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EDITORIAL COMMENT

Deciphering the Electrophysiological Mechanisms for Ibrutinib-Induced Ventricular Arrhythmias*

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Ibrutinib, an oral irreversible Bruton's tyrosine kinase inhibitor, is rapidly becoming the treatment of choice for patients with chronic lymphocytic leukemia, Waldenström macroglobulinemia, mantle cell lymphoma, and marginal zone lymphoma, as well as chronic graft-versus-host disease (1). While generally well tolerated, ibrutinib is associated with bleeding and increased risk of infection. A recent meta-analysis of randomized clinical trials found that ibrutinib recipients are at ~4-fold increased risk for developing atrial fibrillation (AF) as compared with other cancer therapeutics (1,2). In 2002, a study assessed the effects of tyrosine kinase inhibitors on the cardiac sodium current (I_{Na}) and showed that phosphorylation of this pathway plays an important role in regulating the current in rabbit ventricular cardiomyocytes (3). Furthermore, tyrosine kinase inhibitors not only reversibly inhibited I_{Na}, but they also significantly prolonged the time course of sodium channel recovery from inactivation. Recent studies have also shown that calmodulin kinase II and protein kinase C mediate the effect of increased intracellular calcium to enhance the late $I_{Na\text{-}L}$ in cardiomyocytes (4,5). Collectively, these studies support the hypothesis that enhanced $I_{Na\text{-}L}$ in part mediates ibrutinib-associated AF. Another potential mechanism by which ibrutinib may increase AF risk is by regulating the phosphoinositide 3-kinase–Akt pathway, important for stress-induced cardiac protection (6) with a recent report showing that both Bruton tyrosine kinase and related kinases reduced phosphoinositide 3-kinase–Akt activity in a transgenic mouse model associated with AF (7,8).

Although animal and clinical studies have reported an association between ibrutinib and development of ventricular arrhythmias and sudden cardiac death, the underlying molecular mechanisms are poorly understood (3,4). Importantly, the role of age and hypertension, known risk factors for the development of AF, in ibrutinib-induced ventricular arrhythmias is unknown. In this issue of *JACC: CardioOncology*, Du et al. (9) hypothesized that ibrutinib increases susceptibility to ventricular arrhythmias by calcium cycling dysfunction and membrane repolarization dysregulation in hearts with advanced age and cardiomyopathy. The elegant set of studies using state-of-the-art mapping techniques examined the acute effects of ibrutinib on ventricular arrhythmia susceptibility, cytosolic calcium dynamics, and membrane electrophysiology in young (10 to 14 weeks) and old (10 to 14 months) spontaneous hypertensive rats (SHRs). The investigators showed that acute treatment with ibrutinib failed to induce ventricular fibrillation in young SHRs but did so in old SHR hearts with enhanced action potential duration (APD) alternans and APD spatial discordance, longer calcium transient duration 50, lower calcium amplitude alternans ratio, and shorter time-to-peak calcium amplitude. In contrast, ibrutinib treatment in young SHRs failed to alter calcium and APD dynamics.

The study findings are novel, provide insights into the underlying molecular mechanisms by which ibrutinib increases susceptibility to ventricular arrhythmias and may have important clinical implications for

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patients treated with this Bruton's tyrosine kinase inhibitor for cancer. This is the first study to show that acute treatment with ibrutinib enhances spatially discordant APD alternans, a recognized risk factor for arrhythmias and sudden cardiac death, in old SHRs but not in the young. Spatially discordant alternans is particularly arrhythmogenic as it likely converts standard repolarization heterogeneity to become "pathological" creating conduction block and functional re-entry for ventricular fibrillation. Furthermore, a longer calcium transient duration 50 suggests abnormalities in ryanodine receptor 2 activity and a shorter time-to-peak implicates calcium overload and generation of delayed afterdepolarizations, respectively. However, Du et al. (9) showed no changes in the phosphorylation and expression of ryanodine receptor 2, phospholamban, SERCA2a, and other calcium handling proteins. This may in part relate to acute treatment with ibrutinib as chronic treatment enhances calmodulin kinase II expression and phosphorylation of ryanodine receptor 2 (10). Thus, the study findings implicate mechanisms other than phosphorylation of calcium regulatory proteins by which acute ibrutinib treatment induces ventricular arrhythmias.

Adenosine monophosphate-activated protein kinase (AMPK) is a potential pathway by which acute ibrutinib treatment may mediate dysregulation of calcium handling proteins as it activates Akt under metabolic stress and studies have shown that ibrutinib reduces phosphoinositide 3-kinase-Akt activity in cardiomyocytes (8,11). However, Du et al. (9) showed that acute ibrutinib treatment did not change the expression and phosphorylation of AMPK in old SHR hearts. Whereas this may in part relate to reduced AMPK reserve in old SHRs, it is also possible that changes in AMPK involve translocation between subcellular compartments, which is difficult to assess experimentally. Thus, we cannot completely rule out the possibility of AMPK-Akt pathway involvement in mediating ibrutinib-induced changes in calcium handling proteins. Nonetheless, the electrophysiological mechanisms by which both acute and chronic ibrutinib treatment alters calcium transients and dynamics and predisposes to ventricular arrhythmias remains unclear and requires further investigation. Understanding the underlying molecular mechanisms by which ibrutinib predisposes individual patients to increased risk of ventricular arrhythmias is not only important for risk stratification but may also affect their management as the proarrhythmic effects are potentially life-threatening.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood 2016;128:138–40.

2. Byrd JC, Brown JR, O'Brien S, et al. for the RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213–23.

3. Wang Y, Wagner MB, Kumar R, Cheng J, Joyner RW. Inhibition of fast sodium current in rabbit ventricular myocytes by protein tyrosine kinase inhibitors. Pflugers Arch 2003;446:485–91.

4. Ma J, Luo A, Wu L, et al. Calmodulin kinase II and protein kinase C mediate the effect of increased intracellular calcium to augment late sodium current in rabbit ventricular myocytes. Am J Physiol Cell Physiol 2012;302:C1141–51.

5. Qian C, Ma J, Zhang P, et al. Resveratrol attenuates the Na(+)-dependent intracellular Ca(2+) overload by inhibiting H(2)O(2)-induced increase in late sodium current in ventricular myocytes. PLoS One 2012;7:e51358.

6. McMullen JR, Amirahmadi F, Woodcock EA, et al. Protective effects of exercise and phosphoinositide 3-kinase(p110alpha) signaling in dilated and hypertrophic cardiomyopathy. Proc Natl Acad Sci U S A 2007;104:612–7.

7. Pretorius L, Du XJ, Woodcock EA, et al. Reduced phosphoinositide 3-kinase (p110alpha) activation increases the susceptibility to atrial fibrillation. Am J Pathol 2009;175:998–1009.

8. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood 2014;124:3829–30.

9. Du B, Chakraborty P, Azam MA, et al. Acute effects of ibrutinib on ventricular arrhythmia in spontaneously hypertensive rats. J Am Coll Cardiol CardioOnc 2020;2:614–29.

10. Jiang L, Li L, Ruan Y, et al. Ibrutinib promotes atrial fibrillation by inducing structural remodeling and calcium dysregulation in the atrium. Heart Rhythm 2019;16:1374–82.

11. Sharif-Askari B, Doyon D, Paliouras M, Aloyz R. Bruton's tyrosine kinase is at the crossroads of metabolic adaptation in primary malignant human lymphocytes. Sci Rep 2019;9:11069.

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