To the editor:

Validation of cytogenetic-based risk stratification in primary myelofibrosis

Primary myelofibrosis (PMF) is a Philadelphia chromosome–negative myeloproliferative neoplasm whose diagnostic criteria have been recently updated.[1] Roughly one-third of the patients have an abnormal karyotype for the most part corresponding to deletions of chromosome 13, of chromosome 20q and to partial duplication of chromosome 1q.[2] Current prognostication in PMF is based on the International Prognostic Scoring System (IPSS).[3] Different studies demonstrated that individual cytogenetic abnormalities may affect survival of patients with PMF.[4-6] Hussein et al[7] have just developed a cytogenetic-based prognostic model useful to predict survival in patients with PMF by grouping cytogenetics as favorable (sole +9, sole 20q−, sole 13q−), normal, unfavorable (complex karyotype or sole +8), and other abnormalities. A significant impact on survival was also obtained by merging cytogenetics into larger categories such as favorable/normal and unfavorable/other abnormalities. To validate this prognostic stratification, we evaluated 114 patients with PMF whose cytogenetics was available at diagnosis. Approval was obtained from the Pavia Institutional Review Board. Informed consent was provided in accordance with the Declaration of Helsinki. Patients have been regularly followed at the Division of Hematology of Pavia between 1975 and 2009. Quinicrine banding (1975-1989) and Giemsa banding (1990-2009) analyses were performed on 24- and 48-hour bone marrow cultures or peripheral blood.[8] Median age was 59 years (range, 18-84 years) with a male/female ratio of 70/44. According to IPSS, 34 (30%) patients had low-risk PMF, 29 (25%) intermediate-1, 29 (25%) intermediate-2, and 22 (20%) high-risk. Among 52 patients evaluated for *JAK2* status, 28 (54%) were *JAK2*V617F-positive. Median follow-up was 3.1 years (range, 0.6-20 years). Although missing abnormalities could not be ruled out in patients evaluated many years ago, karyotype was favorable in 2 patients (sole 20q−, sole +9), normal in 92, unfavorable in 8 (sole +8 in 5, complex karyotype in 3), and included other abnormalities in 12 patients. We did not find 13q deletions. The low number of patients belonging to the favorable category does not allow a meaningful comparison among groups. So, we carried out survival analysis by stratifying patients into larger categories: favorable/normal (n = 94) and unfavorable/other abnormalities (n = 20). We found that patients with unfavorable/other cytogenetic profile had a significant shorter survival than patients with favorable/normal cytogenetic profile ($P = .012$). Figure 1 shows Kaplan-Meier estimate of survival in the 2 groups: median survival was 2.9 years in the group with low-risk profile and 7.8 years in that with high-risk profile. After adjusting for IPSS in a multivariable Cox proportional hazard regression, the cytogenetic-based prognostic stratification retained its significant impact on survival with a hazard ratio of 2.19 (95% confidence interval 1.13-4.26; $P = .021$). This means that patients with high-risk profile have a 2.19-fold higher risk of death than those with low-risk profile. To rule out the effect of the *JAK2*V617F mutation, we performed a multivariable analysis with cytogenetic-based risk categories, *JAK2* mutation status, and IPSS groups as covariates in 52 patients with known *JAK2* status. Cytogenetics remained an independent predictor of survival ($P = .027$).

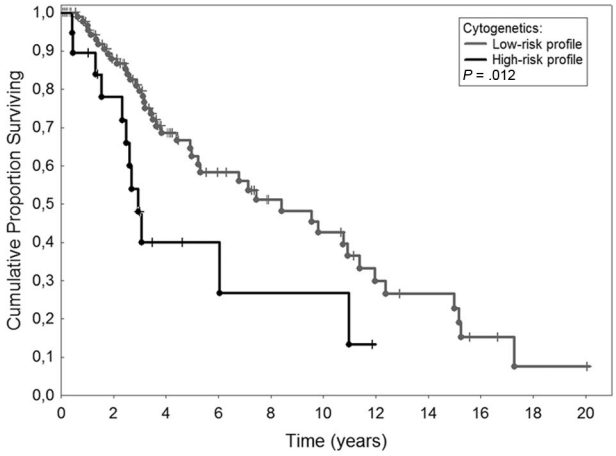

Figure 1. Kaplan-Meier estimate of survival in 114 patients with primary myelofibrosis according to cytogenetic profile at diagnosis. Low-risk profile included 20 patients with sole +9, sole 20q−, and normal karyotype. High-risk profile included 94 patients with complex karyotype, sole +8, or other abnormalities. The 2 survival curves were significantly different ($P = .012$).

