Response

The 2008 World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: a paradigm of effective collaboration among clinicians, pathologists, and scientists

Drs Samuelson, Parker, and Prchal raise several concerns regarding the recently published proposal for the revision of the 2001 World Health Organization (WHO) diagnostic criteria for polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).[1] For the record, the particular document has now been formally incorporated, in its entirety, into the upcoming revised 2008 WHO "Blue Book" on the Pathology and Genetics of Tumors of Hematopoietic and Lymphoid Tissues (in press).

At several points in their letter, Samuelson et al reiterate the need for "validation by data," which is a convenient rhetoric that is more often said than done. None of the current diagnostic systems for *BCR-ABL*-negative myeloproliferative neoplasms (MPNs) are systematically validated by data because of the lack of credible gold standards. Instead, they are all based on "consensus statements," a standard methodology where a panel of experts convenes to establish an authoritative international consensus, supported by scientific publications where appropriate. The same strategy was used in developing the 2008 WHO document, which we believe is a significant improvement over its predecessor because of the incorporation of the recently described MPN-specific molecular markers, including *JAK2* and *MPL* mutations. It is common knowledge that mutation screening now neither helps discriminate one MPN from another nor influences therapeutic decision making. However, this does not undermine its value in reliably excluding the diagnostic possibility of secondary polycythemia or reactive thrombocytosis/myelofibrosis, when a mutation is present, and that of PV, when either *JAK2*V617F or *JAK2* exon 12 mutation is absent.[2,3]

The concern regarding the general applicability of disease-specific histologic descriptions included in the WHO document is appropriate. However, "lack of expertise" does not necessarily mean "lack of value" and we believe that the correct action in this regard is to call attention to rather than undermine the value of bone marrow histology. Furthermore, according to the revised WHO criteria, histology is seldom used alone to make a diagnosis. In fact, bone marrow examination might not even be required for the diagnosis of PV. Similarly, non–histology-based minor criteria are used to validate histologic impression in the diagnosis of PMF. The histologic distinction between PMF and "myelofibrosis associated with nonmyeloid disorders" is facilitated by the demonstration of *JAK2*V617F, *MPL*W515L/K, or cytogenetic abnormalities in the majority of patients with PMF, and as is clearly stated in the criteria, in the absence of clonal markers, other neoplasms or inflammatory disease that can lead to marrow fibrosis must be excluded.

Finally, Samuelson et al mention extremely rare causes of erythrocytosis, such as those associated with germ line mutations of the von Hippel-Lindau (*VHL*) or erythropoietin receptor (*EPOR*) genes, to suggest that their morphologic distinction from PV has not been formally studied and might be problematic. We find this argument practically irrelevant because all PV patients are identified by the presence of either *JAK2*V617F or *JAK2* exon 12 mutations,[2,3] whereas a different set of genetic mutations and serum erythropoietin (Epo) profiles define congenital erythrocytosis.[4] Similarly, although we note the authors' astute observation regarding an inaccuracy in the 2001 WHO document regarding serum Epo level in patients with *EPOR* mutations, we fail to appreciate its relevance to the revised WHO criteria.

In closing, we would like to remind Samuelson et al that several members of the Myeloproliferative Disorders Research Consortium, including its principal investigator, have participated in the preparation of the revised WHO criteria and are accordingly identified as coauthors.

Respectfully submitted,

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

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To the editor:

Late effects of myeloablative bone marrow transplantation (BMT) in sickle cell disease (SCD)

We are greatly encouraged to read the report by Bernaudin et al,[1] showing excellent outcomes for children and adolescents receiving myeloablative allogeneic bone marrow transplantation (BMT) for sickle cell disease (SCD). Approximately 200 children worldwide have undergone BMT after myeloablative conditioning with busulfan and cyclophosphamide, with or without antithymocyte globulin, with a follow-up period approaching 10 years.[1-3] With this experience, outcome has improved with an event free survival of 95% in the most recent patient cohort, and children undergoing BMT can now reasonably expect to be cured of SCD.

The reports to date contain valuable information including rates of engraftment, graft rejection, graft-versus-host disease