

Atrial fibrillation associated with Ibrutinib in Waldenström's macroglobulinemia.

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To the Editor:

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib recently became the first U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved therapy for patients with symptomatic Waldenström's macroglobulinemia (WM). A multicenter phase 2 trial in previously treated WM patients demonstrated high overall and major response rates, as well as durable progression free and overall survival. Although generally well tolerated, atrial fibrillation (AF) is a known adverse event among patients with B-cell malignancies treated with ibrutinib, including WM. Three cases of AF were reported among the 63 (5%) WM patients treated on the pivotal trial that supported ibrutinib approval.¹ Our objective in this study was to further characterize the risk of AF associated with ibrutinib in a larger cohort of WM patients with prolonged follow-up.

We identified 112 patients with WM/LPL (111 WM, 1 IgG LPL) that received ibrutinib, including 43 patients treated at our institution in the previously reported multicenter study.¹ The baseline characteristics for these patients are shown in Figure 1 (upper panel). With a median time on ibrutinib of 11.8 months (range, 0.20-43.1), 12 (10.7%) cases of AF were diagnosed of whom 6 (50%) had a prior history of AF. Three patients had a history of paroxysmal AF, two had active but well-controlled AF, and one had an ablation five years prior to ibrutinib initiation. One patient with a history of AF also had hypertension.

For the six patients without a prior history of AF, five (83%) were male, three (50%) were ≥ 65 years old at ibrutinib initiation, and three (50%) had a cardiac predisposition with a history of hypertension (n=2), coronary artery disease (n=1), premature ventricular contractions (n=1), or cardiac amyloidosis (n=1).

The cumulative incidence of AF at one, two, and three years was 5.4%, 7.1%, and 8.9%, respectively (Figure 1, lower panel). Furthermore, the annualized incidence rate was 0.0818 AF events per person-year of ibrutinib therapy for all patients, and 0.0418 in patients with no history of AF. The time on ibrutinib was 146.76 and 143.52 person-years for all patients and patients with no history of AF, respectively. By comparison, the annualized incidence of new onset AF was 0.0124 AF events per person-year based on data from the Framingham Heart Study.² An increased rate of AF events among all 112 patients (incidence rate ratio [IRR], 6.60; 95% CI, 3.72-11.7), including new cases in patients without a prior history of AF (IRR, 3.37; 95% CI, 1.51-7.54), was therefore observed for patients on ibrutinib versus an age comparable population.

The median time to the first AF event on ibrutinib for all 12 patients was 14.2 months (range, 1.2-43.1 months). Patients with a prior history of AF had a shorter time to AF compared to patients without a history of AF (3.9 versus 33.4 months; log-rank $p=0.003$) with a hazard ratio (HR) of 4.02 (95% CI, 2.73-46.5) (Figure 1B). At the time of AF event, 10 patients were on a dose of 420 mg, and 2 on a dose of 280 mg per day of ibrutinib. Cardiological intervention following the AF event included: initiation of anti-coagulation ($n=2$, 17%) with warfarin ($n=1$) or rivaroxaban ($n=1$), anti-arrhythmics ($n=4$, 33%), beta-blockers ($n=4$, 33%), cardioversion ($n=3$, 25%), calcium channel blockers ($n=1$, 8%), and ablation with dual-chamber pacemaker placement ($n=1$, 8%). Five patients (42%) held ibrutinib in response to AF for a median of 12 days, and all restarted ibrutinib. Notably, all but one patient who was discovered to have cardiac amyloidosis continued on ibrutinib after the AF event. Five (42%) patients had their ibrutinib dose reduced to 280 mg per day following the AF event.

The overall AF risk of 10.7% reported herein is higher than recognized in our previous study of ibrutinib in WM patients, and likely reflects a larger sample size and longer follow-up for many

patients included in that study. Importantly, the higher incidence of AF observed in this patient population is in line with recent studies showing an AF risk up to 16% among chronic lymphocytic leukemia patients treated with ibrutinib.³⁻⁵ Similar to the crude excess risk we observed relative to the general population, the randomized RESONATE and RESONATE-2 trials also reported 10- and 6-fold increased risks of AF in their ibrutinib treatment arms, respectively.^{3,4} In our study, patients with a known history of AF experienced an event earlier than those patients without a history of AF (Figure 1B). It remains unclear whether the late development of AF in the former cohort suggests that prolonged ibrutinib exposure increases the propensity for AF over time, or that these patients were at a higher risk of developing AF due to advancing age and exposure to other AF related morbidities such as hypertension, prolonged disease exposure, and effects of prior therapeutics. Cardiac amyloidosis is highly associated with arrhythmias and may have contributed to AF in one patient. The findings nonetheless continue to support an increased risk of AF for WM patients on ibrutinib therapy. The causal mechanism for ibrutinib related AF remains under investigation, though inhibition of cardiac PI3K-Akt signaling has been hypothesized.⁶

Despite the increased risk of ibrutinib associated AF, the overall efficacy and safety data of this agent in WM continues to support its use. Many adverse events common to other WM therapies are absent with ibrutinib, including uninvolved immunoglobulin depletion, peripheral neuropathy, myelosuppression, disease transformation, and increased risk of secondary cancers, including treatment related myelodysplasia and acute myeloid leukemia.¹ Moreover, a prior history of AF does not appear to prohibit treatment with ibrutinib, as 11 of 12 patients (92%) with an AF event continued on ibrutinib following cardiology intervention. A baseline electrocardiogram appears warranted as to screen for arrhythmias prior to ibrutinib initiation.

