TABLE 45-8 REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELODYSPLASTIC SYNDROMES

PROGNOSTIC SUBGROUPS (% OF PATIENTS)	CYTOGENETIC ABNORMALITIES	MEDIAN SURVIVAL (YR)*	MEDIAN EVOLUTION TO AML, 25%† (YR)*	HAZARD RATIOS OS/AML*	HAZARD RATIOS OS/AML‡
Very good (3-4%‡)	−Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
Good (66-72%)	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1	1/1
Intermediate (13-19%‡)	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5	1.5/1.8	1.6/2.2
Poor (4-5%‡)	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities	1.5	1.7	2.3/2.3	2.6/3.4
Very poor (7%‡)	Complex: >3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9

AML, Acute myeloid leukemia; NR, not reached; OS, overall survival.
*Multivariate analysis, $N = 7012$; data from patients in the International Working Group for Prognosis in MDS (IWG-PM) database.
†*AML*, 25% indicates time for 25% of patients to develop AML.
‡$N = 2754$; Data from Schanz J, Tüchler H, Solé F, et al: New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes and oligoblastic AML following MDS derived from an international database merge, *J Clin Oncol* 30:820–829, 2012.

hundreds of thousands of genes, pathways, and biologic processes in cancer samples. Whole-genome sequencing of untreated MDS samples has revealed that at least 78% of patients carry one or more oncogenic mutations. Although more than 40 genes are recurrently mutated in MDS, most are altered in less than 5% of MDS patients, reflecting the enormous biologic heterogeneity of this disorder. Genes implicated in MDS are involved in cell signaling, DNA methylation, chromatin regulation, and most importantly, RNA splicing. Several studies have shown that several individual gene mutations, including *EZH2, DNMT3A, SF3B1, TET2, NRAS, TP53, RUNX1*, and *ASXL1*, predict MDS outcomes independent of IPSS classification and can improve on prognostication based on clinical features alone.

Comprehensive genomic screening of diagnostic MDS samples occurs largely in academic centers. However, as technology advances, it is likely that novel prognostic models incorporating these mutational signatures will be adopted into the clinical care of patients.

PROSPECTUS FOR THE FUTURE

The field of stem cell biology is rapidly changing. The study of HSC function in marrow failure syndromes provides hints of specific molecular pathways disturbed in many diseases of hematopoietic and nonhematopoietic stem cells. These observations are furthering our knowledge about the complex interplay among AA, PNH, and MDS. Understanding stem cells' plasticity and regulatory roles promises new therapeutic avenues for a wide array of diseases.

UCB stem cells represent a potential source of donor cells for allogeneic stem cell transplantation in patients with primary hematologic diseases lacking other HLA-matched marrow donors. Nonmyeloablative stem cell transplantations (i.e., mini-transplantations) employing low-dose conditioning and immunosuppressive regimens represent another emerging treatment option for older patients with primary marrow failure syndromes.

The TPO agonist eltrombopag and the anti-CD52 antibody alemtuzumab show promise in restoring normal hematopoiesis in refractory AA patients. Novel agents targeting the unique biologic features of ineffective hematopoiesis in marrow failure syndromes have improved outcomes for many patients over the past few years: eculizumab in PNH; 5-azacytidine in transfusion-dependent MDS; immunosuppressive drugs in AA and MDS subsets; lenalidomide in 5q− MDS.

Discoveries elucidating the complex genomic landscape of MDS have revealed that almost 80% of cases are characterized by at least one oncogenic mutation, and more than 40 unique genes are recurrently mutated in this disorder. Much research remains to be done to determine how best to incorporate this vast amount of information into the clinical care of MDS patients and to tailor therapeutic options for these unique biologic signatures.

For a deeper discussion of these topics, please see Chapter 156, "Hematopoiesis and Hematopoietic Growth Factors," in Goldman-Cecil Medicine*, 25th Edition.*

SUGGESTED READINGS

Bejar R, Stevenson KE, Caughey BA, et al: Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes, J Clin Oncol 30:3376–3382, 2012.

Hillmen P, Muus P, Roth A, et al: Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria, Br J Haematol 162:2–73, 2013.

Marsh JC, Kulasekararaj AG: Management of the refractory aplastic anemia patient: what are the options? Blood 122:3561–3567, 2013.

Olnes MJ, Scheinberg P, Calvo KR, et al: Eltrombopag and improved hematopoiesis in refractory aplastic anemia, N Engl J Med 367:11–19, 2012.

Papaemmanuil E, Gerstung M, Malcovati L, et al: Clinical and biological implications of driver mutations in myelodysplastic syndromes, Blood 122:3616–3627, 2013.

Risitano AM: Paroxysmal nocturnal hemoglobinuria and the complement system: recent insights and novel anticomplement strategies, Adv Exp Med Biol 735:155–172, 2013.

Scheinberg P, Nunez O, Weinstein B, et al: Activity of alemtuzumab monotherapy in treatment-naive, relapsed, and refractory severe acquired aplastic anemia, Blood 119:345–354, 2012.