vaso-occlusive crisis. Whether zinc loss can be reduced by prevention of recurrent ischemia or the use of bisphosphonates should be studied in a prospective clinical trial. Life-long urinary wasting of zinc in SCD may justify supplementation of zinc in sickle cell patients.

Authorship Contributions

M. Schimmel, E. Nur and B.J. Biemond had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: MS, EN, LV, BB.

Acquisition of data: MS, ROE.

(Statistical) analysis and interpretation of data: MS, EN, DB, ROE, LV, BB.

Drafting of the manuscript: MS, EN and BB.

Critical revision of the manuscript for important intellectual content: all named co-authors.

Acknowledgment

The authors would like to thank Huib Bout, Ismael Derraz, Yvonne van der Heide and Natasja Huisman (Slotervaart Hospital, Amsterdam) for their laboratory work and support with collection of samples. We thank Marjolein Spiering (Academic Medical Center, Amsterdam) for study support.

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Additional Supporting Information may be found in the online version of this article

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Conflict of interest: Nothing to report.

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Received for publication: 10 March 2016; Accepted: 13 March 2016
Published online: 19 March 2016 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/ajh.24364

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Atrial fibrillation associated with ibrutinib in Waldenström macroglobulinemia

To the Editor: The Bruton 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 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 Table 1. 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 5 years prior to ibrutinib initiation. One patient with a history of AF also had hypertension.

TABLE 1. Patient Characteristics with Waldenström's Macroglobulinemia at Time of Ibrutinib Initiation

Characteristic	Patients (N=112)
Median age (range) – yr	66 (30–93)
Sex – no. (%)	
Male	76 (68)
Female	36 (32)
Previous therapy for Waldenstrom's 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)
>4,000 mg/dl – no. (%)	40 (36)
Hemoglobin level	
Median (range) – g/dl	10.3 (6.4–14.2)
<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)

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 (Fig. 1A). 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 with patients without a history of AF (3.9 vs. 33.4 months; log-rank $P = 0.003$) with a hazard ratio (HR) of 4.02 (95% CI, 2.73–46.5) (Fig. 1B). At the time of AF event, 10 patients were on a dose of 420 mg, and 2 on a dose of 280 mg/day of ibrutinib. Cardiological intervention following the AF event included: initiation of anticoagulation ($n = 2$, 17%) with warfarin ($n = 1$) or rivaroboxan ($n = 1$), 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/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 (Fig. 1B). It remains unclear whether the late development of AF in the

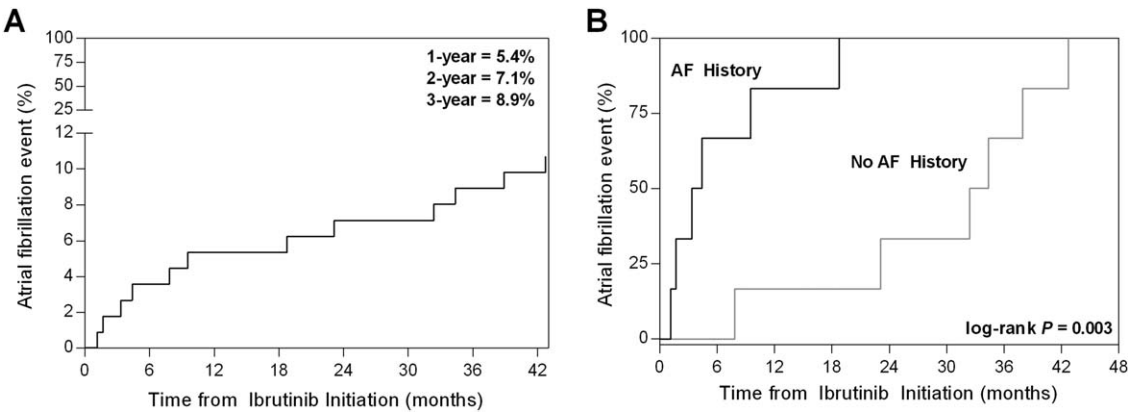

Figure 1. Cumulative incidence of atrial fibrillation events over time among all patients (**A**), and median time to atrial fibrillation in WM patients stratified by known history of atrial fibrillation (**B**).

