Curr. Treat. Options in Oncol. (2020) 21: 67
DOI 10.1007/s11864-020-00764-6

Cardio-oncology (MG Fradley, Section Editor)

Cardiovascular Toxicities of Bruton's Tyrosine Kinase Inhibitors

Ricardo Pineda-Gayoso, MD[1]
Mohammed Alomar, MD[1]
Dae Hyun Lee, MD[1]
Michael G. Fradley, MD[2,*]

Address
[1]Division of Cardiovascular Medicine, University of South Florida Morsani College of Medicine and H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA
[*,2]Division of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA
Email: michael.fradley@pennmedicine.upenn.edu

Published online: 30 June 2020

This article is part of the Topical collection on *Cardio-oncology*

Keywords BTK inhibitor · Cardiotoxicity · Atrial fibrillation · Ibrutinib · Cardio-oncology

Opinion statement

There has been a significant shift in the management of B cell malignancies over the past decade. Initial strategies involving the use of systemic chemotherapies have been gradually replaced by more targeted therapies to improve survival and overall tolerability. Bruton's tyrosine kinase inhibitors are breakthrough drugs that have been approved to treat many B cell malignancies. Despite their demonstrated benefits, unintended events still occur including various cardiotoxicities. In this review, we discuss the rationale behind developing these agents, their common cardiovascular toxicities, and associated management challenges.

Introduction

Traditional approaches to treating B cell malignancies include chemotherapy, immunotherapy, and a combination of both. Initial approaches consisted of monotherapy with alkylating agents such as chlorambucil, which was the gold standard for decades, purine analogs such as fludarabine, and anti-CD20

antibodies such as rituximab [1, 2]. Combinations of chemotherapy and immunotherapy have been shown to have synergistic effects, such as rituximab with fludarabine or fludarabine-cyclophosphamide [3]. The combination of fludarabine, cyclophosphamide, and rituximab (FCR) was the first-line therapy for young patients with symptomatic chronic lymphocytic leukemia (CLL) [4], with an overall response rate of 95% in previously untreated patients and a complete remission rate of 44%, double than those with fludarabine and cyclophosphamide alone (44% vs 22%) [5]. However, most of these therapies require intravenous infusion and safety monitoring due to their cytotoxic side effects. Patients with CLL who are older than 65 years of age are less likely to tolerate fludarabine-based therapy, with increased toxicity often leaving them unable to complete the necessary cycles [5]. In addition, patients with certain mutations, such as the deletion of the short arm of chromosome 17 (del 17p13.1), have a decreased overall response rate and decreased progression-free survival [6]. This led to the paradigm shift in cancer moving towards targeted treatments, thus leading to the development of Bruton's tyrosine kinase (BTK) inhibitors [6].

BTK, a member of the Tec kinase family, is an essential enzyme in the activation of downstream signaling pathways required for survival and proliferation of malignant B cells [7, 8]. The pathogenesis of CLL and various other B cell malignancies consists of the upregulation of this B cell receptor pathway [9, 10]. Inhibition of BTK in malignant B cells leads to diminished proliferation, decreased tumor survival, and impaired adhesion and migration of the malignant B cells to their growth-promoting microenvironment [11, 12]. As such, two BTK inhibitors, ibrutinib and acalabrutinib, have gained Food and Drug Administration (FDA) approval for the treatment of various B cell malignancies, with several others currently under active clinical investigation and/or development.

