JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 4, NO. 12, 2018

PUBLISHED BY ELSEVIER

TOPIC REVIEW

Ibrutinib-Associated Atrial Fibrillation

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ABSTRACT

Ibrutinib, a novel and potent Bruton tyrosine kinase inhibitor, is an effective and well-tolerated treatment for a variety of B-cell lymphomas. However, its use is associated with an increased incidence of atrial fibrillation (AF), ranging from 4% to 16%. We reviewed the original clinical trials that led to the approval of ibrutinib, as well as several other prospective and retrospective studies, to better appreciate the incidence of ibrutinib-associated AF. Based on 16 studies included in our analysis, the incidence of ibrutinib-associated AF was 5.77 per 100 person-years, which is much higher than rates previously reported with ibrutinib and compared with the general adult population. New onset AF in cancer patients is associated with a significantly higher risk of heart failure and thromboembolism, even after adjusting for known risk factors. In addition, ibrutinib poses unique challenges due to its interactions with many medications that are commonly used to manage AF. Ibrutinib also inhibits platelet activation and decisions regarding anticoagulation have to be carefully weighed against this increased risk of bleeding. Ibrutinib's interaction with calcium channel blockers, digoxin, amiodarone, and direct oral anticoagulants can result in either ibrutinib or other drug-related toxicity and careful selection and dose adjustment may be needed. Ibrutinib-associated AF can be a therapy-limiting side effect and physicians should be familiar with the special management considerations imposed by this agent. We review the potential mechanisms and incidence of ibrutinib-associated AF and propose an algorithm for its management. (J Am Coll Cardiol EP 2018;4:1491–500)

Cancer and cardiovascular diseases are the fastest growing and most prevalent diseases in the United States; hence, significant overlap is expected (1). In patients without cancer, atrial fibrillation (AF) is a common arrhythmia and its incidence is increased in patients with malignancies. In rare instances, AF occurs due to direct tumor invasion of the heart, but more commonly, it is secondary to surgery, chronic inflammation, dysautonomia, metabolic abnormalities, and chemotherapy (2). In cancer patients, new onset AF is associated with a significantly higher risk of thromboembolism and heart failure, even after adjusting for known risk factors (3). Ibrutinib, a novel and potent Bruton tyrosine kinase

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received March 15, 2018; revised manuscript received June 6, 2018, accepted June 6, 2018.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2018.06.004

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BTK = Bruton tyrosine kinase

CCB = calcium-channel blocker

CLL = chronic lymphocytic leukemia

CYP = cytochrome P

MCL = mantle cell lymphoma

P-gp = P-glycoprotein

TEC = Tec protein tyrosine kinase

WM = Waldenstrom macroglobulinemia

(BTK) inhibitor, is approved by the U.S. Food and Drug Administration for use in chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenstrom macroglobulinemia (WM), and marginal cell lymphoma (4). It is effective and generally well tolerated. However, an increase in the incidence of both ventricular and atrial arrhythmias has been reported in patients receiving ibrutinib (5–7). Ventricular arrhythmias including frequent premature ventricular contractions, and ventricular tachycardia can occur in the absence of structural abnormalities, ischemia, or QT interval corrected for heart rate prolongation and can increase the risk of sudden cardiac death (7). AF occurs in up to 16% of patients on ibrutinib and can be a therapy-limiting side effect (5,6). In addition to the increased incidence of AF, treatment of AF in patients on ibrutinib poses unique challenges. Specifically, ibrutinib has an inherent tendency to increase bleeding (8–12), and there are significant drug-drug interactions between ibrutinib and medications commonly used to manage AF. We review the potential mechanisms and incidence of ibrutinib-associated AF and provide guidance on the management of AF in this challenging patient cohort.

IBRUTINIB

MECHANISM OF ACTION. Signaling from the B-cell antigen receptor regulates multiple cellular processes, including proliferation, differentiation, apoptosis, and cell migration, and is essential for normal B-cell development and survival. The B-cell antigen receptor pathway is implicated in the pathogenesis of several B-cell malignancies, including diffuse large B-cell lymphoma, follicular lymphoma, MCL, CLL, and WM (13). BTK, a member of the Tec kinase family, is a signaling molecule positioned early within the B-cell antigen receptor signaling cascade (14). Ibrutinib (PCI-32765) is an oral covalent inhibitor of BTK, an essential enzyme in B-cell receptor signaling, homing, and adhesion. It covalently binds to the cysteine-481 amino acid of the BTK enzyme and inhibits numerous processes, including extracellular signal-regulated kinase-1 signaling, nuclear factor κB deoxyribonucleic acid binding, cytosine-phosphate-guanine-mediated cell proliferation, and tumor-cell migration without toxic effects on normal T cells (15,16).

