Current Approaches to the Diagnosis and Management of Myelodysplastic Syndromes

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Author's disclosures of potential conflicts of interest are found on page 4 and at the end of this article.

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Abstract

The myelodysplastic syndromes (MDS) are a group of heterogeneous myeloid stem-cell malignancies most prevalent in the seventh and eighth decades of life. Since most patients are elderly, are treated as outpatients, and often have comorbidities, management of MDS presents challenges to oncology practitioners. Allogeneic hematopoietic stem-cell transplantation is the only potential cure for MDS, but it is not an option for most patients based on age and comorbidities. Three agents (azacitadine, decitabine, and lenalidomide) have recently been approved for treatment of MDS, and treatment guidelines continue to evolve. Selection and goals of treatment are based on International Prognostic Scoring System risk category, other disease-specific factors, and patient characteristics, such as comorbidities and performance status. Recent data showing survival benefit for azacitadine have led to a shift in the goals of treatment from symptomatic improvement to increased overall survival. With all active therapies, however, treatment response requires several months, and patient education and supportive care are needed to allow the patient to continue treatment long enough to realize benefits. Myelosuppression is the most common toxicity with all active therapies, and it may get worse before improvement is seen. Advanced practitioners can help set patient and family expectations and educate them about clinical management strategies to reduce the frequency and severity of adverse effects.

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The myelodysplastic syndromes (MDS) represent a group of myeloid malignancies with variability in clinical presentation, disease trajectory, prognosis, and treatment recommendations (Kurtin & Demakos, 2010). The peak incidence of MDS is in the seventh and eighth decades of life, presenting unique challenges for patients and health-care providers. Until recently, MDS has been poorly understood and often included in the spectrum of myeloid leukemias or myeloproliferative disorders but described by clinicians as a blood disorder, bone marrow failure, or a form of anemia (Sekeres, 2011). Because of the constellation of molecular and clinical findings, inclusion in the Surveillance, Epidemiology and End Results (SEER) database, and use of chemotherapeutic agents for treatment, MDS is now recognized as a myeloid malignancy (Sekeres, 2011).

Diagnostic and response criteria specific to MDS have evolved over the past 15 to 20 years, and more recent clinical trials have led to both US Food and Drug Administration (FDA) approval of three therapeutic agents for the active treatment of MDS, as well as recommendations for supportive care strategies. Given the relatively recent approval of these agents, these guidelines continue to evolve, and combination regimens are being explored. Allogeneic hematopoietic cell transplantation (Allo-HCT) remains the only potential cure for MDS.

The advanced practitioner (AP) in oncology plays an integral role in the clinical management of MDS, including coordination of the diagnostic process, performance of bone marrow biopsies to obtain a tissue diagnosis, collaboration with physicians for treatment selection based on risk analysis, and, perhaps most important, effective management of adverse events to minimize severity and allow continued treatment for optimal response. Since the majority of patients are managed in the outpatient setting, the oncology AP is in a unique position to prepare the patient and caregivers by setting expectations and offering tools for monitoring progress, reporting symptoms promptly, and managing less serious symptoms independently.

Epidemiology

The first epidemiologic data specific to MDS in the United States were collected between 2001 and 2003. Based on these data, the estimated age-adjusted incidence of MDS in the United States was 3.4 per 100,000 persons, or approximately 10,000 new cases per year with an estimated 60,000 existing cases (Ma, Does, Raza, & Mayne, 2007). The median age at diagnosis was 76 years, with the majority (86%) of patients > 60 years of age (Ma et al., 2007). More recent data suggest much higher estimates of both incidence and prevalence. Cogle, Craig, Rollison, and List (2011) evaluated the incidence of MDS using a claims-based algorithm to evaluate the SEER-Medicare database using the International Classification of Diseases, 9th Revision codes, confirmatory blood counts, and bone marrow analysis. The estimated incidence of MDS in 2005 for persons ≥ 65 years of age was 75 per 100,000, considerably higher than the SEER estimates of 20 per 100,000 for that same year. It is important to note that all of these data preceded the availability of active therapies, which will likely increase the prevalence rates (Sekeres, 2011; Kurtin & Demakos, 2010). Additional factors thought to contribute to a rise in incidence and prevalence rates are inclusion of MDS in the differential diagnosis of cytopenias in elderly patients, the expected increase in the elderly population, improved familiarity with diagnostic features of MDS, and the expected rise in secondary or treatment-related MDS (Kurtin, 2011).

Accurate estimates of incidence and prevalence are critical to determining the disease burden, assessing the effect on patients and health-care services, and developing effective management and support strategies. The anticipated increase in incidence and prevalence of MDS is of particular significance to the oncology AP as the majority of these patients are older, will be managed in the outpatient setting, and will require comprehensive management of both their MDS and common comorbid conditions (Kurtin, 2010).

