

Ibrutinib-Associated Cardiotoxicity: From the Pharmaceutical to the Clinical

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Abstract: Ibrutinib is the first-in-class Bruton tyrosine kinase (BTK) inhibitor that has revolutionized the treatment of B cell malignancies. Unfortunately, increased incidences of cardiotoxicity have limited its use. Despite over a decade of research, the biological mechanisms underlying ibrutinib cardiotoxicity remain unclear. In this review, we discuss the pharmacological properties of ibrutinib, the incidence and mechanisms of ibrutinib-induced cardiotoxicity, and practical management to prevent and treat this condition. We also synopsise and discuss the cardiovascular adverse effects related to other more selective BTK inhibitors, which may guide the selection of appropriate BTK inhibitors.

Keywords: ibrutinib, cardiotoxicity, BTK inhibitors, atrial fibrillation, cardio-oncology

Introduction

The use of oral tyrosine kinase inhibitors (TKIs) is becoming increasingly common in cancer therapies because of their convenience and patient preference.^{1,2} However, idiosyncratic adverse events of this class of medications are relatively unknown to physicians and pharmacists.³

Bruton tyrosine kinase (BTK) is a 659 amino acid enzyme that is mainly involved in the catalyzation of phosphate groups from ATP to tyrosine residues.⁴ BTK consists of five domains, each having the potential to critically regulate the interactions involved in intracellular signaling.⁵ The PH domain can bind to several crucial signaling proteins, such as protein kinase C (PKC) and the prolyl isomerase Pin1, both of which are negative regulators of BTK.⁶ As a metalloprotein enzyme requiring Zn²⁺ for optimal activity and stability,^{7,8} the TH domain in BTK contains a highly conserved zinc finger motif. Together with the kinase domain, the SH2 domain forms an allosteric interface that is critical for BTK activation.⁹ Although tyrosine Y223 phosphorylation in the SH3 domain is important, it is Y551 in the kinase domain initiates the catalytic activation of BTK upon the upstream kinase SYK or SRC.¹⁰ The cysteine residue at position 481 (C481), which is also located in the kinase domain, is the main binding site for small-molecule chemical inhibitors.¹¹ BTK is predominately expressed in immune cells such as B cells, macrophages, and mast cells, but not in T lymphocytes.^{12,13} As such, targeted inhibition of BTK has revolutionized the treatment landscape of B cells' malignancies.¹⁴

Ibrutinib is a once-daily oral medication that acts as a BTK inhibitor by irreversibly and covalently binding to C481 of the BTK kinase domain.¹¹ Ibrutinib has profoundly transformed the treatment landscape of B cell malignancies. Phase 3 RESONATE and RESONATE-2 trials demonstrated the superiority of ibrutinib over ofatumumab, a CD20 antibody, in relapsed/refractory chronic lymphocytic leukemia (CLL) and over chlorambucil in previously untreated older patients with CLL or small lymphocytic lymphoma (SLL).^{15,16} The final analysis of the RESONATE study, which had a median follow-up of 65.3 months, revealed that the median progression-free survival (PFS) of patients in the ibrutinib arm

remained significantly longer than that of patients in the ofatumumab arm by approximately 36.1 months.¹⁷ Furthermore, the 5-year follow-up of RESONATE-2 study demonstrated consistent benefit in patients with high prognostic risk, mainly in those with TP53 mutation, 11q deletion, and/or unmutated IGHV. The overall response rate was 92% in the ibrutinib arm.^{18,19} In addition, the results of a Phase 2 study that included 111 patients revealed that ibrutinib exhibited durable single-agent efficacy in relapsed or refractory mantle cell lymphoma (MCL).²⁰ Updated safety and efficacy results after a median 26.7-month-long follow-up showed that the overall response rate (ORR) was 67%.²¹ Currently, ibrutinib has been approved as the first-line treatment for CLL and SLL, MCL, marginal zone lymphoma (MZL) and Waldenström macroglobulinemia (WM). Moreover, it has emerged as an interesting therapeutic candidate for coronavirus disease 2019 (COVID-19) owing to the reported elevated levels of BTK activity in critically ill patients.^{22–24}

Despite the significant advantages of ibrutinib in the treatment of B cell neoplasms, its long-term use has resulted in adverse effects. Mediated by both on- and off-target multiple tyrosine kinases, the most common toxicity profile of ibrutinib includes cutaneous toxicity, hypertension infection, diarrhea, arthralgias, cardiotoxicity and bleeding.^{25,26} These side effects are generally mild. However, bleeding and cardiotoxicity may present as severe and intractable adverse effects.²⁷ A multicenter, retrospective analysis that included 616 ibrutinib-treated CLL patients confirmed that intolerance, rather than progressive disease, is the most common reason for treatment discontinuation with atrial fibrillation (AF) and bleeding being the most common reasons for discontinuation.^{28–30} AF, characterized by an irregular and often rapid heart rate, is the most common cardiac arrhythmia related to ibrutinib.^{31–33} In patients treated with ibrutinib, AF incidence in the first 18 months is 3–7%, increasing to 9–16% in a longer follow-up period of up to 60 months. New-onset of AF is associated with a higher risk of thromboembolism, stroke, and heart failure, leading to ibrutinib discontinuation.^{34–37} The optimal choice of anticoagulation in ibrutinib-treated patients with AF in turn increases the risk of bleeding. In addition, significant drug–drug interactions between ibrutinib and medications that are commonly used to manage AF have been noted.^{38,39} Ibrutinib treatment is also associated with an increased risk of ventricular arrhythmia and sudden death, with an estimated risk of 2 in 100 person-years in ibrutinib-treated versus 0 in non-ibrutinib-treated CLL patients. Several cases of recurrent polymorphic ventricular tachycardia and sudden death have been reported since the drug approval occasionally.^{40,41} Although no common features have been observed among the sporadic reports, in the literature, a preclinical study has found parallel myocardial inflammation and fibrosis injury in the animal models.⁴² A rare case of takotsubo cardiomyopathy (TC) was recently reported.⁴³ This study aims to review the incidence and potential underlying mechanisms of ibrutinib-associated cardiotoxicity, as well as the recommended management options from the pertinent clinical-pharmaceutical aspect.

