■ Article

Update on the Science of Myelodysplastic Syndromes

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Scientific research is only just beginning to shed light on the pathobiology underlying the various subtypes of myelodysplastic syndromes (MDS), a heterogeneous group of clonal stem cell disorders characterized by cytopenias that can progress to acute myeloid leukemia. Increased understanding of the disease and prognostic implications of specific clinical features has aided in the development of prescribing guidelines and new treatments for MDS. Because oncology nurses have frequent interactions with patients during diagnostic and therapeutic evaluations, an understanding of the science behind disease classification, prognostic scoring, and the goals of treatment for low- and high-risk disease is important to answer questions regarding diagnostic results, treatment outcomes, and adverse event monitoring.

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Myelodysplastic syndromes (MDS) represent a group of myeloid malignancies characterized by cytopenias of one or more blood lineages (Kurtin & Demakos, 2010). The heterogeneity of the clinical presentation, disease trajectory, prognosis, and risk of leukemic transformation requires a precise diagnostic evaluation (see Table 1). Cytogenetic and diagnostic staging advances have resulted in refinement of MDS prognostic staging systems that better evaluate the expected disease trajectory and risk of leukemic transformation. The clinical presentation and diagnostic evaluation provide the foundation for therapeutic selection. This article focuses on recent advances in diagnostics, refinements of common prognostic staging systems, and new clinical data on the natural history of MDS as well as the goals of available therapeutic treatments.

Diagnostic Advances: Cytogenetic and Molecular Attributes

Initially, diagnosis of MDS focused solely on cell morphology and blast counts (National Comprehensive Cancer Network [NCCN], 2011). Advances in karyotypic analysis have demonstrated that MDS is characterized by multiple cytogenetic defects that affect diagnosis, prognosis, and treatment (Garcia-Manero, 2010; Haase et al., 2007). Conventional metaphase cytogenetic analysis is the gold standard in karyotypic analysis in hematology; the analysis typically examines 20 actively dividing cells in metaphase to identify chromosomal abnormalities. Use of metaphase cytogenetic analysis to study a large cohort of untreated patients revealed that the survival of patients with cytogenetic abnormalities was significantly shorter than those with normal cytogenetics, and a greater number of abnormalities were associated with shorter survival (Haase et al., 2007). In addition, certain abnormalities were associated with better or worse clinical outcomes (see Table 2). However, patients with normal karyotypes (as determined by metaphase analysis) had a wide variability in clinical outcomes.

Because metaphase cytogenetic analysis cannot detect abnormalities in nondividing cells, new technologies have been developed to enhance sensitivity of karyotype analysis (Tiu, Visconte, Traina, Schwandt, & Maciejewski, 2011). The single-nucleotide polymorphism array overcomes this limitation; it detects copy number alterations below the limit of standard

metaphase cytogenetic analysis detection and identifies abnormalities in nondividing cells (Gondek et al., 2008; Maciejewski & Mufti, 2008). Use of a single-nucleotide polymorphism array allows for the identification of abnormalities in specific genes that have prognostic significance, some of which have demonstrated differential responses to certain therapies (Graubert, 2011; Tiu et al., 2011). For example, the *TET2* gene produces an enzyme that affects the DNA methylation state, and its dysregulation may have a role in epigenetic alterations in MDS (Garcia-Manero, 2010). A small study (N = 13) showed that mutated *TET2* was an independent prognostic factor for increased response rate to azacitidine therapy (Itzykson et al., 2011). In contrast, mutation of the tumor suppressor gene (TSG) *TP53* is an independent predictor of poor prognosis and inferior response to hypomethylating agents and the immunomodulatory agent lenalidomide (Jadersten et al., 2009, 2011; Link, Baer, James, Jones, & Karpf, 2008). Flow cytometry (FC) immunophenotyping provides an additional tool for characterization of MDS clones. FC is used to define hematologic disorders on the basis of quantitative and/or qualitative cell receptor or internal protein expression. Several studies examining FC as an MDS diagnostic tool have indicated the need for additional refinement and standardization of quantification measures before incorporating FC into the routine diagnostic evaluation of MDS (Westers et al., 2011). Despite lack of consensus on the appropriate diagnostic parameters, CD34-related parameters are good candidates because the CD34-positive stem cell compartment in MDS is altered.

Detailed diagnostic testing knowledge can aid nurses when counseling patients. Many patients have acquired sophisticated knowledge about their disease from the Internet and may request tests that have not been proven clinically relevant. In addition, knowledge of the science behind cytogenetic and molecular testing can aid explanations for treatment delays while waiting for testing to become available.

TABLE 1. Diagnostic Evaluation of MDS

Diagnostic Study	Clinical Significance
Medical history and medication profile	Document onset of suspicious symptoms, acute episodes of illness, and prior transfusion history. Review medication profile to identify any potential medication-induced cytopenias; comorbid conditions and effective management may play a critical role in determining potential therapies.
Peripheral Blood	
Complete blood count, differential, platelet count, reticulocyte count	Evaluate for presence of cytopenias, peripheral blasts, morphologic abnormalities, and bone marrow response to anemia.
Serum iron, ferritin, TIBC, folic acid, vitamin B_{12}	Evaluate for other possible causes of anemia.
Lactate dehydrogenase, haptoglobin, antiglobulin	Evaluate for possible underlying hemolysis.
Serum erythropoietin	Baseline evaluation of levels to determine role for growth factors versus active therapies in patient needing treatment
Other Laboratory Studies	
Thyroid profile	Immunomodulatory agents may be associated with hypothyroidism, which can contribute to anemia.
Serum testosterone	Hypogonadism is associated with fatigue and may be effectively treated.
Renal and hepatic profile	Many MDS treatments may have renal and hepatic toxicities or may be affected by renal or hepatic insufficiencies.
Bone Marrow	
Aspirate should include spicules and be cellular enough to assess 500 cells or more	Used for flow cytometry, FISH analysis, and cytogenetics to determine dysplasia, blast percentage, and number of monocytes, ringed sideroblasts, and atypical megakaryocytes. Results allow for FAB/WHO classification.
Biopsy (adequate size for evaluation is 1–2 cm)	Evaluate cellularity, topography, presence of atypical localization of immature precursors (considered a poor prognostic finding), exclusion of other bone marrow disorders, or bone marrow infiltration by solid tumors.
Cytogenetics	Evaluation for possible nonrandom chromosomal abnormalities More than two metaphases from 20 samples with the same abnormality are considered nonrandom.