Who Is at Risk?

The leading risk factor for developing MDS is advanced age, which is thought to be related to hematopoietic senescence. Other risk factors include male gender; occupational or environmental exposure to organic solvents, agricultural chemicals, pesticides and other solvents; tobacco exposure; and antecedent hematologic malignancies (Sekeres, 2011). Treatment-related MDS appears to be dose dependent and varies in onset, with a latency period of 2 to 3 years after exposure to topoisomerase inhibitors and late onset (5 to 10 years) after exposure to alkylating agents such as cyclophosphamide, or in patients treated with radiation (Sekeres, 2011).

Pathobiology of MDS and Associated Clinical Features

Myelodysplastic syndromes are a group of heterogeneous, clonal, myeloid stem-cell malignancies characterized by ineffective hematopoiesis, progressive bone marrow failure, and a variable risk of leukemic transformation (Kurtin, 2011). MDS is thought to result from complex interactions between the malignant clone and the bone marrow microenvironment.

The initiating event is often uncertain; however, self-renewal capability of the malignant clone is thought to be a prerequisite for the development of MDS (Bejar, Levine, & Ebert, 2011). Subsequent

events key to the evolution of MDS include ineffective differentiation, increased proliferative capacity, genetic or epigenetic instability, resistance to apoptosis, and evasion of the immune system (Bejar et al., 2011). Together, these factors lead to abnormalities in bone marrow cellularity (hypercellular most common) and peripheral cytopenias with variable severity and duration. In general, as the disease progresses, bone marrow function declines, producing increased risk of infections, bleeding, and symptomatic anemia.

Both intrinsic (characteristic of the malignant clone) and extrinsic (bone marrow microenvironment) factors contribute to the evolution of the disease and in part explain the heterogeneity and variable risk of leukemic transformation (Kurtin, 2011) (Table 1).

Genetic abnormalities are common in MDS and include a number of chromosomal abnormalities and gene mutations, which are known to influence disease prognosis. The clinical utility of routine testing for genetic mutations remains questionable because of conflicting reports of prognostic significance, and it will likely remain restricted to the clinical trial setting or large referral centers until further characterized.

Diagnostic Evaluation, Clinical Presentation, and Disease Classification

A typical patient with MDS is older (median age, 71 years) and presents with vague symptoms, such as fatigue, exertional dyspnea, recurrent infections, or unexplained bruising or bleeding as a result of underlying cytopenias. On routine evaluation, many patients are found to have cytopenias with no associated symptoms. The differential diagnosis of MDS requires exclusion of other causes of cytopenias, particularly anemia. A bone marrow biopsy and aspirate is required to obtain the tissue diagnosis, the hallmark findings being dysplasia, one or more cytopenias, abnormal blasts, and the presence or absence of cytogenetic abnormalities.

The diagnostic evaluation allows confirmation of the MDS diagnosis, classification, and risk stratification of the disease (Figure 1). MDS is classified using the French-American-British (FAB) classification system (morphology based) (Bennett et al., 1982) and the World Health Organization classification system (molecular based) (Arber et al., 2008; Vardiman, Harris, & Brunning, 2002). The International Prognostic Scoring System (IPSS) assigns a risk category based on the number of cytopenias, cytogenetic abnormalities, and percentage of blasts in the bone marrow sample (Greenberg et al., 1997). The score correlates with one of four risk groups (low, intermediate-1, intermediate-2, and high), each with projected median survival and risk of leukemic transformation (Table 2). It is important to note that this system was developed before the availability of active therapies and is only applicable at the time of initial diagnosis. A revised IPSS has been proposed and will include additional risk factors, including transfusion burden, depth of cytopenias (thrombocytopenia in particular), revised cytogenetics, and bone marrow fibrosis. It will also add a fifth risk category and allow for application throughout the disease trajectory (Greenberg et al., 2011b) (Table 2).

Risk-Adapted Treatment Selection and Goals of Therapy

The first consensus guidelines for the treatment of MDS were released by the National Comprehensive Cancer Network (NCCN) in 2004. At that time, only one active agent, azacitidine (Vidaza) had been approved (Celgene, 2009a), and the guidelines focused primarily on supportive care. Two additional agents are now FDA approved: lenalidomide (Revlimid) approved in 2005 (Celegene, 2009b) and decitabine (Dacogen) approved in 2006 (Eisai, 2008); see Table 3. The most recent guidelines include updated risk-adapted treatment recommendations categorizing patients into two primary groups: low/intermediate-1 or intermediate-2, high risk, based on expected survival using the IPSS scores (Greenberg et al., 2011a). The current guidelines also include recommendations for the use of erythropoietin-stimulating agents, granulocyte-stimulating proteins, and treatment of iron overload, which is common in transfusion-dependent patients. The goals of therapy for a low/intermediate-1 risk patient are to improve hematopoiesis and, therefore, immediate treatment may not be necessary. A patient with intermediate-2, high risk disease may die very quickly of the disease or as a result of leukemic transformation, and treatment is generally necessary at the time of diagnosis.

