MAYO CLINIC

Improving Prognostic Tools for Patients With Myelodysplastic Syndromes

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Myelodysplastic syndromes (MDS) is a term used to refer to a very complex group of myeloid stem cell disorders.[1] It most frequently affects older individuals and those previously treated with chemotherapy and/or radiation therapy. Several genetic predisposition syndromes that can affect younger individuals have also been described. In general, most patients present with cytopenia that will trigger a diagnostic procedure. Today, this process should include evaluation of the morphology of the cellular elements in the bone marrow, a cytogenetic analysis, and targeted next-generation sequencing. With this information, the clinician will attempt to calculate the prognosis of an individual patient. More commonly used variables for this analysis include the percentage of blasts in the marrow, the number and degree of peripheral blood cytopenias, and cytogenetic results. The most commonly used prognostic score is the International Prognostic Scoring System (IPSS).[2] This simple score divides patients into 4 categories on the basis of blast percentage, a simple cytogenetic classification and specific thresholds of hemoglobin, and platelet and neutrophil counts. This initial prognostic score was published in 1997 but still is the classification that we use most frequently at MD Anderson Cancer Center. The IPSS has several limitations, some relevant, others more academic. For instance, it was designed using a cohort of untreated patients and included a subgroup of patients with chronic myelomonocytic leukemia. Most importantly, it is not a very precise method to predict prognosis in the lower-risk categories (low and intermediate-1) and it underestimates the prognostic impact of cytogenetic alterations.[3] Some of these limitations have been found to be of little if any consequence. For instance, the IPSS can predict outcomes of patients who have received prior therapy or have therapy-related disease, and it is a good discriminator of outcome for patients with chronic myelomonocytic leukemia. Although age was not incorporated in the IPSS, the impact of age can be calculated based on the IPSS scoring system.[2] Because of some of these limitations, multiple groups have attempted over the past 15 years to improve on the IPSS. Examples include the WPSS (World Health Organization Classification-Based Prognostic Scoring System),[4] the Global MD Anderson Model,[5] the Lower-Risk MD Anderson Risk Model,[6] and, more recently, the Revised IPSS (IPSS-R).[7] This last score was a major effort from multiple centers around the world and should be considered the standard classification for patients with MDS.

The question, then, is why the IPSS-R has not been widely adopted or why there is a need to develop more advanced systems. There are several explanations. First, the IPSS-R is a complex system that requires detailed morphologic analysis (for instance, being able to discriminate more or less than 2% blasts) and uses as its backbone a complex cytogenetic classification.[3] These features result in a 5 subgroup classification instead of 4 as in the original IPSS: very high, high, intermediate, low, and very low risk. Of importance, similar to the original IPSS, the IPSS-R only includes untreated patients, does not include age, and, more importantly, does not include molecular data. It should be noted that when the IPSS-R was designed, we did not have access to the considerable amount of genomic data that we currently have. Furthermore, no drug has yet been approved using IPSS-R criteria. In addition, the intermediate IPSS-R group of patients is not well defined. For instance, my colleagues and I recently reported on the significant heterogeneity of patients with intermediate-risk disease that makes treatment selection difficult for this group of patients.[8]

After the development of the IPSS-R, multiple groups have reported on the genomic architecture of MDS following the discovery of multiple genomic alterations in

Mayo Clin Proc. ■ October 2018;93(10):1340-1342 ■ https://doi.org/10.1016/j.mayocp.2018.08.025
www.mayoclinicproceedings.org ■

this disease.[9] Examples include the discovery of mutations in genes involved in splicing, or mutations in genes such as *TET2* (for expansion of gene symbols, use search tool at www.genenames.org), *DNMT3A*, *RUNX1*, and *ASXL1*, and multiple others already known to occur in other malignancies, such as *TP53*.[9] At the present time, no prognostic scoring system has been developed that systematically includes these genomic alterations. A large international effort, based on the IPSS-R, is trying to merge genomic data with the IPSS-R.