FAB—French-American-British; FISH—fluorescent in situ hybridization; MDS—myelodysplastic syndromes; TIBC—total iron-binding capacity; WHO—World Health Organization

Note. From "Myelodysplastic Syndromes: Diagnosis, Treatment Planning, and Clinical Management," by S.E. Kurtin, 2007, *Oncology (Williston Park), 21*(11, Suppl. Nurse Ed.), p. 42. Copyright 2007 by UBM Medica. Reprinted with permission.

Classification and Prognostic Scoring Systems

Two primary MDS diagnostic classification systems are in use: the French-American-British (FAB) system, based on morphology and blast percentage, and the World Health Organization (WHO) system, with the addition of cytogenetics (Bennett et al., 1982; Vardiman et al., 2009) (see Table 3). These morphology-based systems have come under scrutiny. Analysis of 915 patients referred to MD Anderson Cancer Center (MDACC) from 2005 to 2009 showed a discordance in diagnosis of MDS between the referring practice and MDACC in 16% of patients (150 of 915) (Naqvi et al., 2010). The data underscore the diagnostic complexity of MDS, value of expert hematopathologists, current morphology-based disease classification limitations, and MDS diagnostic discrepancies between referral and tertiary care centers. More recently, prognostic models have been developed to estimate prognosis and risk of leukemic transformation. The International Prognostic Scoring System (IPSS) categorized four groups of previously untreated patients based on a scoring method involving cytopenias, cytogenetics, and percentage of blasts in the bone marrow (Greenberg et al., 1997) (see Table 4). Median survival time and the time to

TABLE 2. Cytogenetic Abnormalities by Associated Clinical Outcome Based on the MDS Cytogenetic Scoring System

Prognostic Subgroup	Cytogenetic Abnormalities	Survival (Months)	Hazard Ratio
Very good	del(11q), –Y	60.8	1
Good	normal, der(1;7), del(5q), del(12p), del(20q), double including del(5q)	48.5	2.1
Intermediate	–7/7q–, +8, i(17q), +19, +21, any other single, double, independent clones	24	3.4
Poor	der(3)(q21)/der(3)(q26), double including –7/7q–, complex (three abnormalities)	14	6
Very poor	complex (more than three abnormalities)	5.7	9.3

N = 2,901

der—derivative; i—inversion; MDS—myelodysplastic syndromes

Note. Based on information from Schanz et al., 2010.

transformation to acute myeloid leukemia (AML) consistently decreased as IPSS score increased (see Table 5). Two important limitations of the IPSS method are that it underemphasizes the impact of cytogenetics and is designed for use only at initial diagnosis (Garcia-Manero, 2011). Based on observations that transfusion dependence (TD) was an independent prognostic factor for lower-risk IPSS subgroups, the WHO Prognostic Scoring System (WPSS) was developed to incorporate WHO subgroups, IPSS cytogenetics, and red blood cell transfusion requirements (Malcovati et al., 2007). Because this model was designed to be used at any time during follow-up, it can be used for implementing risk-adapted treatment strategies at any point after diagnosis. In particular, the WPSS is useful in identifying patients with low-risk disease who may benefit from early disease-modifying treatment (Navada & Silverman, 2011). However, the WPSS has two key limitations: lack of ability to directly account for cytopenias other than anemia and inability to be applied to patients who lack a WHO subtype description (Komrokji et al., 2010; Komrokji, Zhang, & Bennett, 2010). The MDACC developed a prognostic scoring system that does not rely on WHO scoring and can be used to determine prognosis at any time during the course of MDS (Kantarjian et al., 2008) (see Tables 4 and 5). In addition, Greenberg et al. (2011) are currently developing a revised IPSS (IPSS-R) system based on a database of more than 7,000 patients. The IPSS-R will include five risk groups (very low, low, intermediate, high, and very high) with estimated overall survival and risk of AML transformation (Greenberg

TABLE 3. MDS Classification Systems

FAB	World Health Organization 2000	World Health Organization 2008	Dysplasia	Blast Percent (BM/PB)
Refractory anemia	Refractory anemia MDS unclassified RCMD del(5q)	RCUD Refractory anemia Refractory neutropenia Refractory thrombocytopenia RCMD Isolated del(5q) MDS unclassified	– Erythroid Nonerythroid Nonerythroid Erythroid with other Erythroid with megakaryocytic Unilineage with pancytopenia or RCMD/RCUD with 1% PB blasts	All: less than 5/1 or less
RARS	RARS RCMD-RS	RARS RCMD-RS	Erythroid only Erythroid plus other (all greater than 15% ringed sideroblasts)	Less than 5/less than 1
RAEB	RAEB-1 RAEB-2	RAEB-1 RAEB-2	1 or more lineage 1 or more lineage	5–9/2–4 10–19/5–19 with or without Auer rods
RAEB in transformation	Acute myeloid leukemia	Acute myeloid leukemia	Myeloid with or without other	20 or more/—
CMML	MDS/MPD CMML JMML Atypical CML MDS/MPD unclassified	MDS/myeloproliferative neoplasm CMML JMML BCR-ABL–negative CML MDS/MPD unclassified	Variable greater than 1×10^9/L monocytosis	All: less than 20/—