Several key principles are considered when

Table 1. Intrinsic and Extrinsic Abnormalities Contributing to the Pathobiology of Myelodysplastic Syndromes

	Intrinsic abnormalities (properties of the malignant clone)
Abnormality and estimated frequency in MDS	**Prognostic implications**
TET2 mutation (14%–26%)	Most common gene mutation in MDS; conflicting reports of prognostic significance Involved in epigenetic regulation of gene expression TET2 mutation is associated with improved response to azacitidine
RUNX1 (15%–20%)	Second most common gene mutation in MDS; more common in treatment-related MDS Increased risk of leukemic transformation
ASXL 1 (10%–15%)	Unknown prognostic significance in MDS; more common in CMML
5q- (15%)	Most common cytogenetic abnormality in MDS; favorable prognosis as a sole cytogenetic abnormality Prognosis declines when associated with additional abnormalities Favorable response to lenalidomide
Complex karyotype (≥ 3) (10%–15%)	Poor prognosis; associated with leukemic transformation
TP53 (5%–10%)	Located on 17p; poor prognosis with treatment resistance common Common in complex karyotypes Increased risk of leukemic transformation
-7/7q (5%–10%)	Poor prognosis; common in tMDS (~50% of cases)
Trisomy 8 (+8) (5%–8%)	Intermediate risk–reduced survival when compared with normal cytogenetics (22.0 vs. 53.4 months) Improved response to immunosuppression when associated with HLADR15
EZH2 (6%)	Poor prognosis; commonly associated with 7q abnormalities
20q- (2%–5%)	Common in myeloproliferative disorders and AML; no known disease-associated prognostic significance in MDS
-Y (2%–4%)	Considered common in aging; no known disease-associated prognostic significance
Epigenetic changes: DNA hypermethylation (common)	Potentially reversible heritable abnormalities outside the DNA genetic code Hypermethylation of the promoter region of the genes results in silencing of the tumor-suppressor genes Hypermethylation is a continuous process in MDS and is associated with leukemogenesis Explains in part the utility of DNA methyltransferase inhibitors in the treatment of MDS and the need to continue treatment until disease progression or unacceptable toxicity
	Extrinsic abnormalities (bone marrow microenvironment)
Bone marrow stroma	Network of fibroblasts, fat cells, and adhesion molecules may foster abnormal hematopoiesis and the dysplastic changes that are the hallmark findings in MDS; several novel therapies target stromal elements
Medullary angiogenesis	Vascular endothelial growth factor and other inflammatory cytokines such as TNFα are increased in patients with MDS, contributing to abnormal erythropoiesis Elevated VEGF levels contribute to myeloblast self-renewal and survival of malignant clone
Proliferation and apoptosis	The balance between proliferative rate and apoptosis varies throughout disease trajectory *Early disease:* proliferative rate and thus differentiation are blunted and programmed cell death (apoptosis) is faulty, leading to the characteristic findings of a hypercellular bone marrow with peripheral cytopenias *Advanced disease:* proliferation outpaces cell death and an increase in blasts is noted; common in leukemic transformation

Note. AML = acute myeloid leukemia; ASXL1 = additional sex-comb like 1'; CMML = chronic myelomacrocytic leukemia; HLA = human leukocyte antigen; TET2 = ten eleven translocation-2; tMDS = treatment-related MDS; TNFα = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor.
Information from Bejar et al. (2011), Garcia-Manero & Fenaux (2011), Steensma & Stone (2011), Kurtin (2010), Scott & Deeg (2010), Tiu et al. (2011), Jadesrten et al. (2011).

