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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Bruton's tyrosine kinase Inhibitors and Cardiotoxicity: More Than Just Atrial Fibrillation

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Abstract

Purpose of Review The purpose of this review is to summarize the epidemiology, mechanisms, and management of cardiovascular complications of Bruton's Tyrosine Kinase inhibitors (BTKIs).

Recent Findings Ibrutinib increases the risk of atrial fibrillation, bleeding, and hypertension compared with non-BTKI therapies. The evidence to support an association between ibrutinib and other cardiovascular complications including ventricular tachyarrhythmias or cardiomyopathy is limited. Ibrutinib metabolism can be inhibited by some medications used to treat cardiovascular complications. The cardiovascular effects of more selective BTKIs, such as acalabrutinib, remain to be determined.

Summary Future research should address the mechanisms underlying the cardiovascular complications of BTKIs and how best to manage them. The risks and benefits of more selective BTKIs as compared with ibrutinib require further evaluation.

Keywords Bruton Tyrosine Kinase · Tyrosine kinase · Cardio-oncology · Cardiac side effect · Atrial fibrillation · Hypertension · Bleeding · Anti-platelet effect · Ventricular arrythmias · Cardiomyopathy · Cardiac death · Heart failure

Introduction

Inhibition of Bruton's tyrosine kinase (BTK) is effective at inhibiting B-cell neoplasm growth [1]. Ibrutinib, the first BTK inhibitor (BTKI) approved, improves progression-free and overall survival compared with alternative therapies in both relapsed/refractory and treatment-naïve chronic lymphocytic leukemia (CLL). In addition, ibrutinib has been demonstrated effective in mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), and marginal zone lymphoma (MZL) [2–10].

While ibrutinib is an important treatment for B-cell neoplasms, a key limitation is its cardiovascular adverse effects. In seminal trials of ibrutinib, associations between ibrutinib use and atrial fibrillation (AF), hypertension, and bleeding were noted. Recently, BTKIs with higher selectivity for BTK than ibrutinib have been developed. Among these, acalabrutinib has been evaluated in patients with CLL, MCL and WM [11–17] and zanubrutinib has been used in patients with refractory MCL and WM. It has been postulated that these more selective BTKIs may lead to less off-target cardiovascular adverse effects [18, 19]. Here, we review the current knowledge of the cardiovascular adverse effects of the BTKIs.

Atrial Fibrillation

Epidemiology

AF was the first recognized cardiac adverse effect of ibrutinib [20] (Fig. 1). In a meta-analysis of 8 randomized clinical trials of ibrutinib, the pooled risk ratio for AF in the ibrutinib arms was 4.69 (95% CI; 2.17–7.64) [21, 22]. Pooling data from 20 clinical studies, we found the incidence of AF in these populations to be 3.3 (95% CI 2.5–4.1) per 100 person-years vs 0.84 (95% CI 0.32–1.6) per 100 person-years in non-ibrutinib

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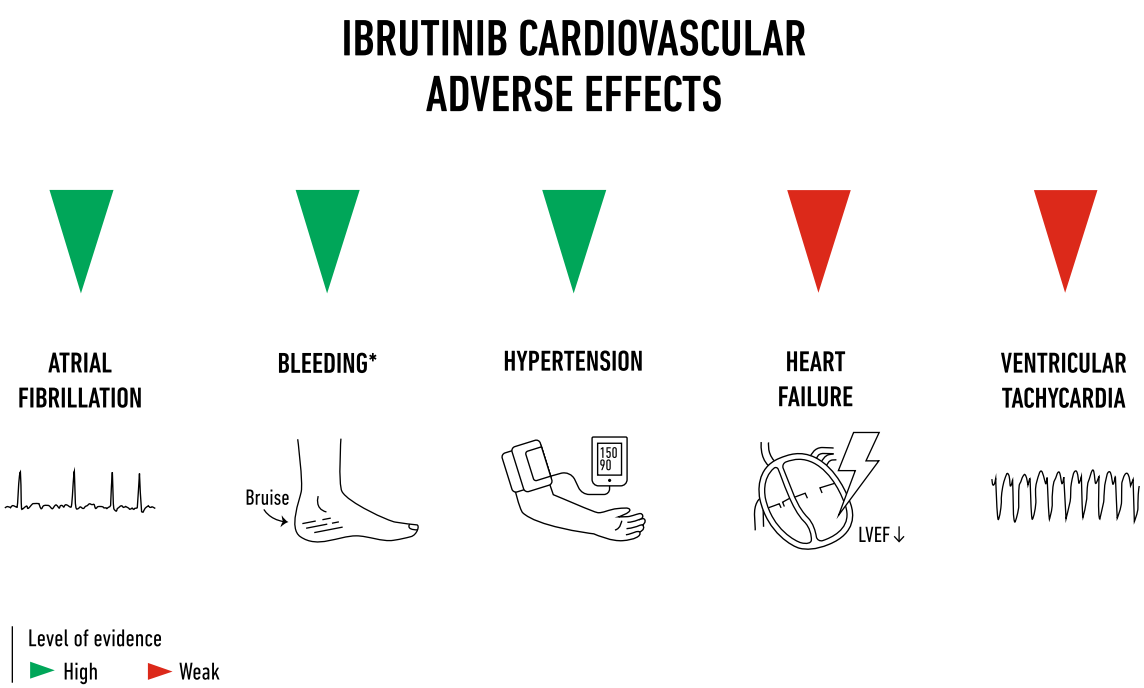

