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*Use of new classification and prognostic scoring systems is key to optimizing management of patients with MDS.*

## Myelodysplastic Syndromes: Diagnosis and Staging

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*Myelodysplastic syndromes (MDS) represent a heterogeneous group of hematologic disorders characterized by ineffective hematopoiesis and an increased risk of developing acute myelogenous leukemia (AML). Accurate diagnosis of MDS can be difficult, and its classification requires evaluation of cytopenias, bone marrow morphology, blast percentage, and cytogenetics. These factors, as well as patient performance status and red blood cell transfusion dependence, can be used to predict prognosis in MDS. Accurate diagnosis and classification are essential for subgroup identification and prognostic assessment of patients with MDS. This article reviews essential criteria for staging and subgroup classification and summarizes prognostic scoring systems that aid in risk stratification and selection of optimal therapy.*

*Classification systems such as the World Health Organization (WHO) classification are widely used but do not always provide sufficient prognostic information. This limitation led to the creation of the International Prognostic Scoring System (IPSS). However, this system was designed to be used only at diagnosis and may not be suitable for serial assessment of patients whose disease can evolve over time. The WHO classification-based prognostic scoring system (WPSS) permits dynamic estimation of survival and risk of AML transformation at multiple time points during the natural course of MDS. Prognostic scoring systems such as WPSS allow for prediction of survival and risk of leukemic evolution at any time during the course of the disease. Such an approach may provide a useful adjunct for clinical decision making, including selection of appropriate treatment options.*

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*Abbreviations used in this paper: MDS = myelodysplastic syndromes, AML = acute myelogenous leukemia, RBC = red blood cell, WHO = World Health Organization, IPSS = International Prognostic Scoring System, WPSS = WHO classification-based prognostic scoring system.*

### Introduction

Myelodysplastic syndromes (MDS) constitute a group of clonal hematopoietic disorders characterized by bone marrow failure, dysplasia, and an increased likelihood of evolution to acute myeloid leukemia (AML). MDS is generally classified as “primary” (or *de novo*) and “treatment-related” (secondary to prior cytotoxic chemotherapy).<sup>1</sup> These disorders are thought to arise due to abnormalities in hematopoietic stem cell self-renewal and differentiation. The incidence of MDS increases with age, perhaps as a result of ongoing acqui-

sition of DNA damage, natural depletion of stem cells, and/or accumulated exposure of the bone marrow to environmental stresses or toxins.<sup>2</sup>

Many different conditions are grouped together under the “MDS” umbrella based on common clinical characteristics, thus accounting for the wide heterogeneity observed. Diagnosis of patients with this disease can be difficult at times. Similarly, the assigning of prognosis and the selection of appropriate therapy require careful application of prognostic scoring systems taking into account clinical characteristics (eg, cytopenias age, performance status) and cytological parameters (eg, blast count, morphology, karyotype).<sup>3,4</sup> Factors such as poor cytogenetics are associated with decreased survival in MDS. Knowing the specific cytogenetic abnormality can assist in the selection of therapy for certain subgroups of MDS patients (eg, lenalidomide for patients with 5q- syndrome). Inadequate diagnosis can lead to delayed or incorrect classification of MDS that could result in inappropriate treatment decisions, such as relying only on best supportive care.

Several factors have been identified that can significantly impact the prognosis and selection of therapy for MDS patients, such as cytogenetics, patient performance status, and red blood cell (RBC) transfusion dependence. Numerous studies have shown that patient performance status is inversely associated with overall or event-free survival in patients receiving intensive chemotherapy for MDS or AML, particularly older individuals.<sup>5,8</sup> Current treatment guidelines suggest that performance status be considered when evaluating therapeutic options since it affects the ability of higher-risk patients to safely undergo aggressive treatments such as intensive induction chemotherapy or hematopoietic stem cell transplantation.<sup>9</sup> Older MDS patients, who are more likely to have lower performance status and major comorbidities than younger patients, may not be able to tolerate such intensive therapy. Some patients whose performance status is suboptimal may benefit from treatment with azacitidine or decitabine as a bridging therapy prior to transplantation.

Recent advances in the diagnosis and prognostic assessment of MDS, accompanied by a greater number of effective treatment options, have improved patient outcomes based on proper selection of therapy. This review summarizes the current classification systems used to subcategorize MDS. Evolving prognostic scoring systems that facilitate assessment of patient survival and risk of progression to AML at diagnosis as well as during the course of their disease are discussed. Additionally, factors that can adversely affect survival such as cytogenetics, performance status, and RBC transfusion dependence are examined, along with criteria that can be used for the selection of appropriate therapy for individual MDS subgroups.