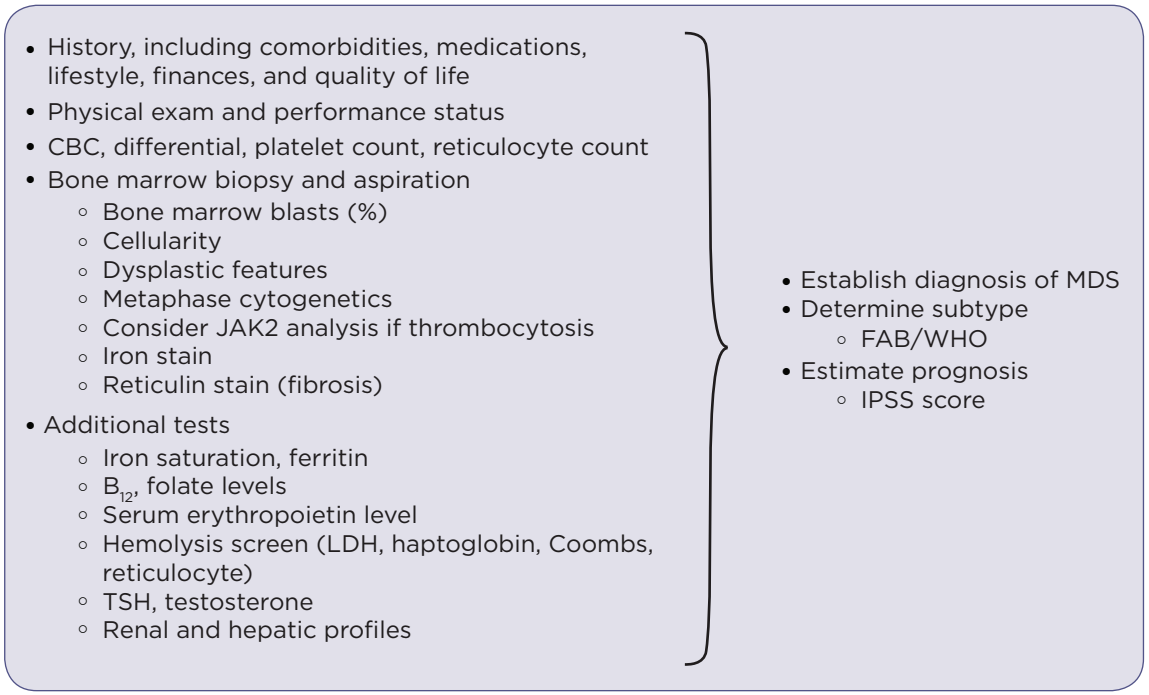

Figure 1. Diagnostic evaluation of myelodysplastic syndromes.
FAB = French-American-British; IPSS = International Prognostic Scoring System; LDH = lactate dehydrogenase; MDS = myelodysplastic syndromes; TSH = thyroid-stimulating hormone; WHO = World Health Organization.

deciding on treatment: (1) characteristics of the individual patient, including comorbidities, performance status, lifestyle, finances, and quality of life; (2) characteristics of the disease, for example, IPSS risk category and individual disease characteristics; and (3), currently available treatment options with selection based on risk analysis (Table 4). It is important to consider the most recent clinical trial data to guide treatment selection (Figure 2). For example, patients with the 5q deletion are known to benefit when treated with lenalidomide, based on data from the Myelodysplastic Syndrome (MDS)-001 and MDS-003 trials (List et al., 2005; 2006).

More recently, the first survival data for any active MDS therapy were published, showing a survival advantage in patients receiving azacitadine (AZA-001 trial) compared with conventional chemotherapy (Fenaux et al., 2009). Based on these data, azacitadine has been listed as the preferred agent for treatment of intermediate-2 or high-risk MDS by the National Comprehensive Cancer Network (NCCN). Also noted in the AZA-001 trial is that cytopenias associated with treatment improved over a 3- to 4-month period, again reinforcing the importance of aggressive management of cytopenias in the early months of therapy to allow continuation of potentially beneficial treatment.

Based on these data, the goals of therapy have shifted from symptomatic improvement to improved overall survival (OS) (Kurtin & Demakos, 2010). Other key findings in recent clinical trials have refined the administration of selected agents to allow outpatient management or reduce specific toxicities. For example, when it was originally approved in 2006, decitabine required inpatient administration and a hospital stay of at least 3 to 4 days. More recently, in the Alternate Dosing for Outpatient Treatment (ADOPT) trial, an outpatient regimen using daily dosing for 5 days was found to be equally effective and also less likely to be associated with hospitalization, infections, or mortality (Kantarjian et al., 2007a; 2007b).

Treatment response in most cases requires a minimum of 4 to 6 months of active therapy, and the best response may not be evident for up to 9 months (Kurtin & Demakos, 2010). To improve the potential benefit, it is critical to prepare the patient and family for this timeframe and reinforce a commitment to at least 4 to 6 months of therapy before response can be adequately evaluated. In the meantime, the most common toxicity associated with all active therapies for MDS is myelosuppression, which most

Table 2. Risk Stratification of Myelodysplastic Syndromes—International Prognostic Scoring System and Proposed Revisions With Survival and Risk of Acute Myeloid Leukemia Transformation