Fig. 1 Ibrutinib's cardiovascular adverse effects. An asterisk denotes that bleeding alone has been shown to be a cardiovascular adverse event of acalabrutinib (LVEF, left ventricular ejection fraction)

controls. This rate of AF among ibrutinib recipients exceeds the incidence rate of AF of 0.55 (95% CI 0.42–0.71) per 100 person-years observed in a population-based cohort study of similar aged adults [23] (Table 1).

In most BTKI studies, AF has been identified by reporting as a treatment emergent adverse event and systematic screening for AF was not performed. As AF is frequently paroxysmal, the more intensively it is screened for, the higher its incidence. In a prospective cohort study of 53 patients with a B cell neoplasm for whom ibrutinib therapy was planned, patients were followed with palpation of the pulse and electrocardiography every 3 months. The ibrutinib-related cumulative AF incidence rate was 23% (95% CI 9–35%) at 12 months [30]. While the population described in this study was highly selected, referred to a specialist cardio-oncology clinic, these data suggest that the incidence of AF may be higher than previously reported.

Acalabrutinib is a more selective BTKI than ibrutinib. In ELEVATE-TN, an open-label RCT, the incidence of AF was 3% in acalabrutinib-obinutuzumab recipients, 4% in acalabrutinib monotherapy recipients, and 1% in obinutuzumab-chlorambucil recipients at a median of 28.3 months [16]. In the ASCEND trial, 5% of acalabrutinib recipients and 3% of participants receiving the investigator's choice of therapy developed AF at a median of 15.7 months [13]. The results of head-to-head trials comparing acalabrutinib with ibrutinib are expected in the near future. These studies may provide insights into whether the risk of AF is lower with acalabrutinib than with ibrutinib. Until these and further data are available, the risk of AF among those treated with acalabrutinib remains uncertain.

In the ASPEN study, zanubrutinib, another highly selective BTKI, was compared with ibrutinib for symptomatic WM. AF/atrial flutter occurred at a rate of 1.0 events per 100 person-months among ibrutinib recipients vs 0.1 events per 100 person-months among zanubrutinib recipients (p=0.0004), suggesting that the risk of AF may be lower with zanubrutinib than ibrutinib [29]. However, in these trials, AF was not specifically screened for and ascertainment bias cannot be excluded, as these trials were open-label.

Pathogenesis

The mechanisms by which ibrutinib increases AF remain speculative with both BTK-mediated pathways and off-target pathways under investigation. BTK and Tec, a non-receptor tyrosine kinase, are expressed in cardiac atrial tissue [31]. The phosphoinositide 3-kinase (PI3K)-Akt pathway is regulated by BTK and Tec and may play a role in the cardiac response to stress [32]. Patients with AF have significantly lower cardiac PI3K-Akt activity [33]. In a murine study, increased PI3K activity decreased atrial fibrosis and improved cardiac conduction [34]. Ibrutinib targets the alpha-subunit of P13K (the predominant P13K isoform expressed in cardiovascular tissues) and attenuates the Akt response after P13K stimulation by IGF1 [32]. This evidence suggests that BTK inhibition could predispose towards atrial fibrosis, which is a hallmark of AF. However, in a murine study, Xiao et al. demonstrated that mice with genetically mediated loss of BTK activity did not have increased AF inducibility. When these mice were treated with ibrutinib, AF inducibility increased, while

Table 1 Major randomized controlled trials of Bruton's tyrosine kinase inhibitors and rate of cardiac adverse events. *AF*, atrial fibrillation; *BTKI*, Bruton's tyrosine kinase inhibitor; *CLL*, chronic lymphocytic leukemia; *F/u*, follow-up; *n/a*, not reported; *MCL*, mantle cell lymphoma; *SLL*, small lymphocytic lymphoma; *WM*, Waldenström's macroglobulinemia