This issue of *Mayo Clinic Proceedings* includes a very important initiative by investigators from the Mayo Clinic and the National Taiwan University Hospital delivering a large integrated new prognostic system for patients with MDS.[10] This score includes genomic data and is designed to overcome some of the limitations of the IPSS-R. To do so, the authors used a very large cohort (N=685) of very well molecularly annotated patients from both centers. In addition to clinical characteristics, they also used a simplified cytogenetic score and genomic analysis that included 15 of the most commonly mutated genes in MDS. Using all these characteristics, the authors developed a very powerful scoring system that divides patients into 4 categories (Table). For survival analysis, 2 distinct cohorts were used for validation (Mayo and Taiwan). This system has several advantages compared to the IPSS-R: it includes age, sex-adjusted thresholds of hemoglobin, simpler cytogenetic scoring systems (the 3-tier Mayo Clinic Score), and genomic data. Furthermore, patients could have previously received therapy. In addition, there are several interesting aspects of this analysis. The first is that the presence of *TP53* mutations is not part of the score because of its close association with monosomal karyotype and the fact that by both univariate and multivariate analysis, several of the IPSS-R variables are not significant. Also of interest is that although survival trends were similar between both cohorts, outcomes appear better in the Taiwan subset. One limitation of the article is that there are limited data on the risk of leukemic transformation.

TABLE. Characteristics of the New MDS Scoring System[a]

Variable	Points
Monosomal karyotype	4
Non–monosomal karyotype	1
RUNX1 mutation	1
ASXL1 mutation	1
Absence of *SF3B1* mutation	1
Age >70 years	2
Severe anemia	2
Platelet count $<75 \times 10^9$/L	1
Bone marrow blasts %	1

[a]Using this score, patients are then grouped into 4 different risk categories by adding their total number of points: low (0-2 points), intermediate-1 (3-4 points), intermediate-2 (5-6 points), and high (>6 points). The median survival of patients with low risk is 85 months with an 87% 3-year survival; for patients with intermediate-1 risk, 42 months (3-year survival of 54%); for patients with intermediate-2 risk, 22 months (27% 3-year survival); and for the high-risk group, 9 months (0% 3-year survival). Severe anemia is defined depending on age: hemoglobin level <8 g/dL for women and <9 g/dL for men.

The question is, what is going to happen now to this score? In my experience, this initiative will need to undergo a dynamic assessment in future prospective analysis, particularly in the context of therapy. For instance, the IPSS-R or the new Mayo-Taiwan score may indeed allow the prediction of survival but mainly outside the context of specific therapy. As an example, the clinician will predict survival based on the model and then will advise the patient on different treatment strategies. This could include observation, for instance for patients in the Mayo low-risk category (who have an expected 5-year survival of 73%); the model may lead to the recommendation of allogeneic stem cell transplant, perhaps for a patient in the high-risk category (who have a median survival of 9 months and a 0% percent chance of 3-year survival). But these assumptions may not be accurate. For instance, it is possible that patients in the worse category may not have their outcomes improved by transplant. As an example, it is known that the presence of mutations in the *TP53* gene is associated with poor outcomes with transplant.[11] Therefore, it will be important to better understand the impact of different treatment modalities when using this score. Likely, the behavior of the model will be affected by the future use of different treatment strategies. This is very important because it is possible that a number of new therapeutic approaches will be gradually incorporated into the care of patients with

MDS. The use of transforming growth factor β pathway modulators, newer epigenetic drugs, targeted approaches, and newer immune-based or transplant technologies are all likely to substantially affect the natural history of MDS and therefore the use of these models.

In summary, Tefferi et al[10] present a new and very important scoring system for patients with MDS that finally includes genomic data and is easy to use. I plan to test it in my clinic.

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Potential Competing Interests: The author reports no competing interests.

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