IPSS risk categories (1997), prior to active therapies

Score	0	0.5	1.0	1.5	2.0
Bone marrow myeloblasts	< 5%	5%–10%		11%–20%	21%–30% (considered AML)
Karyotype	Normal, del(5q), del(Y), del(20q) as sole abnormalities	Other abnormalities	del(7), 7+, or ≥ 3 abnormalities		
Number of cytopenias	0, 1	2, 3	Anemia (hemoglobin < 10 g/dL), neutropenia Absolute neutrophil count < 1,800/μL) and/or thrombocytopenia (platelets < 100,000/μL)		

IPSS (1997) and proposed revised IPSS (IPSS-R[a]) with survival and risk of leukemic transformation

IPSS (1997) (n = 816)				Proposed revisions to IPSS: IPSS-R (n = 4,417)		
Category	Score	MS	Evolution to AML (25%)	Risk category, proposed changes	MS	Evolution to AML (25%)
Low	0	5.7 yr	9.4 yr	Very low	6.8 yr	NR
Intermediate-1	0.5–1.0	3.5 yr	3.3 yr	Low	4.3 yr	10.1 yr
Intermediate-2	1.5–2.0	1.2 yr	1.1 yr	Intermediate	2.3 yr	2.8 yr
High	≥ 2.5	0.4 yr	0.2 yr	High	1.5 yr	1.2 yr
				Very high	0.9 yr	0.7 yr

Proposed revisions[a]

Karyotype
Very good: del(11q), -Y
Good: normal, del(5q), del(12p), del(20q), double incl. del(5q)
Intermediate: +8, i(17q), +19, +21, any other single, any other double, independent clones
Poor: der(3)(q21)/der(3)(q26), double incl. -7/7q-, complex 3 abnormalities
Very poor: complex (> 3 abnormalities)

Cytopenias
Adverse risk: thrombocytopenia at presentation, high transfusion burden

Other factors considered in overall survival: elevated LDH, elevated ferritin, bone marrow fibrosis, comorbidity score

Note. AML = acute myeloid leukemia; IPSS = International Prognostic Scoring System; R-IPSS = proposed revisions to IPSS; LDH = lactate dehydrogenase; MDS = myelodysplastic syndromes; MS = median survival.
Adapted, with permission, from Yarbro, C. H. *Cancer Nursing: Principles and Practice*. 7th ed, 2011; Jones & Barlett Learning, Burlington, MA. www.jblearning.com. Data from Garcia-Manero & Fenaux (2011), Greenberg et al. (2011), Schanz et al. (2010), Greenberg et al. (1997), P. Greenberg (personal communication, June 13, 2011).
[a] IPSS-R is still being modified by the International Working Group for Prognosis in MDS (IWG-PM) including assignment of scores and the final attributes of each category.

often consists of moderate but asymptomatic cytopenias that may be present for extended periods of time without the need for any intervention (Kurtin & List, 2009). Aggressive supportive care should be instituted for all patients, and each drug has specific recommendations for dose modifications or drug holidays in the presence of more severe or symptomatic cytopenias.

Allo-HCT is an option for a selected group of patients with MDS. Adequate performance status, adequate major organ function, controlled or limited comorbidities, treatment-sensitive disease with minimal residual disease, a suitable donor, and availability of a consistent caregiver are common eligibility criteria for Allo-HCT (Kurtin, 2010; Cutler, 2010). Hypomethylating agents are commonly used

