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Case Report

# Ibrutinib-Associated Cardiovascular Events in a Patient Wearing an Implanted Loop Recorder

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**Abstract. Ibrutinib is a well-tolerated and effective therapy used for the treatment of chronic lymphocytic leukemia (CLL). However, its use has been associated with cardiovascular events such as atrial fibrillation (Afib), hypertension, and ventricular arrhythmias. Cardiac arrhythmias represent a significant cause of morbidity and mortality. Implanted loop recorders have been integrated into our clinical practice and have been considered a useful tool in guiding the management of patients with cardiac arrhythmias. We report a case that describes our experience on a patient diagnosed with CLL treated with ibrutinib.**

**Keywords:** .

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**Introduction. Learning objectives.**

- The importance of Ibrutinib-related cardiovascular events.
- Differential diagnosis of patients with a newly diagnosed tachyarrhythmia.
- The role of an implanted loop recorder for the management of ibrutinib-associated arrhythmias.

**History of presentation.** The patient is a 67 y.o. man, who in February 2017 presented to the emergency center with a chief complaint of dizziness, lightheadedness, and palpitations. He was found to be hypotensive, and his physical exam was remarkable for tachycardia with an irregularly irregular heart rhythm.

**Past Medical History.** The patient had a history of hyperlipidemia treated with atorvastatin and well-controlled essential hypertension treated with losartan/hydrochlorothiazide. In 2015 he was diagnosed with CLL with chromosome 11 deleted and IGHV mutated. In October 2016, the patient required treatment because of progressive disease and started therapy on a clinical trial with ibrutinib at the dose of 420 mg daily.

**Differential diagnosis.** Laboratory evaluation did not show electrolyte imbalances or thyroid dysfunction. An echocardiogram did not detect valvular or structural abnormalities and showed an LVEF of 61% with no regional wall motion abnormalities or evidence of myocardial disorders. The patient was admitted with the diagnosis of Afib with a rapid ventricular rate (RVR) and a CHADSVASc of 2.

**Investigations and Management.** The patient was initially treated with amiodarone without success; electrical cardioversion was performed, achieving normal sinus rhythm (NSR). The patient was discharged on amiodarone, 400 mg daily, apixaban 5 mg BID, and the ibrutinib dose was reduced to 140 mg daily. However, fifteen days after the event, due to the concern of the interaction between ibrutinib and amiodarone, which could reduce Ibrutinib clearance and, consequently,

increase the risk of bleeding due to its interaction with apixaban, these two drugs were discontinued.

Ibrutinib was increased to its total dose of 420 mg daily, and the patient was started on metoprolol 12.5 mg daily and aspirin 81 mg daily. At this time, the cardiology team implanted a subcutaneous insertable loop recorder (Reveal) to optimize the monitoring of future arrhythmias. The next phase of his treatment on clinical trial consisted of venetoclax at the dose of 400 mg daily.

Over the next 2 months, the loop recorder detected 2 episodes of Afib, which were asymptomatic and, on one occasion, followed by a non-sustained monomorphic ventricular tachycardia (NSVT) with no hemodynamic sequela. (**Figure1 A** and **B**). The patient at this time was asymptomatic with a CHADSVASc of 2 and HAS-BLED of 1. Due to the presence of recurrent arrhythmias, a Pharmacological nuclear EKG stress test was done and showed normal myocardial perfusion with no evidence of stress-induced ischemia and normal left ventricular systolic function with a left ventricular ejection fraction of 66%. His treatment was optimized with a change of metoprolol 12.5 mg daily to metoprolol XL 50 mg daily.

Between May 2017 and February 2018, the implantable loop recorded continued to detect Afib with a burden that remained <6%, but no further episodes of VTs (**Table 1**). The patient continued to experience borderline hypertension (**Table 1**).

