Comment on: "The impact of category, cytopathology and cytogenetics on development and progression of clonal and malignant myeloid transformation in inherited bone marrow failure syndromes"

The paper by Cada *et al*. published in Haematologica uses data from the Canadian Inherited Marrow Failure Registry to examine the prognostic value of the category, cytopathology and cytogenetics (CCC) classification for pediatric myelodysplastic syndrome (MDS).[1] We have previously expressed some reservations about this classification system, and remain concerned about its utility.[2] The CCC classification, introduced in 2002, has not been widely employed, while a simpler description of childhood MDS was published more recently by the World Health Organization (WHO) in 2008.[3] In our opinion, the application of the CCC system to the Canadian Registry introduces more confusion than clarity into our understanding of MDS or leukemia in patients with inherited bone marrow failure syndromes (IBMFS). In addition, the introduction of new abbreviations such as CMMT (clonal and malignant myeloid transformation) and CMCA (clonal marrow cytogenetic abnormalities) make it hard to compare or combine results from the Canadian Registry with other IBMFS registries.

We have several specific concerns. First, the paper states a plan to examine the prognostic utility of the three components of the CCC classification. The first component, category, has "syndrome" as part of the case definition for the Registry, and thus in fact cannot be analyzed. The second component, cytology, includes RC, refractory cytopenia without dysplasia. The supplement to the paper states that patients are enrolled in the Registry "if they have chronic bone marrow failure", which appears to be very similar to their definition of RC. Hence this component of the CCC definition also appears difficult to analyze.

Second, we have concerns about the representativeness of the patients with identified syndromes. The authors report that 30% of the patients were "unclassified" – but does this mean they are "unclassifiable", or simply not thoroughly tested? The numbers of the patients with known syndromes are individually small, which led to many of the analyses using the total group of 11 different disorders. But, what does a physician learn from a survival curve involving 11 different diagnoses? How does this enable him/her to counsel a patient with a specific syndrome? Lumping syndromes only serves to increase heterogeneity and decrease specificity, the opposite of precision medicine.[4]

Finally, the entire dataset includes 45 patients out of 320 who had any type of CMMT at onset, and up to 75% risk of development of CMMT by 10 years of follow-up (in Fanconi anemia). This is puzzling, since in several other cohorts, unbiased by entry criteria, we found a risk of acute myeloid leukemia of 15% and of MDS of 30-40% by the age of 40 years,[5] an impossible outcome in the analysis by Cada *et al*. since they stated that they stopped their follow-up at the age of 18 years (216 months). This too is confusing, since Table 2 has patients whose CMMT was detected at up to 756 months, which is 63 years. Furthermore, most of the data in the paper lack *P* values, justifiably, since most of them are based on inadequate sample sizes.

In summary, we believe the experience of patients enrolled in the Canadian Registry is potentially very valuable, but we would very much prefer to see syndrome-specific analyses, using standard definitions of MDS and acute myeloid leukemia, until the collective hematology community develops improved classifications.

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References

1. Cada M, Segbefia CI, Klaassen R, et al. The impact of category, cytopathology and cytogenetics on development and progression of clonal and malignant myeloid transformation in inherited bone marrow failure syndromes. Haematologica. 2015;100(5):633-642.
2. Alter BP, Elghetany MT. The CCC system: is it really the answer to pediatric MDS? J Pediatr Hematol Oncol. 2003;25(5):426-428.
3. Baumann I, Niemeyer CM, Bennett JM, Shannon K. Childhood myelodysplastic syndrome. In: Swerdlow SH, Campo E, Harris NL, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC; 2008. p. 104-107.
4. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372(9):793-795.
5. Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol. 2010;150(2):179-188.