INDICATIONS. Between November 2013 and January 2015, ibrutinib was approved by the U.S. Food and Drug Administration for use in patients with various types of B-cell malignancies including CLL, MCL, WM, and marginal zone lymphoma (4). In patients with CLL, it improved progression-free survival, overall response rates, and overall survival when compared with the anti-CD20 antibody, ofatumumab, and chlorambucil. This was seen consistently across refractory or relapsed cases and when used as initial therapy (8–10). Similar outcomes were noted in patients with refractory or relapsed intermediate- to high-grade MCL, in patients with WM, and in those with relapsed or refractory marginal zone lymphoma (11,12).

ADVERSE EFFECTS. Ibrutinib is generally well tolerated but its use is associated with both hematologic and nonhematologic side effects. The main hematologic side effects include neutropenia and thrombocytopenia and are seen with longer duration of therapy. Ibrutinib-related neutropenia and thrombocytopenia are mostly reversible, although dose modification or discontinuation is sometimes required. The most frequent nonhematologic adverse events noted with ibrutinib are diarrhea, fatigue, upper respiratory tract infection, pyrexia, and nausea. Cardiovascular side effects include hypertension, AF, and excessive bleeding (8–12). Among these, AF and the increased risk of bleeding can be therapy-limiting side effects (5,6).

INCIDENCE AND MECHANISM OF IBRUTINIB-ASSOCIATED AF. AF is the most common sustained arrhythmia affecting 1.5% to 2% of the general population, and this prevalence increases to 10% at 80 years of age (17). In addition to aging, several cardiovascular as well as noncardiovascular conditions predispose to the development of AF. Given the increased incidence of cancer with advancing age and the coexistence of other conditions predisposing to AF in cancer patients, an association between cancer and AF has been noted more frequently.

Many antineoplastic agents including anthracyclines, gemcitabine, cisplatin, melphalan, and interleukin 2 have been associated with AF, for a variety of reasons such as direct cytotoxic effects, development of cardiomyopathy, valvular heart disease, autonomic imbalance, or electrolyte abnormalities (18). However, the incidence of new onset AF in patients receiving long-term ibrutinib therapy is higher than that seen in the general population and with other chemotherapeutic agents (5,6,8–11,19).

The incidence of AF in the initial randomized controlled trials leading to the approval of ibrutinib was around 4% to 6% (8–12). However, in a recent phase II trial (PCI-32765 for Special Cases of Chronic

TABLE 1 Incidence of AF and Major Bleeding in Various Ibrutinib Studies

First Author, Year of Publication (Ref. #)	Population	Average Age (yrs)	Median Follow-Up (months)	Number of Subjects Who Received Ibrutinib (Sample Size Weight)	Ibrutinib Dose (mg)	Number of Subjects Who Developed AF in Ibrutinib Arm	Number of Subjects Who Developed AF in Control Arm	Number of Subjects Who Developed Grade 3 or Higher Bleeding
Byrd, 2013 (9)	Relapsed/refractory CLL	66	20.9	85 (3.92)	420 (n =51) 840 (n =34)	3 (3.5)	No control arm	4 (4.7)
Wang, 2013 (11)	Relapsed/refractory MCL	68	15.3	111 (5.12)	560	5 (4.5)	No control arm	5 (4.5)
O'Brien 2014 (20)	Frontline CLL	71	22.1	31 (1.43)	420–840	2 (6.5)	No control arm	Not reported
Byrd, 2014 (RESONATE Study) (10)	Relapsed/refractory CLL	67	9.4	195 (9.8)	420	10 (5)	1 (1)	2 (1)
Treon, 2015 (12)	Relapsed/refractory WM	63	19.1	63 (2.9)	420	3 (5)	No control arm	4 (6.3)*
Burger, 2014 (21)	Frontline and relapsed/ refractory CLL	63.2	18	40 (1.84)	420	2 (5)	No control arm	5 (12.5)†
Burger, 2015 (RESONATE-II Study) (8)	Frontline CLL	73	18.4	136 (6.27)	420	8 (5.9)	1 (0.75)	6 (4)
Farooqui, 2015 (19)	Frontline and relapsed/ refractory CLL	>65 (35) >18 (51)	28	86 (3.97)	420	14 (16) [11 (79) patients were >65 yrs of age and 3 (21) were <65 yrs of age]	No control arm	Not reported (study is ongoing)
Stilgenbauer, 2015 (RESONATE-17 trial) (24)	Relapsed/refractory CLL with del 17p	64	11.5	144 (6.64)	420	11 (6)	No control arm	7 (5)‡
Jaglowski, 2015 (25)	CLL/SLL/PLL	>65	12.5	71 (3.27)	420	6 (8.4)	No control arm	7 (10)
Romisher, 2015 (28)	CLL/MCL	65	Not stated	32 (1.47)	Not stated	5 (16)	No control arm	Not stated
Chahan-Khan, 2016 (22)	Relapsed/refractory CLL/SLL	64	17	289 (13.34)	420	21 (7.2)	7 (2.4)	12 (4)
Dreyling, 2016 (23)	Relapsed/refractory MCL	68	20	139 (6.41)	560	5 (3.5)	2 (1.4)	14 (10)
Wang, 2016 (26)	Relapsed/refractory MCL	67	16.5	50 (2.35)	560	7 (14)	No control arm	3 (6)
Gustine, 2016 (27)	WM	66	14.2	112 (5.17)	420	12 (10.7)	No control arm	Not reported
Wiczer, 2017 (6)	CLL, MCL, WM, other	65	32	582 (26.86)	420-560	76 (13)	No control arm	34 (5.8)§
Total			18.32	2,166		190 (8.15)‖		