Study/ authors	Disease	Agent and dose	F/u, months	Rate of cardiac adverse events									
				Atrial fibrillation		Bleeding Any (major)		Hypertension		Ventricular tachyarrhythmia		Heart failure	
				Control	BTKI	Control	BTKI	Control	BTKI	Control	BTKI	Control	BTKI
Chanan-Khan; HELIOS [24]	CLL/SLL	Ibrutinib 420 mg vs placebo	17	7/289 (2.4%)	21/289 (7.3%)	42/289; 15% (5/289; 1.7%)*	89/289; 31% (11/289; 3.8%)*	5/289 (1.7%)	13/289 (4.5%)	n/a	n/a	n/a	n/a
Burger; RESONATE-2 [3]	CLL/ALL	Ibrutinib 420 mg vs chlorambucil	18.4	1/133 (0.8%)	8/136 (5.9%)	(3/133; 2.3%)*	(6/136; 4.4%)*	0/132 (0%)	20/135 (15%)	n/a	n/a	n/a	n/a
Byrd; RESONATE [2, 22]	CLL/SLL	Ibrutinib 420 mg vs ofatumumab	9.4	1/191 (0%)	6/195 (3.1%)	24/196; 12% (2/196; 1.0%)**	86/195; 44% (3/195; 1.5%)**	4/191 (2.1%)	10/195 (5.1%)	n/a	n/a	n/a	n/a
Dreyling; RAY [4]	MCL	Ibrutinib 560 mg vs temsirolimus	20	2/141 (1.4%)	5/139 (3.6%)	(9/141; 6.4%)*	(14/139; 10%)*	5/139 (3.6%)	16/139 (12%)	n/a	n/a	n/a	n/a
Dimopoulos; iNNOVATE [25]	WM	Ibrutinib 420 mg + rituximab vs placebo + rituximab	26.5	2/75 (2.7%)	11/75 (15%)	n/a	n/a	3/75 (4.0%)	10/75 (13%)	n/a	n/a	n/a	n/a
Huang [26]	CLL	Ibrutinib 420 mg vs rituximab	17.8	0/52 (0%)	6/104 (5.8%)	n/a	n/a	3/52 (5.8%)	6/104 (5.8%)	n/a	n/a	n/a	n/a
Woyach [10]	CLL	Ibrutinib 420 mg vs ibrutinib 420 mg + rituximab vs bendamustine + rituximab	43	5/176 (2.8%)	27/361 (7.5%)	n/a	n/a	25/176 (14%)	113/361 (31%)	n/a	n/a	n/a	n/a
Moreno; iLLUMINATE [27]	CLL	Ibrutinib 420 mg + obinutuzumab vs chlorambucil + obinutuzumab	31	0/115 (0%)	14/113 (12%)	n/a	n/a	5/115 (4.3%)	19/113 (17%)	n/a	n/a	n/a	n/a
Munir; RESONATE final analysis [28]	CLL/SLL	Ibrutinib 420 mg vs chlorambucil	65.3	n/a	24/195 (12%)	n/a	19/195 (10%)*****	n/a	41/195 (21%)	n/a	2/195 (1.0%)	n/a	9/195 (4.6%)
Sharman; ELEVATE-TN [16]	CLL	Acalabrutinib 100 mg BID +/− obinutuzumab vs chlorambucil + obinutuzumab	28.3	1/169 (0.6%)	13/357 (3.6%)	20/169; 12% (0/169; 0%)	146/357; 41% (6/357; 1.7%)	5/169 (3.0%) (grade ≥3)	9/357 (2.5%) (grade ≥3)	0/169 (0%)	0/357 (0%)	n/a	n/a
Ghia; ASCEND [13]	CLL	Acalabrutinib 100 mg BID vs idelalisib + rituximab vs bendamustine + rituximab	15.7	1/153 (0.7%)	3/154 (1.9%)	11/153; 7.2% (4/153; 2.6%)*	40/154; 26% (3/154; 1.9%)*	5/153 (3.3%)	5/154 (3.2%)	0/153 (0%)	0/154 (0%)	2/153 (1.3%)	1/154 (0.6%)
Tam; ASPEN [29]	WM	Zanubrutinib 160 mg twice daily vs ibrutinib 420 mg	32.7	Zanubrutinib: 0.1 events per 100 person-months Ibrutinib: 1.0 events per 100 person-months		Zanubrutinib: 4.4 (0.3)* events per 100 person-months Ibrutinib: 7.0 (0.6)* events per 100 person-months		Zanubrutinib: 0.7 per 100 person-months Ibrutinib: 1.2 per 100 person-month		n/a	n/a	n/a	n/a

*Severe bleeding defined by grade ≥ 3 or CNS

**Severe bleeding defined by grade ≥3, transfused or hospitalized

***Central nervous system hemorrhagic events

****Hypertension and related end-organ damages

*****Hemorrhagic event grade ≥ 3 in severity, or one of the following: intraocular bleeding causing vision loss, need for transfusion of ≥ 2 units of red cells or equivalent, hospitalization, or prolongation of hospitalization

AF inducibility was not increased by the more selective BTKI, acalabrutinib, suggesting that pathways independent of BTK may mediate the susceptibility to AF seen among mice treated with ibrutinib. The authors then screened cardiac tissue to identify other kinases that might be inhibited by ibrutinib. Of these, C-terminal src kinase inhibition in a murine model produced an AF phenotype [35]. However, other signaling pathways may also play a role in the pathogenesis of ibrutinib-associated AF since ibrutinib inhibits at least 19 other kinases [36].

