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RECENT CLINICAL AND BIOLOGIC ADVANCES IN THE MYELODYSPLASTIC SYNDROMES

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Abstract

The myelodysplastic syndromes (MDS) are a heterogeneous spectrum of myeloid clonal hemopathies. The Revised International Prognostic Scoring System (IPSS-R) provides a recently refined method for clinically evaluating the prognostic risk of MDS patients. Molecular profiling has recently generated extensive data describing critical biologic derangements contributing to the patients' clinical phenotypes. Current molecular insights have shown roles of specific somatic gene mutations for the development and clinical outcomes of MDS, including their propensity to progress to more aggressive stages such as acute myeloid leukemia (AML). This review will focus on these recently reported clinical and underlying molecular pathogenetic findings. Discussion will focus on providing a synthesis of the prognostic clinical and molecular abnormalities intrinsic to aberrant marrow hematopoiesis in MDS.

The myelodysplastic syndromes (MDS) consist of a heterogeneous spectrum of myeloid clonal hemopathies. Factors associated with the clinical and biologic nature of MDS incorporate the two major discerning features of the disease—the poor differentiation of the patients' hematopoietic cells resulting in marrow failure with associated peripheral blood cytopenias and expansion of the abnormal clone for those patients who undergo evolution to or toward acute myeloid leukemia (AML). Pathogenetic mechanisms contributing to the patients' clinical phenotypes relate to critical molecular and biologic features.

This review will focus on recent clinical risk analysis and molecular advances which describe major components of these variable clinical and underlying pathogenetic features. Particular attention will be given to those prognostic features associated with disease stability or progression.

Prognostic Risk Analysis

The International Prognostic Scoring System (IPSS) has been an important standard for assessing the prognosis of primary untreated adult MDS patients (1). However, since its publication in 1997 modification of existing parameters and additional prognostic systems have been suggested as providing meaningful differences for patients' clinical outcomes (2-5), and the World Health Organization (WHO) hematopathologists added morphologic refinement of the French-American-British (FAB) classification (6,7). In addition, the WHO Prognostic Scoring System (WPSS) (2,3)

provided new insights into prognostic variables, adding RBC transfusion dependence along with IPSS cytogenetic classification and WHO dysplastic categories. Importantly, newer cytogenetic groupings have been reported to be prognostically valuable and to refine those features used in the IPSS (8).

To refine the IPSS and evaluate many of the suggested prognostic features defined over the past decade, MDS patient databases were recently coalesced from multiple institutions in 11 countries by the International Working Group for Prognosis in MDS (IWG-PM) project in order to assemble a large combined database of 7012 untreated primary MDS patients for more precise analysis (9). This system comprehensively integrated the numerous known clinical features into a method analyzing MDS patient prognosis more precisely than the initial IPSS. Bone marrow cytogenetics, marrow blast percentage and cytopenias remained the basis of the new system (the Revised IPSS, IPSS-R) (10). Novel components of this scoring method included: five rather than three cytogenetic prognostic subgroups with specific and new classifications of a number of less common cytogenetic subsets, splitting the low marrow blast percentage value, and depth of cytopenias. This model defined five rather than the four major prognostic categories which are present in the IPSS.

A variety of other differentiating features in the IPSS-R were additive to the five major parameters for predicting survival albeit not for AML evolution: age, performance status, serum ferritin and LDH levels. Thus, compared to the IPSS, the IPSS-R demonstrated improved predictive prognostic power with more precise

prognostic categories (five) vs four groups in the IPSS.

Molecular Abnormalities

Multiple pathogenetic features underlying MDS relate to primary disease-specific intrinsic hematopoietic stem cell (HSC) and progenitor lesions combined with an altered intramedullary stromal microenvironment. These findings demonstrate that cytogenetic abnormalities and oncogenic mutations, as well as epigenetic changes are associated with disease progression in MDS. A major final common pathogenetic pathway causing ineffective hematopoiesis in MDS has been the varying degrees of apoptosis of the hematopoietic precursors and their progeny, with increased apoptosis in lower risk compared to higher risk disease (11-14). This apoptotic process in hematopoietic precursors is increased early in the disease with associated peripheral cytopenias and diminishes with disease progression, thus permitting expansion of the abnormal clone.

Recent findings have provided major molecular insights into specific gene mutations playing critical roles for the development and clinical outcome of MDS and its propensity to progress to a more aggressive stage. Somatic point mutations have been identified in more than 70% of MDS patients, including most cases with a normal karyotype, some of which have major prognostic value (15-19). Spliceosome mutations were found in 51% of the patients (20). These abnormalities involve genes engaged in molecular signaling and differentiation, regulation of cell cycle progression, apoptosis, transcription, translation and epigenetics. Genetic alterations have included oncogenic

mutations, amplifications or deletions, transcriptional RNA splicing abnormalities, epigenetic changes and/or altered telomere dynamics.

Some mutations were mutually exclusive, whereas others were associated with other mutations, suggesting the co-dependence of these mutations being related to disease status. Five gene mutations (*TP53*, *EZH2*, *ETV6*, *RUNX1*, *ASXL1*), present in 3-14% of the patients, have been shown to be associated with poor overall survival. There was an inverse correlation between gene mutation number and overall and leukemia-free survival.

Studies have recently defined numerous molecular abnormalities in chronic myelomonocytic leukemia (CMML). Nine mutations were particularly frequent, of which 93% patients had at least one such lesion (21). The *SRSF2* mutation, a member of the spliceosome complex, was generally associated with a good prognosis, whereas worse prognosis was found in patients with *U2AF1* and *DNMT3A* mutations (22).

Patients with del(5q) cytogenetics have a distinctive form of MDS, with a remarkably high erythroid and cytogenetic responsiveness to the drug lenalidomide. However, the durability of that response and potential for AML evolution of these patients is quite variable. Long term outcomes are poorer in del(5q) patients with additional cytogenetic lesions compared to those with del(5q) alone (23). Recent data using very sensitive next generation sequencing techniques demonstrated that a higher than expected subset of lower risk del(5q) patients (18%) have *TP53* mutations (24). These patients with mutated *TP53* had poorer erythroid

and cytogenetic responses to lenalidomide and a higher potential for AML evolution.

Conclusions

The IPSS-R, with its risk-based method of characterizing primary untreated MDS, has been shown to possess improved prognostic ability for survival and AML evolution compared to the IPSS and other prior classification systems. As such, it is beneficial for clinical determination of prognostic status of patients and to aid design and analysis of clinical trials for this disease. Combining these clinical features with the recently defined molecular lesions should markedly enhance our ability to provide more precise diagnostic and prognostic analyses for these patients.

The molecular data presented herein provide insights into mechanisms underlying MDS and their propensity to progress to more aggressive stages. Specific genetic alterations present in individual MDS patients explain much of the clinical heterogeneity shown by this spectrum of diseases. Molecular analysis of the clonal architecture in MDS demonstrated that genetic evolution and disease progression to AML is a dynamic process shaped by multiple cycles of mutation acquisition and clonal selection (25). Extending the use of more comprehensive and sensitive methods for molecular profiling using next generation sequencing techniques to evaluate MDS marrow cells will likely define further critical biologic lesions underlying this spectrum of diseases. As such, these findings have the potential to generate discovery of valuable targets for future biospecific therapy of MDS patients.

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