BM—bone marrow; CML—chronic myeloid leukemia; CMML—chronic myelomonocytic leukemia; FAB—French-American-British; JMML—juvenile myelomonocytic leukemia; MDS—myelodysplastic syndromes; MPD—myeloproliferative disorder; PB—peripheral blood; RAEB—refractory anemia with excess blasts; RARS—refractory anemia with RS; RCMD—refractory cytopenia with multilineage dysplasia; RCUD—refractory cytopenia with unilineage dysplasia; RS—ringed sideroblasts

Note. From "Myelodysplastic Syndromes Classification and Risk Stratification," by R.S. Komrokji, L. Zhang, and J.M. Bennet, 2010, *Hematology/Oncology Clinics of North America, 24,* p. 446. Copyright 2010 by Elsevier. Adapted with permission.

et al., 2011). The International Working Group on Prognosis in MDS continues to refine the attributes of each risk group.

Understanding the advantages and limitations of the various diagnostic, staging, classification, and prognostic systems is necessary to answer patients' questions as well as to facilitate diagnostic testing and treatment decisions. Those systems continue to evolve, incorporating new data on the biology and natural history of MDS, and to better reflect current clinical practice. More than one system may be used in a setting based on the advantages and limitations of the various systems, particularly with respect to patients with low-risk disease.

TABLE 4. Risk-Stratification Models in MDS

Variable	Score
International Prognostic Scoring System	
Bone marrow blast (%)	
Less than 5	0
5–10	0.5
11–20	1.5
21–30	2
Karyotype[a]	
Good	0
Intermediate	0.5
Poor	1
Cytopenia[b]	
0/1	0
2/3	0.5
World Health Organization Prognostic Scoring System	
World Health Organization category	
RA, RARS, del(5q)	0
RCMD, RCMD-RS	1
RAEB-1	2
RAEB-2	3
Karyotype[a]	
Good	0
Intermediate	1
Poor	2
Transfusion dependence[c]	
Yes	1
No	0
MD Anderson Cancer Center	
Platelets (× 10^9/L)	
Less than 30	3
30–49	2
50–199	1
Age (years)	
60–64	1
65 or older	2
Bone marrow blasts (%)	
5–10	1
11–29	2
Performance status (2 or greater)	2
Hemoglobin (less than 12 g/dl)	2
White blood cell count (greater than 20 x 10^9/L)	2
Chromosome 7 or complex karyotype	3
Transfusion	1

[a] Good cytogenetics includes normal, –Y, del(5q), del(20q); intermediate includes other karyotypic abnormalities; poor includes complex (three or more abnormalities) or chromosome 7 abnormalities.

[b] Hemoglobin less than 10 g/dl; absolute neutrophil count less than 1,800/mcl; platelets less than 100,000/mcl

[c] Transfusion dependence was defined as having one or more red blood cell transfusions every eight weeks over a period of four months.

MDS—myelodysplastic syndromes; RA—refractory anemia; RAEB—RA with excess blasts; RCMD—refractory cytopenia with multilineage dysplasia; RS—ringed sideroblasts

Note. Based on information from Kantarjian et al., 2008; National Comprehensive Cancer Network, 2011.

Natural History and Goals of Treatment

MDS have heterogeneous natural histories and disease trajectories, including survival and risk of leukemic transformation (Greenberg, 2010). Two primary subgroups have been identified: lower-risk disease (IPSS low-risk and intermediate-1–risk categories) and higher-risk disease (IPSS intermediate-2– and high-risk categories). Therapy for low-risk MDS aims to treat symptoms by reducing cytopenias and transfusion requirements, whereas the goal for patients with high-risk disease is to prolong time to leukemic transformation and overall survival. In both cases, altering the natural history of the disease is necessary to achieve these outcomes. Table 6 lists regional drug approval regulatory agencies, Table 7 details the international approval status of the agents commonly used to treat MDS, and Table 8 summarizes key registrational trial outcomes for commonly approved agents.

In the United States, the NCCN is a common source for clinical practical guidelines, including MDS (NCCN, 2011). The NCCN's clinical practice guidelines for MDS are written and regularly updated by a panel of experts who review current evidence-based literature and drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDS. Guidelines for drug approval and subsequent treatment recommendations vary worldwide. However, similarities between the United States and other countries exist in the decision-making process for treatment, role of supportive care, and use of specific drugs in MDS. Importantly, best supportive care (BSC) is appropriate for all patients throughout the disease continuum. According to the NCCN guidelines, BSC for patients with MDS includes clinical monitoring, psychosocial support, quality of life (QOL) assessment, transfusion of blood products, antibiotics, bleeding prophylaxis, iron chelation, and cytokine administration (NCCN, 2011). These topics are discussed in detail in the Thomas, Crisp, and Campbell (2012) and Shah, Kurtin, Arnold, Lindroos-Kolqvist, and Tinsley (2012) articles in this supplement.

Therapeutic Strategies for Low-Risk Myelodysplastic Syndromes

The goal for low-risk MDS treatment is management of the symptomatic cytopenias and concomitant symptoms (e.g., fatigue). Packed red blood cell transfusion is a common treatment strategy for anemia (Greenberg, 2010). Because of the negative impact of long-term TD (e.g., iron overload, negative impact on QOL, transfusion-related complications), use of erythroid-stimulating agents (ESAs) to improve anemia has been integrated into the treatment of low-risk MDS (Greenberg, 2010). Analysis of 1,000 patients with low- and intermediate-1–risk MDS from the European LeukemiaNet Registry demonstrated