Pharmacokinetics and Pharmacodynamics of Ibrutinib

The recommended dose of ibrutinib for patients with CLL and WM is 420 mg once daily, and 560 mg orally once daily for patients with MCL who have received at least one prior therapy.⁴⁴ Pharmacokinetic data of ibrutinib collected from clinical trials demonstrated that the T_{max} ranged from 1 to 2 hours and the mean elimination half-time ranged from 4 to 6 hours.^{45,46} A dose-proportional increase in C_{max} and area under the curve (AUC) values was noted with doses up to 840 mg. Based on noncompartmental pharmacokinetic analysis, the geometric mean ibrutinib steady-state daily AUC was 707–1159 (50–72%) ng·h/mL and 865,978 (69–82%) ng·h/mL following 420 mg and 560 mg daily, respectively.⁴⁷ However, the relationship between plasma/serum ibrutinib concentration and ibrutinib efficacy remains unclear because of the high inter-individual pharmacokinetic variability caused by food–drug or drug–drug interactions. The plasma concentration of ibrutinib increases approximately twofold after consuming a high-fat meal compared with that after an overnight fast.⁴⁸ Cytochrome P450 (CYP) 3A4 has been identified as the primary enzyme responsible for ibrutinib metabolism, and three major metabolites have been observed. M35 is the hydroxylation product of the phenyl form of ibrutinib, and piperidine opens to form the metabolites M25 and M34. The ethylene on the acryloyl moiety epoxidized and subsequently hydrolyzed to form dihydrodiol, which is known as the metabolite dihydrodiol ibrutinib (DHI).^{49,50} Current evidences do not clearly show the exact relationship between the plasma level of DHI and the adverse events. However, because DHI has a longer elimination half-life than the parent drug, monitoring DHI levels in addition to ibrutinib, may be a useful evaluation for adherence to therapy.

Characteristics of Ibrutinib-Induced Cardiotoxicity

Cardiac diseases and cancer are two major public health concerns. Emerging evidence supports a strong and independent association between the risk of new-onset cardiac diseases and cancer incidence of cancer therapies. For instance, it has been suggested that there are many drugs that increase the risk of new-onset cardiac diseases.^{51,52} The magnitude of this risk depends on the choice of therapeutic drugs. Traditional chemotherapy, such as the anthracycline-based cancer drug doxorubicin, can cause heart failure in a dose-dependent manner and decrease the asymptomatic left ventricular ejection fraction by approximately 10–15%.^{53–55} Increased use of targeted therapies and indefinite inhibition of critical kinases may result in more specific cardiac toxicities. Immune checkpoint inhibitors (ICIs), such as anti-CTLA-4 antibodies or anti-PD-1 monoclonal antibodies, cause fatal toxic myocarditis, with a mortality rate up to 40%.⁵⁶ Tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptor (VEGFR), sunitinib or sorafenib cause hypertension in at least 25% of all patient cases.⁵⁷

Incidence of Ibrutinib-Induced Atrial Arrhythmia

CLL is the most common type of leukemia, with a significantly higher prevalence in older patients (aged >65 years), especially in the Western countries.⁵⁸ Ibrutinib, which targets the B cell receptor (BCR) signaling pathway, is an ideal therapeutic candidate for CLL. However, its cardiotoxicity prevents its long-term use in patients with CLL. Atrial arrhythmia (AA) disorder is the most common adverse event in ibrutinib-induced arrhythmias. A retrospective study that quantified the incidence rates and risk of AA in 137 patients treated with ibrutinib and in 106 patients diagnosed with B cell malignancies and treated with chemotherapy confirmed that the use of ibrutinib is an independent risk factor for the incidence of AA.⁵⁹ Ibrutinib use was also associated with a 5.2-fold increased risk of AA development, 14% in the ibrutinib-treated group versus 3% in the chemotherapy group.

