



Michele Sassi. *Baldwin Hill Farm*. Photograph. North Egremont, Massachusetts.

*The current strategies for classification, prognosis and treatment of myelodysplastic syndrome are reviewed.*

# Classification, Treatment Goals, and Management Principles for Myelodysplastic Syndromes

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Myelodysplastic syndromes (MDS) constitute a group of acquired clonal stem cell disorders.<sup>1</sup> Occurring primarily in persons 65 years of age and older, these conditions are characterized by peripheral cytopenias and dysplasia of bone marrow progenitor cells.<sup>2</sup> In later stages of MDS, clonal evolution produces progressive bone marrow failure and progressive accumulation of marrow blasts.<sup>3</sup> While management of patients with MDS is challenging, the physician's armamentarium includes tools to assist in developing an individualized care plan for each patient. The plan of care may be designed to provide palliation, stabilization, or cure. This article reviews current MDS classification and risk stratification tools, general treatment principles and therapy goals, and International Working Group (IWG) criteria to assess clinical response and quality of life parameters.

## Classification of Myelodysplastic Syndromes

For many years, the French-American-British (FAB) system was the primary classification system for MDS (Table 1).<sup>4,5</sup> While it was readily applied and somewhat useful, it was suboptimal for prognostic stratification.<sup>6,8</sup> To improve prognostic utility, the World Health Organization (WHO) published a new standard classification system.<sup>2,9,10</sup> Regardless of the precision in classifying disease characteristics, a classification system alone does not predict outcomes. While the WHO has added some important cate-

gorizations (eg, the recognition of the negative prognostic import of multilineage dysplasia, even in the absence of excess blasts or with ringed sideroblasts), additional prognostic information is needed for the management of the patient with MDS.

The International Prognostic Scoring System (IPSS) provides a framework to guide the caregiver in discussions with the patient and identification of treatment goals.<sup>11-13</sup> Created in a study that pooled observational data from numerous longitudinal MDS trials, the IPSS study examined risk factors beyond cell morphology that might be associated with MDS prognosis — specifically, factors that might be useful in predicting the level of risk of progressing to pathologically defined acute myeloid leukemia (AML), ie,  $\geq 30\%$  blasts in the FAB classification. The IPSS score was derived from an analysis of the outcomes of 816 patients with de novo MDS who were enrolled in large institutional or national trials. Centrally reviewed, this analysis produced the world's largest data-

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base (at that time) of previously untreated patients with MDS.<sup>11</sup> Risk factors that were studied included those that had been promulgated as potentially important prognostic factors in smaller studies: cytogenetic analysis, FAB classification, percentage of blasts, peripheral cytopenias, age, sex, and other clinical parameters used in previously published scoring systems. Definitions of cytopenias and cytogenetic stratifications used in the IPSS are provided in Table 2.

The IPSS system uses three clinical factors — percentage of marrow blasts, karyotype, and number of cytopenias — to calculate a prognostic risk score (Table 3)

**Table 1. — French-American-British Classification of Myelodysplastic Syndromes**

	Bone Marrow Blasts	Peripheral Blasts	Ringed Sideroblasts
Refractory anemia (RA)	0–5%	0%	<15%
Refractory anemia with ringed sideroblasts (RARS)	0–5%	0%	>15%
Refractory anemia with excess blasts (RAEB)	6–19%	1–4%	Variable
Refractory anemia with excess blasts in transformation (RAEB-T)	20–29%	5–29%	Variable

Data from Steensma et al,<sup>2</sup> Bennett et al,<sup>5</sup> and Silverman.<sup>18</sup>

**Table 2. — International Prognostic Scoring System Definitions of Cytopenias and Cytogenetic Classifications**

Cytopenias	Neutrophils:	<1,500/μL
	Hemoglobin:	<10 g/dL
	Platelets:	<100,000/μL
Cytogenetics	Good:	Normal or -5q, -Y, -20q as sole abnormalities
	Poor:	Complex (ie, ≥3 abnormalities) or chromosome 7 abnormalities
	Intermediate:	All other abnormalities

From Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89: 2079-2088. Copyright American Society of Hematology, used with permission.