## Diagnosis

The differential diagnosis of MDS can be challenging, given its heterogeneous nature and the subjective assessment of dysplasia. Accurate diagnosis of MDS-associated dysplasia requires a review of the peripheral blood smear as well as a bone marrow aspirate and biopsy. Morphological analysis is performed to determine the percentage of myeloblasts; it is also performed because specific cytological abnormalities can be found in the blood and bone marrow.<sup>10,11</sup> Peripheral blood smears may reveal hypogranulated neutrophils with hyposegmented nuclei (the pseudo-Pelger-Huet anomaly) and large platelets, while bone marrow dysplasia affects the erythroid, myeloid, or megakaryocytic lineages.<sup>1</sup> The bone marrow is usually normocellular or hypercellular, but up to 20% of MDS patients have hypocellular marrow.<sup>3</sup>

Cytopenias are the most common clinical feature of MDS, particularly anemia. A diagnosis of MDS must be distinguished from other causes of anemia such as aplastic anemia or paroxysmal nocturnal hemoglobinuria (PNH).<sup>3</sup> Hairy cell leukemia, which can also mimic MDS clinically, should also be excluded by careful evaluation of the bone marrow. Bone marrow findings can also exclude a diagnosis of natural killer cell leukemia. Occasionally, human immunodeficiency virus (HIV) can cause cytopenias that mimic MDS.<sup>12</sup> Unexplained anemia that commonly occurs in the elderly also must be excluded.<sup>13</sup> Other factors can cause MDS-like bone marrow dysplasia, including vitamin B<sub>12</sub> or folate deficiencies, viral infections, and exposure to certain toxic agents (eg, chemotherapy, lead, benzene), but their effects are generally transient. The presence of fibrosis in some patients requires that a diagnosis of primary myelofibrosis be ruled out.<sup>14</sup>

Several groups have demonstrated that flow cytometry may have diagnostic utility for the immunophenotyping of MDS.<sup>15-17</sup> For example, using flow cytometric analysis, Malcovati et al<sup>18</sup> found a higher proportion of immature erythroid cells and immature myeloid cells in MDS. A significant correlation was found between multiparameter flow analysis and both the International Prognostic Scoring System (IPSS) score and the degree of morphologic dysplasia. Flow cytometry can also be used to rule out a diagnosis of PNH or large granular lymphocytic leukemia. This technique may serve as a useful adjunct in the diagnosis and staging of MDS, although it is not routinely performed in many diagnostic pathology laboratories outside of research or academic institutions.

Appropriate diagnosis and classification of MDS depends on accurate assessments of both clinical features and laboratory/pathology findings (eg, blast count, peripheral blood counts, cytogenetics). To this end, well-prepared bone marrow smears and biopsy specimens are essential. Close collaboration between the oncologist and pathologist is key for proper evalu-

ation of clinical findings together with bone marrow morphology, karyotype, and any additional data such as flow studies or immunophenotyping.<sup>19</sup>

### Cytogenetics

Cytogenetic analysis of the bone marrow is indicated in MDS not only to detect characteristic chromosomal abnormalities, but also to assess for clonal evolution. Chromosomal abnormalities have been documented in 40% to 70% of patients presenting with MDS and in the majority of patients with treatment-related MDS. A review of the literature, involving more than 3,000 cases, indicated an incidence of chromosomal aberrations of approximately 48% at time of presentation.<sup>20</sup> While the remaining cases appear to have a normal karyotype, technical failures such as inability to obtain sufficient analyzable metaphases may reduce the actual proportion of abnormal cases. Fluorescence *in situ* hybridization (FISH) has been used to assess chromosomal changes in MDS not detected by standard cytogenetic analysis. It is particularly useful in cases where insufficient numbers of metaphases are available for standard G-banding. FISH has been used to detect 5q- alterations in patients with a seemingly normal karyotype<sup>21</sup>; its greater sensitivity is useful for detecting minimal residual disease or early relapse. This technique, however, detects alterations only at defined loci and requires genetic probes specific for the region(s) of interest. Current MDS staging systems do not yet incorporate FISH or other molecular analyses.

While no chromosomal abnormalities are pathognomonic for MDS, several cytogenetic alterations have been consistently noted. Chromosomal deletions are most common, although translocations and loss or gain of whole chromosomes can also occur.<sup>22</sup> In patients with primary MDS, the most common cytogenetic alteration consists of interstitial deletion of the long arm of chromosome 5 (5q-), which is found in up to 30% of cases.<sup>22,23</sup> Other common changes include trisomy 8 (19%) and 7q- or monosomy 7 (15%). Additional reported karyotypic aberrations, including loss of chromosome Y, 17p-, isochromosome 17q, and interstitial deletions of 3, 11, 12, 13, and 20, are frequently observed in more advanced disease (Table 1).<sup>22,23</sup> Between 10% and 20% of patients with primary MDS have complex karyotypes.<sup>24</sup>