AF is the most common atrial rhythm disorder. The incidence of AF in CLL patients is rapidly increasing with increasing age of this population. Early in 2014, the RESONATE clinical trial demonstrated the superiority of ibrutinib over ofatumumab chemotherapy regardless of age or clinical stage, with an AF incidence as high as 5% (10/195).¹⁶ Later, the extended follow-up study revealed that approximately 4% AF cases occurred within the 12-month treatment period. The RESONATE 2 trial studied the efficacy of ibrutinib in patients who were aged ≥ 65 years, and found that AF occurred in 6% (8/136) of the study population.⁶⁰ With a median follow-up of 60 months from the RESONATE 2 study, AF with any grade occurred in 16% of patients.¹⁵ A pooled analysis from four randomized controlled trials (RESONATE, RESONATE 2, HELIOS, and RAY) reappraised the incidence of ibrutinib-induced-AF.^{61,62} A total of 1505 patients with CLL and MCL were analyzed, with 756 patients randomized to the ibrutinib group. The pooled rate of AF in the ibrutinib-treated group was 6.5% at the 16.6-month follow-up, and 10.4% at the 36-month follow-up, respectively. An additional updated long-term safety analysis of the RESONATE study reported that 11% (10/94) of the total population had grade 3 AF.⁶²

AF is frequently paroxysmal and often asymptomatic. The prevalence of AF significantly increases from < 0.2% in adults aged < 55 years to 10% those aged ≥ 85 years, with a median age at CLL diagnosis of approximately 72 years.^{63–66} Though the latest recommendation statement from the United States Preventive Services Task Force cannot determine the balance of advantages of screening for AF in asymptomatic adults, the potential benefits of early AF detection in patients with cancer with concurrent hypercoagulable changes should be extended beyond stroke prevention.^{35,67–69} AF is usually accompanied by an increased heart rate.³⁴ The profile of BTK-treated patients presenting with AF exhibits remarkable increases when this condition is intensively screened. Consequently, screening for asymptomatic AF or monitoring the cardiac rhythm before ibrutinib prescription should be considered an excellent recommendation. However, the precise timepoint of AF screening remains uncertain. According to safety analyses from randomized clinical trials (RCTs), ibrutinib-induced AF is more likely to occur in the first 3 months, with a median time of onset of 2.8 months and late onset of 18 months post-medication.⁴⁷ Therefore, continuous monitoring during the period of long-term inhibitory effect of ibrutinib may guide for future clinical management of this condition.

Incidence of Ibrutinib-Induced Ventricular Arrhythmia

In addition to AF, ventricular arrhythmia (VA) also results in a significant burden of arrhythmia, leading to high rates of medication discontinuation and morbidity in the patient population. The use of ibrutinib has been constantly associated with recurrent polymorphic ventricular tachycardia and sudden death.⁴¹ Severe electrical storms have also been thought to be associated with ibrutinib.⁴⁰ Limited information is available on ibrutinib-induced VA compared with ibrutinib-induced AF. In

a single-center retrospective data analysis including 72 patients, 43% were documented with non-sustained ventricular tachycardia. Long-term follow-up of the incidence of symptomatic VAs was investigated using data from patients in the registry cohort. The results revealed that 11/582 patients developed VA symptoms, 7 of whom had a probable association with ibrutinib.⁷⁰ A disproportionality analysis using the Vigibase database (the EROCA study) identified 0.52% VAs in 13,572 individual case safety reports, with a median onset time of 70 days, ranging from 28.5 to 152.5 days. Furthermore, rare unexplained sudden cardiac death may occur.²⁶ Heart failure was also observed with a median time of 54 days. Concerns about ibrutinib-associated VAs have been emerged as a result of an increasing trend reported in the Vigibase database. Moreover, the occurrence of VAs was associated with older age in the spontaneously hypertensive rats.⁷¹

Incidence of Ibrutinib-Induced QT Interval Changes

According to current clinical trials, the effect of ibrutinib on other electrocardiographic parameters has been controversial, and this aspect has thus attracted less attention compared with other cardiac arrhythmias. In the EROCA study, QT interval prolongation was detected in 0.07% patients, and no correlation between the medication and cardiac repolarization was noted.²⁶ However, in another study, Fradley et al retrospectively analyzed 137 patients and found that the incidence of short QT intervals tended to increase after ibrutinib exposure.⁵⁹ Furthermore, a sequential administration of single doses of therapeutic and super-therapeutic concentrations of ibrutinib revealed that ibrutinib shortened the QTc interval and prolonged the PR interval, which was consistent to the results from the Phase 1b/2 study 1102.⁷² In conclusion, QT interval change is not strongly correlated with ibrutinib-induced cardiotoxicity.

Incidence of Other Cardiac Complications or Cardiomyopathy

Despite much focus on ibrutinib-induced arrhythmias, little information is available from individual case reports on ibrutinib-associated cardiomyopathy that is irrelevant to arrhythmias. Reversible nonischemic cardiomyopathy was reported to be associated with the use of ibrutinib. Systolic dysfunction, deterioration of the left ventricular ejection fraction, and reversible heart failure were probable symptoms.^{42,73,74} Takotsubo cardiomyopathy (TC), also called *apical ballooning syndrome or stress cardiomyopathy*, was a reported adverse effect in patients with cancer treated with TKIs.⁷⁵ A case report described mid-cavitary Takotsubo cardiomyopathy post ibrutinib therapy.⁴³

Cardiac disorders are a common condition seen in the ibrutinib-treated cancer population because of multiple shared risk factors. Although AF remains a major concern in ibrutinib-related cardiotoxicity, an increasing number of case reports documenting cardiomyopathy and sudden death at home have been published to describe long-term outcomes⁷⁶ (Figure 1A). The intrinsic relationship between arrhythmia and heart failure remains difficult to define.

