Ventricular Tachycardia Storm in a Patient Treated With Ibrutinib for Waldenstrom Macroglobulinemia

Anantha Sriharsha Madgula, MBBS,a Meghana Singh, MBBS,a Mansour Almnajam, MD,a,b Christopher C. Pickett, MD,a,b Agnes S. Kim, MD, PhD,a,b

A 68-year-old Caucasian man with a history of Waldenstrom macroglobulinemia (WM) on treatment with ibrutinib for 2 years presented with syncope. He had no prior cardiovascular history or risk factors. On the day of presentation, he had an episode of dizziness followed by a sudden loss of consciousness while watching television. Two minutes later, he spontaneously regained consciousness. Upon initial evaluation by emergency medical services, he was found to be in atrial fibrillation (AF). In transit to the hospital, he had 4 episodes of polymorphic ventricular tachycardia (VT) that required multiple debrillations (Figure 1). In the emergency department (ED), he was hemodynamically stable. Physical examination revealed normal S1 and S2 with no murmurs, equal peripheral pulses with warm and well-perfused extremities, and unremarkable neurological and pulmonary findings. His home medication list included only ibrutinib and no over-the-counter medications. In the ED, he was started on amiodarone for recurrent episodes of VT and admitted to the cardiac intensive care unit.

DIFFERENTIAL DIAGNOSIS

Myocardial ischemia: Leading the differential diagnosis of polymorphic VT in a 68-year-old man was acute coronary syndrome.

Heart failure (HF): He did not have symptoms or signs of hyperviscosity syndrome or HF. Systemic amyloidosis associated with WM leading to amyloid cardiomyopathy was also considered.

Drug toxicity: A high index of suspicion was maintained about the potential association between ibrutinib and ventricular arrhythmia (VA).

CLINICAL COURSE

Electrocardiogram at the time of evaluation by emergency medical services showed AF with a ventricular rate of 120 beats/min and nonspecific ST/T-wave abnormalities. Complete blood count, serum electrolytes, and renal function were within normal limits at the time of admission, and serial serum troponin levels were undetectable. A transthoracic echocardiogram showed normal biventricular size and function with no regional wall motion abnormalities. Furthermore, coronary angiography demonstrated very mild luminal irregularities without obstructive disease. In the cardiac intensive care unit, he was noted to have multiple premature ventricular complexes and nonsustained VT with a left bundle branch block morphology and right superior axis, indicating an origin at the right ventricular apex (Figure 2). He underwent cardiac magnetic resonance imaging, which demonstrated a small area of mid-myocardial delayed enhancement in a nonvascular
distribution in the basal inferolateral and anterolateral free wall of the left ventricle. The etiology of this scar was unclear because the patient had no prior cardiac history, and to our knowledge, ibrutinib had not been known to be associated with myocardial scar. No abnormality was noted in the right ventricular apical region, which was the likely origin of his VA.

**MANAGEMENT**

Initially, the patient was managed with intravenous amiodarone for recurrent VT. After extensive multidisciplinary discussions among cardiology, electrophysiology and oncology teams, ibrutinib was discontinued due to its potential association with VT. The patient was started on metoprolol, and an implantable cardioverter-defibrillator (ICD) was placed for secondary prevention. In terms of AF, his CHA2DS2-VASc score was 1, and anticoagulation was deferred, particularly given the potential bleeding risks with ibrutinib (1).

Although it remained uncertain if ibrutinib played an integral role in the pathophysiology of VT, the medication was discontinued with close outpatient cardiology and oncology follow-up. Because he had been in remission for several years, he was not started on alternative therapy for WM. On follow-up visits with close surveillance every 3 months with CBC, comprehensive metabolic panel, and IgM levels, he continued to be without evidence of symptomatic cytopenias, hyperviscosity, hepatosplenomegaly, lymphadenopathy, neuropathy, amyloidosis, cryoglobulinemia, or cold agglutinemia and did not meet criteria for reinitiation of therapy. On ICD interrogation at 3 months after cessation of ibrutinib, there were no further arrhythmias.

**DISCUSSION**

Ibrutinib is an oral, irreversible Bruton’s tyrosine kinase inhibitor used to treat a broad spectrum of B-cell proliferative disorders, including chronic lymphocytic leukemia (CLL) as first-line therapy, mantle cell lymphoma, marginal zone lymphoma, and WM (2). Cardiovascular toxicities associated with ibrutinib are...
supraventricular tachyarrhythmias, VAs (VT and ventricular fibrillation) sudden cardiac death, conduction disorders, HF, hypertension, CNS hemorrhagic events, and CNS ischemic events (3). Its association with AF has been well-described. In a meta-analysis of 4 RCTs, the pooled incidence rate of AF in patients treated with ibrutinib was 3.3 per 100 person-years compared with 0.84 per 100 person-years in those who received non-ibrutinib therapy (4).