Clinical Features and Management Considerations

AF may be symptomatic, presenting with palpitations, dizziness, syncope, fatigue, or complications such as heart failure or thromboembolism; or asymptomatic, detected by clinical screening or by smart watch and smart phone applications. It is recommended that AF be screened for in individuals prescribed ibrutinib in order to identify asymptomatic AF. Screening for AF can range from palpation of the pulse and cardiac auscultation to cardiac rhythm monitoring for 24 h to 2 weeks at a time, or even invasive cardiac rhythm monitors that remain in situ for months. It is uncertain how intensively patients prescribed a BTKI should be monitored for AF. While more intensive monitoring may lead to a higher AF detection rate, it incurs increased cost and patient inconvenience, and the clinical importance of very brief paroxysms of asymptomatic AF is not certain. In the general population, there is a positive association between AF burden (the proportion of time in AF) and the risk of complications, such as thromboembolism [37]. The relationship between very brief episodes of AF (<6 min) and thromboembolism is not known [37]. The burden of AF that occurs with BTKI use is also unknown. In one study in which data from 4 randomized trials were pooled, AF occurring among ibrutinib recipients featured a higher rate of multiple AF events (44.9% in the ibrutinib arms vs 16.7% in the comparator arms) and longer mean duration of AF episodes (mean±standard deviation 12.6±29.5 days in the ibrutinib group vs 5.1±5.5 days in the comparator group) [38]. Further research is needed to evaluate the burden of AF, and the relationship between AF burden and AF complications among BTKI recipients.

Important complications of AF include heart failure and arterial thromboembolism leading to stroke or other acute ischemic syndromes. Strategies to prevent heart failure from AF-related tachycardia-induced cardiomyopathy include rate control (in which a target resting heart rate <110 beats per minute is sought) and rhythm control (in which interventions to promote sinus rhythm are implemented). Rate-controlling drugs include beta-blockers; calcium antagonists (verapamil and diltiazem); and digoxin [39]. Of these, beta-blockers are preferable because diltiazem and verapamil may inhibit ibrutinib metabolism. Therefore, if diltiazem or verapamil must be used, the dose of ibrutinib should be reduced. Similarly, amiodarone, which is effective in rhythm control strategies for AF, may increase ibrutinib concentrations [40].

The appropriate use of anticoagulation is fundamental in the prevention of thromboembolism in AF. Caution is recommended when using antithrombotic therapy with a BTKI because they are known to have antiplatelet effects and to increase bleeding risk [41–43] (Fig. 2). In the general population, risk scores are used to inform the risk-benefit of anticoagulation in patients with AF. According to American College of Cardiology guidelines, anticoagulation should be prescribed for a CHA2DS2-VASC score ≥2 in men and ≥3 in women [39, 44] (Table 2). However, a HAS-BLED score ≥3 indicates that anticoagulation should be prescribed cautiously because of increased bleeding risk (Table 3). These scores have not been validated for use in patients with B cell neoplasms on BTKI [48], and whether the absolute thromboembolic or bleeding risk estimated using such scores can be extrapolated to patients taking BTKI, with its demonstrated anti-platelet effects, is unknown. We recommend that the decision to prescribe anticoagulants to patients on a BTKI who develop AF be individualized, taking patient preferences into consideration. More data are needed on the bleeding risk among BTKI recipients who are also taking an anticoagulant to inform this decision-making process. Until such data are available, it may be reasonable to consider BTKI use as contributing 1 point to the HAS-BLED score. Our approach to the patient with AF while taking a BTKI is to provide an estimate of the patient's thromboembolic and bleeding risk. We then participate in shared decision-making with them, which includes the patient's values and preferences. Typically, we do not strongly advocate for an anticoagulant to be taken with ibrutinib unless the CHA2DS2-VASC score is ≥3 or (if additional risk factors for bleeding are present) ≥4.

Among BTKI-treated individuals who develop AF, it is uncertain if or when the BTKI should be dose-reduced or discontinued. AF can often be managed without the need to discontinue the BTKI. This is important because of the need for continuous BTKI treatment of the patient's hematologic disease. However, in some individuals, AF can prove challenging to manage. Brown et al. pooled data from 1505 CLL and MCL patients enrolled in 4 RCTs and reported that half of patients who developed ibrutinib-associated AF had their ibrutinib dose reduced. They also reported that patients with ibrutinib interruption of ≥7 days had a similar survival to those with an interruption of <7 days [38]. However, this post hoc analysis may not be powered to detect a survival difference according to the duration of ibrutinib interruption and it is unclear whether there is a dose-response relationship between ibrutinib and AF burden (i.e., whether reducing ibrutinib dose reduces AF burden). The decision to reduce a BTKI dose in those who develop AF should be made in concert with the patient, the hematologist, and the cardiologist. The patient's hematologic response to therapy should be taken into consideration, as a