Mechanisms of Ibrutinib-Induced Cardiotoxicity

Ibrutinib has demonstrated impressive efficacy against at least 19 kinases, including BTK, tyrosine kinase expressed in hepatocellular carcinoma (TEC), vascular endothelial growth factor (EGFR), B-lymphoid tyrosine kinase (BLK), bone marrow kinase on the X chromosome (Bmx), C-terminal Src kinase (CSK), fetal growth restriction (FGR) and Janus kinase 3 (JAK3) (Table 1).^{77–79} Multiple mechanisms have been documented regarding the pathogenesis of ibrutinib-induced arrhythmia in both on- and off-target effects (Figure 1B).

On-Target Effect of the Cardiotoxic Adverse Events

Atrial-Specific Pro-Arrhythmic Effect of Ibrutinib

Although ibrutinib presents an atrial-specific pro-arrhythmic effect in the clinical trials and real-world studies, it is hard to reproduce the drug response with a predominance of ventricular cells in the in-vitro model. A stem cell-derived cardiomyocyte model was used to investigate ibrutinib-induced AF in vitro.⁸⁰ Unlike acalabrutinib and tirabrutinib, which are second-generation BTK inhibitors, ibrutinib demonstrated atrial-specific pro-arrhythmic effect not observed in ventricular cardiomyocytes. The number of differentially expressed genes was markedly decreased in the RTK pathway after treatment with ibrutinib, followed by a decrease in action potential duration (APD₈₀) and increased calcium transient duration (CaTD₈₀). A mouse model also suggested that the arrhythmogenic mechanisms are associated with structural remodeling and Ca²⁺ handling disorders in the atrium.⁸¹ These

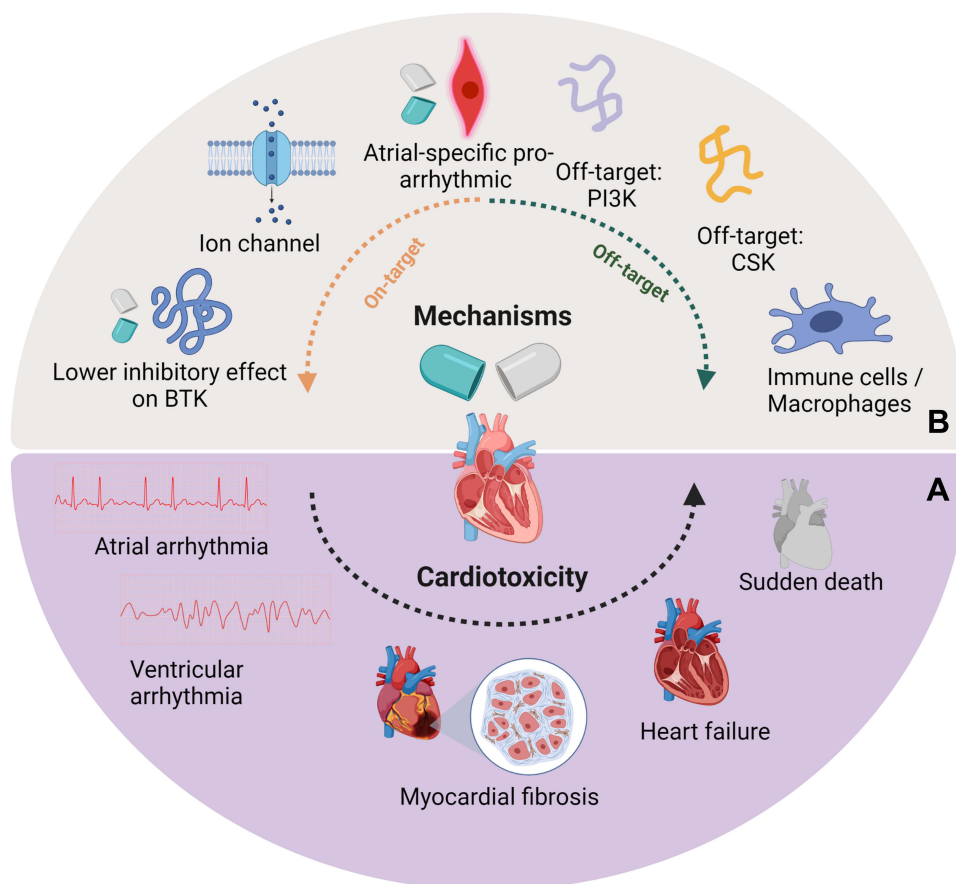


Figure 1 (A) Schematic diagram of the ibrutinib-induced cardiotoxicities. Ibrutinib is associated with several cardiotoxicities: atrial arrhythmias, mainly atrial fibrillation; ventricular arrhythmias. Serious ventricular tachycardia may cause sudden death. Myocardial fibrosis and injury are also reported in the clinical trials and research studies. **(B)** Schematic diagram of the mechanism of ibrutinib-induced cardiotoxicity. Both on- and off- target effects are involved in the ibrutinib-induced cardiotoxicities. Ibrutinib present and atrial-specific pro-arrhythmic effect. Ion transient disturbance was noticed in the chamber-specific toxicity. Low inhibitory effect of ibrutinib on target kinase is considered be another on- target effect, but clear evidence is still needed to address the issue. PI3K- and CSK- related signaling pathway inhibition are linked to ibrutinib-induced cardiotoxicity in an off-target aspect. Macrophages are also hypothesized to participate in the cardiotoxicity. Created with BioRender.com.