Values are n (%), unless otherwise indicated. *Grade 2 or higher bleeding. †Grade 2 bleeding only. No higher grade bleeding reported in this study. ‡Grades 2 and 3 bleeding. §Bleeding outcomes reported only for patients who developed AF. ‖Adjusted incidence weighted according to sample size of all studies.

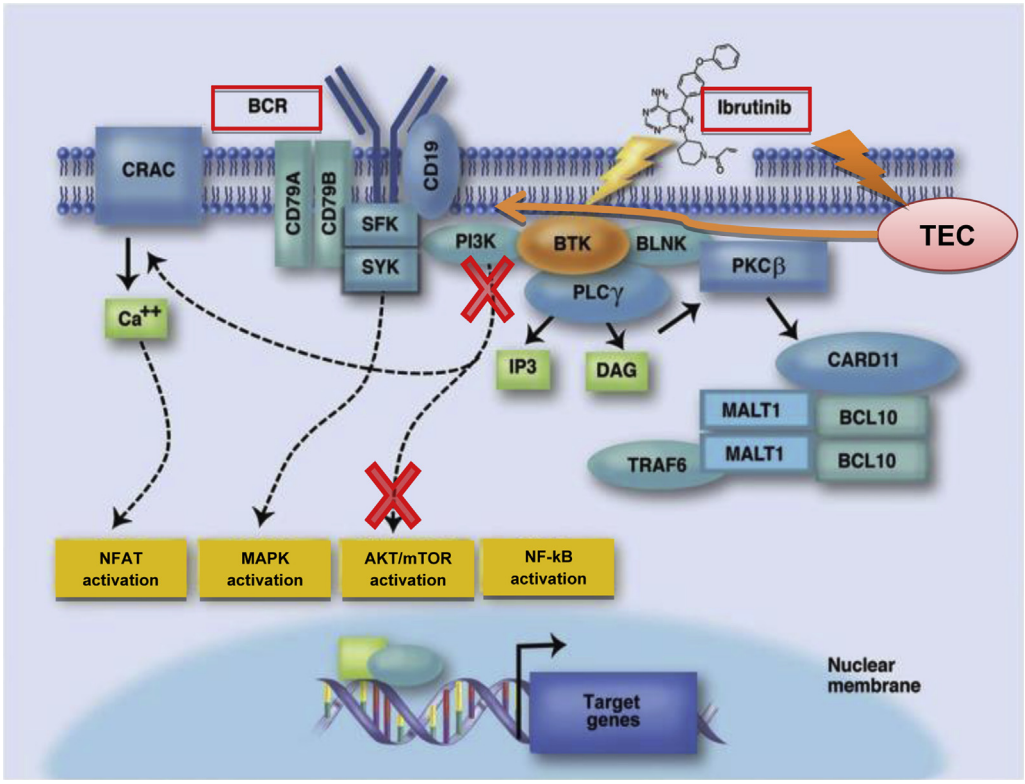
AF = atrial fibrillation; CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; PLL = prolymphocytic leukemia; SLL = small lymphocytic lymphoma; WM = Waldenstrom macroglobulinemia.

Lymphocytic Leukemia or Small Lymphocytic Lymphoma; NCT01500733), 16% patients developed AF at 28 months. This higher incidence was likely due to the longer duration of follow-up (19).

We undertook a systemic review and analyzed the incidence of ibrutinib-associated AF based on 16 studies (**Table 1**) (6,8-12,19-28). Over a median follow-up of 18.32 months, of 2,166 patients, 190 (8.15% adjusted incidence weighted according to sample size) developed AF. The incidence of ibrutinib-associated AF was 5.77 per 100 person-years, which is significantly higher than rates previously reported with ibrutinib therapy and compared with the general adult population. In the Rotterdam study (29), among 7,983 community-dwelling adults, ages 60 to 64 years, screened by electrocardiogram twice during a mean duration of 6.9 years, the incidence of AF was 0.55 (95% CI: 0.42 to 0.71) per 100 person-years. In the Framingham study (30), AF incidence among men ages 65 to 74 years was 1.8 per 100 person-years, and among women ages 65 to 74 years, it was 1.0 per 100 person-years.

