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CORRESPONDENCE

Bone Marrow Fibrosis and Diagnosis of Essential Thrombocythemia

TO THE EDITOR: In a recent article by Campbell et al[1] published in *Journal of Clinical Oncology*, a significant association between the degree of bone marrow (BM) fibrosis at diagnosis and progression of disease as well as risk of arterial thrombosis was found in patients with essential thrombocythemia (ET). The patients reported on were mostly included in previously published studies on ET, also coauthored by Campbell.[2,3] In a broad sense, the result is in agreement with previous findings in myeloproliferative neoplasms concerning the relationships of clinical data with BM fibrosis at diagnosis and its prognostic significance.[4,5] However, there are serious issues to be raised concerning the authors' analysis of the clinical data, the criteria used to diagnose ET, and the quantification of fibrosis. Altogether the authors compared a heterogenous patient database, which included 311 patients evaluated for presenting features, 299 for response to therapy, 361 for complication rates, 97 for progression of fibrosis, and four for reversal of BM fibrosis, so no single cohort with consistent features was described throughout the study of 361 patients. For example, for the analysis of progression of fibrosis, only 97 (12%) of the original 809 patients entered in the UK-PT1 trial[2] were evaluated. Hemoglobin and platelet values were analyzed only in the 299 patients with known *JAK2* status (37% of the original 809 patients).[2] The reasons for the selection are unclear, particularly given that the *JAK2* status was shown to be irrelevant for this analysis. Moreover, according to the authors, participating physicians were encouraged to switch therapy from anagrelide to hydroxyurea in high-risk ET patients after the study ended. Out of an unknown number of patients who changed therapy, results from only four were selected to support the conclusion that fibrosis associated with anagrelide therapy may be reversed by hydroxyurea. Although some of the selection process could have been because of the lack of availability of BM specimens, the process applied should be more explicitly stated.

Of most concern is that nearly 60% of the patients presented with significantly increased BM fibrosis at disease onset (226 of 361 patients), including more than 20% with moderate to overt myelofibrosis grades 3 and 4,[6] occasionally accompanied by osteosclerosis.[3] Although patients entered in previous studies reported from this group[1-3] were considered to meet the Polycythemia Vera Study Group criteria for ET, the cohort of patients with overt myelofibrosis described in the current article is definitely not consistent with the original[7] or updated[8] Polycythemia Vera Study Group diagnostic guidelines, nor are they in keeping with the WHO classification.[9] Following the WHO classification, ET patients have only minimal reticulin fibrosis, if any at all.[5,10-12] This significant heterogeneity of the patient population, as well as inconsistencies of study design and evaluation, may explain why a previously published article by the same group[3] showed poor reproducibility of the WHO diagnostic criteria.[9] Whether the myelofibrotic patients might represent patients with primary fibrosis (PMF) with pronounced thrombocythemia at diagnosis rather than ET is a possibility that must be seriously considered.[10]

As shown in this study, the correlation between the WBC count, in turn related to granulocytic proliferation and degree of fibrosis, gives even more credence to the assumption that patients diagnosed as ET with presenting fibrosis would have most likely met the criteria for a diagnosis of PMF were the WHO classification criteria[9] applied. In the WHO scheme, granulocytic proliferation is considered characteristic of PMF, particularly in the early stages, but is not considered to be a feature of ET.

The crucial discrimination of ET from patients with PMF with presenting thrombocythemia is based on the identification of specific histologic BM patterns[13] as outlined in the WHO classification,[9] an approach that has been shown to be reproducible by a number of studies from independent groups.[12,14,15] The lack of a leukoerythroblastic blood film, overt anemia, or palpable splenomegaly would not be a convincing argument against the diagnosis of early stage PMF, because these features may be borderline or even not all expected early on.[5,9] However, it is unusual that of the 80 patients with grades 3 and 4 myelofibrosis,[6] only a few expressed these features at presentation without history of preceding therapy.[5] The general consensus is that such a discrimination between ET and PMF by applying the WHO criteria[9] is essential in regard to survival and progression to myelofibrosis.[4,5,10-12]

In addition, a proportion of the biopsies entered were prepared not from paraffin but plastic embedded tissue. Because of the well-known significant differences in section thickness between those techniques, it is doubtful that the quantification of fibrosis would yield comparable results in the two groups.

Lastly, in view of recent findings emphasizing the importance of an elevated WBC count for arterial thrombosis,[16] the reader is wondering why the rate of arterial thrombosis was only correlated with the degree of fibrosis but not with the WBC count and granulocyte cellularity.

In conclusion, we have serious concerns regarding the selection of patients for the various analyses in this study, and suspect that a large number of the patients reported are more likely to represent thrombocythemic patients with PMF rather than ET.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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