TABLE 5. Prognostic Outcomes of Common Risk-Stratification Models

Risk Group	Sum Score	Median OS	AML Prognosis
International Prognostic Scoring System[a]			
		Without Therapy[b]	25% Progression Without Therapy
Low	0	5.7 years	9.4 years
Int-1	0.5–1	3.5 years	3.3 years
Int-2	1.5–2	1.1 years	1.1 years
High	2.5 or greater	0.4 years	0.2 years
World Health Organization Prognostic Scoring System[c]			
			Probability of AML Progression
		Without Therapy	2 Years / 5 Years
Very low	0	141 months	0.03 / 0.03
Low	1	66 months	0.06 / 0.14
Int	2	48 months	0.21 / 0.33
High	3–4	26 months	0.38 / 0.54
Very High	5–6	9 months	0.8 / 0.84
MD Anderson Cancer Center[d]			
		Without Therapy	
Low	0–4	54 months	NR
Int-1	5–6	25 months	
Int-2	7–8	14 months	
High	9 or greater	6 months	

[a] Used only at initial prognosis for planning purposes

[b] Data generated prior to availability of disease-modifying therapies

[c] Can be used at any point in disease for dynamic prognostic estimation

[d] Accounts for disease duration and prior therapy

AML—acute myeloid leukemia; Int—intermediate; NR—not reported; OS—overall survival

Note. Based on information from Kantarjian et al., 2008; National Comprehensive Cancer Network, 2011.

that patients with TD had significantly shorter overall survival and progression-free survival compared with transfusion-independent patients ($p < 0.0001$) (De Swart et al., 2011). Additional factors associated with overall survival included high ferritin levels and IPSS scores.

Erythropoiesis Agents and Other Growth Factors

In the United States, treatment with an ESA (with or without granulocyte colony–stimulating factor) is recommended for patients with MDS lacking del(5q) with serum erythropoietin levels less than 500 mU/ml and who require fewer than two units of packed red blood cell transfusions per month (Greenberg, 2010). The Eastern Cooperative Oncology Group (ECOG) conducted a prospective, randomized, controlled phase III trial of erythropoietin with or without granulocyte colony–stimulating factor and BSC (n = 53) versus BSC alone (n = 57) in patients with lower-risk MDS (Greenberg et al., 2009). The erythroid response rate in the erythropoietin-only arm was 36% versus 9.6% for BSC alone, demonstrating better outcomes with ESAs versus BSC alone; granulocyte colony–stimulating factor was added to erythropoietin and induced an additional response for six patients, for an overall response rate of 46.6%. Erythroid response was associated with improved patient-reported QOL and improved survival compared with nonresponders. No differences in incidence of AML transformation were identified in this study (Greenberg et al., 2009).

In March 2007 and 2008, the FDA announced safety warnings for the use of ESAs (Greenberg, 2010; Rizzo et al., 2010). An increased risk of mortality, inferior response to treatment, and incidence of thromboembolic events were observed in patients without MDS receiving ESAs when dosing to targeted hemoglobin levels less than 12 g/dl. Although no studies in patients with MDS have demonstrated a deleterious impact of ESAs on survival or AML transformation, the data emphasize the importance of hemoglobin monitoring for patients receiving ESAs with the goal of achieving hemoglobin levels of 12 g/dl or less. Guidelines for ESA use with MDS are available online and have been published (NCCN, 2011; Rizzo et al., 2010).

Thrombopoiesis agents: Thrombocytopenia remains a challenge when managing patients with MDS and can result in life-threatening bleeding events. Guidelines for platelet transfusions are set by individual institutions, but less than 10,000 platelets per mcl is a common transfusion threshold (Kurtin, 2007). Platelet transfusions have short-term efficacy, and chronic use can lead to alloimmunization. As a result, thrombopoiesis–stimulating agents currently approved for use in idiopathic thrombocytopenia purpura have been evaluated in MDS clinical trials for impact on thrombocytopenia.

The thrombopoietin receptor agonists eltrombopag and romiplostim have shown efficacy in treating thrombocytopenia in patients with MDS (Kantarjian et al., 2010; Wroblewski, Shi, Mudd, & Aivado, 2010). Romiplostim promotes thrombopoiesis through activation of the thrombopoietin receptor. Despite positive results showing platelet responses in 88% of patients in a long-term open-label extension study, romiplostim is not recommended for use in patients with MDS following the results of a randomized phase III clinical trial demonstrating increased risk of AML progression in the romiplostim arm compared with placebo (Fenaux, Kantarjian, et al., 2011; Giagounidis et al., 2011). Risk of progression was higher for patients with refractory anemia with excess blasts 1 (RAEB-1) MDS compared with lower-risk subtypes. Eltrombopag also binds to the thrombopoietin receptor (Wroblewski et al., 2010). Currently, a phase I/II study of eltrombopag conducted in a multicenter, double-blind, randomized, placebo-controlled fashion is accruing adult patients with MDS.

Immunomodulatory Agents

Lenalidomide: Approved in 2005 in the United States for the treatment of TD anemia in patients with lower-risk MDS with a del(5q) abnormality, lenalidomide is a novel immunomodulatory agent

Guidelines for Use of Erythroid-Stimulating Agents

Guidelines for erythroid-stimulating agents for use with myelodysplastic syndromes are available online at www.esa-apprise.com.

TABLE 6. International Approval Agencies for Myelodysplastic Syndromes (MDS) Therapies

Country or Region	Approval Mechanisms for Drugs Used to Treat MDS
Canada	Although coverage varies by province for approved drugs, Health Canada is the drug approval body for Canada. New drugs are approved when a notice of compliance is issued. Regardless of status of notice of compliance from Health Canada, all oncology drug submissions are reviewed by the pan-Canadian Oncology Drug Review board, which provides approval recommendations to the provinces.
Europe	European Medicines Evaluation Agency (EMEA) Availability may vary by country.
Japan	Pharmaceuticals and Medical Devices Agency
Nordic countries	Nordic MDS Group
United Kingdom	National Institute for Health and Clinical Excellence approval is required for general coverage. EMEA approval is required to permit private insurance coverage.
United States	U.S. Food and Drug Administration approval is required for commercial availability.