Table 3. FDA-Approved Agents for Treatment of Myelodysplastic Syndromes

	Azacitidine	Decitabine	Lenalidomide
Indication	All 5 FAB subtypes (RA[a], RARS[a], RAEB, CMML, RAEB-T)	Int-1/Int-2/high risk per IPSS, as well as tMDS	Transfusion-dependent MDS low-int-1 MDS with del(5q) with or without additional chromosomal abnormalities
Therapeutic target	DNA methyltransferase inhibitor RNA and DNA Proteins and microenvironment	DNA methyltransferase inhibitor DNA specific Direct cytotoxic effect	Immunomodulatory drug (IMiD) Del(5q)—possible direct cytotoxic effect on the clone Without del(5q)—drug may target the disease microenvironment
Sensitivity	No data on use after decitabine failure	May be effective in patients previously treated with azacitidine	Most effective in patients with del(5q) Activity has been demonstrated in non-del(5q) patients
Key clinical trials	Registration trial: CALGB 9221, phase I/II CALGB 8421 phase II continuation (2000) Established efficacy and safety (Silverman et al., 2002) Expansion trial: AZA-001, phase III international, multicenter Int-2, high-risk MDS First survival data for active therapies in MDS (Fenaux et al., 2009)	Registration trial: D-0007, phase I/II (2003) Established efficacy and safety (Kantarjian et al., 2007) ADOPT trial (Kantarjian et al., 2007b), phase III randomized, multicenter trial Established new dosing guidelines Decitabine 20 mg/m^2 IV given over 1 h days 1–5 Outpatient treatment feasible	Registration trial: MDS-001, phase I/II (2002) Established efficacy and safety (List et al., 2005) Expansion trials: MDS-003, phase II multicenter trial, lenalidomide in del(5q) led to FDA approval based on efficacy and safety (List et al., 2006) MDS-002, phase II multicenter trial, lenalidomide in non-del(5q) low–Int-1 MDS. Confirmed activity in non-(del)5q MDS; confirmed safety and efficacy (Raza et al., 2008)
Primary end points met (IWG)	Improved overall survival Hematologic improvement (trilineage) Transfusion independence Cytogenetic response Safety and efficacy	Hematologic improvement (trilineage) Transfusion independence Cytogenetic response Safety and efficacy	Hematologic improvement Transfusion independence Cytogenetic response Safety and efficacy
Common adverse events and treatment considerations	Myelosuppression is most common Injection site reactions Nausea and vomiting Constipation Contraindicated in patients with hepatic tumors Use with caution in renal impairment May cause fetal harm	Myelosuppression is most common Nausea and vomiting Constipation Hyperbilirubinemia Use with caution in renal impairment May cause fetal harm	Myelosuppression is most common Rash Diarrhea Requires renal dose adjustment Nonteratogenic in animal studies Analog of thalidomide Must be prescribed through RevAssist program for safety
Mode of use	SC or IV x 7 days Every 28 days Outpatient regimen Treat until unacceptable toxicity or disease progression	IV daily for 5 days over 1 hour every 28 days Treat until unacceptable toxicity of disease progression	10 mg orally days 1–21 every 28 days

Note. ADOPT = Alternate Dosing for Outpatient Treatment; CALBG = Cancer and Leukemia Group B; CMML = chronic myelomacrocytic leukemia; FAB = French-American-British; FDA = US Food and Drug Administration; IPSS = International Prognostic Scoring System; IWG = International Working Group; MDS = myelodysplastic syndromes; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts; tMDS = treatment-related myelodysplastic syndromes.
Information from Fenaux et al. (2009), Kantarjian et al. (2007), Kantarjian et al. (2007), Kurtin & Demakos (2010), Raza et al. (2008), Scott & Deeg (2010), Silverman et al. (2002), Silverman et al. (2008).

Table 4. Key Principles for Treatment of Myelodysplastic Syndromes

- Selection of therapy based on IPSS risk category, disease-specific attributes, individual patient characteristics, including comorbidities and performance status, is recommended.
- Almost all active therapies for MDS require several months of treatment (4–6) before determining overall response, and the best response may not be evident for up to 9 months.
- Myelosuppression is the most common toxicity with all types of active therapy for MDS.
  - Cytopenias commonly get worse before overall and sustained improvement.
  - Moderate asymptomatic cytopenias may persist for months or years in patients responding to treatment.
- Supportive care of the patient is essential to continue therapy long enough to realize the benefit of treatment.
  - Close monitoring of cytopenias is needed during the first 8 to 12 weeks of therapy.
  - Dose adjustment, drug holidays, or administration of growth factors may be needed to allow safe continuation of therapy.
- Setting patient and family expectations for expected cytopenias, and reviewing necessary monitoring and available treatment strategies will reduce severe adverse events.
- Anticipating common adverse events will limit the severity and duration of adverse events:
  - All agents:
    - Myelosuppression (may also be disease related): anemia, neutropenia, thrombocytopenia
    - Nausea and vomiting, constipation
    - Renal and hepatic toxicities
- Drug-specific adverse events:
  - Azacitadine: injection-site reactions
  - Lenalidomide: rash, pruritus, diarrhea. Must be prescribed with safety program.
- Iron overload: Chelation therapy may be associated with cytopenias, renal and hepatic toxicities.

Note. IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes.

as a bridge to transplantation, based on effective reduction in disease burden and limited sustained cytopenias (Kim et al., 2011). Data specific to outcomes in patients > 65 years of age undergoing Allo-HCT are limited, with very few patients included in clinical trials, although 80% of the patients receiving treatment for MDS are > 60 years (Giralt, Horowitz, Weisdorf, & Cutler, 2011). In addition, Medicare reimbursement for Allo-HCT was only recently approved (August 4, 2010) with specific criteria for reimbursement, including eligibility and participation in an Allo-HCT clinical trial that addresses clinical questions specific to the older patient with MDS undergoing transplant (Giralt et al., 2011). Factors found to predict OS in recent clinical trials evaluating Allo-HCT in patients > 60 years include advanced disease stage at the time of transplant, donor-recipient human leukocyte antigen disparity, increasing donor age, and recipient's performance status (Lim et al., 2009; McClune et al., 2010).