In patients with treatment-related MDS, certain cytogenetic alterations are associated with exposure to specific leukemogenic agents. Monosomy 7, 7q-, monosomy 5, and 5q- are the most common changes related to alkylating agent exposure. Alterations at 11q23 are generally found following treatment with topoisomerase inhibitors.<sup>25</sup> These chromosomal aberrations are associated with a poor prognosis in patients

**Table 1. — Common Cytogenetic Alterations in MDS**

MDS Subtype	Frequency	Chromosomal Aberrations
RA	25%	del(5q), del(20q), -Y, -7, +8
RARS	10%	del(5q), del(20q), -Y, -7, +8, idic(X)(q13)
RCMD	50%	del(5q), -7, +8
RCMD-RS	50%	del(5q), -7, +8
RAEB-1	50%	del(5q), -7, +8, del(20q)
RAEB-2	50%–75%	del(5q), -7, +8, -17p, del(11q), t(11q23), -13, del(13q)
MDS del(5q)	100%	del(5q)

Data from Mufti<sup>20</sup> and Fenaux.<sup>22</sup>

with treatment-related MDS. In contrast to primary MDS, where translocations may be balanced, many unbalanced translocations were noted in patients with treatment-related AML.<sup>26</sup>

Currently used MDS prognostic scoring systems include cytogenetics as a key variable, considering both the presence and type of chromosomal alterations. In the IPSS, for example, a normal karyotype or the presence of -Y, del(5q), or del(20q) is classified as good risk, while the presence of three or more abnormalities (ie, complex cytogenetic abnormalities) or chromosome 7 abnormalities connotes poor risk. All other abnormalities are considered intermediate risk. These criteria are also used in the World Health Organization (WHO) classification-based prognostic scoring system (WPSS).<sup>27</sup> Cytogenetic risk factors, in combination with other prognostic factors such as bone marrow blasts and cytopenias, are used to assess overall outcome as well as risk of transformation to acute leukemia. Thus, IPSS “low-risk” MDS patients with a good-risk karyotype, < 5% blasts, and 0 or 1 cytopenias have a median survival of 5.7 years compared with IPSS “high-risk” patients who have a median survival of only 0.4 years.<sup>28</sup>

### 5q- Syndrome

Some patients with the 5q- deletion are categorized by the WHO classification as having a distinct type of MDS (the “5q- syndrome”), characterized by < 5% blasts in the bone marrow (with no Auer rods), thrombocytosis, typical dysmegakaryopoiesis, macrocytic anemia, and an isolated 5q- abnormality.<sup>9</sup> Such patients, who are predominantly female, typically have a low frequency of progression to AML (10%) and favorable survival compared with other MDS subgroups. Cytogenetic and FISH analyses have shown that this deletion is present in the pluripotent hematopoietic progenitor cells (CD34<sup>+</sup>, CD38<sup>-</sup>) of MDS patients.<sup>29</sup>

Until recently, such patients were thought to respond poorly to available therapy, responding only to RBC transfusions. However, the immunomodulatory drug lenalidomide has been found to be extremely effective in the treatment of RBC transfusion-dependent, low-

to intermediate-risk MDS patients with 5q- abnormalities (alone or with other cytogenetic alterations). Lenalidomide therapy leads to transfusion independence in more than two-thirds of cases, with frequent cytogenetic remissions being achieved. In a study of 148 MDS patients treated with 10 mg of lenalidomide daily, 112 (76%) had a reduced need for transfusions and 99 (67%) became transfusion-independent.<sup>30</sup> Of 85 evaluable patients, 62 had cytogenetic improvement, 38 of whom had a complete cytogenetic remission. On the basis of these results, lenalidomide was approved by the US Food and Drug Administration for the treatment of transfusion-dependent patients with low- to intermediate-risk MDS and chromosome 5q deletion.<sup>31</sup>

While outcomes may vary among patients with different 5q deletions, patients with the 5q- syndrome generally have a longer survival.<sup>26</sup> One study found that patients with 5q- and no other karyotypic changes had a median survival of 76 months compared to 42 months for MDS patients with a normal karyotype.<sup>32</sup> The presence of additional (complex) chromosomal changes or an increased bone marrow blast count significantly reduces median survival in patients with a 5q- deletion. In a study of 66 MDS patients, median survival for those with only 5q- was 146 months vs 45 months for patients with additional chromosomal changes ( $P = .0085$ ).<sup>33</sup> Survival was shorter still if the amount of blasts was greater than 5%.

A recent study implicated haploinsufficiency of a specific gene as causing some of the features of the 5q- syndrome. Using a novel RNA interference (RNAi) screening approach, Ebert et al<sup>34</sup> found that inactivation of the gene encoding the RPS14 ribosomal protein could favor hematopoietic cell differentiation in a manner consistent with the thrombocytosis and anemia found in the 5q- syndrome.<sup>34</sup> The RPS14 protein functions in the processing of pre-ribosomal RNA and the formation of the 40S ribosomal subunit. A similar defect in a gene involved in ribosomal processing (the *RPS19* gene) is seen in another bone marrow failure

syndrome, Diamond-Blackfan anemia.<sup>35</sup> These results suggest that haploinsufficiency of critical ribosomal gene products could account for these disease phenotypes and imply that translational control is dysregulated in hematologic malignancies.

