Response to comments from Drs. Alter and Rosenberg

We thank Drs. Alter and Rosenberg for their comments[1] on our paper[2]. In adults, and more so in children, the classifications of myelodysplastic syndrome (MDS) are still debated, and modifications are periodically proposed. Controversy prevails with regard to whether some MDS groups need to be combined together or further split, and whether some cases should be classified as MDS or acute myeloid leukemia (AML). The inclusion criteria of pediatric MDS vary in different published studies and sometimes are not precisely stated. In particular, there are no "standard definitions" of MDS in inherited bone marrow failure syndromes (IBMFS). We stated in the Discussion of our paper that two classifications for pediatric MDS have been proposed; the 2002 Category, Cytopathology and Cytogenetics (CCC) classification[3] (revised in our current paper) and the 2003 World Health Organization (WHO) classification[4] (revised in 2008[5]). The advantage of the CCC classification is that it was designed to include all categories of MDS (*de novo*, therapy-related and syndrome-associated). In contrast to the WHO classification, the CCC classification includes the category of refractory cytopenia with ringed sideroblasts since despite its rarity, this cytopathology exists in children as evidenced by this series and other reports in the literature.[6] Had we used the pediatric WHO MDS classification we could not have categorized either of our cases of refractory cytopenia with ringed sideroblasts. In addition, the significance of refractory cytopenia with dysplasia has not been systematically and thoroughly studied in IBMFS; therefore, this category was included in our classification while in the WHO classification it was omitted.

The first component of the CCC classification refers to the etiology of MDS, which we termed "category". In our classification, the category can be general (e.g. syndromic MDS) or more specific (e.g. Fanconi anemia-associated MDS). We analyzed the differential risk of disease progression and survival among patients with various syndromic diagnoses.

We used the diagnostic criteria for MDS published by Hasle and colleagues.[4] This also applied to cases with refractory cytopenia. The only exception was a patient with constitutional trisomy 8, who led us to propose expansion of the published criteria. As explained in the Discussion, this patient clearly had MDS, since he had an MDS/AML predisposition syndrome (constitutional trisomy 8), progressive cytopenia and a hypercellular marrow. He had no prominent dysplasia, no ringed sideroblasts, no excess blasts, no cytogenetic abnormalities and no indication of any other dietary, metabolic or infectious etiologies that could account for the blood dyscrasia.

With regard to the cases of unclassified IBMFS, we stated in the *Online Supplementary Data* that patients who fulfilled specific diagnostic criteria for an IBMFS were recruited by hematologists at each center submitting data to the registry.[7] Patients were considered to have unclassified IBMFS if they did not fit the clinical, laboratory and genetic diagnostic criteria of known IBMFS.[7] The majority of these patients underwent extensive genetic testing, which was negative. Genetic testing was performed at the discretion of the referring physician.

As stated in the Methods of our paper, when we compared the risk of clonal and malignant myeloid transformation (CMMT) among the different syndromes, we selected IBMFS categories that had more than ten patients for our analyses. Therefore, four categories were analyzed and not 11. Also, to assess the impact of category on progression and overall survival of patients with CMMT, we included only syndromes that had more than three patients with CMMT: Fanconi anemia, Shwachman-Diamond syndrome and unclassified IBMFS. Thus, three syndromes were used for this analysis and not 11.

In the Canadian Inherited Marrow Failure Registry we enroll children and adults with a diagnosis of IBMFS. Nowhere in the paper was it stated that the follow-up of patients was stopped at the age of 18 years. We instead state that "Some analyses (e.g. risk of CMMT) were stopped at the age of 18 years, due to the possibility of referral bias of patients with CMMT who are older than 18 years and are not treated at pediatric centers." This statement clearly explains why some patients, who are older than 18 years of age were included in the report and why some analyses did not include patients older than 18 years of age.

All the comparative analyses in our paper included *P*-values (See Figures I-C, 2-I, 2-E, 2-J, 3A-D, 3E-I, 4-A and 4B). We discussed the conclusions that can be drawn from results that were statistically significant (half of the analyses) and from results that were not significant.

We found the statement of Drs. Alter and Rosenberg about their preference to see syndrome-specific analysis particularly surprising in view of their previous published attempts to characterize malignancies and survival patterns among their cohort of IBMFS patients.[8] Unfortunately, their studies were based on either review of cases from the literature or a non-population-based cohort, where families contacted the investigation team for enrollment. Data from population-based studies are needed to evaluate risks and prognostic factors accurately. As we stated in the Discussion, given the rarity of the IBMFS the numbers of patients in certain categories, cytopathology and cytogenetic groups were small. Enrolling more patients and longer follow-up are important for replicating our results and finding additional cytogenetic and genetic variables as risk factors.

In summary, to our knowledge our study tested, for the first time, the prognostic significance of a MDS classification in a large cohort of patients with IBMFS-associated MDS or CMMT. The data in our study help to define the impact of categories, cytopathology and bone marrow cytogenetic abnormalities on the characteristics and prognosis of IBMFS-associated CMMT.

Yigal Dror and Michaela Cada

Marrow Failure and Myelodysplasia Program, Division of Hematology/Oncology, Department of Paediatrics and the Genetics and Genome Biology Program, Research Institute, The Hospital for Sick Children and the University of Toronto, Ontario, Canada

Correspondence: yigal.dror@sickkids.ca

doi:10.3324/haematol.2015.130898

Key words: inherited bone marrow failure syndromes, CCC classification, clonal and malignant myeloid transformation.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Alter BP, Rosenberg PS. Comment on "The impact of the category, cytopathology and cytogenetics development and progression of clonal and malignant myeloid transformation in inherited bone marrow failure syndromes. Haematologica. 2015;100(9):xxx
2. Cada M, Segbefia C, Klaassen R, et al. The impact of the category, cytopathology and cytogenetics on development and progression of

clonal and malignant myeloid transformation in inherited bone marrow failure syndromes. Haematologia. 2015;100(5):633-642.
3. Mandel K, Dror Y, Poon A, Freedman MH. A practical, comprehensive classification for pediatric myelodysplastic syndromes: the CCC system. J Pediatr Hematol Oncol. 2002;24(7):596-605.
4. Hasle H, Niemeyer CM, Chessells JM, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia. 2003;17(2):277-282.
5. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937-951.
6. Huijgens PC, van der Veen EA, Meijer S, Muntinghe OG. Syndrome of Shwachman and leukaemia. Scand J Haematol. 1977;18(1):20-24.
7. Teo JT, Klaassen R, Fernandez CV, et al. Clinical and genetic analysis of unclassifiable inherited bone marrow failure syndromes. Pediatrics. 2008;122(1):e139-148.
8. 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.