In addition to the on-target inhibitory effects on cardiac BTK, ibrutinib has off-target inhibitory effects on Tec protein tyrosine kinase (TEC). Recently it has been shown that both BTK and TEC transcripts are expressed in human cardiac tissue and their expression is higher in atrial tissue during AF than sinus rhythm ($p < 0.05$), suggesting that BTK and TEC may have functional roles under conditions of cardiac stress (31). One of the pathways regulated by BTK and TEC is the phosphoinositide 3-kinase-Akt pathway. This pathway is a critical regulator of cardiac protection under conditions of stress (32). Pretorius

FIGURE 1 BCR Signaling Pathway as a Therapeutic Target for the BTK Inhibitor Ibrutinib and Mechanism of Ibrutinib-Associated AF



The B-cell antigen receptor (BCR) signaling pathway shows target and off-target effects of ibrutinib. In addition to the on-target inhibitory effects on cardiac Bruton tyrosine kinase (BTK), ibrutinib has off-target inhibitory effects on Tec protein tyrosine kinase (TEC). The phosphoinositide 3-kinase (PI3K)-Akt pathway, which is thought be a critical regulator of cardiac protection under conditions of stress is shown to be regulated by BTK and TEC. Down-regulation/inhibition of this pathway by ibrutinib's effects on BTK and TEC predisposes arrhythmia. Reproduced with modifications with permission from Rossi and Gaidano (15). AF = atrial fibrillation; BCL10 = B-cell lymphoma/leukemia 10; BLNK = B-cell linker; CARD11 = caspase recruitment domain-containing protein 11; CD = cluster of differentiation; CRAC = calcium release-activated channel; DAG = diacyl glycerol; IP3 = inositol triphosphate; MALT1 = mucosa-associated lymphoid tissue lymphoma translocation protein 1; MAPK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor κB; PKCβ = protein kinase β; PLCγ = phospholipase Cγ; TRAF6 = tumor necrosis factor receptor-associated factor 6.

et al. (33) showed that surgical specimens from human atrial appendages undergoing coronary bypass or mitral valve surgery exhibited lower phosphoinositide 3-Akt activity in patients with AF compared with those from patients in sinus rhythm. Therefore, it is plausible that ibrutinib increases vulnerability to atrial arrhythmias by down-regulation or inhibition of this pathway (**Figure 1**) (16).

Enhanced automaticity due to inhibition of phosphoinositide 3-kinase and subsequent increase in the late sodium current after chronic exposure to ibrutinib is another potentially implicated proarrhythmic mechanism. This may lead to prolongation of cardiac action potential duration and as a consequence, increased vulnerability to early and delayed after-depolarizations that in-turn may increase the risk of both atrial and ventricular arrhythmias (34,35).

ASSESSMENT AND DIAGNOSIS. Given the increased probability of developing AF on ibrutinib therapy, a higher level of suspicion should be maintained for the diagnosis of AF. For any patient presenting with cardiovascular symptoms, a detailed history and cardiovascular examination should be performed. Standard diagnostic approaches for AF such as electrocardiogram, Holter, and event monitoring should be considered. Once the diagnosis is established, an echocardiogram should be performed to rule out structural heart disease. Blood tests to assess thyroid

TABLE 2 Interaction Between Ibrutinib and Common Medications Used for Management of AF

Medication	Level of Interaction	Effect	Mechanism of Interaction
Diltiazem/verapamil	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by diltiazem/verapamil
Digoxin	Moderate	Increases plasma level of digoxin	P-glycoprotein inhibition by ibrutinib
Amiodarone/dronedarone	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by amiodarone/dronedarone
Factor Xa inhibitor (rivaroxaban, apixaban, edoxaban)	Moderate	Increases plasma level of factor Xa inhibitors	CYP450 3A4 induction and P-glycoprotein inhibition by ibrutinib
Direct thrombin inhibitor (dabigatran)	Major	Increases plasma level of dabigatran	P-glycoprotein inhibition by ibrutinib

CYP450 = cytochrome P450.

function should also be conducted to identify a potentially reversible cause of AF.

MANAGEMENT STRATEGIES. Although there are robust guidelines for the management of AF among broad groups of patients (36), AF in cancer patients poses unique challenges. Whereas thromboembolism and heart failure are common complications of AF, new-onset AF in patients with malignancy is associated with a 2-fold increased risk of thromboembolism and a 6-fold higher risk of heart failure, even after adjustment for known risk factors (3). There is a paucity of randomized clinical trial data addressing rate versus rhythm control strategies and optimal anticoagulation in cancer patients receiving active cancer therapy. Current guidelines for the management of AF are based on randomized controlled trials that have generally excluded patients with active malignancy.