## MDS Classification Systems

Staging systems are key for accurate MDS diagnosis and selection of therapy. MDS staging and classification schemes have evolved significantly over the past few decades to address our evolving understanding of the biology of this disease and its subtypes. A review of the literature reveals that a variety of classification systems have been used, thus making comparisons of the types of patients enrolled in different clinical trials quite challenging. The recent use of uniform classification systems has remedied this problem. However, some systems, developed to assess patients at diagnosis, may not be well suited for evaluating patients following disease progression. Newer and hopefully improved classification schemes may advance this situation.

### French-American-British Classification

The French-American-British (FAB) classification is the oldest and most well-established scheme for the classification of MDS and AML (Table 2). Developed in 1982, the FAB MDS classification scheme includes five subtypes of MDS, based largely on the proportion of blasts in the peripheral blood and bone marrow and the presence or absence of ringed sideroblasts or increased circulating monocyte numbers. Median survival and time to AML transformation vary according to FAB subtype, allowing for assigning prognosis and in some cases predicting response to therapy (eg, RARS patients generally have a low rate of response to erythropoietin).<sup>28</sup> It was noted, however, that FAB subtypes are not homogeneous within each group, suggesting limitations of this system. Also, the FAB scheme does not accurately reflect the biology of the disease, such as the number of lineages with dysplasia.

Table 2. — French-American-British (FAB) Classification for MDS

Classification	Characteristics
Refractory anemia (RA)	Cytopenia of 1 PB lineage; normo- or hypercellular marrow with dysplasias; < 1% blasts in PB and < 5% bone marrow blasts
Refractory anemia with ringed sideroblasts (RARS)	Cytopenia and dysplasia, with same percentage blast as RA; > 15% ringed sideroblasts in bone marrow
Refractory anemia with excess blasts (RAEB)	Cytopenia of ≥ 2 PB lineages; dysplasia involving all 3 lineages; < 5% PB blasts and 5%–20% bone marrow blasts
Refractory anemia with excess blasts in transformation (RAEB-t)	Same hematologic features as RAEB; > 5% blasts in PB or 21%–30% blasts in bone marrow or presence of Auer rods in blasts
Chronic myelomonocytic leukemia (CMML)	Monocytosis in PB; < 5% blasts in PB and up to 20% bone marrow blasts

PB = peripheral blood. Adapted from Catenacci DV, Schiller GJ. Myelodysplastic syndromes: a comprehensive review. *Blood Rev.* 2005;19(6): 301-319. Reprinted with permission. © 2008 Elsevier.

## WHO Classification

A variety of clinical and morphological issues led to the development of a new MDS staging system by the WHO to further refine the classification criteria and improve the assignment of prognosis for intermediate-risk cases.<sup>36,37</sup> The WHO scheme is based on the FAB system but better defines each class by use of specific criteria for assigning dysplasia to one or more lineages in the bone marrow cells.<sup>38</sup> Refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) are considered as erythroid dysplasia with < 10% dysplasia in the myeloid or megakaryocytic lineages. Refractory anemia with excess blasts (RAEB) is considered as RAEB-1 (5% to 9% blasts) or RAEB-2 (10% to 19% blasts). A new category, refractory cytopenia with multilineage dysplasia, was added. Chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (CML), and juvenile myelomonocytic leukemia (JMML) are classified under myelodysplastic/myeloproliferative disorders. The 5q- syndrome is considered as a separate subgroup under the WHO. In addition, AML was defined based on a lower minimum criterion for percentage of bone marrow blasts compared to FAB (20% vs 30%). The WHO system has demonstrated prognostic value in predicting overall and leukemia-free survival (both  $P < .001$ ).<sup>39,40</sup> Some clinicians, however, do not support the elimination of RAEB-t from the FAB classification. This stems in part from the important heterogeneity that exists for patients with 20% to 30% blasts. By not distinguishing those with MDS from those with AML, tracking their outcome will be difficult using the WHO system.<sup>37,41-45</sup>

## Prognostic Scoring Systems

Various prognostic systems have been proposed aimed at improving the ability to predict survival and progression in MDS patients. While the IPSS has been the most widely used, the implementation in the clinical practice of the WHO classification compelled a refinement of prognostic factors and the development of new prognostic scoring systems, such as the WPSS.