In conclusion, this study confirms that having a complex karyotype or abnormalities other than sole 20q− or sole +9 implies a shorter survival in PMF.

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To the editor:

Proposal for a revised classification of systemic mastocytosis

Historically, mast cell disease (MCD) signified overt infiltration of one or more organs by cytologically abnormal mast cells.[1] In adults, the condition almost always involves the bone marrow (BM), a cardinal feature of systemic mastocytosis (SM). We now recognize SM as a hematopoietic stem cell disease that often harbors a KIT mutation and is sometimes associated with non–mast cell lineage clonal myeloproliferation. The World Health Organization (WHO) classification system recognizes 4 major SM subcategories: indolent SM (ISM; little or no evidence of organ dysfunction), aggressive SM (ASM; presence of disease-related organopathy), SM associated with a clonal hematologic non–mast cell lineage disease (SM-AHNMD), and mast cell leukemia (MCL; presence of $\geq 20\%$ mast cells in BM aspirate).[2] Although we fully endorse the current classification system, it has its limitations, and we hope to initiate a constructive dialogue that may lead to a consideration for revisions.

1. Unlike the case with blast-phase chronic myelogenous leukemia (CML) or leukemic conversion of *BCR-ABL1*–negative myeloproliferative neoplasms (MPN), most MCL cases develop de novo rather than represent transformation of preexisting SM. Such was the case in the majority of MCL cases identified in a recent review of 342 MCD patients from our institution.[3] The mere presence of *KIT*D816V in some MCL cases (the sole MCL case tested in the aforementioned study was negative for the mutation) does not justify the status quo, because the pathogenetic contribution of *KIT*D816V in SM and its use as a therapeutic target are uncertain and definitely not as well defined as they are for *BCR-ABL1* or *FIP1L1-PDGFRA*. From a practical standpoint, the clinical features and treatment of MCL are more akin to acute leukemia than SM.

2. The clinical relevance of the SM-AHNMD subcategory has not been convincingly made, since the SM component is often not the dominant process from the standpoint of clinical features, diagnosis, bone marrow histology, or treatment. Again, for the reasons outlined in the previous paragraph, the presence of *KIT*D816V should not be used as an excuse to lump together a clinicopathologically heterogenous group of diseases that are prognostically diverse. The observations from our recent review of 123 cases with SM associated with other myeloid malignancies underscore this point.[4]

3. The current proposal fails to address the prognostic relevance of the provisional ISM subvariants, smoldering SM (SSM) and BM mastocytosis (BMM).

Based on the above discussion, we propose the following revisions to the current SM classification (Table 1):

1. MCL should be eliminated as a subcategory of SM and instead be included under the WHO category of "Acute myeloid leukemia (AML) and related myeloid neoplasms." The frequent

Table 1. Proposed revised classification of systemic mastocytosis (SM)

Class	Name	Criteria
I	Indolent systemic mastocytosis (ISM)	Meets criteria for SM; no "C" findings; no evidence of SM-MDS, SM-CMML, SM-AL, or AML with BM mastocytosis; minimal or no MPN features
II	Smoldering systemic mastocytosis (SSM)	As above for ISM; 2 or more "B" findings
III	Aggressive systemic mastocytosis (ASM)	Meets criteria for SM; no evidence of SM-MDS, SM-CMML, SM-AL, or AML with BM mastocytosis; 1 or more "C" findings; MPN features allowed
IV	Systemic mastocytosis associated with myeloproliferative neoplasm, unclassifiable (SM-MPN)	No "C" findings

SM indicates systemic mastocytosis; MPN, myeloproliferative neoplasm; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; AL, acute leukemia; AML, acute myeloid leukemia; and BM, bone marrow.