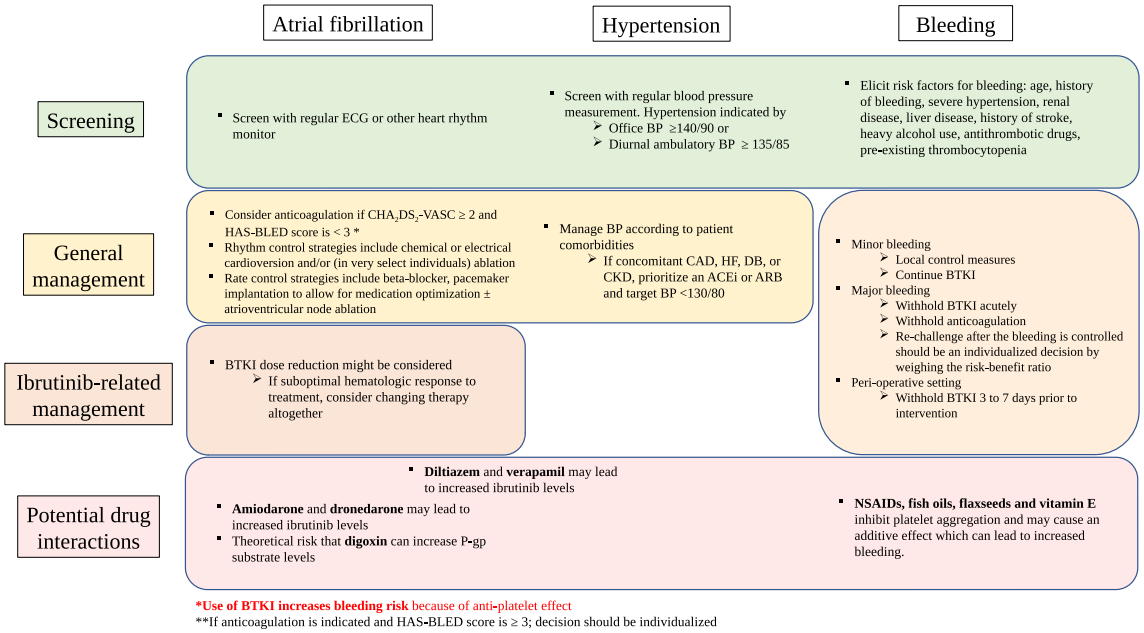

Fig. 2 Screening, management, and potential drug interactions of Bruton's tyrosine kinase inhibitors. Most of these recommendations are based on ibrutinib which is the most studied Bruton's tyrosine kinase inhibitor (BTKI). ECG, electrocardiogram; BP, blood pressure; CAD, coronary heart disease; HF, heart failure; DB, diabetes; CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs

suboptimal hematologic response may prompt a change in therapy for the B cell neoplasm rather than a dose reduction. Treatment alternatives for the patient who develops AF on ibrutinib are increasing and may include more selective BTKIs and venetoclax-based strategies. The burden of AF and its management in patients treated with non-ibrutinib BTKIs are not well characterized; more data are needed on AF outcomes among those prescribed acalabrutinib or zanubrutinib. The consequences of switching from ibrutinib to another BTKI or venetoclax are uncertain at the present time.

When AF persists and is difficult to control with medical therapy (and, when appropriate, electrical cardioversion or BTKI dose reduction), invasive strategies, such as permanent pacemaker implantation followed by atrioventricular node ablation, should be considered. While this approach would prevent tachycardia-related complications, it does not reduce the thromboembolic risk associated with AF. The role of pulmonary vein isolation and other AF ablation procedures in the context of ibrutinib use is unclear.

Table 2 CHA_2DS_2VASC score. In patients with atrial fibrillation, thromboembolic risk can be estimated by using the CHA_2DS_2VASC score (*TIA*, transient ischemic attack; *TE*, thromboembolic event; *MI*, myocardial infarction; *PAD*, peripheric artery disease) [45]. Note that this score has not been validated in populations with a B cell neoplasm

CHA_2DS_2VASC score			
	Points	Total score	Adjusted stoke rate (% per year)
Congestive heart failure	1	0	0%
Hypertension	1	1	1.3%
Age > 75 years old	2	2	2.2%
Diabetes mellitus	1	3	3.2%
Stroke/TIA/TE	2	4	4.0%
Cardiovascular disease (prior MI, PAD or aortic plaque)	1	5	6.7%
Age 65 to 74 years old	1	6	9.8%
Female sex	1	7	9.6%
MAXIMUM SCORE	9	8	6.7%
		9	15.2%

Table 3 HAS-BLED score. In patients with atrial fibrillation, bleeding risk can be estimated with the HAS-BLED score [46, 47]. Note that this score has not been validated in populations with a B cell neoplasm nor if taking an inhibitor of Bruton's tyrosine kinase, which might be considered a bleeding predisposition