### International Prognostic Scoring System

Following the proposal by the FAB cooperative group, several studies have been performed to improve our ability to evaluate prognosis in MDS. In 1997 an International MDS Risk Analysis Workshop defined the IPSS. The IPSS was derived on a regression model based on 816

patients with primary MDS from seven previous studies.<sup>28</sup> The scoring system integrates bone marrow blast percentage scored into four ranges, number of peripheral cytopenias, and karyotype categorized in three groups. An IPSS score is obtained by summing the individual scores for the three variables, resulting in stratification of patients into one of four risk groups: low (score of 0), Int-1 (score of 0.5 to 1.0), Int-2 (score of 1.5 to 2.0), or high (score > 2.0) (Table 3). The four risk groups showed significantly different overall survival and risk of transformation to AML. Median survival ranges from 5.7 years for patients with low risk (score of 0) to 0.4 years for those with high risk (score of 2.5 or greater). The IPSS has been extensively validated in independent patient populations and has become a benchmark for clinical trials and clinical decision making.

To improve prognostication in MDS, a working party of seven Austrian and German groups identified elevated lactate dehydrogenase (LDH) as an additional prognostic variable and proposed a refinement of IPSS by including the LDH.<sup>46</sup> The IPSS+LDH was capable of separating a new group of “very-low-risk” patients. Also, for patients in the Int-2 and high-risk groups, the addition of the LDH results in meaningful stratifications.

The limitation of the IPSS to stratify patients with lower-risk disease (ie, low or Int-1 risk) was also addressed by Garcia-Manero et al.<sup>47</sup> They developed a prognostic scoring system specifically designed to identify among patients with low-risk disease those with poor prognosis who may be eligible for early interventions or enrollment in a clinical trial. These investigators analyzed 856 patients with low or Int-1 IPSS risk, and they developed a model that computes the pres-

Table 3. — International Prognostic Scoring System (IPSS) for MDS

Prognostic variable	Survival and Acute Myelogenous Leukemia Evolution Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	<5	5–10	—	11–20	21–30
Karyotype*	Good	Intermediate	Poor	—	—
Cytopenias**	0 or 1	2 or 3	—	—	—
* Good = normal or any 1 of the following: -Y, del(5q), del(20q); Intermediate = other abnormalities; Poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.					
** Cytopenias: neutrophil count < 1,500/μL, platelets < 100,000/μL, hemoglobin < 10 g/dL.					
	IPSS Risk Category				
	Low	Int-1	Int-2	High	
Combined score	0	0.5–1.0	1.5–2.0	≥ 2.5	
Leukemic death	19%	30%	33%	45%	
Median time to AML (yr)	9.4	3.3	1.1	0.2	
Median survival (yr)*	5.7	3.5	1.2	0.4	
Int-1 = intermediate-1, Int-2 = intermediate-2, AML = acute myelogenous leukemia. This research was originally published in Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. <i>Blood</i> . 1997;89(6):2079-2088. Reprinted with permission. © 2008 American Society of Hematology.					

ence of poor cytogenetics, age, hemoglobin, platelets, and percentage of marrow blasts. This led to a scoring system that allows patients to be classified into three prognostic groups, with median survival ranging from 80.3 months to 14.2 months. For low-risk patients, this approach may improve the identification of those with a more aggressive disease who may benefit from appropriate early therapy or inclusion in clinical trials.

### WHO Classification-Based Prognostic Scoring System

Although IPSS is the most commonly used prognostic staging system for MDS, it does have limitations,<sup>26</sup> which were emphasized following introduction of the WHO classification. The IPSS retains significance within the WHO subgroups. However, the two systems are redundant mainly because the IPSS blast intervals have been substantially maintained by the WHO classification. In addition, the number of peripheral cytopenias fails to retain significant value when the number of dysplastic marrow lineages is included in the analysis. Therefore, when accounting for blast percentage using WHO categories, the only other IPSS variable adding prognostic information is cytogenetics. Finally, the assimilation of MDS with more than 20% blasts to acute leukemia resulted in a significant cutback of the higher-risk IPSS groups.

A further limitation of IPSS is that, as with other traditional prognostic scoring systems, it provides estimates of risk and survival based on assessment of clinical variables at the time of diagnosis, irrespective of disease progression. Consequently, its application during the course of the disease could introduce bias.

To address these limitations, Malcovati et al<sup>27</sup> developed a dynamic prognostic model based on the variables introduced by the WHO classification-based prognostic scoring system (WPSS). The WPSS score integrates the three most important prognostic factors in MDS patients classified according to WHO criteria: karyotype, WHO

subgroup, and requirement for RBC transfusion as an indicator of symptomatic anemia. This model estimates the relationship between variables repeatedly measured during follow-up and outcome and, therefore, provides dynamic prognostic information throughout the clinical course. Patients are assigned a score of 0 to 3 according to WHO categories (Table 4). Patients with isolated erythroid dysplasia (ie, RA and RARS according to WHO criteria), as well as those with MDS with isolated del(5q), have a very good prognosis (score 0) compared to those with multilineage dysplasia (RCMD and RCMD-RS, score 1). Among patients with excess of bone marrow blasts, the two categories of RAEB identify subgroups with significantly different survival and risk of leukemic evolution (RAEB-1 scored 2; RAEB-2 scored 3). Karyotype is grouped according to the IPSS criteria, but its relative weight in the model is higher compared to the original scoring system, with good, intermediate, and poor cytogenetic risk groups being scored from 0 to 2. The third variable in the score is transfusion requirement. Patients developing a need for regular RBC transfusion have a worse prognosis (score 1) compared to those without a transfusion need (score 0).

