Synergistic Interactions of Molecular and Clinical Advances for Characterizing the Myelodysplastic Syndromes

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The myelodysplastic syndromes (MDS) are a heterogeneous spectrum of myeloid clonal hemopathies that provide a clinical model for evaluating the potential evolution of a relatively benign group of hematologic malignancies into one that is frankly aggressive (acute myeloid leukemia [AML]). Clinical and biological complexity has become apparent in this spectrum of disorders. To help to more clearly define the clinical status, prognosis, and therapeutic strategies for these patients, several clinical risk-based classification systems have been developed. In addition, investigations using next-generation molecular technology have permitted clarification of the exomic gene mutational landscape of marrow cells from these patients, describing critical biologic derangements that contribute to the patients’ clinical phenotypes. Proposals have been generated to attempt to effectively incorporate these developments into current management strategies. Given these features, the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MDS have been modified to reflect these relevant advances.1 This article focuses on describing a synthesis of recently reported clinical features and underlying molecular pathogenetic findings intrinsic to the aberrant marrow hematopoiesis generating patient outcomes in MDS.

To aid clinical characterization of patients with MDS, the standard risk-based International Prognostic Scoring System (IPSS) was recently refined and superseded by the Revised IPSS (IPSS-R),2 as reviewed in the current NCCN Guidelines for MDS.1 Advances within the IPSS-R methodology include 5, rather than the previous 3, cytogenetic prognostic subgroups, with specific new classification of several less-common cytogenetic subsets, a split of the low marrow blast percentage value, and scores based on depth rather than the number of cytopenias. This model provides 5 major prognostic categories rather than the 4 that are represented in the IPSS. Various other differentiating features in the IPSS-R are additive to the 5 major parameters for predicting survival, albeit not for AML evolution: age, performance status, serum ferritin levels, and lactate dehydrogenase levels. Compared with the IPSS, the IPSS-R has shown improved predictive prognostic power. The IPSS-R has been extensively validated,3 and has also been shown to be useful for predicting clinical outcomes in patients with secondary MDS and after various forms of therapy (chemotherapy or hematopoietic stem cell transplantation).4–6 The WHO classification–based Prognostic Scoring System (WPSS), which uses WHO morphologic categories in addition to other features of the IPSS-R, has also been updated and shown to have comparable prognostic efficacy.7

Pathogenetic mechanisms contributing to the patients’ clinical phenotypes include the impact of a disparate group of somatic gene mutations. Recent investigations have provided major molecular insights into specific mutations within hematopoietic cells that play a critical role in clinical outcomes. Point mutations have been identified in more than 90% of patients with MDS, including most patients with a normal karyotype.8–10 These mutational features encompass abnormalities involving genes engaged in molecular signaling and differentiation, regulation of cell cycle progression, apoptosis, transcriptional RNA splicing, translation, and epigenetic changes. Some of these mutations are mutually exclusive, whereas others are coexpressed, suggesting

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that disease status is codependent on these abnormalities. Although approximately 50 to 100 genes are frequently mutated in MDS, consistent mutations exist in only approximately 10% of patients.

Spliceosome mutations are those most commonly found in MDS, and are present in approximately 50% of patients. Few (usually 1–3) driver mutations are found at disease presentation, along with numerous passenger mutations that generally increase with disease evolution. Analysis of the clonal architecture of MDS has shown that genetic evolution, and disease progression to AML is a dynamic process shaped by multiple cycles of mutation acquisition and clonal selection.

These molecular findings have also provided prognostic information. An inverse correlation exists between the number of mutations and overall and leukemia-free survival. At least 25 mutations have been associated with poor prognosis in MDS, with good reproducibility for at least 5 specific mutations (TP53, E2H2, ETV6, RUNX1, ASXL1) that are present in 3% to 14% of patients. TP53 mutations have major negative prognostic implications for patients with MDS, particularly in those with del(5q) cytogenetic abnormalities, complex cytogenetics, or secondary forms of MDS. In contrast, SF3B1 mutations, present in virtually all patients with ring sideroblasts, are associated with a good prognosis.

Studies have recently defined molecular abnormalities in chronic myelomonocytic leukemia, with more than 90% of patients with this disease having 1 of 9 specific mutations (TET2, SRSF2, ASXL1, RAS, RUNX, CBL, E2H2, JAK2, IDH1/2). The SRSF2 mutation was generally associated with a good prognosis, whereas poor outcomes were found in patients with U2AF1 and DNMT3A mutations.

However, in addition to somatic mutations occurring in patients with MDS and other myeloid malignancies, recent studies have also shown these lesions in individuals without hematologic abnormalities, particularly as they age. An increased proportion of such individuals (ie, with clonal hematopoiesis of indeterminate prognosis) may subsequently develop a myeloid malignancy.

Given these findings, major issues have arisen as to the use and timing of molecular testing for clinical evaluation. Because no mutation is specific for MDS, and not all patients with MDS have mutations, these molecular features are not diagnostic of the disease. Thus, although these findings can establish somatic (acquired) versus congenital (germline) abnormalities, information obtained from molecular studies should be used in the appropriate clinical context—after clinical and cytogenetic features have established the diagnosis of MDS. After the diagnosis has been made, these molecular findings provide additive prognostic information. The previously noted genes associated with poor prognosis have been shown to alter clinical risk associations by shifting patients into a higher IPSS or IPSS-R clinical risk category. Also, germline abnormalities may exist in certain individuals, particularly those who are relatively young or have familial hematologic disorders. Thus, evaluating nonhematopoietic tissue (eg, skin, buccal smears) for the mutations is important in these circumstances. In addition, more consistency in analysis is needed because differing results may be reported when nonuniform molecular platforms have been used.

Despite these molecular advances, much work is needed to clarify the roles of many of these disparate mutational features, particularly for those lesions that are less commonly present. In addition, the sequence and coexpression of such aberrancies and their relation to either AML progression or marrow failure remains to be defined.

To further clarify such issues, a global multi-institutional collaborative project (the International Working Group for Prognosis in MDS-Molecular Project, coordinated under the aegis of the MDS Foundation) is currently obtaining and analyzing molecular abnormalities from marrow samples in a large group of patients with MDS to define the clearer implications of these findings.
In addition to exomic mutational data, transcriptional studies using microarray platforms,1,2,3,4,5 and more recently with RNA sequencing,6,7 have shown alterations of gene expression patterns from MDS CD34+ marrow cells related to their clinical stages and outcomes, with significant and distinctive differences in gene expression between MDS and normal marrow. Specific clustering of the differentially expressed genes showed alterations in functional pathways and biologic processes that are highly relevant for MDS. These transcriptomic data provide valuable information complementary to exomic gene mutational findings that contribute to further understanding of the biologic mechanisms underlying MDS.

These recent advances that demonstrate methods for characterization of patients with MDS are harbingers of future MDS classifications that will incorporate both molecular and clinical features to refine the diagnostic and prognostic status of these patients. This approach will permit a molecularly based classification within this heterogeneous disease spectrum. Further, as the pathogenetic features related to molecular mutations underlying MDS are more clearly discerned, this “next-generation comprehension” should lead to the discovery of valuable novel therapeutic targets for these patients.

References