Note. Based on information from European Medicines Agency, 2012; Greenberg, 2010; National Institute for Health and Clinical Excellence, 2012; Nordic MDS Group, 2011; Pan-Canadian Oncology Drug Review, 2011; Pharmaceuticals and Medical Devices Agency, 2012; U.S. Food and Drug Administration, 2012.

with direct cytotoxic activity against the del(5q) MDS clone and also enhances erythropoiesis by stimulating expression of the fetal hemoglobin gene (Heise, Carter, Schafer, & Chopra, 2010). Multiple trials have demonstrated that treatment with lenalidomide induced cytogenetic responses and durable transfusion independence in patients with IPSS lower-risk del(5q) MDS (Fenaux, Giagounidis, et al., 2009; List et al., 2006). Adverse events requiring monitoring and potential intervention included neutropenia, thrombocytopenia, thrombosis, rash, pruritus, and fatigue.

Immunosuppressive Agents

Impaired immune function has been implicated in MDS pathogenesis (Sloand & Barrett, 2010). Studies showing improvements in patients with MDS treated with immunosuppressive drugs have suggested that the apoptosis of bone marrow cells observed during early MDS may be the result of immune attack rather than solely the result of intrinsic genetic alterations (Molldrem et al., 1998; Sauntharajah et al., 2002; Sloand, Wu, Greenberg, Young, & Barrett, 2008). Although not approved in the United States for treatment of MDS, several immunosuppressive agents, including cyclosporine, antithymocyte globulin (ATG), and alemtuzumab, have been used off-label for the treatment of MDS and are still under investigation.

Cyclosporine is an immunosuppressant commonly used in organ transplantation to inhibit immune rejection. An early study with cyclosporine for the treatment of patients with refractory anemia (RA) and variable marrow cellularity resulted in responses and transfusion independence in 82% of patients (n = 17) (Jonasova et al., 1998). Cyclosporine is generally well tolerated in the low doses used for the treatment of MDS, although a risk exists for renal toxicity that may require treatment discontinuation.

ATG, used to treat aplastic anemia as well as selected subtypes of MDS, is an immunosuppressive, T cell–depleting agent that exists in two forms: rabbit and equine (Sloand & Barrett, 2010). Both forms deplete T cells; however, equine ATG has a transient effect, whereas rabbit ATG induces prolonged immunosuppression. Factors associated with positive responses to ATG therapy in patients with MDS include younger age (60 years or younger), shorter duration of disease, human leukocyte antigen (HLA)-DR15 genotype, and hypocellular disease (Passweg et al., 2011; Sauntharajah et al., 2002; Sloand et al., 2008). A nonrandomized phase II clinical trial is ongoing to develop an immune-guided response signature to evaluate the efficacy of immunosuppressive agents in MDS (Epling-Burnette, List, & Komrokji, 2011). This study confirmed the prognostic impact of HLA-DR15 in the 21 patients currently evaluated as well as the shorter duration of disease combined with T cell activation markers. The results suggest that the immunosuppressive intervention of T cell–mediated bone marrow failure may be most effective early in the disease before widespread bone marrow damage has occurred. Common side effects include fever, chills, and myalgia. ATG requires specific administration guidelines because of the potential for hypersensitivity reactions and serum sickness and is most often administered in the inpatient setting (Bevans & Shalabi, 2004).

Alemtuzumab is an antibody to the CD52 receptor found on many mature immune cells, including T and B cells, with demonstrated activity in patients with lower-risk MDS (Sloand et al., 2010). Results from a nonrandomized phase II study of alemtuzumab in patients meeting criteria for immunosuppressive therapy showed responses in 77% of patients listed as intermediate-1 (17 of 22) and 57% of those listed as intermediate-2 (4 of 7). In addition, 40% of patients with TD (10 of 25) achieved transfusion independence by three months, and 78% of responders (7 of 9) remained transfusion independent at one year. Alemtuzumab may be beneficial to a wider population of patients with MDS compared with ATG because age and bone marrow cellularity are not predictors for responses. However, it does result in more prolonged lymphopenia than ATG, although no reactivation of herpes viral infections was observed.

Therapeutic Strategies for High-Risk Disease

Patients with higher-risk MDS (IPSS intermediate-2 or high) who have a reasonable performance status (ECOG 0–2) with adequate organ function should be considered for treatment (Blum, 2010). Without intervention, the median overall survival of patients with higher-risk MDS varies from 4 to 12 months (Greenberg et al., 1997). The primary goal of treatment for high-risk MDS is prolonged survival (Garcia-Manero & Fenaux, 2011). As the only proven cure for MDS, allogeneic hematopoietic stem cell transplantation (HCT) should be considered

for transplantation-eligible patients with high-risk disease. Hypomethylating agents are an option for patients ineligible for transplantation.

Hypermethylation of DNA results in gene silencing and has been associated with tumorigenesis (Esteller, 2008). Reduced TSG expression has been demonstrated in MDS and is correlated to areas of hypermethylated DNA (Figueroa et al., 2009; Jiang et al., 2009). The data support the theory that the pathophysiology of MDS is partly from hypermethylation and aberrant TSG silencing. Two hypomethylating agents are available in the United States: 5-azacytidine (azacitidine) and 5-aza-2-deoxycytidine (decitabine). Both agents are believed to lead to re-expression of silenced genes and are used in the treatment of all MDS risk groups (Yoo & Jones, 2006).