In summary, a higher incidence of AF is associated with the use of ibrutinib in WM patients than previously reported, with a shorter time to AF event observed in patients with versus without a prior history of AF. Nearly all patients who developed AF were able to continue ibrutinib following cardiological intervention and/or ibrutinib dose reduction.

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Authorship

J.N.G., S.P.T., and J.J.C. designed the study and wrote the manuscript. J.N.G., S.P.T., and J.J.C. performed the data analysis. J.N.G. and K.M. collected the patient data. J.J.C., S.P.T., and T.E.D. provided patient care.

Conflicts of Interest

JNG, KM, TED: No conflicts of interest to disclose.

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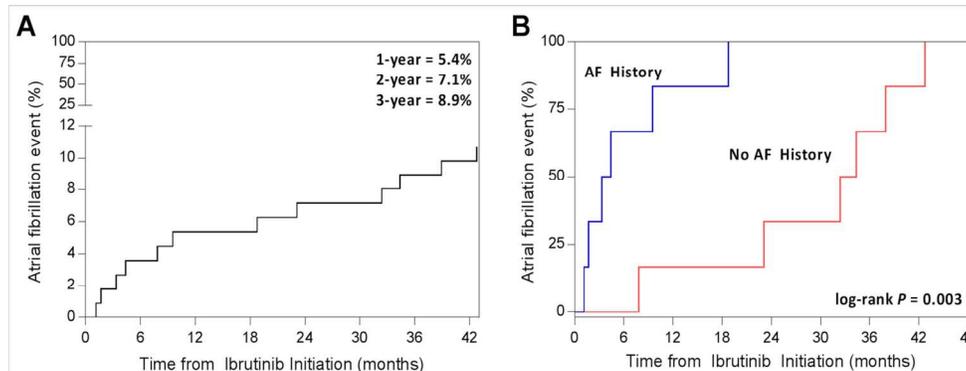
References

1. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. *N. Engl. J. Med.* 2015;372(15):1430–1440.
2. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet.* 2015;386(9989):154–162.
3. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N. Engl. J. Med.* 2014;371(3):213–223.
4. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. *N. Engl. J. Med.* 2015;373(25):2425–2437.
5. Farooqui M, Valdez J, Soto S, et al. Atrial Fibrillation in CLL/SLL Patients on Ibrutinib [abstract]. *Blood.* 2015;126(23):Abstract 2933.
6. McMullen JR, Boey EJH, Ooi JYY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood.* 2014;124(25):3829–3830.

Figure legend

Upper panel: Characteristics of patients with Waldenström macroglobulinemia (WM) at time of ibrutinib initiation. **Lower panel:** Cumulative incidence of atrial fibrillation events over time among all patients (A), and median time to atrial fibrillation in WM patients stratified by known history of atrial fibrillation (B).

Characteristic	Patients (N=112)
Median age (range) – yr	66 (30-93)
Sex – no. (%)	
Male	76 (68)
Female	36 (32)
Previous therapy for Waldenstrom macroglobulinemia	
Median no. of treatment regimens (range)	2 (0-8)
Type of therapy among previously treated – no. (%)	
Monoclonal antibody	101 (93)
Glucocorticoid	65 (60)
Proteasome inhibitor	57 (52)
Alkylator	55 (51)
Nucleoside analog	23 (22)
Other	44 (40)
Untreated – no. (%)	3 (3)
Serum IgM	
Median (range) – mg/dl	3370 (227-10,000)
>4000 mg/dl – no. (%)	40 (36)
Hemoglobin level	
Median (range) – g/dl	10.3 (6.4-14.2)
<11 g/dl – no. (%)	66 (59)
<10 g/dl – no. (%)	47 (42)
Platelet count	
Median (range) – g/dl	220,000 (24,000-639,000)
<100,000/mm ³ – no. (%)	12 (11)
Median bone marrow involvement (range) - %	60 (0-95)



Upper panel: Characteristics of patients with Waldenström macroglobulinemia (WM) at time of ibrutinib initiation. Lower panel: Cumulative incidence of atrial fibrillation events over time among all patients (A), and median time to atrial fibrillation in WM patients stratified by known history of atrial fibrillation (B) 217x254mm (300 x 300 DPI)