Response

Additional data needed for a better understanding of the potential relationship between atrial fibrillation and ibrutinib

Atrial fibrillation (AF) is a common cardiac arrhythmia observed in elderly patients who are representative of those who require therapy for chronic lymphocytic leukemia. A higher frequency of AF was noted with ibrutinib in the RESONATE phase 3 trial comparing the covalent Bruton's tyrosine kinase inhibitor vs ofatumumab.[1] In an attempt to address a possible role of ibrutinib in this process, McMullen et al[2] used a specific mouse model to evaluate the inhibition of the related phosphatidylinositol 3-kinase (PI3K) pathway and susceptibility to AF in dilated cardiomyopathy with depressed left ventricular function. Limitations of this study include species- and disease-specific electrophysiologic properties of cardiac cells that can lead to major functional differences between human and nonhuman heart.[3,4] To the best of our knowledge, there is no evidence of the inhibition of PI3K p110 alpha (p110α) activity by ibrutinib in vivo or in vitro. The lack of a clear dose response for ibrutinib (Figure 1B[2]) suggests that these effects may not be directly related to inhibition of PI3Kα by ibrutinib. Moreover, the expression of many genes in the atrium are different when AF and sinus rhythm are compared.[5-7] Such changes observed by the authors (Figure 1A[2]) could reflect underlying susceptibility to AF or could be a reflection of AF itself. Furthermore, the authors present no functional evidence for an effect of ibrutinib on myocytes or direct evidence for the role of Bruton's tyrosine kinase.

When evaluating the differences in the rate of AF in the RESONATE study, the relatively small numbers of AF events and the fact that duration of exposure to ibrutinib was approximately twice that for ofatumumab (mean, 8.6 vs 4.3 months) must be considered. AF events were reported in older patients (median age, 73 years), particularly those with cardiac risk factors, acute infection, and/or a history of AF. Among patients enrolled in RESONATE, the proportion of patients with a medical history of AF was higher in the ibrutinib arm (11 patients; 5.6%) vs ofatumumab (5 patients; 2.6%). AF reported in the context of ibrutinib has generally been manageable and not therapy limiting.[1,8-10] Six of 10 AF events in the RESONATE study resolved during follow-up, and 4 were considered ongoing at the time of the interim analysis. AF events were typically of short duration, frequently 1 to 2 days (range, 1 to 11 days), with only 1 patient permanently discontinuing ibrutinib because of AF.[1] Further clarification of the risk of AF is required in other patient groups, particularly in patients with fewer comorbidities; these data will soon be available from a number of randomized controlled phase 3 trials that are under way.

It is important to interpret any risk of AF within the context of the significant clinical benefits of ibrutinib. Specifically, on the RESONATE trial, ibrutinib significantly reduced the rate of progression or death by 78% (hazard ratio, 0.22; $P < .001$) and the rate of death by 57% (hazard ratio, 0.43; $P = .005$) compared with ofatumumab.[1] Thus, the clinical benefit-risk profile remains favorable for ibrutinib treatment in light of the AF events observed in the RESONATE trial. Prior history of AF or development of this medical condition while receiving ibrutinib neither prohibits use of nor necessitates discontinuation of treatment with this effective therapy. Additional data on the use of anticoagulants (if necessary) for AF in the context of ibrutinib therapy are needed for the optimal management of these patients.

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