In February 2018, the patient developed an erythematous rash which was attributed to ibrutinib. CLL re-staging was found to have achieved complete remission with undetectable measurable residual disease on bone marrow test. Ibrutinib was, therefore,

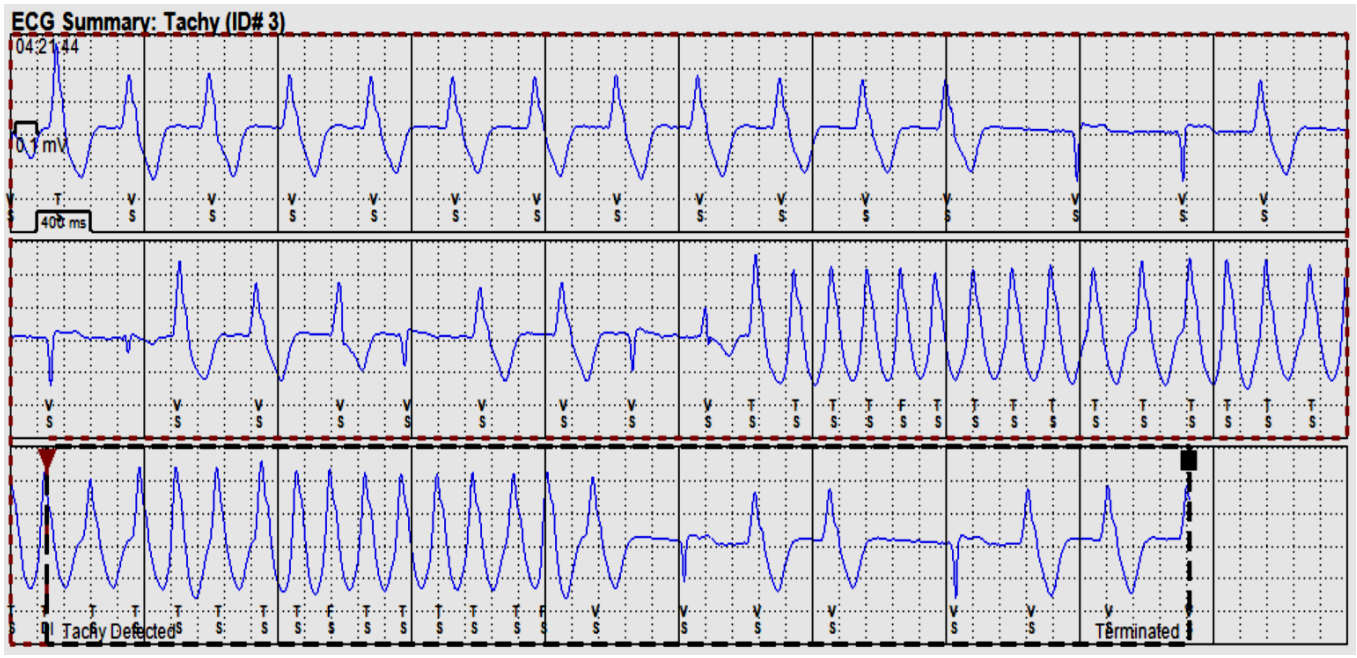


**Figure 1 A.** Electrocardiogram showing non-sustained monomorphic ventricular tachycardia (NSVT).

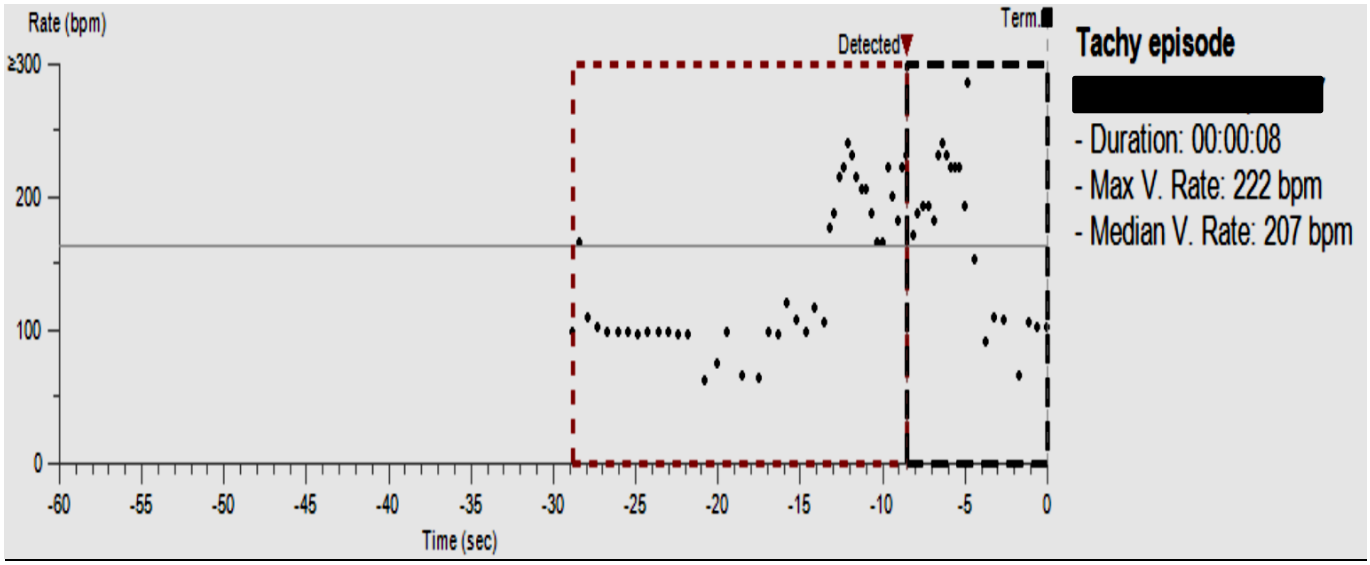


**Figure 1 B.** Reveal LINQ monitor interrogation: Percentage of time in Atrial tachycardia/ Atrial Fibrillation: 4.3%. Findings: One Ventricular tachycardia episode was noted with rates of 207-222 bpm. Two Afib episodes.

**Table 1.** The burden of Atrial fibrillation, Blood pressure readings, and management.

| DATE | CLL THERAPY | % OF THE TIME IN AFIB | SYSTOLIC BP | DIASTOLIC BP | CARDIAC TREATMENTS |
|---|---|---|---|---|---|
