

MDS: Separating the Forest of Cytogenetic Abnormalities From the Trees (Targets)

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Myelodysplastic syndrome (MDS) is the term for a collection of clonal abnormalities affecting hematopoietic development. For the past several years we have been able to identify high-risk patients by WHO classification and IPSS score, but until two years ago, few if any active therapies were available. Over the past two years, three drugs have been approved for treatment of patients with MDS, 5-azacytidine (azacitidine), 5-aza-2'-deoxycytidine (decitabine), and lenalidomide. We are now in a position to define sub-groups of patients with MDS based upon molecular phenotyping data.

Dr. Pierre Fenau of the Université Paris in Bobigny, France, led off the session with a discussion of the 5q minus syndrome (del(5q)), which accounts for approximately 10 percent of cases of MDS. He pointed out that the "del(5q) syndrome" is characterized by severe anemia, frequent thrombocytosis, dysmegakaryopoiesis with a specific hypo-lobulated morphology, rare AML transformation (10 percent), and favorable clinical course. Despite a good prognosis, until the approval of lenalidomide, the only therapeutic intervention possible was transfusions. Patients with this syndrome are certainly a distinct clinical entity easily differentiated from other MDS with cytogenetic abnormalities, including those with del(5q) with or without additional abnormalities. Nevertheless, results indicate that lenalidomide is generally active in MDS with del(5q), with and without additional cytogenetic abnormalities. Lenalidomide was approved this year for transfusion dependent patients with MDS and del(5q). Treatment led to transfusion independence in over 75 percent of patients with low- and intermediate-risk 1 MDS. Also, it has activity in treating patients with intermediate-risk 2 and high-risk MDS, but this use would be off-label. Of note, lenalidomide not only led to transfusion independence in the majority of these patients, treatment also was associated with complete molecular remission in 45 percent.

Next, Dr. James W. Vardiman discussed issues regarding hematopathologic classification of MDS and the importance of bone marrow examination. He pointed out that, although the hallmark of diagnosis is based on the biopsy specimen, the biopsy is also necessary to exclude other diagnoses that can have similar clinical presentations, such as hairy-cell leukemia, lymphoma, or metastatic tumors. Also, since the most common initial manifestation of MDS is in the erythroid lineage, it is important to recognize that inter-observer agreement regarding dyserythropoiesis is notoriously poor. Recent data indicate that flow cytometry is an important and useful tool in evaluating cases of MDS. Furthermore, cytogenetic abnormalities are very diagnostically useful; however, these are associated with 40-60 percent of cases, and are even less frequent in the lower grade lesions. However, if present, cytopenias and immunophenotypic and chromosomal abnormalities are usually sufficient for diagnosis, even in cases where morphology is not obvious. Dr. Vardiman concluded by discussing the controversy surrounding the WHO classification system by proponents of the FAB system.

In the final part of the session, Dr. Charles A. Schiffer discussed case-based approaches to clarify controversies and issues of treatment interventions. He discussed the complex management of patients with myelodysplasia (MDS) who present with variable clinical manifestations as well as complicating co-morbidities.

For those interested in learning more about MDS, Soriano et al. (abstract #160) evaluated azacitidine, valproic acid (histone deacetylase inhibitor or HDACI), and ATRA in patients with AML. Gore et al. (abstract #517) evaluated azacitidine combined with MS-275 (HDACI) and demonstrated cytogenetic remissions with this well-tolerated regimen. Wu et al. (abstract #2629) present data indicating that methylation of SOCS1 gene occurred in 47 percent of evaluated patients with MDS, and this methylation was correlated with unfavorable prognostic features such as RAS mutation and poor-risk karyotype.