Ibrutinib

Ibrutinib is an oral, once-a-day, BTK inhibitor that works by forming an irreversible covalent bond with a cysteine residue, demonstrating an improvement in overall and progression-free survival in various B cell malignancies [13, 14]. Unlike other regimens used for B cell malignancies, this BTK inhibitor does not have toxic effects on normal T cells [15]. The randomized phase 3 RESONATE trial in patients with previously treated CLL or small lymphocytic lymphoma (SLL) demonstrated a statistically significant 57% reduction in the rate of death vs. ofatumumab, with an overall survival rate of 90% at 12 months, and increased overall response rate (42.6% vs 4.1%) [16]. Similarly, in a phase 2, open-label, multicenter study that assessed the activity of ibrutinib in 145 patients with relapsed or refractory CLL with del17p or SLL who had experienced poor response rates after chemoimmunotherapy, 120 patients (83%) had an overall response at a median follow-up of 27.6 months. The 24-month progression-free survival was 63%, while the 24-month overall survival was 75% [17]. In a phase 2 study that included 111 patients with relapsed or refractory mantle cell lymphoma, patients treated with ibrutinib had a complete response rate of 21% and a partial response rate of 47% [18]. In another phase 3 trial, 150 patients with Waldenström's macroglobulinemia (WM) were assigned to receive ibrutinib plus rituximab or placebo plus rituximab; it was found that at 30 months, the progression-free survival rate was 82% with ibrutinib-rituximab versus 28% with placebo-rituximab [19]. Similarly, a multicenter, open-label study evaluating the efficacy of ibrutinib in patients with chronic graft versus host disease (cGVHD) demonstrated an overall response rate of 67% at a median follow-up of 13.9 months [20].

As a result of these various studies, ibrutinib is currently approved for the treatment of CLL, SLL, mantle cell lymphoma, WM, 17p deletion CLL, and cGVHD [21]. Despite its many clinical benefits, ibrutinib has several cardiotoxic effects including atrial and ventricular arrhythmias and hypertension, which have been associated with increased morbidity and mortality in this population [22••]. Moreover, ibrutinib is also associated with increased bleeding which further complicates the management of these patients [22••]. As such, it is imperative that both cardiologists and hematologists/oncologists recognize and appropriately manage these issues to allow for the continued optimal cancer treatment while mitigating long-term cardiovascular risk.

Atrial fibrillation and other atrial arrhythmias

Atrial fibrillation is one of the most common cardiac side effects related to ibrutinib therapy (Table 1) [29]. Incidence of atrial fibrillation has been reported in up to 16% of patients treated with ibrutinib [30]. Although patients with a prior history of atrial fibrillation are more prone to recurrence with this medication, patients with no known history of atrial fibrillation can also develop this arrhythmia. In the RESONATE trial, 3% of patients developed grade 3 or higher atrial fibrillation, while another 2% of patients developed grade 1 or 2 atrial fibrillation [16]. After a 19-month median follow-up, a total of 7% of patients developed atrial fibrillation with a 5.1-month median time to onset [23]. In another randomized phase 3 trial (RESONATE-2), 269 patients age 65 years or older with previously untreated CLL or SLL were randomized to receive either ibrutinib or chlorambucil, with 6% of ibrutinib-treated patients developing atrial fibrillation after a median exposure of 17.4 months in contrast to only 1 patient in the chlorambucil group [13]. The 5-year follow-up of the RESONATE-2 trial showed a total of 16% had

Table 1. Ibrutinib studies reporting atrial fibrillation

Study	Number of patients	Percent of patients who developed atrial fibrillation	Median time to follow-up (months)
Byrd et al. 2014 [16]	195	5.13% any grade (3% grade 3 or higher)	8.6
Brown et al. 2018 [23]	195	7% any grade (3.6% grade 3)	19
Munir et al. [24]	195	12% any grade (6% grade 3 or higher)	65.3
Burger et al. 2015 [13]	136	6% any grade (1.5% grade 3)	17.4
Burger et al. 2019 [25]	136	16% any grade (5% grade 3 or higher)	60
Byrd et al. 2015 [21]	132	6% grade 3 or higher	36
O'Brien et al. [17]	144	6% grade 3 or higher	27
Fradley et al. [26]	137	14% any atrial arrhythmia	N/A
Dimopoulos et al. [19]	75	15% any grade (12% grade 3 or higher)	26
Reda et al. [27]	43	16% any grade	8
Mato et al. [28]	183	11.3% any grade	7

developed atrial fibrillation at any time, with 5% having developed a grade 3 event. Interestingly, only 4% had continued episodes of AF at 5 years [25]. In a phase 2, open-label, multicenter study of 144 patients with relapsed or refractory CLL or SLL with the 17p deletion, 6% developed atrial fibrillation after a median of 27 months of follow-up, similar to the reported rate in RESONATE [17].