| 2/17 | Ibrutinib 420 mg | Pre- loop recorder | 80 | 50 | Amiodarone + apixaban |
| 3/17 | Ibrutinib 140 mg | Loop recorder implanted - 0 | 139 | 78 | metoprolol + aspirin |
| 4/17 | Ibrutinib + Venetoclax | 4.3 | 143 | 81 | metoprolol + aspirin |
| 5/17 | Ibrutinib + Venetoclax | 3.1 | 123 | 84 | metoprolol + aspirin |
| 8/17 | Ibrutinib + Venetoclax | 2.9 | 138 | 77 | metoprolol + aspirin |
| 10/17 | Ibrutinib + Venetoclax | 1.6 | 138 | 81 | metoprolol + aspirin |
| 12/17 | Ibrutinib + Venetoclax | 3.0 | 138 | 81 | metoprolol + aspirin |
| 2/18 | Ibrutinib + Venetoclax | 2.2 | 138 | 76 | metoprolol + aspirin |
| 4/18 | Venetoclax | 0 | 123 | 83 | metoprolol + aspirin |
| 6/18 | Venetoclax | 0 | 126 | 79 | metoprolol + aspirin |
| 9/18 | Venetoclax | 0 | 127 | 80 | metoprolol + aspirin |

discontinued in February 2018 and venetoclax monotherapy was continued for one additional year until January 2019 when all treatments were discontinued.