Evaluation of comorbidities and performance status is perhaps as important as an accurate clinical diagnosis. Recent studies have demonstrated the significance of comorbidities to survival and tolerance of active therapies (Kurtin, 2010). The University of Texas MD Anderson Cancer Center has developed a tool for incorporating a comorbidity score into a prognostic model for MDS. Naqvi and colleagues (2009) studied 600 MDS patients with a median age of 66 years, the majority with low/intermediate-risk disease. Each patient was evaluated for comorbidities using the Adult Comorbidity Evaluation-27, which assigns risk groups based on the presence of selected comorbidities. Median survival for all patients combined was 18.6 months; however, for those with no comorbidities median OS was 31.8 months compared with 9.7 months in those with severe comorbidities ($p < .001$; hazard ratio [HR], 2.3), indicating a 50% decrease in OS in those with severe comorbidities independent of age or IPSS score.

A retrospective review of 1,394,343 Medicare Standard Analytic Files in 2003 yielded 2,253 newly diagnosed MDS patients with a median age of 77 years, translating to an incidence rate of 162 per 100,000 persons (Goldberg et al., 2011). Comorbidities, including diabetes (40.0% vs. 33.1%), dyspnea (49.4% vs. 28.5%), hepatic disease (0.8% vs. 0.2%), and infections (22.5% vs. 6.1%), were higher in the patients with MDS compared with the general Medicare population ($p < .001$). Patients with MDS who were transfusion dependent had a higher incidence of dyspnea, hepatic dis-