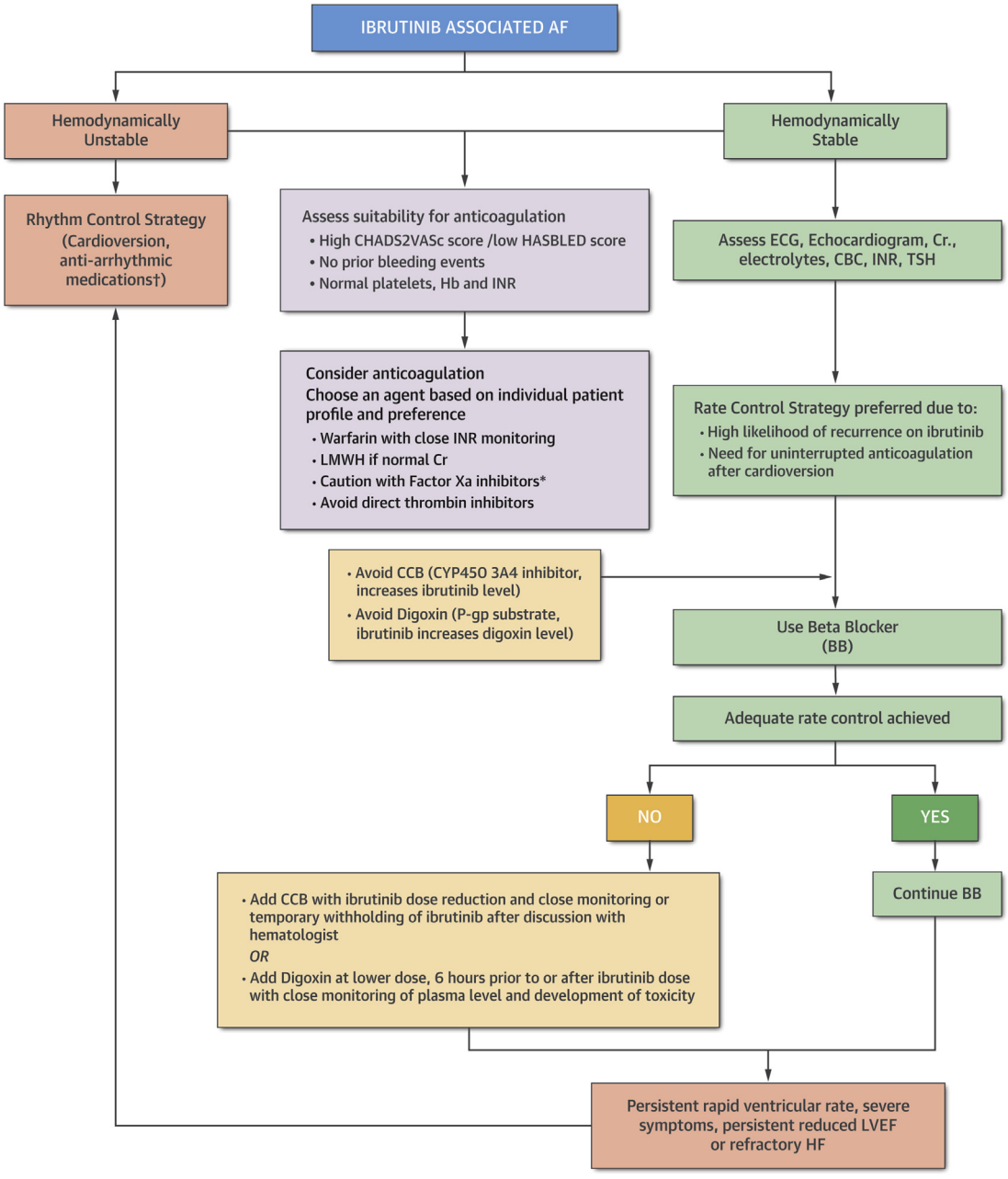
Cancer itself is a prothrombotic state, thus further increasing the risk of thromboembolic events in patients with AF. However, cancer has not been incorporated in thromboembolic risk prediction scores. In a large cohort of 24,125 patients with newly diagnosed cancer, although the $CHADS_2$ (Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack or Thromboembolism) score was predictive of thromboembolism risk in patients with pre-existing AF, it did not accurately predict thromboembolic events in those with new-onset AF. For any given score, the risk of thromboembolism was higher in patients with new-onset AF (3). This makes the usual scoring system a less reliable predictor in patients with cancer and new-onset AF.

On the other hand, some malignancies and cancer therapies increase the risk of bleeding. Furthermore, the response to anticoagulation may not be predictable either due to potential interaction with concomitant medications or metabolic disorders associated with cancer. Vitamin K antagonist therapy for deep venous thrombosis in patients with malignancies, compared with patients without cancer, was associated with a nearly 6-fold higher risk of hemorrhage (37).