Abbreviations: BTK, Bruton tyrosine kinase; CSK, C-terminal Src kinase; PI3K, Phosphoinositide-3 kinase.

results provide another off-target possibility for ibrutinib with respect to its chamber-specific cardiotoxicity and disturbance of ion transient.

Lower Inhibitory Effect of Ibrutinib on Target Kinase

The relation between ibrutinib's inhibitory effect on BTK and its pro-arrhythmia is controversial. No clear evidence has been shown to prove the issue. The first head-to-head comparison of two irreversible BTK inhibitors, namely ibrutinib and acalabrutinib, revealed that a 100-mg twice-daily dose of acalabrutinib resulted in noninferior PFS with fewer cardiovascular adverse events compared with ibrutinib.⁸² As ibrutinib can irreversibly bind to BTK and non-BTK kinases with analogous cysteine residues at lower nanomolar concentrations, it is presumed that an on-target effect may be contributing to the observed cardiotoxic adverse events. However, in another phase 3 trial of zanubrutinib vs ibrutinib, ibrutinib patients experienced a 10-fold higher incidence of atrial fibrillation than zanubrutinib patients, while zanubrutinib exhibited a higher degree of selectivity of BTK. As we conclude in [Table 1](#), the safety and tolerability profiles of BTK inhibitors may be consistent with high selectivity vs off-target kinases.

Table 1 The IC₅₀ of Approved Irreversible BTK Inhibitors

Drug Name	On-Target Activity: BTK IC ₅₀ (nM)	Off-Target Activity	Diseases
Ibrutinib	0.5	ITK: 11, TEC: 78 BLK: 0.5 Bmx: 0.8 CSK: 2.3 FGR: 2.3 JAK3:3.9 HER2: 9.4	CLL, MCL, WM, MZL, SLL, cGVHD
Zanubrutinib	0.3	ITK: 56, TEC: 2 JAK3: 200 HER2: 661	MCL, CLL, WM, SLL
Acalabrutinib	3	-	MCL, CLL
Tirabrutinib	2.2	TEC: 5.3	PCNSL
Orelabrutinib	1.6	-	MCL, CLL, SLL

Abbreviations: BTK, Bruton's kinase tyrosine; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; WM, Waldenström macroglobulinemia; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; cGVHD, chronic graft-versus-host disease; PCNSL, primary central nervous system lymphoma; ITK, interleukin-2 inducible T-cell kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma; BLK, B-lymphoid tyrosine kinase; Bmx, bone marrow kinase on the X chromosome; CSK, C-terminal Src kinase; FGR, fetal growth restriction; JAK3, Janus kinase 3; HER2, human epidermal growth factor receptor 2.

Off-Target Effect of the Cardiotoxic Adverse Events

Involvement of the PI3K Pathway

Upon activation by antigen binding, BTK can be phosphorylated by upstream SYK or LYN, activating the downstream NF- κ B and phosphatidylinositol 3-kinase (PI3K) cascades.^{83–86} PI3K(p110 α) activation is a key regulator in sinus rhythm maintenance.⁸⁷ According to the study of Jenny et al, the expression of BTK and TEC was higher in AF tissue than in the normal heart.⁸⁸ When ibrutinib impaired the activity of PI3K/Akt, patients were highly susceptible to AF. PI3K was also hypothesized to increase susceptibility to VAs via disruption of calcium cycling and membrane repolarization in a spontaneously hypertensive rat model.⁷¹ These observations highlight that the cardiotoxicity of ibrutinib is an off-target adverse effect.

Involvement of C-Terminal Src Kinase (CSK)

In a study by Xiao et al, an off-target effect for AF induction was also identified as the mechanism leading to AF.⁸⁹ Chemoproteomic kinase profiling of ibrutinib and acalabrutinib, which has a low cardiotoxicity profile, was performed to screen the potential mechanism associated with AF. The results revealed CSK as the culprit. In a previous study using a transgenic mouse model, it was suggested that CSK loss in the myocardium led to an increase in AF susceptibility. Pharmaceutical profiling of the CSK inhibitor also confirmed that kinase inhibitors with higher C_{max}/IC₅₀ values had the tendency to induce AF.⁸⁰