The excess risk of developing atrial fibrillation with ibrutinib has been shown in multiple studies. In a retrospective study, 137 patients diagnosed with B cell malignancies treated with ibrutinib were compared with 106 patients treated with chemotherapy for the same cancers. The incidence of atrial arrhythmias was 14% in the ibrutinib group, compared with 3% in patients treated with chemotherapy ($p = 0.009$). In multivariable analysis, patients treated with ibrutinib had a fivefold increased risk of developing atrial arrhythmias (odds ratio = 5.18, 95% confidence interval 1.42 to 18.89) and ibrutinib was an independent risk factor for developing atrial arrhythmias [26]. Additionally, in a randomized trial of 150 patients, comparing placebo-rituximab and ibrutinib-rituximab, atrial fibrillation occurred in 15% of patients treated with ibrutinib vs 3% in the placebo group. Notably, 27% of patients in the ibrutinib group had a prior history of atrial fibrillation [19]. In a retrospective case-control study of 183 patients with CLL treated with ibrutinib, 11.3% developed atrial fibrillation at a median time of 7 months from ibrutinib initiation [28]. In another study where 43 CLL patients were assessed before starting ibrutinib therapy, atrial fibrillation occurred in 16.3% of patients after a median follow-up of 8 months. Of those, 57.1% were started in anticoagulation, and 71.4% were started on beta blockers or amiodarone [27]. Lastly, a recent observational retrospective analysis, which was the largest and most extensive clinical characterization of cardiovascular adverse drug reactions, identified 303 cardiovascular deaths related to ibrutinib out of 13,572 individual case safety reports. In addition, the median time from initiation of treatment with ibrutinib to onset of supraventricular arrhythmia (SVA) was approximately 2–3 months with a total of 959 (7.07%) cases, 93% of which were atrial fibrillation. The reported odds ratio was 23.1 with associated rates of heart failure and death in 11.9 and 10% respectively [22••].

Mechanism of atrial fibrillation

Although the actual mechanism of ibrutinib-related atrial fibrillation is still unknown, it is thought to be related to the inhibition of cardiac PI3K-Akt signaling [31]. However, the effects on PI3K-AKT signaling alone may not be sufficient to explain the mechanism of ibrutinib-induced atrial fibrillation as only a few cases of atrial fibrillation were documented with acalabrutinib, a second-generation, selective, irreversible inhibitor of Burton's tyrosine kinase inhibitor [32]. In a mouse model, potential mechanisms for ibrutinib-associated atrial fibrillation included atrial structural remodeling and fibrosis, dysregulated calcium handling in atrial myocytes,

enhanced delayed afterdepolarization, and increased activity of CaMKII, an enzyme kinase implicated in many cardiac pathologies [33].

Risk factors

Multiple risk factors for developing atrial fibrillation with ibrutinib therapy have been identified.

Brown and colleagues evaluated over 1500 ibrutinib-treated patients with CLL and mantle cell leukemia from four randomized trials and found that a history of atrial fibrillation, ibrutinib therapy, and older age (> 65 years) were independent risk factors in multivariate analyses for developing atrial fibrillation, while hypertension and hyperlipidemia were additional risk factors in a univariate model [30].

In a "real-world" retrospective study where patients with prior history of atrial fibrillation were excluded, ibrutinib use, age, hypertension, and previous use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aspirin were independently associated with incident arrhythmias in univariate analyses [26]. A retrospective case-control study of 183 consecutive patients with chronic lymphocytic leukemia treated with ibrutinib identified left atrial enlargement on pre-ibrutinib EKG as a significant predictor of atrial fibrillation development. Interestingly, diabetes mellitus and coronary artery disease were not shown to be strong predictors for atrial fibrillation in this study [28]. In another study, left atrial volume index of ≥ 40 mL/m2 on transthoracic echocardiogram at ibrutinib initiation identified patients at risk for developing atrial fibrillation [27].

