The Dawn of the Molecular Era of the Myelodysplastic Syndromes

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The myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem-cell diseases characterized by cytopenias, dysplasia in one or more of the myeloid cell lines, ineffective hematopoiesis, and an increased risk of acute myeloid leukemia.[1] These diseases exhibit considerable clinical heterogeneity, with variation in the likelihood of evolution to acute myeloid leukemia and in overall survival.[2,3] The diagnosis and classification of the myelodysplastic syndromes are established according to World Health Organization (WHO) criteria, which succeeded the French–American–British (FAB) Cooperative Group criteria a decade ago. The WHO classification system incorporates bone marrow histologic findings, blast count, and cytogenetic findings, thus representing the initial attempt to incorporate genetic abnormalities into risk stratification.[1]

However, approximately 50% of patients with a primary myelodysplastic syndrome have a normal karyotype; hence, the current classification system is still largely based on morphology. In cases of refractory cytopenia with unilineage dysplasia and without increased blasts (in the context of a normal karyotype), the diagnosis of a myelodysplastic syndrome requires the exclusion of secondary causes of dysplasia (e.g., nutritional deficiencies, toxins, medications, inflammation, and infection). Other diagnostic challenges include cases of refractory cytopenias of unknown origin that lack definitive morphologic features of the myelodysplastic syndromes.

The WHO and FAB diagnostic entities are marked by a wide variation in outcomes, probably reflecting genetic heterogeneity in disease pathogenesis; this has spurred efforts to develop prognostic systems that are more accurate with regard to predicting outcomes.[4,5] The International Prognostic Scoring System (IPSS), the most widely used prognostic tool, stratifies patients into four risk groups on the basis of the number of cytopenias, the percentage of bone marrow blasts, and the karyotype.[1,4] Patients classified as having intermediate-2–risk or high-risk disease, characterized by an aggressive course and a short median survival, are generally considered to be candidates for intensive treatment approaches, such as allogeneic stem-cell transplantation, the use of DNA hypomethylating agents, or both.[6] Management options for intermediate-1–risk and low-risk myelodysplastic syndromes include observation, transfusions or growth-factor support, and — for del(5q) myelodysplastic syndrome — lenalidomide.

A major limitation of the IPSS is the heterogeneity within each risk category, particularly the lower-risk categories. In addition, the IPSS was validated in patients with untreated myelodysplastic syndromes at diagnosis, which limits its usefulness as a tool to predict treatment outcomes. Potential prognostic factors not yet incorporated into the IPSS include clinical and demographic factors such as the status with respect to transfusion dependency,[5] severity of thrombocytopenia, and age,[7] as well as genetic factors such as mutations and epigenetic abnormalities.[2,3] There is an urgent need for more refined classification and prognostic scoring systems that include genetic profiling (e.g., mutations, epigenetic states, and gene-expression profiles) and that are linked to therapeutic trials.

In this issue of the *Journal*, Bejar et al.[8] report on a pivotal step toward this goal. By using state-of-the-art technologies, including next-generation DNA sequencing and mass-spectrometry genotyping, to interrogate bone marrow aspirates from 439 patients with myelodysplastic syndromes for 953 mutations (111 genes), Bejar et al. found that the integration of mutation analysis into diagnostic classification and prognostic scoring systems has the potential to stratify a diverse disease into discrete subsets with more consistent clinical phenotypes and prognoses.

What are the key concepts and lessons that can be derived from this study? First, somatic gene mutations are common; 51% of patients had at least one mutation, including one half of the patients examined who had a normal karyotype. Somatic mutations were identified in 18 genes, including 2 genes (ets variant 6 [*ETV6*] and GNAS complex locus [*GNAS*]) for which mutations have not previously been identified in the myelodysplastic syndromes. Second, somatic point mutations are associated with specific clinical features and prognoses. For example, muta-

tions in genes encoding runt-related transcription factor 1 (*RUNX1*), tumor protein p53 (*TP53*), and neuroblastoma RAS viral oncogene homologue (*NRAS*) were associated with severe thrombocytopenia and an increased blast percentage. In a multivariate analysis, mutations in 5 genes (*TP53*, enhancer of zeste homolog 2 [*EZH2*], *ETV6*, *RUNX1*, and additional sex combs–like 1 [*ASXL1*]), which occurred in almost one third of patients, retained independent prognostic significance and predicted poor overall survival. Mutations in these genes allowed further stratification of low, intermediate-1, and intermediate-2 IPSS risk groups and the identification of patients within these subgroups with a poorer prognosis, who may require a more intensive therapeutic approach. Third, illustrative principles on the molecular pathogenesis of the myelodysplastic syndromes emerged — for example, the majority of mutations in these syndromes predict loss of function.

Also informative is the emerging paradigm of mutations in genes (isocitrate dehydrogenase 1 and 2 [*IDH1*/*2*], tet oncogene family member 2 [*TET2*], *EZH2*, and *ASXL1*) involved in the epigenetic regulation of transcription through chromatin modifications and the intriguing observation that mutations often occur in more than one of these genes in the same patient, implying functional cooperation (an exception is that mutations in *IDH1*/*2* and *TET2* are virtually mutually exclusive). In this regard, the analysis of this large series of patients has facilitated the identification of patterns of cooperating mutations and associations with cytogenetic abnormalities. For example, *TET2* mutations occur across the spectrum of cytogenetic subgroups, whereas *TP53* mutations are associated with complex karyotypes and relatively few other mutated genes. These observations supplement our previous understanding of the genetic pathways leading to the myelodysplastic syndromes — for example, the recognition that abnormalities of chromosome 7 occur in conjunction with mutations in *RUNX1* and *NRAS*, suggesting that each lesion drives distinct, but synergistic, steps during the development of the disease.[2,3]

Cytogenetic analysis is the sole genetic testing for the myelodysplastic syndromes currently performed in routine clinical practice. The IPSS and the WHO classification system incorporate only the most common chromosomal abnormalities.[1,4] An international effort is under way to develop a comprehensive cytogenetic scoring system for the myelodysplastic syndromes that incorporates rare cytogenetic subgroups, which will inform an ongoing revision of the IPSS.[9] With the advent of more sensitive techniques already available in the research setting, including next-generation genome and transcriptome sequencing[10] and arrays of single-nucleotide polymorphisms for the detection of copy-number alterations, the rate of discovery will accelerate, and the compendium of genetic alterations in the myelodysplastic syndromes will undoubtedly expand. Detailed analyses of bone marrow samples from a larger number of patients with myelodysplastic syndromes are needed to establish the spectrum and frequency of mutations, the degree of genotypic overlap, and their clinical significance, particularly in predicting outcomes for available therapies.

In conclusion, defining the genetic complexity of the myelodysplastic syndromes holds tremendous promise for elucidating the pathogenesis of these diseases, facilitating diagnosis, refining the prognostic scoring systems, and identifying novel therapeutic targets.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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