

# MDS Matures from Mere Management to Mutation, Methylation, Manipulation

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The Education Session on Myelodysplastic Syndromes at 9:30 a.m. today and again tomorrow at 7:30 a.m. in Hall A1-A2, focuses on how knowledge of genetic mutation and control of gene expression has resulted in, and continues to impact development of, new MDS drugs. With FDA approval of azacitidine in May 2004, MDS at last became a disease that could be treated rather than merely managed by supportive care. The approval of two additional drugs, decitabine and lenalidomide, has changed the therapeutic landscape of this deadly disease that strikes a predominantly older population. This breakthrough has occurred through understanding the mutations and molecular mechanisms that contribute to initiation and development of the disease. In addition, the session will include a discussion of the clinical implications and management of the red blood cell transfusion dependency seen in many patients with MDS.

Numerous gene mutations are found in MDS and AML cells after exposure to irradiation or chemotherapy (treatment-related MDS, T-MDS, AML, and T-AML). These mutations occur as well in *de novo* MDS and AML, albeit with differing frequencies. In his presentation, Dr. Jens Pedersen-Bjergaard will show that most of the mutations affect three functional classes of genes: tumor suppressors, tyrosine kinase genes, or transcription factors that control gene expression. While seemingly complex, many of the mutations appear to cluster into subgroups that also define clinical subsets of MDS and AML. These similarities indicate that the etiology, pathology, and therapy of T-MDS, MDS, T-AML, and AML are interconnected.

Genetic modification and control of gene expression may be due to biochemical alterations of the chromosome structure without accompanying changes in the primary DNA sequence. This is referred to as epigenetic modification. Methylation and acetylation are the most common epigenetic changes: these have been identified in many types of cancer, including MDS. Dr. Guillermo Garcia-Manero will summarize the clinical experience in treating MDS with DNA-hypomethylating drugs and discuss potential toxicities as well as future strategies for improving treatment outcome.

Dr. Alan List, from H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL, will provide an overview of the adverse impact that severe anemia requiring continued blood transfusions has on the clinical course of MDS. Recent studies suggest therapies that alleviate the anemia not only improve quality of life, but, most importantly, may affect the natural history of the disease. The various therapeutic options that relieve the transfusion burden will be summarized. Primary therapy in this respect should take into account age, transfusion frequency, endogenous erythropoietin levels, and cytogenetics.

In the Plenary Session tomorrow, Dr. Ebert will report on exciting research using RNA interference to identify the causal gene for the 5q- syndrome, a subset of MPD with a block in erythroid maturation. By a lentivirus expressing short hairpin RNAs, they targeted each of 41 candidate genes, assessing their hematopoietic differentiation in marrow CD34+ cells, and determined that only one, the ribosomal protein encoding *RPS14* gene was the causal gene.