**Table 3. — International Prognostic Scoring System for Percentage of Marrow Blasts, Karyotype, and Cytopenias**

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
% Marrow Blasts	<5	5–10	–	11–20	21–30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0 or 1	2 or 3			

Scoring for risk groups:  
 0 = Low  
 0.5–1.0 = Intermediate-1  
 1.5–2.0 = Intermediate-2  
 ≥2.5 = High

From Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89: 2079-2088. Copyright American Society of Hematology, used with permission.

and place the patient into one of four risk categories.<sup>11,14</sup> The four risk levels represented by the cumulative score are low, intermediate-1, intermediate-2, and high. Low is a score of 0, representing low risk of progression to AML or death. Intermediate-1 scores range from 0.5 to 1.0. Intermediate-2 scores range from 1.5 to 2.0. High scores of 2.5 or more represent a high risk of disease progression or death. Survival and progression rates for the four levels of risk are presented in Fig 1. Progression is defined as development of AML based on the FAB classification (accumulation of at least 30% blasts in the marrow).<sup>5</sup>

## Treatment Goals and Principles

The goals of treatment of MDS, whether curative or non-curative, are to prolong survival, improve peripheral blood counts, and improve quality of life.<sup>15</sup> More aggressive care plans involve greater risk for patients. Therefore, it is advantageous to have the most accurate assess-

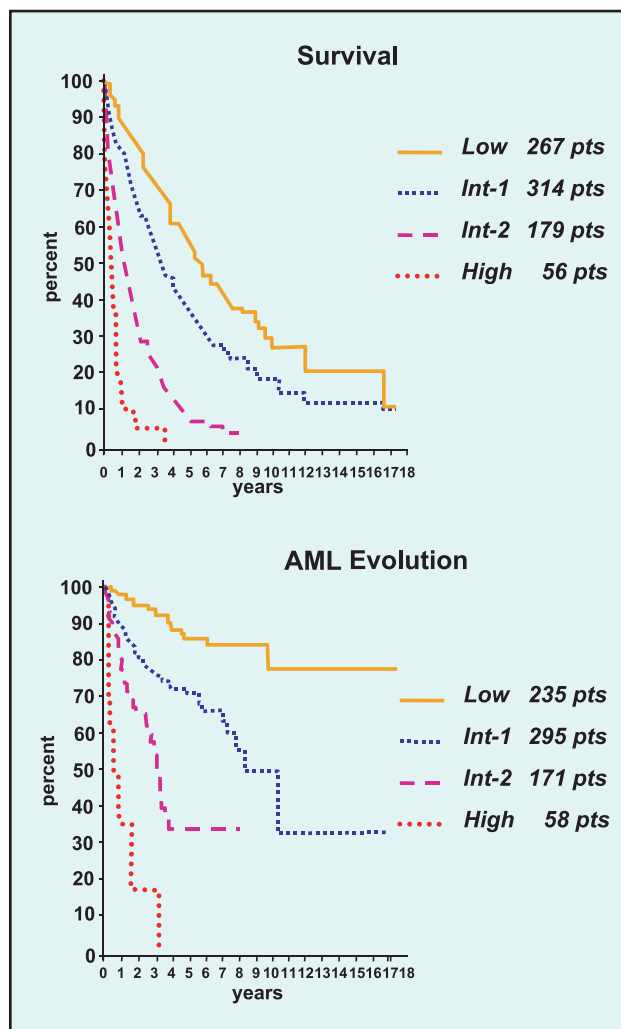


Fig 1. — Survival and progression of 816 patients with myelodysplastic syndrome separated into the four classifications of the IPSS classifications (AML = acute myeloid leukemia). From Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89: 2079-2088. Copyright American Society of Hematology, used with permission.

ment of the patient's prognosis utilizing the IPSS score. It becomes evident that each risk group needs a different approach to treatment.

In the low-risk group, a minority of patients progress to AML. Prevention of leukemia, as an outcome, is not necessarily a dominant concern in this group. However, the median survival in this population is only 7 years. Patients in the low-risk group are at an increased risk of premature death, but death tends to be due to complications of cytopenia. Thus these complications should be the focus of medical care. The three goals of therapy — enhanced quality of life, improved blood counts, and prolonged survival — still apply, but higher-risk therapies may not be appropriate for most low-risk patients in the absence of disease progression.

Compared with low-risk patients, those in the high-risk group have a high rate of evolution to AML. The progression curve of this group overlaps its survival curve, and patients tend to die of progressive disease.<sup>11</sup> Treatments for these patients focus on the improvement of cytopenias as well as prevention of AML evolution. The only known curative treatment for MDS is allogeneic stem cell transplantation.<sup>16</sup> Because allogeneic transplantation has a real cure rate, it needs to be considered early for patients with MDS, but full myeloablative allogeneic transplantation is primarily applicable to a younger subset of patients, with specific age criteria varying among transplant centers. Many patients die of the consequences of the therapy, and not all survivors are cured. For patients who do not elect to receive potentially curative allogeneic transplantation, usually because of the risks of death or transplant failure, treatment goals become palliative. The objectives of palliative treatment include decreasing the frequency of red cell transfusions with its concomitant risks of infection and iron overload, decreasing the incidence of both minor and life-threatening infections, decreasing the risk of bleeding due to thrombocytopenia, and generally improving the patient's quality of life. The physician must examine the patient's specific hematologic needs to identify those requiring palliation. In addition, the physician must also consider the risk of progression to AML. While this consideration was previously not a factor in the absence of allogeneic stem cell transplantation, the recent recognition that DNA methyltransferase inhibitors delay the progression of MDS makes this benefit an important factor to consider in patient discussion and treatment