Role of Macrophages in the Ibrutinib-Induced Cardiotoxicity

It is worth mentioning that infiltration of macrophage lineage cells was detected in an acute toxicity mouse model of ibrutinib, reminding us that macrophages are involved in other immunotherapies associated with cardiotoxicity, such as PD-1 antibodies and CTLA-4 inhibitors.^{90,91} Latest studies have unmasked the role of macrophages in the normal functioning of the heart. For example, tissue-resident macrophages in the normal myocardium were found to couple

electrically to cardiomyocytes via the connexin-43-containing gap junctions and facilitate their electrical activity.⁹² They also have also been proved to be involved in mitochondrial elimination from the myocardial tissue and in the preservation of metabolic homeostasis.⁹³ The anthracycline-based cancer drug doxorubicin, which was notorious for its dose-dependent cardiotoxicity and heart failure side effects, was found to intoxicate splenic marginal zone macrophages, thereby causing splenic contraction and impairing the immediate deployment of monocytes.⁹⁴ Interestingly, ibrutinib treatment was reported to sustain the M2 macrophage population and immunosuppressive profile of nurse-like cells in CLL patients, whereas it inhibited M2 macrophage activation in a BTK-PI3K γ -dependent manner in patients with pancreatic ductal adenocarcinoma.^{95,96} In a zymosan-induced peritonitis model of sterile inflammation, BTK inhibition was correlated with reduced C5a and CCL2 levels, both of which regulate myeloid cell recruitment.⁹⁷ As BTK is predominantly expressed in immune cells including macrophages, it is logical to hypothesize that macrophages may actively be involved in ibrutinib-induced arrhythmias. Further studies may be necessary to clarify this potential involvement.

Clinical Management

Risk Factors of Ibrutinib-Induced Cardiotoxicity

Several risk factors have been implicated in ibrutinib-related cardiotoxicity in clinical trials and clinical practice. A retrospective study of 242 patients receiving ibrutinib or another chemotherapy drug was performed to quantify the real-world incidence rates and risk of AF. The results revealed that prior hypertension, ACEI/ARB use, beta-blocker use, and aspirin use were associated with increased AA incidence.⁹⁸ Prior history of AF, enlarged left atrial diameter and age over 65 years were also variables associated with the development of ibrutinib induced adverse effects.³⁴

Evaluation of Ibrutinib-Induced Cardiotoxicity

Cardiovascular magnetic resonance imaging (CMR) or echocardiography has also been recommended for assessment of the myocardial injury.⁹⁹ A single-center study examined the relationship between myocardial damage and myocardial strain using cardiac biomarkers. The findings revealed that evaluating myocardial strain in conjunction with measuring high-sensitive troponin T is useful for detecting early cardiac drug toxicity secondary to ibrutinib.^{100,101}

For patients with AF, clinical assessment should be performed to estimate the risk of bleeding and stroke. The CHA₂DS₂-VASc or HAS-BLED scoring systems could provide a guide to control this issue. For patients with a low score, mainly CHA₂DS₂-VASc 0 or 1, it is recommended to continue the use of ibrutinib.^{102–104} However, for patients with more than two risk factors, or a score of ≥ 2 , discontinuation of ibrutinib is an optional choice. Although the bleeding risk can also be accessed via the HAS-BLED scoring systems, it is not always appropriate for patients with cancer, according to the European Society of Cardiology position paper. This is because, neither the CHA₂DS₂-VASc nor the HAS-BLED scoring systems consider cancer-specific high-risk bleeding characteristics.¹⁰⁵ Treatment should be patient-customized to manage the bleeding and stroke associated with ibrutinib use.¹⁰⁰

Considerations with Anticoagulants

Patients with ibrutinib-induced AF have a substantially increased risk of stroke, heart failure, and all-cause death, the optimal strategies to prevent or treat this condition remain uncertain.¹⁰¹ In cases where stroke and thromboembolism are major concerns, the selection of systemic anticoagulation agent should be based upon the risk and benefit for a given patient. The intravenous administration of low-molecular-weight heparin (LMWH) is frequently used but required close monitoring. Traditional vitamin K antagonists, mainly warfarin, should be avoided, as an increased rate of subdural hematomas has been reported in MCL patients.²¹ Direct oral anticoagulants (DOACs), such as apixaban, rivaroxaban, or dabigatran, are introduced in the management of AF. In some cases, low dose of aspirin has also been used. Nevertheless, ibrutinib is also associated with bleeding, and it is possible that significant bleeding complications may emerge with concomitant use of anticoagulants or antiplatelets.¹⁰⁶ Over-the counter supplements, such as vitamin E or fish oil, are not acceptable, either.¹⁰⁴

Rate Control vs Rhythm Control

Paroxysmal and asymptomatic AF patients without continuous electrocardiogram monitoring are less likely to be and yet need to be handled by oncologists; however, it is hard to make the decision for cases of symptomatic AF, such as those with palpitations and fluttering. In the case report by Essa, the Atrial Fibrillation Better Care (ABC) pathway was recommended to provide a holistic management for AF patients. Factors favoring rhythm control were as follows: 1) hemodynamic instability; 2) younger cancer patients without structural heart disease; 3) AF secondary to correctable causes; and 4) persistent symptoms despite medical management.¹⁰⁷ A retrospective descriptive study reviewed patients with rhythm-controlled strategies. In that study, amiodarone, flecainide, digoxin and dofetilide were used as rhythm-controlled medication. The Cleveland experience suggests temporarily hold ibrutinib and reintroducing it at either a full or reduced dose after the AF is controlled.¹⁰⁸ Patients with advanced disease and palliative care, proarrhythmogenic chemotherapeutics, drug interactions or frailty were better provided with a rate control policy. Pertaining to rate control, the majority of studies selected a beta-blocker over nondihydropyridine calcium channel blockers (verapamil and diltiazem) or P-glycoprotein substrates (amiodarone).