**Discussion.** Ibrutinib is a first-generation BTK inhibitor that has been effective for the treatment of CLL. BTK inhibition reduces B-cell proliferation, adhesion, and migration.[1,2] treatment with ibrutinib has been associated with cardiovascular toxicities. The proposed mechanisms of the cardiovascular effect are not exactly known; however, it has been thought they are related to off-target effects on kinases different than BTK. Inhibition of cardiac PI3K-Akt signaling, which is a critical regulator of cardiac protection under stress conditions,[3] the binding of ibrutinib to ErbB2/HER2, ErbB4/HER4, and BMX receptors in cardiomyocytes, and inhibition of C-terminal Src kinase have been reported to be involved.[4]

In the case reported here, shortly after starting ibrutinib, the patient began experiencing cardiovascular events such as an increase in blood pressure, recurrent episodes of Afibr, and one episode of VT, which were attributed to ibrutinib therapy.

We observed that our patient had a median systolic BP of 127 mmHg and a diastolic BP of 81 mmHg while receiving treatment with ibrutinib. The development of hypertension has been reported in up to 68% of the patients undergoing treatment with ibrutinib, and worsening HTN is common in patients with pre-existing HTN. The risk for HTN continues for the entire duration of treatment with ibrutinib and can increase the risk of major adverse cardiovascular events such as Afib, stroke, or myocardial infarction.[5]

Our patient experienced one symptomatic Afib episode four months after initiating therapy with ibrutinib, requiring electrical cardioversion. Antiarrhythmic treatment with amiodarone and anticoagulation with apixaban was initially implemented but soon deemed not feasible due to interactions with ibrutinib and increased risk for bleeding. This highlights the complexity in managing these patients with risks for drug interactions with strong or moderate CYP3A4 inhibitors/inducers. Additionally, the concomitant administration of vitamin K antagonists is prohibited in patients receiving ibrutinib, and insufficient data are available on the risk of bleeding in patients receiving DOAC and ibrutinib considering that the coadministration of DOAC and ibrutinib could increase ibrutinib exposure via CYP3A4-mediated interaction.

Consequently, our patient continued metoprolol for rate control. His loop recorder showed a median percentage of time in Afib of 2.2% over 12 months. The patient remained on ibrutinib since he remained asymptomatic with successful medical management. Pooled analysis of 4 randomized trials showed an incidence of ibrutinib related-atrial fibrillation of 3.3 per 100 person-year.[6] However, a higher incidence has been reported in studies, with a longer follow-up being up to 16% of the patients.[7] The common etiologies for ventricular arrhythmias include untreated or unrecognized ischemic heart disease; wherein ischemia can serve as a substrate for ventricular tachycardia. Ventricular arrhythmias have been associated with ibrutinib therapy. Avirup et al. reported a median time-to-event of 16 months with an incidence rate of 617 per 100,000 person-year in the general population and patients without baseline CAD, and heart failure; similar to our patient, the incidence rate was lower at 596 per

100,000.[8] Similarly, the REVEAL AF study performed in the general population in 446 patients, reporting a detection rate at 18 months of 29%, this proved to be of value in detecting undiagnosed AF in patients with risk factors for Afib and stroke.[9]

In this case, Ibrutinib was not discontinued as this patient was asymptomatic with no hemodynamic compromise. Early discontinuation of Ibrutinib can impact the ability to control CLL and affect long-term survival. The risks and benefits of discontinuing ibrutinib must be discussed extensively with the oncology team, cardio-oncology specialists, and patients.[10,11]

**Follow-up.** No further episodes of Afib were observed after discontinuation of ibrutinib. Since then, the patient continues to be without treatment for his CLL, which remains in remission, with good quality of life and no cardiovascular events to date.

**Conclusions.** The management of ibrutinib-related cardiovascular toxicities remains a challenge in daily practice, and their importance is going to increase with the growing number of older patients being treated with this agent. The presence of an implanted loop recorder helps monitor patients, following the impact of treatment modifications, and trigger additional testing to identify contributing factors or alternative etiologies to the observed arrhythmias.

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