blood advances

TO THE EDITOR:

CHIP-*JAK2V617F*, chronic inflammation, abnormal megakaryocyte morphology, organ failure, and multimorbidties

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Thank you so much for giving us the opportunity to comment on the commentary by Barosi et al titled "*JAK2V617F* and ischemic stroke: CHIP or CMD-NBV?"[1] regarding our recent article published in *Blood Advances*.[2] Barosi et al underscore several highly important features of *JAK2V617F*-associated clonal hematopoiesis of indeterminate potential (CHIP), including the increased risk of cardiovascular diseases and higher frequency of splanchnic vein thrombosis. They also underscore common knowledge that *JAK2V617F* encodes a constitutively activated tyrosine kinase in the STAT signaling pathway, which gives rise to myeloproliferation and a chronic inflammatory state. Being different from other somatic mutations, they argue that including the *JAK2V617F* mutation in the definition of CHIP is controversial. In support of their viewpoint, they refer to an article by Cassinat et al, in which the authors argued that the inclusion of *JAK2V617F* in CHIP was misleading because the *JAK2V617F* mutation in otherwise normal individuals often causes deregulated red blood cells and platelet production.[3]

We respectfully disagree with Barosi et al and are happy to address the above concerns in regard to the inclusion of the *JAK2V617F* mutation in the definition of CHIP, because we thereby also have the opportunity to argue for a biological continuum from the CHIP-*JAK2V617F* stage to the development of overt Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs). Thus, based on our experience with follow-up studies on an increasing number of the 613 individuals with *JAK2V617F* from the Danish General Suburban Population Study,[4,5] evidence is rapidly accumulating that CHIP-*JAK2V617F* steadily progresses toward MPN in a substantial proportion of individuals with CHIP-*JAK2V617F*.

Accordingly, based on our studies, a biological continuum exists from CHIP-*JAK2V617F* for decades, and in a subset of citizens, clonal expansion and evolution are recorded with associated elevated blood cell counts. Unfortunately, several such citizens or patients with elevated blood cell counts remain undiagnosed for decades and repeatedly suffer thromboembolic complications (the brain, the heart, the lungs, and elsewhere) before they are ultimately referred to a department of hematology and diagnosed with MPN. In Denmark, ~150 000 citizens carry the *JAK2V617F* mutation, and at least 10 000 citizens have undiagnosed MPN.[4,5] Accordingly, the MPNs are massively underdiagnosed chronic blood cancers. In the pre-MPN phase, they are at an increased risk of other complications and inflammation-mediated comorbidities, including early development of dementia, drusen, age-related macular degeneration, ischemic heart failure (perhaps at an increased risk of heart failure with preserved ejection fraction), hypertension including pulmonary hypertension, aneurysms, peripheral arterial insufficiency with a risk of gangrene, osteoporosis and associated increased risk of fractures, chronic nephropathy, and, not least, an increased risk of second cancers. These diseases associate with a huge health-economic burden, which calls for much earlier diagnosis and treatment of MPN at a disease stage when the "tumor burden" is at a minimum, and accordingly, the chance of successful outcome of

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stem-cell–targeting therapy with interferon-alpha2 (IFN-α2) is likely much higher than in the later myelofibrosis stage, in which *JAK2V617F*-driven chronic inflammation is prevalent along with several patients intolerant or refractory to IFN. In the context of the above considerations, implying a paradigm shift in the diagnosis and treatment of MPNs, sooner better than later, by screening of patients with a high risk of having MPN, such as patients with ischemic stroke or other cardiovascular diseases alluded to above, there is an urgent need for an interdisciplinary collaboration between hematologists, neurologists, cardiologists, and others caring for patients with chronic inflammatory diseases at risk of harboring the *JAK2V617F* mutation. We have proposed that the optimal platform for such a collaboration is a CHIP clinic,[2] where follow-up programs are designed for citizens and patients positive for CHIP-*JAK2V617F*. Thereby, we start a new era of preventive medicine by much earlier diagnosis of MPN and much earlier treatment with stem-cell–targeting therapy with IFN. At the same time, we will open a new horizon and landscape, in which a revision of the World Health Organization criteria for diagnosis of early MPN is needed to include those citizens/patients with the earliest bone marrow changes of MPN. According to our experience with bone marrow biopsies in the CHIP-*JAK2V617F* stage and in the earliest stage of MPN development,[5] these changes are seen in megakaryocyte morphology with hyperplasia and dysplasia. Therefore, we do not believe these citizens/patients have a particular subtype of MPN named "clonal megakaryocyte dysplasia with normal blood values."[6] Rather, we are convinced that they simply represent the bone marrow morphology in the CHIP-*JAK2V617F* stage or early MPN stage in those with ≥1 elevated cell counts.

As part of the MPN research program in our CHIP clinic, we have launched international studies dealing with concomitant measurements of circulating extracellular matrix (ECM) peptides[7] and bone marrow biopsy studies using artificial intelligence–based morphological fingerprinting of megakaryocytes.[8,9] By this approach, we foresee to uncover new insights into the bone marrow architecture in the CHIP-*JAK2V617F* stage and in the earliest stage of MPN development from CHIP and, perhaps, unravel even subtle bone marrow changes to be reflected in the signature of ECM peptides in peripheral blood as assessed by serial measurements of the dynamics of ECM peptides toward overt MPN development. We believe that such studies are of utmost importance to pave the way for novel standards of bone marrow assessment to be included in future improved World Health Organization diagnostic criteria and classification of MPN, using novel techniques with concurrent morphological fingerprinting of megakaryocytes,[8] continuous indexing of fibrosis,[9] and fingerprinting of circulating ECM peptides as biomarkers of inflammation, fibrosis, and neoagiogenesis in the bone marrow.[7]

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