HAS-BLED score			
	Score	Total score	Bleeds per 100 patient-years
Hypertension (systolic blood pression >160 mmHg)	1	0	1.13
Abnormal renal and liver function (1 point each)	1 or 2	1	1.02
Stroke	1	2	1.88
Bleeding tendency/predisposition	1	3	3.74
Labile INRs (if on warfarin)	1	4	8.70
Age >65 years old	1	5	12.5
Drugs or alcohol (1 point each)	1 or 2		
Maximum score	9		

Anti-platelet Effect

Epidemiology

Ibrutinib increases bleeding risk. In a systematic review of randomized trials, the pooled incidence of any bleeding was 20.8 per 100 patient-years (95% confidence interval [CI], 19.1–22.1) among ibrutinib recipients, compared to 11.6 per 100 patient-years (95 % CI, 9.1–14.4) in patients receiving alternate treatments with a pooled relative risk of 2.72 (95% CI, 1.62–4.58; P=0 .0002). The pooled relative risk of major bleeding with ibrutinib, including life-threatening or intracranial bleeding, was 1.66 (95% CI 0.96–2.85) [49]. In the ELEVATE-TN trial, from which patients on an anticoagulant were excluded, grade ≥3 bleeding was reported in 1.7% of those on acalabrutinib-obinutuzumab, 1.7% of those in the acalabrutinib monotherapy group and 0% of those on obinutuzumab-chlorambucil during a median follow-up of 28.3 months [16]. The respective rates of any bleeding were 42.7%, 39.1%, and 11.8%, suggesting that increased bleeding risk may be a class effect common to all BTKIs. In the ASCEND trial, major hemorrhage (defined as any serious or grade >3 hemorrhage or central nervous system hemorrhage) was reported in two (1%) individuals in the acalabrutinib monotherapy and three (2%) participants in the investigator's choice arms respectively [13].

A pertinent clinical dilemma, given the increased risk of AF seen with ibrutinib use, is the safety and efficacy of various anti-thrombotic therapies used together with ibrutinib. However, the data to inform the risks and benefits of antithrombotic therapies when used with BTKIs are limited because individuals with an indication for anticoagulation were excluded from several of the key BTKI trials. In data from two clinical trials of ibrutinib, there were 175 participants who were on both ibrutinib and anticoagulation and/or antiplatelet therapy. Of these individuals, 3% had major bleeding events within 6 months of starting ibrutinib — a rate that is considered high. Three (2%) patients who did not receive concomitant antithrombotic therapy had major bleeding [50]. In a multi-center, retrospective study of 56 patients who developed AF while on ibrutinib, 29% were treated with aspirin, 5% with dual anti-platelet therapy, and 48% with an anticoagulant (most frequently a direct oral anticoagulant). Eight (14%) patients developed grade 3–4 bleeding, although the duration of follow-up of these individuals was not stated [51].

Pathogenesis

CLL itself (including untreated CLL) is associated with decreased collagen-mediated and ADP-mediated platelet aggregation as compared with healthy controls [52]. The anti-platelet effects of ibrutinib are therefore superimposed on a background of a bleeding predisposition inherent to CLL. Ibrutinib has been shown to inhibit collagen-induced platelet aggregation and platelet adhesion onto von Willebrand factor in vitro [53]. However, the effects of ibrutinib on ADP-mediated platelet aggregation may vary with time: after an initial decrease, ADP-mediated platelet aggregation subsequently improved in a small cohort of ibrutinib-treated patients [54]. This laboratory finding is mirrored by the observation that most ibrutinib-associated bleeding occurs within the first 6 months of therapy. However, this clinical finding is not specific to ibrutinib because a spike in bleeding events early after initiating an antithrombotic medication is frequently observed, as clinically occult lesions become apparent when the new antithrombotic precipitates their bleeding.

In a small study comparing the effects of ibrutinib with acalabrutinib in patients with non-Hodgkin's lymphoma, Bye et al. found that both drugs had similar effects on collagen-mediated platelet aggregation. However, ibrutinib but not acalabrutinib inhibited Src kinase, which is active in platelet adhesion to collagen, and led to less in vitro thrombus formation. The results of head-to-head trials of acalabrutinib vs ibrutinib may inform whether these in vitro differences

translate into clinical differences in bleeding risk. Patients treated with BTKIs should be counseled that aspirin, nonsteroidal anti-inflammatory drugs, and fish oils can increase their bleeding risk [52, 55].

Management

In general, we do not recommend withholding a BTKI for minor bleeding. However, treatment decisions in patients who develop distressing levels of minor bleeding need to be individualized. In instances of major bleeding, including life-threatening bleeding, bleeding requiring transfusion, or intracranial bleeding, the BTKI should be withheld. In vitro research suggests that platelet aggregation returns to normal after 5 to 7 days of ibrutinib cessation [53, 56, 57]. Platelet transfusion can be considered in the setting of severe bleeding even if platelet counts are normal. The decision to rechallenge with a BTKI following a major bleed should be individualized and should take into consideration the risk of recurrent bleeding and therapeutic alternatives for the underlying B cell neoplasm. In the perioperative setting, a BTKI should be withheld 3 to 7 days before an invasive procedure [58].