In contrast with the four risk groups identified by the IPSS, the WPSS stratifies MDS patients into five different risk categories: very low (score = 0), low (1), intermediate (2), high (3–4), or very high (5–6) (Table 4). Significant differences can be seen among the five groups in overall survival ( $P < .0001$ ) and risk of AML ( $P < .0001$ ). In an independent cohort of patients with MDS, median survival ranged from 140 months for patients with a score of 0 to 10 months for those with a score of 5 or more.<sup>27</sup> The most significant improvement in prognostic stratification compared with IPSS is observed in patients without excess blasts, primarily due to the strong impact of marrow lineage involvement and transfusion dependency.

The WPSS is based on a time-dependent regression model, and therefore it provides dynamic prognostic information throughout the clinical course. According to this model, a patient is classified into a risk group at the time of diagnosis and stays in the same group as long as the score remains unchanged. If the patient progresses, the WPSS category changes according to the resulting score, and the patient will subsequently be followed in the new risk group. As a consequence, the interpretation of the survival curves resulting from such a model is different from that used for traditional survival curves. Non-time-dependent curves give an estimate of survival and risk of leukemic evolution

**Table 4. — WHO-Based Prognostic Scoring System (WPSS) for MDS**

Parameter	Score			
	0	1	2	3
WHO category	RA, RARS, 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	—
RBC transfusion requirement**	No	Regular	—	—

RA = refractory anemia, RARS = refractory anemia with ringed sideroblasts, RCMD = refractory cytopenia with multilineage dysplasia, RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts, RAEB-1 = refractory anemia with excess of blasts-1, RAEB-2 = refractory anemia with excess of blasts-2.  
 \* Karyotype: Good = normal, -Y, del(5q), del(20q), Poor = complex ( $\geq 3$  abnormalities), chromosome 7 anomalies, Intermediate = other abnormalities.  
 \*\* RBC transfusion requirement = having  $\geq 1$  RBC transfusion every 8 weeks over a 4-month period. Modified from Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol.* 2007;25(23):3503-3510. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

based on data at diagnosis, independent of any further evolution of the disease. In contrast, time-dependent survival curves provide a risk estimate based on the current clinical features. In fact, a patient is followed in the risk group assigned at diagnosis as long as the disease remains stable. In the case of disease progression, the patient is re-scored according to the WPSS, and the time-dependent survival curves for the new risk group will provide an updated estimate of survival and risk of leukemic progression (Fig 1). Such an approach may be helpful for clinical decision making, particularly in low-risk patients who may be candidates for delayed treatment strategies. The ability to determine a risk estimate as long as patients have stable disease is of particular interest in the very low WPSS risk group, in which mor-

tality is not significantly different from that of the general population. This indicates that patients classified as having a very low risk, as long as their disease remains stable, have a life expectancy not significantly different from that of the general population.

The basis of WPSS is the WHO classification, which requires skilled morphologists since the definition of the WHO subgroup may be problematic in occasional patients due to morphologic features that are not clear-cut. In this regard, flow cytometric immunophenotyping might be of help in the future.

### Transfusion Requirements in MDS

The majority of MDS patients are anemic at the time of diagnosis, and moderate or severe anemia is observed in