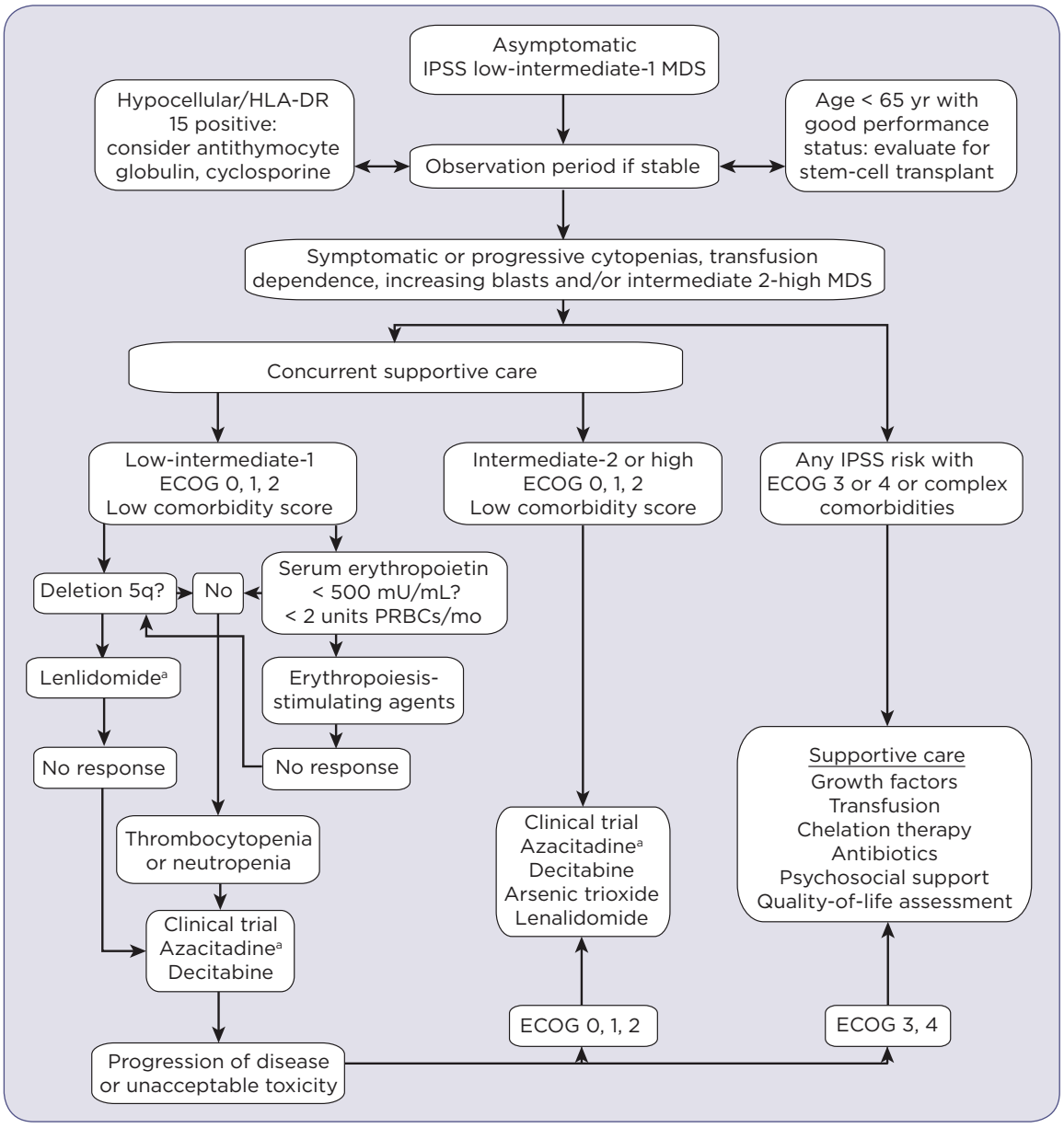

Figure 2. Risk-based treatment algorithm for myelodysplastic syndromes. ECOG = Eastern Cooperative Oncology Group; HLA = human leukocyte antigen; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; PRBCs = packed red blood cells. Based on information from NCCN (2011). Adapted, with permission of Oncology Nursing Society, from Kurtin & Demakos (2010).
[a]NCCN category 1 designation.

ease, and infections (all $p < .001$), and 82% experienced a cardiac event within 3 years of follow-up ($p < .001$). Patients with MDS receiving transfusions had an increased risk of death (age-adjusted) when compared with other MDS patients (HR, 2.41, 95% confidence interval, $p < .001$).

These studies validate the recommendation to institute active therapy for patients with MDS who become transfusion dependent and the need to evaluate these patients for possible chelation therapy (Kurtin & Demakos, 2010).

Supportive Care and Health-Related Quality of Life

All patients with MDS should receive supportive care, including transfusion support, administra-

Table 5. FDA-Approved Therapies for Iron Overload and Recommended Monitoring

	Deferoxamine	Deferasirox		
Route	SC or IV	Oral		
Initial dosing	25–50 mg/kg	20 mg/kg starting dose		
Schedule	Administered for a period of 8–24 h, 5-7 d/wk	Once daily		
Excretion	Urine/feces	Feces		
Recommended monitoring	**Test**	**Monthly**	**Every 3 mo**	**Baseline and yearly**
	Auditory testing			✓
	Granulocytes	✓		
	Serum ferritin		✓	
	Serum transaminase	✓		
	Serum creatinine	✓		
	Liver iron stores (T2 MRI)			✓
	Myocardial iron stores (T2 MRI)			✓
	Ophthalmic testing			✓

Note. FDA = US Food and Drug Administration; MRI = magnetic resonance imaging. Information from Kurtin & Demakos (2010), Greenberg et al. (2011), NCCN (2011).

tion of growth factors when appropriate, and management of comorbidities and any acute diagnoses, including infections. For patients with limited performance status, complex comorbidities, or those not wishing to pursue active therapies, supportive care alone is an appropriate standard of care.

Transfusion-related iron overload is common in patients with MDS and has significant potential clinical consequences. Important considerations when implementing iron chelation therapy are the need for monitoring serum ferritin levels and the total number of transfusions (Kurtin & Demakos, 2010). The agents commonly used to treat iron overload require specific safety considerations, particularly monitoring hepatic and renal function in older adults with MDS (Table 5).

A recent online survey evaluating health-related quality of life (HRQoL) in 199 patients with MDS found that patients with hemoglobin levels < 10 g/dL or platelet counts < 30,000 had the poorest HRQoL (Kurtin & Demakos, 2011). Patients with moderate cytopenias were able to function relatively well and reported better HRQoL. An interesting finding was that patients with thrombocytopenia seemed to be more concerned about bleeding than actually affected by bleeding events. Specifically, patients with lower platelet counts reported that they "worry about serious bleeding," although there was no evidence they bled more since lower platelet counts were not associated with blood in urine or stool. This may reflect the way health-care providers communicate risks associated with cytopenias. Transfusion dependence was also found to have a negative effect on HRQoL, limiting patient and family independence.

Summary

Myelodysplastic syndromes represent myeloid stem-cell malignancies most common in older adults. Transplant remains the only potential cure but is not an option for the majority of patients with MDS. Chronologic age, however, should not exclude active therapy, and supportive care should be provided to all patients with MDS. Active therapies that are feasible in the older adult are the mainstay of therapy for MDS. Oncology APs play

an integral role in educating the patient and family, setting expectations for duration of therapy and expected cytopenias, and instituting clinical management strategies to reduce the frequency and severity of adverse events, including management of comorbidities. Effective management of MDS, unlike other hematologic malignancies, does not require a molecular response, and moderate asymptomatic cytopenias may persist for months or years. Ongoing clinical trials will be necessary to develop novel agents for the treatment of MDS and address the growing problem of treatment-related MDS.

DISCLOSURES

Sandra Kurtin, RN, MS, AOCN®, ANP-C, reported a financial interest/relationship in the form of: Speaker's Bureau: Celgene, Novartis.

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