Myelodysplastic Syndromes: An Historical Perspective

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In 1900, Leube described a patient with severe megaloblastic anemia, preceding the development of overt leukemia. This case was followed by similar reports of patients characterized by cytopenia, dysmaturation of marrow precursors, an increase of marrow blasts and a significant risk of evolving to acute myeloid leukemia. The first classification of the myelodysplastic syndromes published in 1982 by the French-American-British (FAB) group, sorted out the differences between subgroups with and without an increase of marrow blasts, defined sideroblastic anemia by its characteristic accumulation of mitochondrial iron in erythroblasts, and included chronic myelomonocytic leukemia. During the 1990s, it became clear that additional clinical variables, and in particular chromosome analysis, largely contributed to clinical outcome and that survival and risk for leukemic transformation was significantly worse in patients with adverse cytogenetics. In 1997, patient cohorts from the United States, Europe and Japan were put together and reviewed thoroughly in order to form the database of the International Prognostic Scoring System (IPSS). Based on the number of significant cytopenias, percentage of marrow blasts, and cytogenetic risk profile the IPSS divided patients into four risk categories with significantly different probabilities for survival and risk for leukemic transformation. The IPSS has been extremely useful, and not until recently have new validated risk factors been introduced, the most important being presence of a transfusion need.

Myelodysplastic syndromes (MDS) encompass some entities with clearly different biological basis, two of these being sideroblastic anemia (WHO RARS) and the 5q- syndrome (WHO refractory anemia with an isolated del(5q) and less than 5% marrow blasts). Bjorkman introduced sideroblastic anemia in 1956, when he described four cases with refractory anemia and “great amounts of free iron in the normoblasts.” Pure RARS with isolated erythroid dysplasia is characterized by hyperplastic but ineffective erythropoiesis and has a very low risk for leukemic transformation. It was recently described that the cellular iron in RARS is deposited in the mitochondria in the form of aberrant mitochondrial ferritin, and that the erythroid apoptosis is mediated via a mitochondrial release of the pro-apoptotic protein cytochrome c. Lately, a subgroup of RARS with marked elevation of platelet counts was defined. Approximately 50% of these patients present with a JAK2 mutation, thus providing a link between MDS and myeloproliferative disorders. The 5q- syndrome was described by Van Den Berghe in 1974 as the first entity within the group of refractory cytopenias with a common chromosomal aberration, an interstitial deletion of 5q. It took more than 20 years to define the commonly deleted segment (CDS) of 5q and to confirm that the corresponding allele did not contain mutated genes within the CDS. Recently, Ebert et al proposed that the clinical phenotype may be caused by haploinsufficiency of certain genes within the CDS, by showing that downregulation of the ribosomal protein RPS14 induced defect erythroid maturation in normal progenitors, and that restoration of the same gene could rescue the erythroid phenotype in 5q- progenitors. These and other recent advances in understanding the pathogenesis of MDS have already led to new and effective therapies for defined subsets of MDS, a disease that has historically and into the present been so difficult to treat.

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