Azacitidine is approved in the United States for the treatment of FAB subtypes of RA, RA with ringed sideroblasts, RAEB, RAEB in transformation, and chronic myelomonocytic leukemia, and in Spain, Australia, and Canada for IPSS intermediate-2– and high-risk MDS. Two phase III trials have demonstrated that azacitidine improved hematologic responses as well as prolonged overall survival and time to AML progression (Fenaux, Mufti, et al., 2009; Silverman et al., 2002) (see Table 8). Importantly, azacitidine resulted in a survival benefit in virtually every FAB category in patients with higher-risk MDS compared with conventional care regimens (Fenaux, Mufti, et al., 2009). Adverse events requiring monitoring and potential intervention included neutropenia, thrombocytopenia, anemia, leukopenia, injection site reactions, and infection.

The recommended dose and schedule for azacitidine is 75 mg/m^2 subcutaneously for seven days, every four weeks, based on improved overall survival demonstrated in the AZA-001 trial using this dosing regimen (Blum, 2010; Fenaux, Mufti, et al., 2009). Although alternative dosing schedules have been used and investigated for logistical reasons, data have failed to show the same survival benefits in high-risk MDS as the standard dosing strategy (Blum, 2010; Lyons et al., 2009). First responses were observed within six cycles of azacitidine therapy in 91% of patients and can improve in time (Silverman et al., 2011). Therefore, current recommendations are to administer azacitidine as long as the patient receives clinical benefit in the absence of toxicity for at least six cycles.

A multicenter phase I trial evaluated the efficacy of an oral azacitidine formulation for the treatment of MDS (n = 29; 14 lower risk, 14 higher risk, 1 unclassified), AML (n = 8), and chronic myelomonocytic leukemia (n = 4) and demonstrated that the oral route was associated with significantly less exposure and induced significant methylation alterations in fewer gene loci compared with subcutaneous administration (Garcia-Manero et al., 2011). However, oral azacitidine was efficacious, with clinical responses observed in 73% of previously untreated patients (n = 15), including a 40% rate of complete remissions. Duration of responses ranged from 30 to 483 days. The data demonstrate both biologic and clinical activity of oral azacitidine with adequate bioavailability relative to subcutaneous delivery.

Decitabine was approved by the FDA for the treatment of de novo and secondary MDS of all FAB subtypes and IPSS-defined intermediate-1–, intermediate-2–, and high-risk MDS (SuperGen, Inc., 2010). Studies have shown that decitabine significantly improved response rates compared with BSC, prolonged progression-free survival, and improved QOL. However, there has yet to be a significant overall survival benefit (Kantarjian et al., 2007; Lubbert et al., 2011) (see Table 8).

The original recommended dose and schedule for decitabine was 15 mg/m^2 via IV for three hours repeated every eight hours for three days, repeated every six weeks (SuperGen, Inc., 2010). Subsequently, a randomized trial evaluated the efficacy of three alternative dosing schedules and found that 20 mg/m^2 via IV one hour daily for five days every four weeks resulted in the

TABLE 7. Internationally Approved Therapeutic Strategies for MDS

Agent	International Availability
Supportive Care	
Erythropoietin, darbepoetin	• Approved for patients with lower-risk MDS in Europe. • Approved for use in the United Kingdom, Nordic countries, and Canada. • Administered in the United States as part of the APPRISE REMS program.
Granulocyte colony–stimulating factor	• Approved for use in Nordic countries. • Administered in the United States off-label or under special conditions.
Deferasirox	• Approved for patients with iron overload in the United States and Nordic countries. • Approved in Europe for patients who are deferoxamine intolerant or unresponsive. • Approved in Canada for patients with retinopathy or deferoxamine allergy.
Deferoxamine	• Approved for iron overload in Canada, Europe, Japan, Nordic countries, the United Kingdom, and the United States.
Disease-Modifying Agents	
Antithymocyte globulin, cyclosporine	• Off-label use for MDS occurs in Canada, Europe, Japan, Nordic countries, and the United States.
5-azacitidine	• Approved for treatment of higher-risk MDS in Europe, Nordic countries, and the United States.
Decitabine	• Approved for treatment of IPSS higher-risk or low-risk MDS with thrombocytopenia or neutropenia in the United States.
Lenalidomide	• Approved for treatment of low-risk MDS with del(5q) in the United States. • Available in Canada for use through a special access program only.

APPRISE—Assisting Providers and Cancer Patients With Risk Information for the Safe Use of Erythroid-Stimulating Agents; IPSS—International Prognostic Scoring System; MDS—myelodysplastic syndromes; REMS—Risk Evaluation and Mitigation Strategy

Note. From "Current Therapeutic Approaches for Patients With Myelodysplastic Syndromes," by P.L. Greenberg, 2010, *British Journal of Haematology, 150,* p. 133. Copyright 2010 by John Wiley and Sons. Adapted with permission.

highest response rate (Kantarjian et al., 2007). The Alternative Dosing for Outpatient Treatment trial further evaluated this dose in a multicenter setting in patients with any FAB subtype of MDS with IPSS scores of 0.5 or greater and found that this dose was the optimal decitabine dosing regimen based on improved efficacy, scheduling convenience, and similar response rates and survival outcomes as those observed in the standard dosing regimen (Steensma et al., 2009). Both of these decitabine dosing schedules are approved by the FDA.

