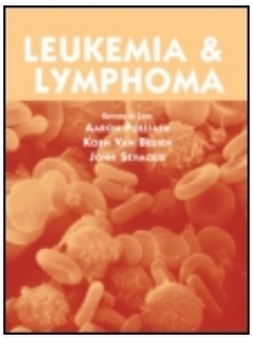

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COMMENTARY

Heterogeneity in the myelodysplastic syndromes: moving toward a better understanding

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The myelodysplastic syndromes (MDS) are a group of heterogeneous, malignant hematopoietic stem cell disorders. While they collectively result in ineffective hematopoiesis, with aberrant cellular maturation resulting in chronic peripheral cytopenias, their clinical presentation and course are quite variable [1]. At one end of the spectrum, low-risk disease has a fairly indolent course, noting that younger patients have a reported median survival of over 11 years [2]. However, those with unfavorable characteristics have a worse prognosis. Patients with high risk features have a poor overall survival (<1 year on average regardless of age at diagnosis), as well as a relatively high propensity for transformation into acute leukemia [2]. The disparity between high and low risk MDS underscores a need to better define its pathogenesis, and determine mechanisms that may explain differences between the various subtypes.

Diagnostic criteria for MDS are clearly defined by the French–American–British (FAB) or World Health Organization (WHO) classification systems [1]. Unfortunately, these do not provide significant insight into the underlying pathophysiology, and by themselves, cannot reliably predict clinical course. To aid in prognostication and help guide treatment decisions, various clinical scoring systems have been developed. The International Prognostic Scoring System (IPSS) is considered the most utilized, as it was validated to predict survival and time to leukemic progression in 816 treatment-naive patients with MDS [2]. This system assigns points to each of three key areas (bone marrow blast percentage, karyotype and peripheral cytopenias), and patients can be grouped into low, intermediate (1 and 2) and high risk categories. Blast percentage and unfavorable cytogenetics are more heavily weighted toward a negative outcome. Median overall survival ranges from 5.7 to 0.4 years for those with low versus high risk disease, and rates of leukemic transformation also correspond with the IPSS scale. A revised scoring system (IPSS-R) was recently published following evaluation of over 7000 patients with MDS [3]. Cytogenetics, bone marrow blast percentage and peripheral cytopenias remain the basis for the new system; however, severity of cytopenias is considered in scoring. In addition, the karyotype is expanded into five risk categories (previously three), and blast percentage >10 is given the highest negative weight compared to >20 in the prior system. Consistent with the original IPSS, overall survival in the IPSS-R was longest in the lowest risk group (8.8 years), noting a progressive decline with less favorable features, and only 0.8 years in the very high risk group. Similarly, median times until 25% of the population developed acute leukemia were >14.5 years and 0.7 years, respectively.

While often helpful, there are several limitations with these prognostic scoring systems. Only those with *de novo* disease were included for evaluation in both the IPSS and revised versions. Patients were also given only supportive therapies until leukemic transformation; it is unclear how more readily available disease-modifying treatments, including hypomethylating agents, lenalidomide or stem cell transplant, would impact survival and leukemic evolution in these scales. And while these can give an indication as to potential clinical course, they still do not address fundamental differences in underlying pathophysiology of MDS subtypes. Indeed, the underlying pathogenesis of MDS is incompletely understood at present.

A possible role of the matrix metalloproteinases (MMPs), and their regulation, has been raised in hematologic malignancies, including MDS [4]. With their ability to cause degradation of many components of the extracellular matrix, a role for MMPs in the invasive and metastatic potential of solid tumors would seem more plausible. However, these proteins may serve other functions, including cell growth and differentiation, which would be more relevant in the hematologic malignancies. In this issue of ***Leukemia and Lymphoma***, Melo *et al*. report a potential role of aberrant regulation of MMPs in MDS [5]. They found significantly lower levels of the tissue inhibitor of metalloproteinase-2 (TIMP-2) in those with acute myeloid leukemia (AML) and MDS compared to healthy controls, with lowest levels being seen in patients with AML or WHO high-risk MDS. Unfortunately, the TIMP-2 levels were not able to differentiate between low and high risk disease based on the IPSS scale, nor were they

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able to predict survival. There was also no difference across subgroups with regard to TIMP-1 levels; the reason for the discrepancy in TIMP-1 and -2 findings is unclear. Whether variable regulation of MMPs adds to the pathogenesis of MDS, partially explains differences in disease subtypes and clinical outcomes, or adds to existing prognostic scales, would need to be evaluated with larger studies.

However, more extensive genetic evaluation has shown considerable promise in explaining the pathology and heterogeneity between the MDS subtypes. Mutations involving components of RNA splicing (*U2AF35*, *ZRSR2*, *SRSF2* and *SF3B1*) were found to be frequent in myeloid neoplasms with dysplastic features [6]. Somatic mutations in the *SF3B1* gene strongly correlated with the presence of ringed sideroblasts, and were independently associated with a lower risk for AML conversion as well as a better overall survival [7]. More recently, previously unreported somatic mutations were identified in 18 genes in patients with MDS through next-generation sequencing and mass spectrometry-based genotyping [8]. Over 50% of the 439-patient cohort harbored one of these mutations, including half of the patients with normal cytogenetics based on conventional analysis. Poor clinical features of severe thrombocytopenia and higher bone marrow blast percentage were strongly associated with mutations in *NRAS*, *RUNX1* and *TP53*. These three, as well as *EZH2* and *ETV6* mutations, were independently associated with negative prognostic significance.

A better understanding of the pathophysiology of MDS, particularly at the molecular level, has already resulted in more directed therapy. The 5q31 deletion is associated with a good prognosis, as well as an excellent clinical response to treatment with lenalidomide [9]. Those with high risk disease have clinical improvement, including decreased transfusion requirements, slower progression to leukemia and better overall survival, with the use of hypomethylating agents such as azacitidine [10]. Further elucidation of disease mechanisms in MDS, particularly highlighting key differences that help explain the heterogeneity among subtypes, may prove helpful in identifying more targeted therapies, in addition to identifying patients who may require a more aggressive treatment approach.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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