selection. The goals of therapy need to be individualized for each patient, with the overall goals of minimizing toxicity, improving blood counts, decreasing transfusions and infections, and prolonging stable disease. It is hoped that meeting these goals will prolong survival and improve quality of life outcomes.

### Patient Response to MDS Therapies: The International Working Group

With no standards in place to assess patient response to treatment, it was difficult in the past to assess MDS therapies presented in the literature. Thus, in 2000, an international working group of clinicians involved in the management of patients with MDS developed a uniform set of guidelines for future clinical trials.<sup>15</sup> The IWG criteria have become the required standardized method of assessing responses in new trials of agents in MDS. The IWG criteria recognize that there are different potential goals of a new treatment modality.

The IWG response criteria defines complete remission as less than 5% blasts in the bone marrow, essentially normalized peripheral blood counts, and the absence of morphologic dysplasia in the bone marrow. A partial remission is identical to complete remission, but with a decrease in blasts by only 50% or less. In addition, a hematologic peripheral blood complete remission with ongoing marrow dysplasia in the marrow would be considered a partial remission by the IWG (Table 4).<sup>17</sup>

The IWG criteria divide hematologic improvements into major and minor categories.<sup>15</sup> The trend is to focus

**Table 4. — Levels of Response to MDS Treatments Defined by International Working Group (IWG) Criteria**

Complete Remission	<5% bone marrow blasts No dysplasia Hemoglobin >11 g/dL Neutrophils $\geq$ 1,500/ $\mu$ L Platelets $\geq$ 100,000/ $\mu$ L
Partial Remission	Same as above except bone marrow blasts decreased by 50% or more
Hematologic Improvements	
Red Blood Cells:	Major: Transfusion independence or >2 g/dL increase in hemoglobin Minor: 50% decrease in transfusion requirements or 1–2 g/dL increase in hemoglobin
Platelets:	Major: Platelet transfusion independence, or increase of 30,000/ $\mu$ L if less than 100,000/ $\mu$ L at baseline Minor: 50% or more increase in platelet count (at least 10,000/ $\mu$ L) if less than 100,000/ $\mu$ L at baseline
Neutrophils:	Major: If ANC <1,500/ $\mu$ L, increase of at least 100% or absolute increase of 500/ $\mu$ L, whichever is greater Minor: If ANC <1,500/ $\mu$ L, increase of at least 100% but absolute increase of <500/ $\mu$ L
ANC = absolute neutrophil count	
Adapted from Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. <i>Blood</i> . 2000;96:3671-3674. Copyright American Society of Hematology, used with permission.	

on the improvements classified as major and thus more clinically significant. In the red blood cell series, a major improvement is transfusion independence or an increase of at least 2 g/dL in hemoglobin. A major improvement in platelets is defined as platelet transfusion independence or an increase of 30,000/ $\mu$ L if the platelet count was less than 100,000/ $\mu$ L at baseline. A major improvement in neutrophil count is a 100% increase in neutrophils or at least an increase of 500/ $\mu$ L, whichever is greater, if the baseline neutrophil count was less than 1,500/ $\mu$ L.

Since quality of life is the primary outcome in palliative therapy trials, the IWG also recommends the inclusion of quality of life instruments in trials investigating new agents in MDS. The use of a validated instrument is recommended to measure physical, functional, emotional, social, and spiritual domains of quality of life.<sup>19,20</sup>

## Conclusions

MDS is composed of a heterogeneous group of hemopathies. The IPSS allows the physician to design a personalized care plan for each MDS patient, quantitatively assessing the risk of disease progression and death. Proper classification and risk stratification are essential in defining an appropriate care plan and selecting therapy. The treatment principles and goals focus on individualizing care, minimizing toxicity, and improving hematologic parameters to enhance quality of life and prolong survival. Future MDS treatment algorithms should recognize these principles and report the efficacy of new agents in accordance with the IWG criteria.

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