Management of ibrutinib-associated atrial fibrillation

Management of ibrutinib-associated atrial fibrillation can be challenging; however, discontinuation of ibrutinib solely due to atrial arrhythmias is generally not recommended [34]. When considering a rate control strategy (primarily for those patients with minimal symptoms), beta blockers are preferred due to fewer drug-drug interactions. Due to the inhibition of cytochrome P450 3A4, non-dihydropyridine calcium-channel blockers such as diltiazem and verapamil are generally avoided as they can increase concentrations of ibrutinib [35, 36]. Conversely, ibrutinib can affect digoxin metabolism via p-glycoprotein leading to potential digoxin toxicity due to its narrow therapeutic window [32]. From a rhythm control perspective, amiodarone should be used with caution due to its effects on CYP 3A4 metabolism. Little data exists regarding other antiarrhythmic medications. Moreover, the safety and efficacy of ablation have not been specifically evaluated in this population [37].

Stroke risk prediction

The most commonly used stroke risk prediction tool is the CHADS VASc score, which has been extensively validated in the general cardiology patient population [24]. However, its accuracy in predicting stroke risk in the cancer population is unclear, as it does not incorporate certain characteristics such as the

presence of malignancy and life expectancy into its calculations [32]. In a recent study from Denmark, patients in a nationwide registry with cancer and AF had higher rates of thromboembolism at low CHADS VASc scores (0–1) but lower rates with scores of 2+ when compared with non-cancer patients [38]. Similarly, in a study from Taiwan, higher CHADS VASc scores had less impact on predicting the risk of ischemic stroke in the setting of AF and cancer [39].

Stroke risk reduction

The antiplatelet effects of ibrutinib make it challenging to choose the appropriate stroke risk reduction strategy in the setting of atrial fibrillation. Ibrutinib is known to increase the risk of bleeding by inhibiting glycoprotein VI collagen-activation pathway and glycoprotein 1b–mediated platelet function, thus decreasing platelet aggregation and adhesion to von Willebrand factor [40–42]. In a phase II study with mantle cell lymphoma, almost 4% of patients developed subdural hematoma following episodes of trauma, while on aspirin or warfarin, leading to the discouragement of warfarin use [43]. The use of direct oral anticoagulants appears to be generally safe; however, careful monitoring is necessary given the potential for drug-drug interactions [44]. For example, ibrutinib can increase concentrations of direct oral anticoagulants metabolized by CYP 3A4, including apixaban and rivaroxaban, which can lead to an increased risk of bleeding. In addition, ibrutinib can increase the levels of dabigatran, a direct thrombin inhibitor, via its effects on the P-glycoprotein system [37]. Although bleeding risk scores such as HAS-BLED are used to assess bleeding risk in patients receiving anticoagulation, its applicability in cancer patients lacks validation [45].

Ventricular arrhythmia

Ibrutinib use has been associated with ventricular arrhythmias but with less frequency than atrial fibrillation. Ibrutinib-associated ventricular arrhythmias are not driven by QT prolongation and early afterdepolarizations as is the case with many other cancer therapeutics [46–48]. The incidence of ibrutinib-associated ventricular arrhythmias was recently reported in a study of 582 patients. After a median follow-up of 32 months, 1% developed symptomatic ventricular arrhythmias related to ibrutinib exposure. In a subset of those without prior history of coronary artery disease or heart failure, the incidence of ventricular arrhythmia events was estimated to be 596 per 100,000 person-years [49••]. In the HELIOS study, a randomized, double-blind, phase 3 study that assessed the safety of adding ibrutinib to bendamustine plus rituximab for previously treated CLL or SLL, 2% of patients developed grade 3 or more ventricular arrhythmias, cardiac arrests, and sudden deaths in the ibrutinib-containing arm, consistent with 1991 events per 100,000 person-years [46, 50, 51].

Hypertension

Ibrutinib exposure has also been linked to the development of hypertension. In the HELIOS trial, the incidence of hypertension was 3.5% in patients treated with ibrutinib after a median follow-up of 17 months [51]. After a three-year