As discussed, ibrutinib has been reported to cause AF in 3% to 16% of patients, but the incidence of grade 3 or higher AF (based on the Common Terminology Criteria for Adverse Events: grade 3: symptomatic and incompletely controlled medically, or controlled with a device [e.g., pacemaker]; grade 4: life-threatening [e.g., arrhythmia associated with congestive heart failure, hypotension, syncope, shock]; grade 5: death) (38) was relatively low (8–12). Although temporary or longer-term discontinuation of ibrutinib was required in a small number of patients with AF in clinical trials (8–12), the majority continued this potentially life-extending therapy and AF was managed medically. In patients receiving ibrutinib, the management of AF is particularly challenging due to its interactions with multiple medications required for rate/rhythm control and anticoagulation (**Table 2**) (39). Ibrutinib is metabolized primarily by cytochrome P (CYP)450 CYP3A, and to a minor extent by CYP2D6. CYP3A inducers and inhibitors affect both the efficacy and toxicity of ibrutinib (4). Moreover, ibrutinib affects several platelet-signaling pathways and increases the risk of bleeding even without concomitant use of anticoagulants, and that risk increases further when anticoagulation is required (40,41).

Rate versus rhythm control. The decision to embark on a rate versus rhythm control management strategy in patients with AF is multifactorial, based on hemodynamic stability, chronicity, persistence of a potential trigger, symptoms, presence or absence of cardiomyopathy and heart failure, patient preference, and their candidacy for short- and long-term

CENTRAL ILLUSTRATION **Proposed Algorithm for Ibrutinib-Associated AF Management**



Ganatra, S. et al. J Am Coll Cardiol EP. 2018;4(12):1491–500.

This figure illustrates the proposed algorithm for ibrutinib-associated atrial fibrillation (AF) taking various drug-drug interactions as well as elevated bleeding risk with ibrutinib into consideration. *Factor Xa inhibitor interacts with ibrutinib and increases the bleeding risk. Factor Xa or ibrutinib dose reduction may be considered based on individual case. †Amiodarone interacts with ibrutinib and increases the risk of ibrutinib-associated adverse events. Temporary withholding of ibrutinib or dose reduction might be considered. BB = beta blocker; CBC = complete blood count; CCB = calcium-channel blocker; CHA_2DS_2VASc = Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack or Thromboembolism, Vascular Disease, Age 65 to 74 Years, Sex Category; Cr. = creatinine; CYP450 = cytochrome P450; ECG = electrocardiogram; HASBLED = Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or Alcohol; Hb = hemoglobin; HF = heart failure; INR = international normalized ratio; LVEF = left ventricular ejection fraction; LMWH = low molecular weight heparin; P-gp = P-glycoprotein; TSH = thyroid stimulating hormone.

anticoagulation. In the hemodynamically stable patient with AF secondary to ibrutinib, rate control may be preferable to rhythm control because the ability to maintain sinus rhythm after cardioversion may be limited by the persistent presence of ibrutinib as a trigger for AF. Antiarrhythmic agents such as amiodarone inhibit CYP3A4 and thereby increase ibrutinib levels and toxicity (4). Furthermore, electrical or chemical cardioversion should only be considered in those patients who can tolerate anticoagulation, at least in the short run, given the increased risk of thromboembolic events in the post-cardioversion period.

