

## Letters to the Editor

### The CCC System: Is It Really the Answer to Pediatric MDS?

*To the Editor:*

Drs. Mandel et al. (1) recently proposed a new classification for pediatric myelodysplastic syndromes (MDS), which they designated the "CCC system." We certainly support their concern that the usual schema for MDS, the French-American-British (FAB) classification and, more recently, the World Health Organization (WHO) classification, were developed for adults and may not be optimal for pediatric cases. Their new classification acknowledges the potential impact of inherited bone marrow failure syndromes on the development and outcome of MDS compared with patients without these syndromes. In addition, the proposal implies, although it does not clearly state, that cytogenetics alone could be used as the sole criterion for the diagnosis of MDS in the absence of morphologic changes. The CCC system (Table 1) is provocative, but there are some components that warrant clarification.

Since their study is mostly concerned with the classification of pediatric MDS, definitions and patient selection are of utmost importance. However, the authors' definition of MDS, "relatively cellular bone marrow but ineffective hematopoiesis or morphologic dysplasia and variable degrees of peripheral cytopenias," lacks clarity and reproducibility (1). Cellularity "relative" to what? Based on aspirates or biopsies? Based on standards for age (considering that pediatric marrows are normally cellular), and if so from what source? How much increase compared with normal? How is "ineffective hematopoiesis" defined or identified? What are the objective criteria for "morphologic dysplasia"? How many dysplastic cells in each lineage, how many lineages, and what are the lineage-specific dysplastic features? How much "cytopenia," at what levels for each lineage, and how many lineages? Furthermore, it seems that the authors make the arbitrary decision that having an inherited bone marrow failure syndrome of the type listed by the authors provides automatic entry into the system and assumes that MDS is inevitable. The authors have applied this concept

and deviated from their definition of "MDS" to the extent of including cases lacking both cytogenetic and cytologic abnormalities. There are some inherent problems here, one of which is the assumption that all such patients will develop MDS, and that all of those will develop acute myeloid leukemia (AML). At least in the context of Fanconi anemia (FA), we have suggested that these assumptions may not be appropriate (2,3). In addition, dyskeratosis congenita should not have been excluded from the list by Mandel et al., because there are several cases who did have MDS (4).

Thus, it seems that the first step in the use of the CCC system would be to clarify the entry criteria. We have previously suggested that a separation of morphologic and cytogenetic findings is important for prognosis, at least in FA (2). In addition, we used cytochemical stains to supplement the diagnosis of MDS in borderline cases. Our proposed diagnostic criteria for cases are outlined in Table 2 (5-7).

Lineage-specific dysplastic features are as follows:

- Erythroid: megaloblastic, multinucleated, nuclear fragments, increased immature forms;
- Myeloid: increased immature forms/blasts, hypo-/hypergranulation, hyposegmentation, bizarre hypersegmentation;
- Megakaryocytes: hypo-/hyperlobulated, small forms, increased nuclear-cytoplasmic ratio.

We also have concerns with regard to the individual components of the CCC and to their use. Is one goal ultimately to develop a formal prognostic score? Which combination of items in the CCC will be considered more important? In fact, the differences among the first "C" (Categories) may be best reserved for subset analyses, which would then permit scientific evaluation of the differences between what is called "MDS" in each of the categories. The authors do acknowledge that the type of syndrome influences the risk for developing AML. This, of course, would reduce the "CCC System" to the "CC System."

The second "C," Cytology, is addressed in our introductory comments. The cytologic appearance must be classified objectively, so that there can be no doubts. Inclusion of

**TABLE 1. CCC system**

Category	Cytology	Cytogenetics
Idiopathic/de novo	RCRS (refractory single/multilineage cytopenia with ring sideroblasts)	CG+ (abnormal cytogenetics)
Syndrome-related	RC (refractory single/multilineage cytopenias without obvious dysplasia)	CG- (normal cytogenetics)
Treatment/toxin-related	RCD (refractory single/multilineage cytopenias with dysplasia)	CG° (cytogenetics not known)
	Any of the above with excess blasts (5-30%) (RCRSEB, RCEB, RCDEB)	The actual cytogenetic abnormality would be specified.

