Untangling the Web of Genome, Epigenome, and Immunity in MDS

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Identification of genetic, epigenetic, and immunologic abnormalities in the pathology and progression of myelodysplasia has led to the development of several successful therapies. The three presentations in the Scientific Committee session on Hematopoietic Cytokine and Factors (offered today at 9:30 a.m.) will summarize how these advances have given, for the first time, the clinician an arsenal of therapies that can improve the debilitating clinical features of this disease. Dr. Ghulam Mufti will describe the successes and pitfalls in using the gene array-based technologies to detect new molecules and molecular pathways unique to specific MDS subtypes. The immense amount of data generated by the arrays has resulted in computational advances that are expected to greatly facilitate continuing therapeutic progress, in part by identifying molecular profiles specific to subsets of patients likely to respond to particular therapies.

Dr. Jean-Pierre Issa will describe how epigenetic changes in the MDS clone, due to aberrant methylation, led to the successful use of azacitidine and decitabine in the treatment of MDS. He raises the question, however, of whether response is entirely due to the mechanism of demethylation attributed to these drugs. Since there is no way to predict which MDS patients will likely respond, and nearly all patients will develop resistance to therapy, further improvements in epigenetic therapy are necessary. Investigations addressing these problems are currently underway, and it is hoped that epigenetic-modifying therapy will eventually offer a cure for at least a subset of patients with this disease.

Dr. A. John Barrett, in his presentation titled "The Role of Cytotoxic T Cells in MDS Pathophysiology" will describe the role that aberrant immune response plays in MDS. Immune suppression has been shown to be therapeutic in MDS patients with a trisomy 8 karyotype. The cells of these patients seem to be in a state of incomplete apoptosis, which accounts for the dysplasia and growth advantage of the clone over normal cells. Whether this type of autoimmune mechanism plays a role in other MDS subtypes is not yet known. The interplay between genome, epigenome, and the proteome is extremely complex, but for patients with MDS, the threads of the "web" are beginning to be untangled.

In a Tuesday simultaneous session on MDS, exciting results from a phase III multi-center study will demonstrate that for the first time survival of high risk patients with MDS may be extended with azacitidine (AZA). The overall survival was 24.4 months among AZA-treated versus 15 months for those receiving conventional therapy.

In other related simultaneous sessions, new therapeutics are generating great interest. For example, lenalidomide has revolutionized treatment of the 5q- syndrome, a subset of MDS, with elimination of transfusion dependence in 67 percent of treated patients.

Finally, although studies of MDS have been limited by lack of a specific animal model, a number of potential animal models, with various clinical manifestations, are available. For example, an NR2F6 mouse transplant model of MDS transforms to acute leukemia (AML). In another model, mice recipients of bone marrow cells of mice expressing a fusion gene NUP98-HOXD13 develop MDS-like findings, including anemia, leucopenia, lymphopenia, and neutropenia in recipients. A third mouse model has a mitochondrial mutation, Polg-D257A, which destroys the mitochondrial DNA proofreading gene, resulting in myelodysplasia without myeloproliferation. These models are hoped to be useful in studying new therapeutic drugs for MDS.