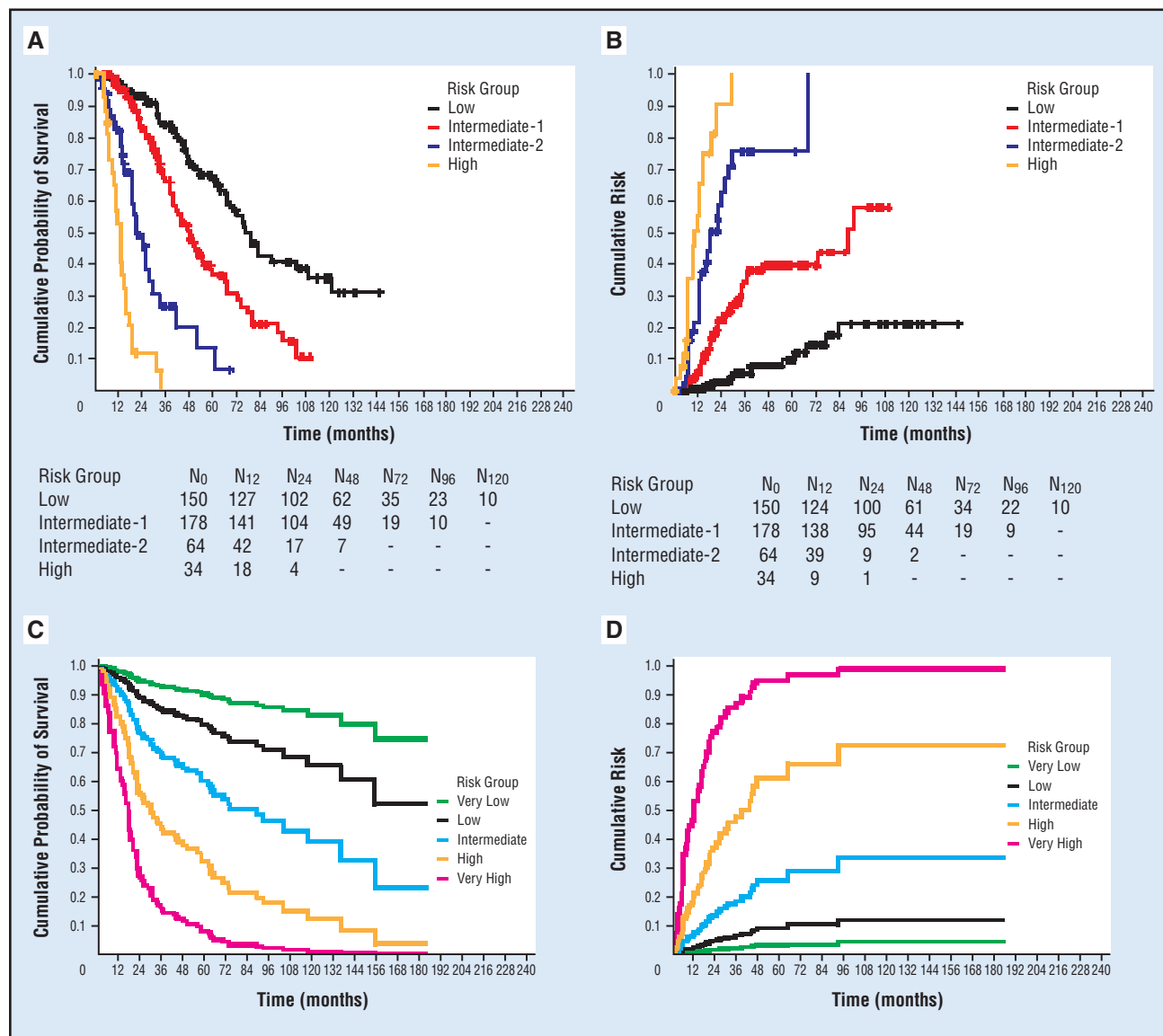


Fig 1. — Analysis of overall survival (A and C) and time to AML transformation (B and D) in a cohort of 271 MDS patients as analyzed by IPSS at diagnosis (upper panels), or by time-dependent WPSS in an independent cohort of 739 German MDS patients (lower panels). The number (N) of patients at risk at 0, 12, 24, 48, 72, 96, and 120 months is shown in panels A and B. From Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol.* 2007;25(23):3503-3510. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

approximately 60% of cases. Severe anemia is usually associated with fatigue, weakness, and other symptoms. Once patients develop symptomatic anemia, standard therapy consists of supportive care measures such as RBC transfusions aimed at preserving quality of life and preventing anemia-related morbidity. The use of hematopoietic growth factors such as erythropoietin, with or without granulocyte colony-stimulating factor (G-CSF), can increase hemoglobin levels without the need for transfusion in a proportion of MDS patients.<sup>48</sup>

Transfusion dependency in MDS is significantly associated with survival.<sup>2</sup> In a study of 467 patients with primary MDS, Malcovati et al<sup>49</sup> demonstrated that transfusion-dependent patients had a significantly shorter survival (hazard ratio [HR] = 2.16;  $P < .001$ ) and higher risk of leukemic progression (HR = 2.02;  $P < .001$ ) compared with those not requiring transfusions. Survival is inversely correlated with severity of transfusion requirement, particularly among patients with low-risk disease (Fig 2).<sup>49</sup> Transfusion-dependent patients have a higher risk of non-leukemic death, which is mainly due to an increased risk of cardiac failure (51% of cases) compared to patients without need for transfusion ( $P = .01$ ). Taken together, these data suggest that the negative effect of transfusion dependency is mainly due to a more severe anemia and more aggressive disease. In addition, indirect evidence suggests that transfusion-related iron overload may also play a role.