Hematopoietic Stem Cell Transplantation

Currently, the only potential cure for MDS is an allogeneic HCT (Center for International Blood and Marrow Transplant

TABLE 8. Outcomes of Key Trials for Approved Agents for Treatment of MDS

Trial	Study	Sample	Clinical Outcomes	Treatment-Related Grade 3 or Greater or AEs Occurring in 10% or More Patients
Azacitidine (Hypomethylating Agent)				
CALGB 9221 Phase III randomized comparison of azacitidine (n = 99) versus basic supportive care (n = 92)	Silverman et al., 2002	All FAB classification system subtypes	Azacitidine significantly improved QOL, reduced TD, and prolonged time to AML or death versus basic supportive care. In low-risk MDS, azacitidine increased median overall survival by 17 months versus basic supportive care.	Neutropenia, 58%; thrombocytopenia, 52%; leukopenia, 43%; infection, 20%
AZA-001 Phase III randomized comparison of azacitidine (n = 179) versus conventional care (n = 179)	Fenaux, Mufti, et al., 2009	IPSS Int-2 or high risk and FAB-defined RAEB, RAEB-t, or CMML[a]	Median follow-up: 21.1 months Azacitidine significantly improved overall survival (24.5 months) versus conventional care (15 months). Rates of hematologic response and improvement were significantly higher with azacitidine versus conventional care.	Neutropenia, 91%; thrombocytopenia, 85%; anemia, 57%
Decitabine (Hypomethylating Agent)				
Phase III randomized comparison of decitabine (n = 89) with basic supportive care (n = 81)	Kantarjian et al., 2006	Any FAB classification with an IPSS score of 0.5 or greater	Decitabine significantly improved rates of response and hematologic improvement. Overall response rate: 17% with decitabine, 0% with basic supportive care No significant overall survival benefit seen	Neutropenia, 87%; thrombocytopenia, 85%; anemia, 12%; febrile neutropenia, 23%; leukopenia, 22%; pneumonia, 15%
EORTC phase III comparison of decitabine (n = 119) versus basic supportive care (n = 114)	Lubbert et al., 2011	Older adults (age 60 or older) with any FAB classification and IPSS Int-1–, Int-2–, or high-risk disease[a]	Decitabine significantly improved response rates and PFS versus basic supportive care. Overall response rate: 25% with decitabine, 0% with basic supportive care No significant overall survival benefit seen Decitabine associated with improved QOL	Febrile neutropenia, 25%; infection, 58%; infection with grade 3 or 4 neutropenia, 47%; hemorrhage: 18%
Lenalidomide (Immunomodulatory Drug)				
MDS-003 Phase II (N = 148)	List et al., 2006	TD with low- and Int-1– risk del(5q)	Median follow-up: 104 weeks Median time to response: 4.6 weeks TI: 67%; median DOR: not reported Cytogenetic response: 73%	Neutropenia, 55%; thrombocytopenia, 44%
Ongoing MDS-004 Phase III comparison of placebo (n = 67) versus lenalidomide 5 mg (n = 69) or 10 mg (n = 69)	Fenaux, Giagounidis, et al., 2011	TD with low- and Int-1– risk del(5q)	Median follow-up: 1.55 years Significantly more RBC-TI and cytogenetic response with lenalidomide compared with placebo ($p < 0.001$) Lenalidomide 10 mg resulted in higher RBC-TI and cytogenetic response compared with 5 mg Median RBC-TI: not reached PFS: 60% and 67%	Neutropenia, 74%–75%; thrombocytopenia, 33%–41%; leukopenia, 9%–13%

[a] With 10% bone marrow blasts and white blood cell count less than 13 x 10^9 cells/L

AE—adverse events; AML—acute myeloid leukemia; CMML—chronic myelomonocytic leukemia; DOR—duration of response; EORTC—European Organisation for the Research and Treatment of Cancer; FAB—French-American-British; Int—intermediate; IPSS—International Prognostic Scoring System; MDS—myelodysplastic syndromes; PFS—progression-free survival; QOL—quality of life; RAEB—refractory anemia with excess blasts; RAEB-t—RAEB with transformation; RBC—red blood cell; TD—transfusion dependence; TI—transfusion independence

TABLE 9. Mechanisms of Action of MDS Therapies Under Investigation

Agent	Target	Mechanism of Action	Trial or Population	Response	Grade 3 or 4 Adverse Events
ARRY-614 (ClinicalTrials.gov, 2011)	P38/Tie-2	Antineoplastic, anti-inflammatory, and antiangiogenic activity	Phase I/low or Int-1 risk (N = 100)	–	–
Entinostat (SNDX-275/MS-275) (Hess-Stumpp et al., 2007)	Histone deacetylase	Class 1 histone deacetylase 1 and histone deacetylase 3 inhibitor	Combination with azacitidine; phase III/ high risk (N = 150) (Gore et al., 2011)	Hematologic response and cytogenetic response did not differ between azacitidine and placebo versus azacitidine and entinostat.	Thrombocytopenia, 63%; fatigue, 23%
Erlotinib (Boehrer et al., 2008)	EGFR signaling leads to DNA synthesis and proliferation	Tyrosine kinase inhibitor that blocks EGFR signaling	Phase II/Int-2 and high risk (N = 24) (Komrokji et al., 2010)	Overall response rate: 17%	Diarrhea, 21%; thrombocytopenia, 17%; rash, 17%
Everolimus (RAD-001) (Klumpen et al., 2010)	mTOR	Inhibitor of mTOR that induces G_1 arrest	Phase II/low and Int-1 risk (not yet recruiting) (ClinicalTrials.gov, 2009)	–	–
Ezatiostat (Raza et al., 2009)	GST P1-1	Stimulates proliferation of myeloid precursors	Phase I/Int-2 (N = 45)	Hematologic improvement, 38%	Neutropenia, 7%
Panobinostat (LBH589) (Prince et al., 2009)	Histone deacetylase	Pan deacetylase inhibitor, inhibits differentiation and induces apoptosis	Phase II/relapsed or refractory MDS (N = 10) (Flinn et al., 2010)	70% had stable disease	Thrombocytopenia, 80%; neutropenia, 70%; leukopenia, 60%; anemia, 50%; febrile neutropenia, 20%
Rigosertib (ON-0110.Na) (Oussenko et al., 2011)	Polo-1 kinase, PI3K, AKT	Inhibits mitotic progression and induces apoptosis	Phase II/Int-1, Int-2, high risk (N = 60) (Raza et al., 2011)	50% or greater blast decrease: 27%, including 34% of 38 patients relapsed or refractory after hypomethylating agent Median overall survival: responders, 51 weeks; stable disease, 37 weeks; progressive disease, 15 weeks	Well tolerated without evidence of myelotoxicity

EGFR—epidermal growth factor receptor; GST P1-1—glutathione S-transferase P1-1; Int—intermediate; MDS—myelodysplastic syndromes; mTOR—mammalian target of rapamycin; PI3K—phosphatidylinositol 3-kinase; Tie-2—protein receptor tyrosine kinase (epithelial-specific)

Research, 2011). However, most patients with MDS are not eligible for HCT because of advanced age, presence of significant comorbidities, and/or lack of a compatible donor.