follow-up study of 101 refractory/relapsed (R/R) CLL/SLL patients and 31 treatment-naïve (TN) CLL/SLL patients, 20% of RR patients and 23% of TN patients developed grade 3 or grade 4 hypertension [21]. In the RESONATE trial, with up to 71 months of follow-up after the initiation of ibrutinib therapy, 21% of patients developed hypertension of grade 3 or higher [52]. In a safety analysis of four randomized controlled trials that included 756 patients on ibrutinib and 749 patients on the comparator drug, grade 3 or higher hypertension was reported in 4% versus 1%, respectively. The median time to onset of hypertension was 4.6 months. While no patient required dose reduction due to hypertension, 78% of patients required initiation or escalation of antihypertensive medications [53]. In a study of 562 patients over an average period of 30 months, 78.3% of patients developed new or worsening hypertension, with a mean increase in systolic pressure of 5.2 mmHg. New hypertension developed in 71.6% of patients on ibrutinib. Of those who did not have a previous history of hypertension, 17.7% developed high-grade hypertension with BPs of 160/100 mmHg or greater. New or worsening hypertension was associated with a twofold increase in major adverse cardiac events. Although initiation of antihypertensive medications was associated with a lower risk of major adverse cardiac events, no specific class was identified as superior in preventing or controlling ibrutinib-associated blood pressure elevations [54••]. While the pathophysiology of ibrutinib-associated hypertension is not yet established, it does not appear to be VEGF (vascular endothelial growth factor) mediated.

Acalabrutinib

Acalabrutinib is a novel BTK inhibitor that was designed to improve on the safety and efficacy of first-generation BTK inhibitors such as ibrutinib [55]. In preclinical studies, acalabrutinib did not inhibit epidermal growth factor receptor (EGFR), interleukin-2-inducible T cell kinase (ITK), T cell X chromosome kinase, or tyrosine kinase expressed in hepatocellular carcinoma (TEC) family proteins. This translates into less off-target activity and likely explains the overall improved side effects profile of acalabrutinib [56].

Acalabrutinib was initially granted accelerated approval for the treatment of relapsed or refractory mantle cell lymphoma, based on the efficacy data from an open-label, phase 2 study of 124 patients with mantle cell lymphoma who had received at least one prior therapy [57]. There were no reported cases of atrial fibrillation in this study.

Recently, the FDA granted acalabrutinib Breakthrough Therapy designation for the treatment of adults with CLL or SLL. The approval was based on two randomized clinical trials. The phase 3 ELEVATE TN trial recruited 535 patients with previously untreated CLL, in which patients were randomized in a 1:1:1 fashion to acalabrutinib alone, acalabrutinib combined with intravenous obinutuzumab, or obinutuzumab plus oral chlorambucil. Patients who received acalabrutinib had a longer progression-free survival compared with patients receiving other standard treatments, with atrial fibrillation incidence of less than 4% (60). The second clinical trial (ASCEND) included 310 patients with previously treated CLL and showed that patients receiving acalabrutinib also had longer progression-free survival than patients receiving rituximab in combination with idelalisib or rituximab in combination with bendamustine. The incidence of atrial fibrillation in the

acalabrutinib group in this study was 5% (61). Interestingly, bleeding of any grade with acalabrutinib occurred in 40% in ELEVATE TN and 26% in ASCEND.

Conclusion

The introduction of targeted BTK inhibitors, such as ibrutinib, has revolutionized the management of B cell malignancies. Nevertheless, unique cardiovascular toxicities have been identified including atrial and ventricular arrhythmias and hypertension. These toxicities are primarily associated with ibrutinib and do not appear to be class-related adverse events as low rates are observed with other BTK inhibitors. Atrial fibrillation is now a well-recognized adverse effect of ibrutinib, and while management can be challenging, especially regarding anticoagulation strategies given the enhanced bleeding with ibrutinib, most patients can continue receiving the drug with careful monitoring. Ventricular arrhythmias are quite rare but can be life threatening often requiring treatment discontinuation. Finally, hypertension is commonly identified and can be managed with typical antihypertensive medications. The exact mechanism of these toxicities remains unclear; basic and translational research to understand the pathophysiology is an area of significant future need in order to develop better clinical risk prediction and mitigation strategies so that patients can continue receiving these effective therapies with minimal cardiovascular morbidity.

Compliance with Ethical Standards

Conflict of Interest

Ricardo Pineda-Gayoso declares that he has no conflict of interest.
Mohammed Alomar declares that he has no conflict of interest.
Dae Hyun Lee declares that he has no conflict of interest.
Michael Fradley has received research funding from Medtronic and has received compensation from Novartis for service as a consultant.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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