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 supports 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.

Author Contributions

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

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Conflict of Interest: JNG, KM, TED: No conflicts of interest to disclose. SPT: Consultancy: Janssen, Onyx, Gilead Sciences; Research funding: Pharmacyclics. JJC: Advisory Board: Pharmacyclics, Alexion Pharmaceuticals; Consultancy: Biogen Idec, Otsukua Pharmaceuticals; Research Funding: Gilead Sciences, Millennium Pharmaceuticals, Pharmacyclics. Contract grant sponsors: Peter S. Bing, M.D. and the International Waldenström's Macroglobulinemia Foundation.

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Received for publication: 8 March 2016; Accepted: 13 March 2016

Published online: 19 March 2016 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/ajh.24366

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Effect of systemic bevacizumab in severe hereditary hemorrhagic telangiectasia associated with bleeding

To the Editor: Hereditary hemorrhagic telangiectasia (HHT) is a multisystem autosomal dominant vascular disorder characterized by severe and recurrent epistaxis and gastrointestinal (GI) hemorrhages from muco-cutaneous telangiectases [1]. Other important features include development of arteriovenous malformations (AVM's), most commonly in the lung, liver, brain, and spine [1]. Vascular endothelial growth factor (VEGF) levels in circulation are elevated in patients with HHT [2]. Intravenous (IV) administration of bevacizumab, a VEGF inhibitor, has been shown to be effective in improving epistaxis and telangiectasias; reducing the need for packed red blood cell (PRBC) transfusions, and improvement in the high output cardiac failure [3–6]. However, there have been no large scale studies demonstrating the effect of systemic bevacizumab with the primary goal of reducing bleeding complications in severe HHT. We conducted this study wherein we hypothesize that systemic bevacizumab reduces bleeding, transfusions, and hospitalizations in patients with severe HHT.

Eleven HHT patients who received systemic bevacizumab during January 1, 2009 to December 31, 2014 were identified. Only five subjects were evaluable after exclusion of patients who were treated for high output cardiac failure ($n = 2$), with insufficient documentation ($n = 2$), and lost to follow up ($n = 2$). Demographic and clinical data collected for all subjects included age, gender, race, hemoglobin, and serum creatinine, history of epistaxis, melena, and hematochezia. Other variables obtained included number of PRBC transfusions and emergency room (ER) visits/hospitalizations up to 1 year before and after bevacizumab administration. Adverse events related to medication use (blood pressures, proteinuria, or any other grade III/IV side effects) were captured during and after IV bevacizumab treatment. Adverse events were recorded in four time blocks (each 3 months) following bevacizumab administration to capture early (first time block) or delayed (third and fourth time blocks) side-effects. Each course of bevacizumab consisted of six doses of IV bevacizumab (5 mg/kg body weight) administered every 2 weeks. The primary endpoint of the study was to determine the difference in the number of PRBC units transfused in the year before and after bevacizumab administration. Secondary endpoints included the number of ER visits and hospitalizations for the study patients during this time period, the average length of hospital stay, months following bevacizumab administration before repeat dosing, change in hemoglobin 60 days after bevacizumab administration, and the safety and tolerability of bevacizumab.

The median age of the patients in our study was 54 years (range, 43–61 years) with (5/5 males and 0 females). The median baseline hemoglobin was 9 g/dL (range, 7.3–9.8 g/dL) at the time of bevacizumab administration. Anemia was related to epistaxis in four patients (cases 1–4), and GI bleeding in another patient (case 5). All patients were treated with oral and parenteral iron supplementation. All patients except for case 5 received antifibrinolytic agents and intranasal bevacizumab for control of epistaxis (Supporting Information Table). All patients required PRBC transfusions in the year prior to initiation of bevacizumab therapy. Total number of PRBC units transfused ranged from 2