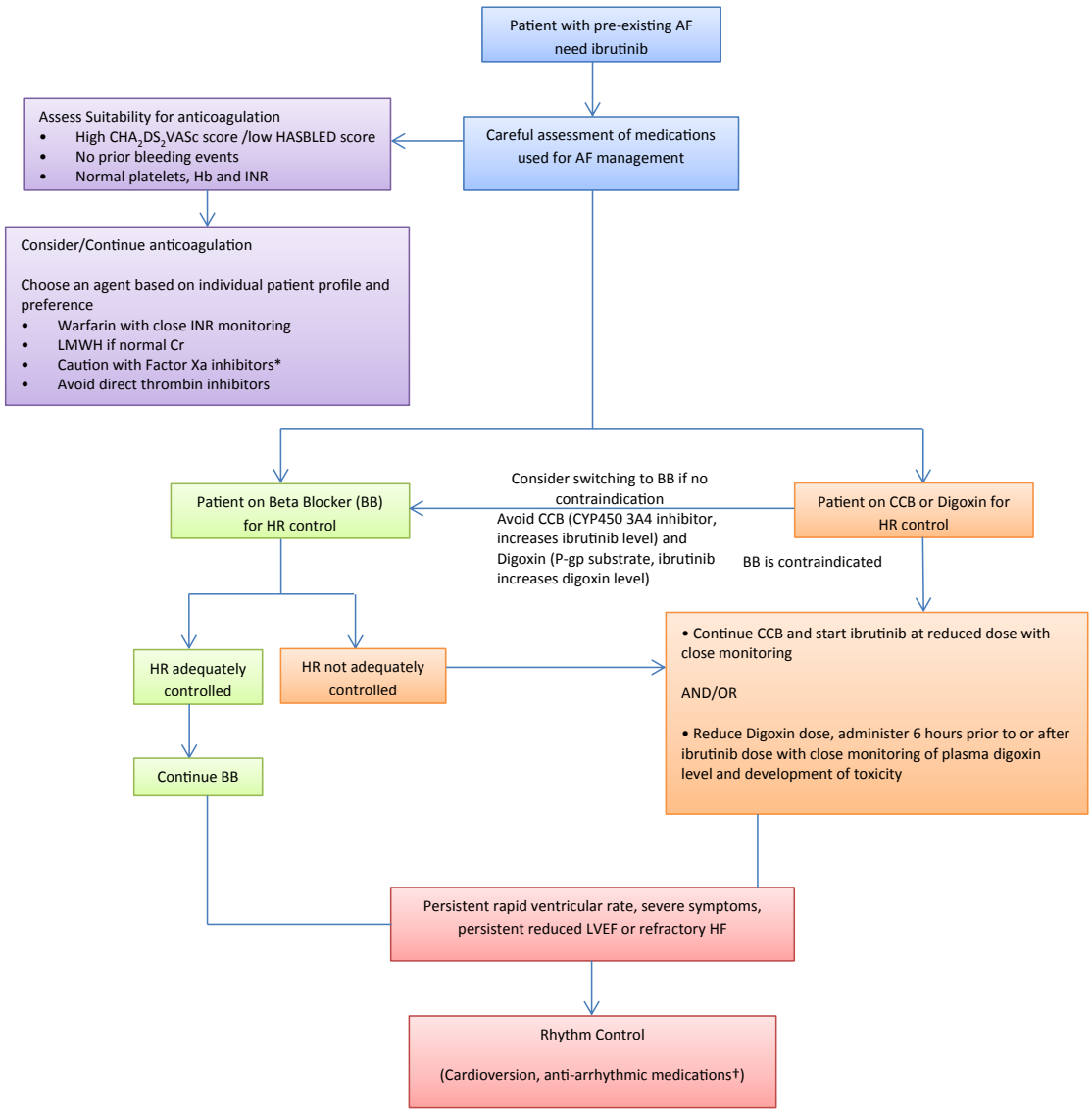
Choice of atrioventricular nodal blocking agent(s). Calcium-channel blockers (CCB) such as diltiazem and verapamil are very effective and frequently used for rate control in AF patients with a rapid ventricular response. However, these agents are moderate inhibitors of CYP450 3A4 and their use in conjunction with ibrutinib, may significantly increase plasma levels of ibrutinib (4). On the other hand, ibrutinib increases plasma levels of digoxin via P-glycoprotein (P-gp) inhibition and the potential for digoxin toxicity (4). Therefore, if needed, smaller doses of digoxin, taken either 6 h prior to or after taking ibrutinib, should be considered with more frequent monitoring of digoxin levels (42). Beta blockers are usually safe, with no known interaction, and should be used as first-line agents when needed for ventricular rate control in this patient population. In many instances, controlling ventricular rate can be challenging and a second agent may be required. CCB can be used in such patients after appropriate dose reduction of ibrutinib and with added vigilance for ibrutinib toxicity (4).

Challenges with anticoagulation. Thromboembolic stroke remains a dreaded complication of AF and anticoagulation for its prevention is a cornerstone of AF management. Conventional methods for assessing risk of thromboembolism (CHA_2DS_2VASc [Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack or Thromboembolism, Vascular Disease, Age 65 to 74 Years, Sex Category] score) and bleeding (HASBLED [Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or Alcohol] score) may not predict risk accurately in this population. Among the many side effects of ibrutinib, bleeding is a major concern with a reported incidence of any grade bleeding complications as high as 44% (10). Higher grade bleeding complications, including intracerebral bleeding, have been noted in up to 6% of patients in the ibrutinib arm of clinical trials (4). In many instances, the bleeding complication occurred either in conjunction with trauma or with concomitant use of anticoagulants. The exact mechanism of action is unclear but it appears that ibrutinib selectively inhibits platelet signaling and functions downstream of the collagen receptor glycoprotein VI and strongly affects firm platelet adhesion on von Willebrand factor under arterial flow (40,41). Thrombocytopenia has also been noted with ibrutinib and may also contribute to the increased bleeding risk (8–12). Ibrutinib is a weak inducer of CYP3A4 and an inhibitor of P-gp (4). Ibrutinib may increase the levels of warfarin via its effects on CYP3A4. The direct thrombin inhibitor, dabigatran, does not have any CYP450 interaction but it is a P-gp substrate and ibrutinib may potentially increase its plasma level and the risk of bleeding significantly. The effect of ibrutinib on factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban is unclear but given its effects on CYP3A4 and P-gp, both of which are involved in the metabolism of factor Xa inhibitors, there is potential for interaction that may increase plasma levels of factor Xa inhibitors and consequently the risk of bleeding. However, ibrutinib use is a not an absolute contraindication for anticoagulation and anticoagulation should be considered for patients at high risk for thromboembolic events after careful review of their bleeding risk. Due to its myriad interactions, there is no consensus regarding the agent of choice for patients on ibrutinib when anticoagulation is warranted. Warfarin might be considered as its plasma level is easily measurable and can be monitored. Also, in case of bleeding complications, a reversal agent is widely available. Low molecular weight heparin was used in clinical trials and can be considered, but fluctuations in kidney function may increase the risk of bleeding. Factor Xa inhibitors may have the least interactions but must be used with caution because there is limited experience with antidote.

