 2015;10(1):e0123868.
11. Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. *J Am Coll Cardiol*. 2000;36(2): 1749-1766.