Drug–Drug Interactions

Ibrutinib is metabolized by the CYP 3A4.¹⁰⁹ For this reason, co-administration of ibrutinib with cytochrome inhibitors should be avoided. Considering the drug–drug interactions of CYP 3A4/5, cardiologist often chose beta-blockers as the first-line therapy. Calcium channel blockers such as diltiazem and verapamil, which inhibit CYP 3A4, increased the concentration of ibrutinib. Amiodarone also inhibits cytochrome 3A4 and can increase the serum concentration of ibrutinib. Ketoconazole is a strong CYP 3A4 inhibitor. In a dedicated drug–drug interaction trial, ketoconazole was found to increase ibrutinib C_{max} by 29-fold and AUC by 24-fold.^{39,109} Ibrutinib also inhibits P-glycoprotein, as well as increases the intracellular concentration of P-glycoprotein substrates, such as digoxin and dabigatran.

Adjustment of Drug Intensity

It remains controversial whether it is appropriate to modify or temporarily interrupt the drug intensity. A clinical trial to examine the impact of prolonged dose delays and reductions in the RESONATE study was conducted, and the results suggested that adherence to the recommended ibrutinib dosage correlated with a higher PFS and improved OS.⁴⁷ When encountered with adverse event management or perioperative holds, dose reduction or interruption are inevitable. In Xiao's work, the *in vitro* chemoproteic profiling experiments demonstrated that the C_{max}/IC₅₀ values were strongly associated with the manifestation of AF adverse effects.⁸⁹ Pertaining to the pharmacology aspect, ibrutinib achieved full occupancy at a dose of 2.5 mg/kg, while the proposed dose of ibrutinib in CLL patients equates to a mean dose of 7.22/kg/day. A pilot study identified a step-down dose cycle, from 420 mg to 280 mg and 140 mg, which did not impact BTK occupancy, and biological and molecular consequences in CLL cells, which is in agreement with the real-world experience from a retrospective analysis where reduced did not affect PFS or OS.^{110–113} Further evidence showed that BTK expression decreased in a time-dependent manner with the prescription of ibrutinib compared with baseline, which supports the lower doses of ibrutinib administration in future clinical management.¹¹⁴

Alternative Treatment Options and Their Cardiotoxicity

Given the crucial role of BTK in B cell maturation and success of ibrutinib, four additional BTK inhibitors have been approved globally and more than 70 inhibitors are currently undergoing clinical or preclinical trials. Second-generation irreversible BTK inhibitors include acalabrutinib, tirabrutinib, zanubrutinib, and orelabrutinib, all of which demonstrated well tolerability regarding cardiovascular diseases (Table 2).^{115–118} Acalabrutinib was approved by the US Food and Drug Administration in 2017 for the treatment of patients with CLL, SLL, or R/R MCL. The IC₅₀ of acalabrutinib of BTK *in vitro* is 3 nM. In a previous study, among the acalabrutinib monotherapy-treated CLL patients, AF was reported in 2 out of 25 patients.¹¹⁵ Long-term data revealed its durable efficacy and safety with a 2% rate of AF-related adverse events.¹¹⁹ A phase 2 study of acalabrutinib in ibrutinib-intolerant patients with R/R CLL demonstrated an ORR of 73% with a median PFS that did not reach the demonstrated durable disease control.¹²⁰ Neither AF nor arrhythmias were included among the most frequent adverse events associated with acalabrutinib use in this population, although two patients experienced a lower grade AF. Zanubrutinib

Table 2 Clinical Trials of Approved BTK Inhibitors Monotherapy

Drug Name	Disease	N	PFS	AA	Reference
Zanubrutinib	R/R MCL	112	25.8	1.8%	[117]
	R/R CLL/SLL	91	NR	0	[126]
	CLL/SLL	123	Estimated 90% at 2 years and 83% at 3 years	4.9%	[127]
	R/R WM	44	60.5% at 2 years	0	[128]
Acalabrutinib	CLL	25	3.2 months	8%	[115]
	CLL	99	Estimated 90% at 4 years	5%	[119]
	R/R CLL	134	Estimated 62% at 45 months	3%	[129]
	WM	106	24-month PFS 90% in naïve and 82% in R/R	5%	[130]
	MCL	124	24-month PFS 49%	0	[131,132]
	Relapsed CLL	61	20-month PFS 95%	0	[133]
Tirabrutinib	Pemphigus	16	CR at 52w, 50%	0	[134]
	WM	27	ORR: 96.3%	0	[135]
	R/R NHL, CLL	17	ORR: 76.5%	0	[136]
	CLL	90	38.5	0	[137]
Orelabrutinib	R/R MCL	86	57.7%	0	[138]

Abbreviations: BTK, Bruton kinase tyrosine; R/R, relapsed/refractory; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; WM, Waldenstrom's macroglobulinemia; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; NR, not reach; CR, complete response; ORR, overall response rate; AA, atrial arrhythmia.