**TABLE 2.** Diagnostic criteria for myelodysplastic syndromes

Major	Intermediate	Minor
Overt dysplasia Clonal cytogenetics	Suggestive dysplasia	Myeloperoxidase deficiency (>5% of segmented neutrophils [5]) Increased dural esterase positivity (>2% of marrow cells [6]) Periodic acid Schiff positive erythroblasts (>0% of erythroblasts [7]) Unexplained ring sideroblasts (>0%)

MDS, 1 major, or 1 intermediate + 1 minor. Overt dysplasia, 2 cell lines with dysplasia in at least 20% of cells. Suggestive, 1 cell line with dysplasia in at least 20% of cells.

patients with hypocellular marrows and refractory single/multilineage cytopenias without obvious dysplasia (RC), such as cases 19 and 38 on one occasion each, is confusing. Perhaps the authors did not mean to call the patients "MDS" at that stage, but this is not clear from their manuscript. The authors did not address some of the inadequacies of the FAB classification that they identified earlier, such as hypocellular MDS and MDS with marrow fibrosis. In parallel, the authors criticized the FAB classification for creating a category for refractory anemia with ringed sideroblasts (RARS), which may not be applicable in children, while creating a closely similar category of refractory single/multilineage cytopenia with ring sideroblasts (RCRS).

The third "C," Cytogenetics, also needs elucidation. Patients were listed by Mandel et al who enter with RC without dysplasia, and without a clone, who then went on to develop either refractory single/multilineage cytopenias with dysplasia (RCD), or a clone, or both. Presumably this inclusion is a posteriori. By necessity, patients with a similar presentation who had not developed dysplasia or a clone would not have been included, but would have been classified as aplastic anemia.

It is clear that we are all struggling to identify patients who have a high probability of development of AML before that transformation occurs. One problem with many of the classification schemes, however, is the assumption that patients with MDS will follow this leukemic path. The most important question is really to identify, among patients who belong to a group who are at risk for MDS and/or AML, which of them will in fact develop MDS, and which among them will develop AML. It is not clear that the CCC system provides all of the answers to this conundrum.

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## REFERENCES

- Mandel K, Dror Y, Poon A, et al. A practical, comprehensive classification for Pediatric myelodysplastic syndromes: the CCC system. *J Pediatr Hematol Oncol* 2002;24:596-605.

- Alter BP, Caruso JP, Drachtman RA, et al. Fanconi anemia: myelodysplasia as a predictor of outcome. *Cancer Genet Cytogenet* 2000;117:125-131.
- Rosenberg PS, Greene MH, Alter BP: Cancer incidence in persons with Fanconi's anemia. *Blood* 2003;101:822-826.
- Dokal I: Dyskeratosis congenita in all its forms. *Br J Hematol* 2000;110:768-779.
- Elghetany MT, Peterson B, MacCallum J, et al. Deficiency of neutrophilic granule membrane glycoproteins in the myelodysplastic syndromes: a common deficiency in 216 patients studied by the Cancer and Leukemia Group B. *Leuk Res* 1997;21:801-806.
- Elghetany MT, Peterson B, MacCallum J, et al. Double esterase staining and other neutrophilic granule abnormalities in 237 patients with the myelodysplastic syndrome studied by the Cancer and Leukemia Group B. *Acta Hematologica* 1998;100:13-16.
- Seo IS, Li C-Y, Yam LT. Myelodysplastic syndrome: diagnostic implications of cytochemical and immunocytochemical studies. *Mayo Clin Proc* 1993;68:47-53.

## Response to Alter and Elghetany

### To the Editor:

In response to the detailed and authoritative critique by Alter and Elghetany of our classification schema for pediatric myelodysplastic syndromes, we offer the following responses.

The purpose for developing a new classification system was to circumvent the frustrating attempts to force-fit pediatric diagnoses into classifications of MDS of adulthood that failed to recognize the diversity and differences of childhood MDS. After compiling the data for the classification in 1998, the first versions of it were presented at three international pediatric oncology meetings for input from our colleagues. Based on the helpful and constructive suggestions that we received, the classification format underwent a series of refinements that culminated into the "CCC System" (1). We are actively promoting the use of the classification because it is practical, comprehensive, and easily accommodates all forms of presentation of pediatric MDS. Indeed, by using the system serially, we have gained valuable information about the evolution and prognosis for individual disorders.

Alter and Elghetany are concerned with definitions and patient selection for inclusion in the classification. The CCC System was not designed to instruct pediatric oncologists in the diagnosis of myelodysplasia, but to provide guidance in what to do with the clinical and laboratory information after the diagnosis is established. Definitions and patient selection are available from standard sources, such as the excellent account by Grier and Civin in Nathan and Oski's *He-*