All patients undergoing long-term RBC transfusions eventually develop iron overload. However, at present there is little evidence for the role of iron in organ damage and the impact of iron overload on the outcome of patients with MDS. Despite the limited evidence, the

available evidence- and consensus-based guidelines recommend iron chelation in MDS patients but only for those in whom long-term transfusion therapy is likely. Patients who are candidates for allogeneic stem cell transplantation may also benefit from chelation therapy since iron overload is associated with increased transplantation-related complications.

## Conclusions

The recent clinical development of multiple new agents for treatment of MDS has resulted in more patients receiving therapy that can potentially change the course of their disease and improve survival. Appropriate selection and application of such treatments, which are highly dependent on correct diagnosis and prognostic classification, are key in providing maximal therapeutic benefit and possibly impacting survival. Thus, cytogenetic analysis is required for diagnosis of patients with 5q- syndrome and subsequent treatment with lenalidomide.<sup>26</sup> Further elucidation of the precise molecular defects present in various subtypes, such as the mutation affecting RPS14 in 5q- syndrome,<sup>34</sup> will allow for more refined prognostic staging and selection of the most appropriate therapy for individual patients. Hypomethylating agents such as azacitidine, which has shown a survival advantage compared with conventional care in Int-2 and high-risk IPSS subgroups, may be the treatment of choice in these groups.<sup>50</sup> It is likely that additional novel compounds currently in development will prove to have greater activity in select subpopulations as defined by these prognostic classification schemes.

The MDS prognostic scoring systems described here allow physicians to select therapy that is most appropriate based on each patient's specific subclassification. So far, the IPSS — based on percentage of marrow blasts, cytogenetic pattern, and number and degree of cytopenias — has been commonly used for predicting survival and leukemic risk. The use of the WPSS, a novel prognostic scoring system based on WHO classification, may be more useful than IPSS in clinical decision making, particularly among patients without excess blasts. This ability of the WPSS to stratify low-risk MDS patients is mainly due to the strong impact of single- vs multilineage dysplasia on patients and the effect of a regular transfusion requirement as a surrogate of symptomatic anemia.

The impressive heterogeneity of the disease complicates clinical decision making, not only for the choice of the most appropriate therapeutic modality but also for the optimal timing of intervention. In fact, many patients with low-risk MDS are able to survive a long time without signs of disease progression. For these patients,

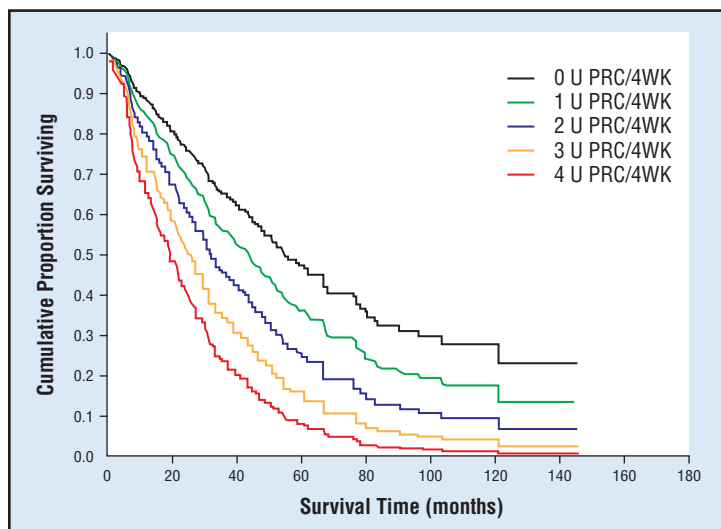


Fig 2. — Severity of transfusion requirements predicting survival in a cohort of 426 Italian MDS patients who were diagnosed according to WHO criteria. Requirement of RBC transfusions was calculated as the number of packed RBC units (U PRC) needed over a 4-week period. From Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica*. 2006;91(12):1588-1590. Obtained from Haematologica/the Hematology Journal website <http://www.haematologica.org>. © 2008 Ferrata Storti Foundation.

the risks of immediate morbidity and mortality associated with transplantation are often thought to be unacceptably high. The use of dynamic prognostic scoring systems, designed for patient assessment not only at diagnosis but throughout the course of their disease, is useful for this type of clinical decision making.

Finally, the presence of comorbid conditions may substantially impact the eligibility of MDS patients to undergo potentially curative therapies. Recently, a hematopoietic cell transplantation-specific comorbidity index (HCT-CI) for predicting risk of nonrelapse mortality has been developed and validated. The HCT-CI provides a reliable base of evidence for assessing the risks of patients who are candidates for allogeneic stem cell transplantation.<sup>51</sup>

## Disclosures

*Dr Nimer has served as a consultant and advisory board member for Celgene Corp, MGI Pharma Inc (now Eisai Inc), Pharmion Corp (now Celgene) and Genzyme Corp.*

*Dr Malcovati reports no significant relationship with the companies/organizations whose products or services may be referenced in this article.*

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