Hypertension

Epidemiology

An office blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic (or an average 24-h ambulatory blood pressure ≥130 mmHg systolic and/or ≥80 mmHg diastolic) is considered as hypertension [59]. In a meta-analysis that included 8 randomized clinical trials of ibrutinib, the risk ratio for hypertension was 2.85 (95% CI; 1.52–5.23) [22]. Dickerson et al. performed a single-arm cohort study to characterize the relationship between ibrutinib use and blood pressure. New hypertension was defined according to a more stringent threshold as a systolic blood pressure ≥130 mmHg on 2 separate visits within 3 months. Worsening hypertension was defined by an increase in hypertension grade using the Common Terminology Criteria for Adverse Events (CTCAE) or an increase in antihypertensive therapy. They found that 78.3% of patients taking ibrutinib developed new or worsening hypertension over a median of 30 months (which may over-estimate the incidence of hypertension if guidelines' definitions of hypertension are applied [59]). Among patients who developed hypertension, 17.7% had a blood pressure >160/100 mmHg [60].

Early evidence suggests that acalabrutinib may not cause hypertension to the same extent as ibrutinib. In the ELEVATE-TN trial, grade >3 hypertension occurred in five (3%) patients in the acalabrutinib-obinutuzumab group, four (2%) patients in the acalabrutinib monotherapy group, and five (3%) patients in the obinutuzumab-chlorambucil group [16]. In the ASCEND trial, the incidence of hypertension of any grade was 3% among acalabrutinib recipients [13]. In the ASPEN trial, the incidence of hypertension among ibrutinib recipients was 1.2 per 100 person-months vs 0.7 per 100 person-months among zanubrutinib recipients. The hazard ratio for incident hypertension in the zanubrutinib group as compared with the ibrutinib group was 0.59 (95% CI 0.29–1.20) [29]. While additional data on the relationship between acalabrutinib or zanubrutinib use and hypertension are desirable, existing information on the effects of the different BTKIs on hypertension risk is relatively unbiased because blood pressure measurement was typically required at each follow-up visit in the BTKI trials reported to date.

Pathogenesis

Numerous tyrosine kinase inhibitors have been shown to cause hypertension. Mechanisms are thought to include inhibition of vascular endothelial growth factor receptor, vascular fibrosis, and cellular remodeling secondary to the inhibition of the PI3K pathway and downregulation of nitric oxide [60]. In an in vitro study, ibrutinib has been shown to have dose-dependent anti-VEGF effects [61]. VEGF inhibition can lead to hypertension by inhibiting endothelial nitric oxide synthetase, thus impairing endothelial function; increased vascular stiffness; activation of the endothelin-1 system; and (somewhat counter-intuitively) reduction in plasma renin [62, 63].

Management Considerations

Patients on BTKI should be monitored regularly for new or worsening hypertension [64]. An office blood pressure ≥140 mmHg systolic and/or ≥90 mmHg diastolic is indicative of hypertension. However, a consequence of the COVID-19 pandemic is that in-person clinical visits have been restricted in many countries and home blood pressure monitoring using off-the-shelf machines may be increasingly adopted. An average awake ambulatory blood pressure ≥135 mmHg systolic and/or ≥85 mmHg diastolic is consistent with hypertension [59].

For patients diagnosed with new or worsening hypertension, lifestyle factors that can reduce blood pressure or its deleterious effects should be considered. These include smoking cessation, regular exercise, weight loss (among those with a body-mass index >30 kg/m^2), salt reduction in those with a very high dietary salt intake, a diet higher in fruit and vegetables, and lower alcohol intake. There are few data to indicate the threshold blood pressure at which antihypertensive medications should be initiated in patients on a BTKI. Given that hypertension and ibrutinib are both risk factors for

the development of AF, antihypertensive medication should be recommended at systolic blood pressures ≥140 mmHg or diastolic blood pressures ≥90 mmHg. In patients with cardiovascular risk factors, including cardiovascular disease, chronic kidney disease, diabetes, or age ≥75 years, a threshold systolic blood pressure ≥130 mmHg might prompt consideration of antihypertensive medication use [65].

There are few data to suggest the optimal class of antihypertensive medication for new or worsening ibrutinib-related hypertension. Medications should be chosen according to patients' comorbidities. For example, angiotensin converting enzyme-inhibitors and angiotensin receptor blockers are beneficial in individuals with diabetes, coronary artery disease, or heart failure with reduced ejection fraction [66]. Also, an awareness of the potential for pharmacokinetic interactions between ibrutinib and other medications is important (as diltiazem and verapamil can increase ibrutinib levels) [67].