The exact timing and optimal conditioning regimen for HCT have yet to be determined and are controversial topics of discussion for patients and healthcare providers (Cutler, 2010). Transplantation has many uncertainties, but the inevitability of MDS disease progression in high-risk disease often forces the decision of HCT to one of patient preference. Although improved outcomes with early transplantation have repeatedly been demonstrated, an inherent bias exists in these analyses because the included patients often represented the best transplantation candidates by disease status, overall health, or other unmeasurable factors (Cutler, 2010). Also, the majority of analyses that have examined the timing of transplantation for MDS have included myeloablative procedures rather than reduced-intensity procedures. Optimal timing of HCT for patients with MDS based on data from several large, nonoverlapping databases recommends the following for patients age 60 or younger (Cutler et al., 2004): delay transplantation until the time of leukemic progression for low- and intermediate-1–risk IPSS disease categories and provide immediate HLA-matched transplantation for intermediate-2– and high-risk IPSS scores.

Because high treatment-related mortality remains a barrier for widespread use of allogeneic HCT, trials and analyses are ongoing to better define the populations of patients with MDS who obtain the most benefit from this procedure. A retrospective analysis of 291 patients with MDS undergoing allogeneic HCT from the Spanish MDS registry found that high-risk cytogenetics, IPSS status pretransplantation, and therapeutic response pretransplantation had statistical impact on survival outcomes (Díez Campelo et al., 2011). The overall survival rate after 2.6 years of follow-up was 33%, and infection (61%) represented the largest cause of transplantation-related mortality (41%).

Unfortunately, trials evaluating reduced-intensity conditioning regimens to limit transplantation-related mortality have shown an increased risk of relapse and leukemic transformation (Cutler, 2010). Additional investigation is necessary to identify patient populations with the best potential for benefit as well as approaches to reduce treatment-associated mortality.

Hypomethylating agents have been used as a bridge to transplantation to achieve disease control before HCT. In a study of 18 patients who received decitabine followed by HCT, successful engraftments were attained in 17 of 18 patients (Jang & Lee, 2011). Importantly, the data suggested that decitabine responders had better survival outcomes compared with nonresponders and that bridging HCT therapy with decitabine should be investigated in additional clinical trials.

Implications for Practice

- Advances in the diagnostic process and refinement of classification, and prognostic scoring systems have provided a framework for risk-adapted treatment selection for myelodysplastic syndromes (MDS).
- The therapeutic goal for low-risk MDS is to improve hematopoiesis and survival by altering the natural history of disease, whereas the goal for high-risk MDS treatment is survival and prolonged time to leukemic transformation.
- Oncology nurses play a critical role in the care of patients with MDS, including through support of clinical trials that are adding to the understanding of the pathobiology and treatment of MDS.

Ongoing Clinical Trials and Nursing Support

Ongoing clinical trials are critical for the advancement of treatment of MDS given that no cure is available for the majority of patients with MDS. Most patients with MDS will ultimately require additional treatments to prolong survival and/or time to leukemic progression. Currently, patients who fail treatment with hypomethylating agents have a short median overall survival, underscoring the need for research into novel therapies (Garcia-Manero, 2011).

Clinical research nurses are vital for ongoing research. Research nurse coordinators assist in identifying prospective clinical trial candidates, conducting informed consent, ensuring adherence to rigorous testing schedules, patient compliance, data management, and upholding the ethical care of study participants.

Although the trial patient is managed closely by the research nurse coordinator, inpatient or outpatient clinic nurses or infusion nurses may assume hands-on responsibility for the daily care of study patients. Their tasks may include monitoring vital signs, administration of the investigational drug, and performance of study-related procedures such as blood draws and electrocardiograms. Familiarity with the study design, drug profile, and administration requirements are critical to ensure safety. Being involved in the development of an investigational drug that offers hope for patients, particularly those with limited treatment options, can be one of the great rewards of nursing.

A number of agents are under investigation for the treatment of patients with high-risk MDS as well as patients who have failed or relapsed on prior hypomethylating agent therapy. Table 9 summarizes these agents, their mechanisms of action, and clinical response rates. As more is learned about the differences in biology of MDS-risk subsets, research on the next generation of therapies is focusing on specific molecular targets and will provide the foundation for the use of rational combinations of novel therapies (List, 2011).

Conclusion

MDS, regardless of risk type, is a complex disease, and research is only beginning to illuminate the various underlying genetic components. As science continues to elucidate the differences among subtypes as well as define new screening criteria, risk stratification systems will continue to evolve and become more accurate. In addition, identification of new therapeutic agents will result in changing treatment paradigms. Therefore, nurses involved in caring for patients with MDS must remain current in their knowledge of this rapidly evolving field to advise and manage patients. In addition to this review, recent nursing publications provide excellent strategies for managing disease- and treatment-related complications associated with MDS (Kurtin & Demakos, 2010). Kurtin and Demakos (2010) identified the contributing role of these effects on the disease burden for patients with MDS. QOL of the patient with MDS, as well as resources for patients and their caregivers, are discussed in detail in Thomas et al. (2012) and Kurtin et al. (2012) in this supplement.

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