The association of ibrutinib with VAs is becoming increasingly recognized (3,5,6). In randomized controlled trials, the incidence of all-grade VAs in patients treated with ibrutinib (n = 1,157) compared with patients in the control arm (n = 958) was 1.0% versus 0.4%, and for grade 3 or greater VAs was 0.3% versus 0% (7). In analyses from a U.S.-based comprehensive cancer registry cohort, male sex, previous AF, HF, coronary artery disease, diabetes, widened QRS, and valvular disease were associated with the development of any arrhythmias (VA and supraventricular tachyarrhythmias) (6). Among those without baseline HF or coronary artery disease, the estimated 100,000 person-year incidence rate for VAs was 596 compared with 48.1 among similar nonibrutinib-treated subjects, which suggested an observed versus expected relative risk of 12.4 (p < 0.001). Regarding drug dosage, in 1 study in which approximately 80% of the patients experienced VAs, 91% were taking at least 420 mg of ibrutinib per day, and only 9% were taking 280 mg or lower per day (3). Among those with ibrutinib-associated VAs, the median time-to-event was 16 months (range 0.7 to 57.6 months) (6).

Ibrutinib has been reported to cause polymorphic VT without QTc prolongation as well as in the absence of structural heart disease (8,9). Tomcsányi et al. (9) reported the case of a 74-year-old woman on ibrutinib for CLL with underlying left bundle branch block and AF who experienced ibrutinib-induced polymorphic VT in the absence of other causes (9). The initiation of VT was not characterized by short-long-short cycles as is seen in torsade de pointes. In polymorphic VT not related to prolonged QT, an alteration in the cardiac calcium homeostasis associated with ryanodine receptor-calmodulin-dependent protein kinase pathways is suspected. As such, it has been hypothesized that an interaction between these and PI3K-Akt pathways could potentially lead to polymorphic VT with ibrutinib (3).

Although the awareness of ibrutinib-associated VA is increasing, there are no published management guidelines. Our patient was initially treated with amiodarone, then started on a beta-blocker. In the case described by Tomcsányi et al. (9), the patient was treated with amiodarone and remained arrhythmia-free for 4 months. Amiodarone was thereafter discontinued due to pulmonary toxicity, and discontinuation led to the recurrence of VT. Sotalol was found to be ineffective, as were Class I antiarrhythmic agents (9). As ibrutinib is
Ibrutinib is a Bruton’s tyrosine kinase inhibitor associated with a well-known side effect of AF. Reported cases of VAs associated with ibrutinib are rare. We present a case of VT storm in a patient receiving ibrutinib for WM.

In general, ICD implantation is recommended for the secondary prevention of sudden cardiac death due to life-threatening VT/ventricular fibrillation in patients in whom a completely reversible cause cannot be identified (10). Our patient had hemodynamically unstable VT episodes requiring resuscitation, and although ibrutinib was felt to be the culprit, the presence of delayed enhancement on cardiac magnetic resonance imaging made it difficult to rule out underlying structural heart disease, such as an infiltrative cardiomyopathy. Additionally, an ICD is indicated if it is expected to improve overall mortality. Because our patient’s long-term prognosis from WM was favorable, it was felt that he would benefit from an ICD, particularly because ibrutinib or another therapy could be indicated in the future. In patients with cancer whose overall prognosis is poor (i.e., low expectation of survival with an acceptable functional status beyond 1 year), ICD therapy is not recommended. As ibrutinib is often used in patients with CLL whose prognosis is generally favorable, ICDs for secondary prevention have a potential for long-term benefit. An additional advantage of an ICD is providing prognostic parameters, such as the burden of atrial arrhythmia, nonsustained VT, and treated episodes of VT/ventricular fibrillation, which could help to risk-stratify patients in the future prior to reintroduction of potentially cardiotoxic drugs.

CONCLUSIONS

Ibrutinib is a Bruton’s tyrosine kinase inhibitor associated with a well-known side effect of AF. Reported cases of VAs associated with ibrutinib are rare. We present a case of VT storm in a patient receiving ibrutinib for WM.

As the recognition of ibrutinib-associated VAs is increasing, more data are needed to guide best management strategies for VAs triggered by ibrutinib.

ADDRESS FOR CORRESPONDENCE: Dr. Agnes S. Kim, Department of Medicine, Calhoun Cardiology Center, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, Connecticut 06030. E-mail: akim@uchc.edu. Twitter: @AgnesSKim2, @HMadgula.

REFERENCES

1. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-associated atrial fibrillation. J Am Coll Cardiol EP 2018;4:1491-500.
2. Byrd JC, Brown JR, O’Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371: 213-23.
3. Salem JE, Manouchehr A, Bretnage M, et al. Cardiovascular toxicities associated with ibrutinib. J Am Coll Cardiol 2019;74:1667-78.
4. Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood 2016;128:138-40.
5. Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. Blood 2017;129: 2581-4.
6. Guha A, Derbala MH, Zhao Q, et al. Ventricular arrhythmias following ibrutinib initiation for lymphoid malignancies. J Am Coll Cardiol 2018;72:697-8.
7. Imbruvica. Highlights of prescribing information. Available at: https://www.imbruvica.com/files/prescribing-information.pdf. Accessed June 10, 2020.
8. Tomcsányi J, Nényei Z, Mátrai Z, Bózsik B. Ibrutinib, an approved tyrosine kinase inhibitor as a potential cause of recurrent polymorphic ventricular tachycardia. J Am Coll Cardiol EP 2016;2:847-9.
9. Tomcsányi J, Mátrai Z, Tomcsányi K. Ventricular tachycardia caused by ibrutinib. J Emerg Med 2017;53:e27.
10. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72:1677-749.

KEY WORDS ibrutinib, ventricular tachycardia, Waldenstrom macroglobulinemia.