Table 3 Clinical Trials of Head-to-Head Comparison of Approved BTK Inhibitors

Drug Name	Disease	N	PFS	AA	Reference
Ibrutinib vs Acalabrutinib	CLL	265 vs 268	38.4 months vs 38.4 months	5.3% vs 2.3%	[82]
Ibrutinib vs Zanubrutinib	WM	99 vs 102	84% vs 85%	15% vs 2%	[121]

Abbreviations: BTK, Bruton tyrosine kinase; PKC, protein kinase C; TH, Tec homology; PH, pleckstrin homology; SH3, Src homology 3; SYK, spleen tyrosine kinase; Pin 1, protein interacting with NIMA 1; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; PFS, progression-free survival; IGHV, immunoglobulin heavy chain; MCL, mantle cell lymphoma; ORR, overall response rate; WM, Waldenstrom's macroglobulinemia; COVID-19, coronavirus disease 2019; AF, atrial fibrillation; C_{max}, maximum concentration; AUC, area under curve; PK, pharmacokinetic; DHI, dihydrodiol ibrutinib; ICIs, checkpoint inhibitors; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed cell death protein 1; TKIs, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor receptor; BCR, B cell receptor; AA, atrial arrhythmia; RCTs, random clinical trials; VA, ventricular arrhythmia; TC, Takotsubo cardiomyopathy; TEC, tyrosine kinase expressed in hepatocellular carcinoma; EGFR, epidermal growth factor receptor; BLK, B-lymphoid tyrosine kinase; Bmx, bone marrow kinase on the X chromosome; CSK, C-terminal Src kinase; FGR, fetal growth restriction; JAK3, Janus kinase 3; RTK, receptor tyrosine kinase; APD, action potential duration; CaTD, calcium transient duration; CCL2, CC chemokine ligand 2; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DOACs, direct oral anticoagulants; OS, overall survival; NR, not reach; CR, complete response; ORR, overall response rate; NHL, non-Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; HER2, human epidermal growth factor receptor 2; ITK, interleukin-2 inducible T-cell kinase; CLL, chronic lymphocytic leukemia; WM, Waldenstrom's macroglobulinemia; AA, atrial arrhythmia.

is a highly selective second-generation irreversible BTK inhibitor developed by the Chinese company Beigene. Structural differences in the pyrimidine ring make zanubrutinib more selective than ibrutinib, with a 10-fold lower IC₅₀ concentration. Pooled analysis to explore the efficacy of zanubrutinib monotherapy demonstrated an equally efficacious and favorable safety profile in R/R MCL patients.¹¹⁷ A trial comparison of acalabrutinib and ibrutinib revealed that acalabrutinib had noninferior PFS with fewer cardiovascular adverse events.⁸² The ASPEN study assessed the effect of zanubrutinib versus ibrutinib on symptomatic WM patients and found that zanubrutinib had a higher rate of complete response and a lower cardiotoxicity profile compared with ibrutinib (Table 3).¹²¹ As data continue to accumulate, more direct head-to-head comparisons will provide a better insight into the selection of BTK inhibitors.

Prospects and Conclusions

Cardiovascular diseases are the second leading cause of morbidity and mortality in cancer patients, next to the development of a second malignancy.¹²² Arrhythmias are a pivotal complication associated with unique management challenges in patients with cancer. Not only atrial and VAs but also other electrolyte abnormalities, such as QT interval changes, are the most common drug related side effects. Among them, AF is a leading cause of significant thrombotic morbidity and overall cardiovascular mortality. AF has become an increasingly common concern, particularly in older patients diagnosed with cancer. In a multi-ethnic representative cohort of patients with early- and late-stage breast cancer, patients with AF onset after 1 year from the onset of breast cancer had a higher mortality rate than patients with new-onset AF.¹²³ Cardiotoxicity from chemotherapies has recently attracted considerable attention from clinicians. The growing awareness of cancer therapy-related cardiac dysfunction has led to the emergence of cardio-oncology.^{124,125} Its goal is to provide optimal prevention and treatment of cancer therapy-related cardiotoxicity and present a better understanding of the relationship between cancer therapeutics and cardiac function.

As data continue to emerge regarding the use of next-generation BTK inhibitors, idiosyncratic drug-specific toxicities may arise, including ibrutinib-related cardiotoxicity, acalabrutinib-related headache or zanubrutinib-related neutrophilia. The unique cardiotoxicity of ibrutinib does not appear to be class-related specific adverse events as lower rates are reported with the use of second-generation BTK inhibitors. Studies have reported that direct comparison data and longer follow-up periods are required to elucidate the safety profile of BTK inhibitors. Furthermore, the continuous and increasingly more common use of selective inhibitors may provide a greater insight into the specific mechanism pertaining to the on-/off-target cardiotoxicity of ibrutinib. To date, ibrutinib remains the most widely used BTK inhibitor which takes up to approximately 97% of market share. Patients or their caregivers should be appropriately informed about cardiotoxicity when initiating therapy. However, it is still too early to make any decision and choose new inhibitors.

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Disclosure

The authors declare that they have no competing interests.

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