Proposed strategy for management of ibrutinib-associated AF. We propose an algorithm for management of ibrutinib-associated AF (**Central Illustration**) considering these factors and our experience. At our institutions we have used this approach successfully for treating several patients with ibrutinib-associated AF.

For patients with pre-existing AF, similar management approach is reasonable. A careful review of medications used for AF management should be conducted prior to the initiation of ibrutinib r to assess for potential drug-drug interactions. If patient is on CCB or digoxin, switching to a beta blocker may

FIGURE 2 Proposed Algorithm for Patients With Pre-Existing AF Who Require Ibrutinib



This figure illustrates the proposed algorithm for patients with pre-existing atrial fibrillation (AF) who require ibrutinib therapy taking various drug-drug interactions as well as elevated bleeding risk with ibrutinib into consideration. *Factor Xa inhibitor interacts with ibrutinib and increases the bleeding risk. Factor Xa or ibrutinib dose reduction may be considered based on individual case. †Amiodarone interacts with ibrutinib and increases the risk of ibrutinib associated adverse events. Temporary withholding of ibrutinib or dose reduction might be considered. HR = heart rate; other abbreviations as in Figure 1.

be reasonable. If a CCB or digoxin needs to be continued, appropriate measures such as dose adjustment and frequent monitoring for toxicity should be taken to reduce the risk of adverse events. Similarly, decisions regarding anticoagulation should be individualized based on a patient's thrombotic and bleeding risk (Figure 2).

There is no experience of AF ablation or left atrial appendage closure devices in this patient population. Neither is an ideal initial strategy given their invasive nature and the requirement for uninterrupted anticoagulation in periprocedural period.

For patients at increased risk of AF development. The clinical implications of ibrutinib-associated AF become greater as the drug is used more in cohorts predisposed to AF, such as elderly patients and patients with cardiovascular comorbidities. Hematologic oncologists should consider referring

patients with multiple risk factors for AF, such as old age (>60 years), hypertension, obstructive sleep apnea, coronary artery disease, cardiomyopathy, heart failure, thyroid or lung disease (43), to cardio-oncology prior to starting ibrutinib therapy. This may provide an opportunity for aggressive management of modifiable precipitating factors and potentially reduce the risk of developing AF. Even if AF develops after starting ibrutinib, referral to a cardio-oncologist who is familiar with the potential drug-drug interactions associated with ibrutinib, may help minimize the risk of complications.

CONCLUSIONS

Ibrutinib is an effective and generally well-tolerated medication for the treatment of multiple B-cell lymphomas including CLL, MCL, WM, and marginal zone lymphoma. The incidence of AF is increased in patients on ibrutinib and is estimated at 3% to 16%. AF can be a therapy-limiting side effect of ibrutinib, primarily due to the various interactions between ibrutinib and medications used to manage AF. An increased risk of bleeding due to inhibition of collagen-induced platelet aggregation by ibrutinib further complicates the management of AF. The optimal strategy for AF management has not been established for patients on ibrutinib but considering these factors, rate control with beta blockers is a reasonable first-line strategy in hemodynamically stable patients. Cardioversion should be deferred as an initial strategy due to the requirement for uninterrupted anticoagulation in periprocedural period and the high likelihood of recurrent AF while the patient continues on ibrutinib. Anticoagulation should be considered based on a careful assessment of the individual patient's thromboembolic and bleeding risks. Low molecular weight heparin can be considered based on renal function. Factor Xa inhibitors may be associated with acceptable bleeding risk, but they should be used with caution given the limited experience with these agents. Warfarin may be associated with increased bleeding risk, but it may be considered with careful monitoring. Rarely, discontinuation of ibrutinib may be needed in patients with hemodynamic instability, refractory symptoms, or unacceptable bleeding risk.

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KEY WORDS anticoagulation, atrial fibrillation, B-cell lymphoma, ibrutinib