Electrocardiographic Changes Associated With Ibrutinib Exposure

Michael G. Fradley, MD1, Allan Welter-Frost, MD1, Matthew Gliksman, BS1, Josephine Emole, MD2, Federico Viganego, MD1, Dae Hyun Lee, MD1, Bijal Shah, MD3, Julio C. Chavez, MD3, Javier Pinilla-Ibarz, MD, PhD3, and Matthew B. Schabath, PhD4

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

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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

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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.

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. 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, 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

| Table 1. Baseline Patient Demographics.a |
|----------------------------------------|
| Age, mean years (SD) | 64 (9.1) |
| Male sex | 16 (76%) |
| BMI: mean (kg/m² [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.

*Bold values are statistically significant.

| Table 2. Changes in ECG Parameters Associated With Ibrutinib Exposure. |
|---------------------------------------------------------------|
| ECG changes | Before ibrutinib (SD) | After ibrutinib (SD) | $P$ value* |
| 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.
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
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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

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