European Bone Marrow Working Group trial on reproducibility of World Health Organization criteria to discriminate essential thrombocythemia from prefibrotic primary myelofibrosis. Haematologica 2012;97(3):360-5 - *Reply*

We are grateful for the critical comments of Thiele *et al.* because they give us the opportunity to underline the difficulties in applying the current World Health Organization (WHO) classification of thrombocytic myeloproliferative neoplasms and to eliminate potential misunderstandings.

1. The study, conducted by the European Bone Marrow Working Group (EBMWG),[1] is not the first to question the criteria inaugurated by the WHO for the classification of myeloproliferative neoplasms (MPN).[2-4] We are not aware of any other chapter of the WHO classification that has provoked contradicting studies by three independent groups.

2. Three out of 4 members of the coordinating committee of the EBMWG participated in the trial. To avoid bias, the co-authors of the WHO chapters did not take part in the study. The conduct of the study was discussed and decided during the assembly of the EBMWG in Szeged in October 2009 and it was announced to non-participating members by circulation of the minutes of the 2009 business meeting. The results were first presented and discussed during the Berlin business meeting of the EBMWG in October 2011. No opposition was raised to the study during either of the meetings or at any other time. Therefore, the trial represents an activity of the EBMWG members and would not have been possible outside the framework of the EBMWG.

3. Thiele and colleagues demand that the WHO criteria, including the vaguely defined category of "borderline values", should be strictly applied and question whether this was also done in our study. Needless to say that in our study the well-established cut-off and range values used at each participating laboratory were applied; in part these are defined by the WHO (e.g. anemia). Consequently, a potential disregard of "borderline values" can be excluded as an explanation of why more than 50% of prefibrotic primary myelofibrosis (PMF) cases by histology were unclassifiable when the minor criteria were taken into account.[1] In fact, almost identical findings were obtained in a recent study by Thiele *et al.*, although this was not stated in the text.[5] In this study, Thiele and co-workers neither defined cut-off values (as required from our study in their criticism) nor did they outline how many of the patients under study fulfilled the WHO minor criteria. From Table 4 in their paper,[5] however, it becomes obvious that none of the 565 patients from the series had a leukoerythroblastic blood picture and more than half of the patients had no anemia. Roughly 50% of patients did not have splenomegaly, and the slight increase of median LDH over 250 U/L suggests that a high proportion of patients had normal values.[5] It becomes inevitably obvious from the compilation of data in Table 4[5] that a considerable proportion of patients could not fulfill the criteria requested by the WHO to diagnose PMF. The authors claim to have validated the WHO criteria, which were "strictly" applied. From studying the data in Table 4 of their paper, the reader would have the opposite impression.[6]

4. Thiele *et al.* quote the above-mentioned study[5] to demonstrate the inadequacy of our own study.[1] As outlined above and stated in a letter to Blood,[6] the authors[5] failed to notice that more than 50% of patients in their study with the diagnosis of prefibrotic PMF did not meet the WHO minor criteria. If there is any inadequacy it refers to the arguments used in the letter by Thiele *et al.* in response to our study.[1]

5. All patients in our study were newly diagnosed patients with clinical suspicion of MPN due to sustained thrombocytosis, as stated in "Material and Study Design". In a recent series of more than 400 patients, we could observe a transformation of essential thrombocythemia (ET) to polycythemia vera in less than 2% of patients.[7] Thus this phenomenon is a rare event and cannot explain the high percentage of unclassifiable cases according to WHO in the EBMWG study.[1] The high percentage of unclassifiable cases was caused by: i) overlapping histomorphological criteria between ET and prefibrotic PMF in 20-40% of cases; and ii) incongruence between major and minor PMF criteria within at least 50% of morphologically typical prefibrotic PMF cases not meeting the minor criteria.

6. We agree with the requirement that new classifications should undergo a consensus process in order to sharpen and to train the corresponding criteria. However, the WHO 2008 histological criteria for discrimination of ET from cellular PMF are not new and were already mentioned in the 2001 edition. All members of the panel are experienced hematopathologists who have used the WHO criteria in their daily practice for many years. Being active members of EBMWG, the members of the panels have attended several presentations by Drs Thiele and Kvasnicka, so the statement that there was "absence of prior consensus or training" is not acceptable. Moreover, this study intended to reflect the reproducibility of the criteria as they are adapted by most hematopathologists from the sources available (publications, books, courses). Consensus conferences are not usually among these sources and are not accessible to most pathologists who try to use the WHO classification. Furthermore, 2 of the panellists are affiliated to the same institution and regularly discuss and exchange cases. Interestingly, the level of concordance between them does not differ from that which was found among the other panellists. This finding suggests that consensus conferences might lead to higher concordance rates for the purpose of a given study. However, the high concordance will most likely not persist under routine diagnostic circumstances.

7. In their letter, Thiele and co-workers quote erroneous values from Table 4 of our paper with regard to kappa values.[1] They mixed up interobserver and intraobserver reproducibility and therefore their conclusions are false.

8. We do not doubt that a variant of thrombocytic MPN, which carries a higher risk of progression to myelofibrosis, can be identified by histopathology. This was first recognized by Burckhard *et al.*[8] who coined the term "megakaryocytic myelosis". Later on Georgii and co-workers changed the label into "megakaryocytic-granulocytic myelosis".[9] The WHO classification adopted this concept in 2001 (renamed as "idiopathic myelofibrosis") and in 2008 (again renamed as "primary myelofibrosis"). We consider it a real achievement that histopathology has been incorporated into the WHO classification of MPN and mainly due to Dr Thiele. Neither this progress nor the discovery of JAK2 mutation

has, however, abrogated those difficulties in subtyping MPN already recognized by Dameshek:[10] "Transitions and overlaps among these various conditions are common, so that where one begins and the other ends is often uncertain… Sometimes, as with the various members of the myeloproliferative syndromes, a supposedly accurate diagnosis can be more inaccurate than the use of the rather vague term of a chronic… myeloproliferative disorder". It should be noted that several distinguished hematologists[11-13] have cast doubt on the value of the diagnosis of "pre-fibrotic myelofibrosis", typically "treating as ET". This, and the large number of unclassifiable cases (if the WHO criteria are strictly followed) has left this part of the WHO classification in need of further scrutiny. Future molecular studies may provide more data that will enable us to more clearly identify various entities. Hence, there is still plenty of room for improvement in MPN diagnosis and this is exactly what we wanted to point out in our study.[1]

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