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CLINICAL TRIALS AND OBSERVATIONS

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Cardiovascular adverse events of ibrutinib

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In this issue of *Blood*, Dickerson et al report on the increased incidence and worsening severity of hypertension and its association with cardiovascular outcomes in 562 patients treated with ibrutinib for B-cell malignancies.[1]

Targeting Bruton tyrosine kinase (BTK) is an effective treatment strategy for patients with B-cell malignancies. Ibrutinib, a first-in-class BTK inhibitor, covalently binds to the cysteine 481 residue in the adenosine triphosphate binding site of BTK, which is a member of the Tec kinase family. Ibrutinib also binds to other Tec kinases such as ITK[2] and ErbB family kinases such as EGFR and HER2,[3] which all harbor a cysteine residue at the homologous active site. These unintended binding sites of ibrutinib, as well as its indirect effects on other signaling pathways such as PI3K/AKT, have been proposed as mechanisms of ibrutinib toxicities, particularly atrial fibrillation and hypertension. The incidence of atrial fibrillation was 3.3 per 100 person-years in a pooled analysis of 4 randomized trials for ibrutinib.[4] Hypertension has been reported in up to 30% of the patients treated with ibrutinib (see table). More recently, a 3-arm randomized trial comparing ibrutinib, ibrutinib plus rituximab, and chemoimmunotherapy reported higher incidences of grade 3 to 4 hypertension in the ibrutinib arms.[5] To date, it has been

Selected studies reporting the incidence of hypertension and atrial fibrillation in patients on ibrutinib monotherapy

Cohorts*	N†	Median follow-up (mo)	Hypertension, any (% or person-years)	Hypertension, grade 3-4 (%)	Atrial fibrillation, any (%)	Comment
Dickerson et al and the Framingham cohort						
Dickerson et al (entire cohort)	562	30	78%	38	13	BP cutoff for hypertension: ≥130/80 mmHg
Dickerson et al (subset)‡	157	30	442/1000 person-years§	NR	NR	BP cutoff for hypertension: ≥140/90 mmHg
Framingham (subset)‡	NR	NR	34/1000 person-years§	NR	NR	BP cutoff for hypertension: ≥140/90 mmHg
Other studies						
RESONATE[7]	195	44	NR	8	11	
RESONATE-2[8]	136	29	NR	5	10	
RESONATE-17[9]	144	28	30%	13	7	
Alliance[5]	182	32	NR	29	9	Grade 3-4 hypertension occurred more frequently in the ibrutinib arms (29%-34%) than in the chemotherapy arm (15%).
PCYC-1102/1103[10]	132	62	NR	27	11 (grade 3-4)	

NR, not reported

*Publications cited in this table are the reports with the longest follow-up to date per cohort.

†Number of patients treated with ibrutinib monotherapy (excluding patients on comparison arms in randomized studies).

‡A selected subset of each cohort who were age 20 to 69 years and had no diabetes.

§Cumulative incidence at 1 year.

unclear whether ibrutinib-related hypertension was associated with adverse clinical outcomes.

Dickerson et al retrospectively reviewed the medical records of 562 patients treated with ibrutinib at a single center and made 2 important observations regarding the cardiovascular toxicities of ibrutinib. First, new or worsening hypertension during treatment with ibrutinib was common (cumulative incidence rate, 78%) and occurred early in the treatment course (1.8 months to cumulative incidence of 50%). The mean systolic blood pressure (BP) increase was 5.2 mmHg with a wide variation within the cohort. More than 80% of the patients had at least a 10-mmHg increase in systolic BP, and 10% of the patients had a 50-mmHg increase. Why was the incidence of hypertension much higher in the Dickerson et al study than in other studies? The index of suspicion for ibrutinib being the cause of hypertension was low in earlier studies, which likely led to underreporting of hypertension as a treatment-related adverse event. Another notable part of their study is a more stringent BP cutoff chosen for a new diagnosis of hypertension, which was based on the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[6] Indeed, when the authors adjusted the BP cutoff to ≥140/90 mmHg, the incidence of new hypertension was reduced to 44%, although this number was the highest in all of published ibrutinib safety reports. The 1-year cumulative incidence rate of new hypertension was 13-fold higher among patients treated with ibrutinib compared with the Framingham cohort with comparable age and comorbidities.

The second key finding from the Dickerson et al study is that new or worsening hypertension during ibrutinib therapy was associated with an increased incidence of major adverse cardiovascular events (MACE), particularly atrial fibrillation. MACE was a composite end point that included arrhythmia, myocardial infarction, stroke, heart failure, and death, which was observed in 17% of the study cohort. MACE was associated with new or worsening hypertension in a multivariable analysis; the risk of MACE was reduced by initiating an anti-hypertensive agent (hazard ratio, 0.4). Interestingly, the majority of MACE was atrial fibrillation (13% of the cohort); ibrutinib was not associated with other MACE such as stroke and heart failure.

In summary, the study by Dickerson et al presents a thoughtful analysis of a large number of patients receiving ibrutinib, and the authors concluded that new or worsening hypertension during ibrutinib therapy can be linked to MACE, especially atrial fibrillation. Although the study has several limitations as a retrospective, single-center study, the authors' observations add new knowledge to the cardiovascular safety profile of ibrutinib and raise an interesting question on how BP and other cardiovascular risks may be managed during ibrutinib therapy. Another unmet need uncovered by this study is the need for a standardized definition of hypertension. Hypertension is defined as systolic/diastolic BP of ≥120/80 mmHg based on Common Terminology Criteria for Adverse Events, ≥130/80 mmHg by the 2017 ACC/AHA guidelines, and ≥140/90 mmHg by The European Society of Cardiology. Prospective studies focusing on age and cancer-specific analyses are needed to determine optimal BP ranges and the clinical benefit of stringent (or relaxed) BP management.

Newer generations of BTK inhibitors that more selectively target BTK have entered the clinic or are under development with the hopes of reducing toxicities and improving long-term adherence to therapy. Randomized studies comparing ibrutinib and other BTK inhibitors with different kinase selectivity are ongoing (NCT02477696 and NCT 03734016).

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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