Ventricular Arrythmias

Epidemiology

There is limited evidence to suggest that BTKIs may increase the risk of ventricular arrhythmia (VA) [68–70]. Salem et al. undertook an analysis of the VigiBase database, which contains voluntary reports of suspected drug adverse effects. They found that the likelihood of a report of a ventricular arrhythmia was higher for ibrutinib as compared with all other drugs in the database pooled together. However, there was no standardized definition of ventricular arrhythmia. Also, no excess reporting of cardiac death among ibrutinib recipients was identified, which is not consistent with higher rates of ventricular arrhythmia [71]. In the general population over 65 years of age, incidence rates of sudden cardiac death are approximately 2 per 1000 person-years [72, 73]. In an analysis of 1000 ibrutinib recipients from RESONATE, RESONATE-2, HELIOS, and RAY, Lampson et al. identified 10 cases of sudden death or cardiac arrest, yielding a pooled incidence rate of sudden death of 7.9 per 1000 person-years [69]. However, the precision of this estimated rate of sudden death is limited by the small number of such events.

While these reports raise the hypothesis that ibrutinib may be associated with an increase in ventricular arrhythmias, the main effects observed in the landmark clinical trials remain highly relevant. In early clinical trials in which participants were randomized to receive ibrutinib or an alternative therapy for CLL, ibrutinib reduced overall mortality, with hazard ratios for death ranging from 0.16 to 0.43. While sudden cardiac death and ventricular tachyarrhythmia were not systematically reported in these trials [2, 3], their findings with respect to overall mortality indicate that any increase in the risk of cardiovascular mortality associated with ibrutinib is likely to be modest if it exists at all, and is markedly outweighed by the beneficial effects of ibrutinib on disease-related mortality. The value of these clinical trials is that their findings are much less susceptible to bias than non-randomized data and there is no ambiguity or ascertainment bias in the outcome of all-cause mortality. There has been recent attention on the apparent excess of cardiovascular deaths observed in a trial of ibrutinib in patients aged ≥65 years [10]. In this trial, there was no difference in overall survival between recipients of bendamustine-rituxmab, ibrutinib, and ibrutinib-rituximab. In total, 2 (1.1%) individuals in the bendamustine-rituximab arm and 11 (3.0%) in the ibrutinib arms experienced unwitnessed death. This number of events is too small to draw a firm conclusion on the causal role of ibrutinib, especially when 3 (1.7%) in the bendamustine-rituximab arm vs 3 (0.8%) in the ibrutinib arms died from myocardial infarction, cerebrovascular, or unspecified causes. The excess unwitnessed deaths in the ibrutinib arms could be explained by play of chance or by variation in the attribution of cause of death.

In ELEVATE-TN and ASCEND, no cardiac deaths were reported among acalabrutinib recipients [13, 16]. There is insufficient evidence to inform whether more selective BTKIs are associated with an increased risk of ventricular arrhythmias.

Pathogenesis

While the empiric clinical evidence to indicate that ibrutinib increases the risk of ventricular arrhythmia is scant, several mechanisms by which ibrutinib might increase arrhythmogenicity have been proposed. In spontaneously hypertensive rats, Du et al. showed that the inducibility of ventricular fibrillation in older animals was increased by ibrutinib [74]. Abnormalities in calcium and repolarization dynamics were also observed. In a randomized, placebo- and positive-(moxifloxacin) controlled, double-blind study, De Jong et al. demonstrated that ibrutinib does not cause prolongation of the QT or corrected QT intervals, even when supratherapeutic doses of ibrutinib (840 and 1690 mg) were administered [75]. Therefore, there is little evidence of an electrophysiologic mechanism by which ibrutinib could increase the risk of *torsades de pointes*.

Heart Failure

There is weak evidence that ibrutinib can cause heart failure [76, 77]. In their analysis of the Vigibase database, Salem et al. found that heart failure was reported more often with ibrutinib use than with other medications in the database [71]. In the long-term follow-up of the RESONATE trial, Munir et al. observed 9 cases (5%) of congestive heart failure after a

median follow-up of 65.3 months [28]. Cardiomyopathy can be caused by AF and related tachycardia, and by hypertension, which are known adverse effects of ibrutinib [78]. No data on heart failure incidence in the ofatumumab arm were provided for comparison and there were too few heart failure adverse events reported in ELEVATE-TN or ASCEND to inform the risk of heart failure in acalabrutinib-treated patients.

Conclusions

There is strong evidence that ibrutinib increases the risk of AF, bleeding, and hypertension. The current evidence to support a direct causal association between ibrutinib and other cardiovascular adverse effects, such as ventricular arrhythmia and cardiomyopathy, is modest and should not preclude the prescription of ibrutinib in most cases. There are only limited data on the cardiovascular safety of acalabrutinib and zanubrutinib and the results of ongoing and future trials of these more selective BTKIs are needed to evaluate whether they offer a better cardiovascular safety profile than ibrutinib.

Abbreviations AF, Atrial fibrillation; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; BTKI, Bruton's tyrosine kinase inhibitor; CI, Confidence interval; CLL, Chronic lymphocytic leukemia; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma; RCT, Randomized, controlled trial; WM, Waldenström's macroglobulinemia

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