Curr Hematol Malig Rep (2011) 6:13–21
DOI 10.1007/s11899-010-0070-x

The Search for Better Prognostic Models in Myelodysplastic Syndromes

Fabio P. S. Santos · Hagop Kantarjian · Guillermo Garcia-Manero · Farhad Ravandi

Published online: 7 December 2010

Abstract Myelodysplastic syndromes (MDS) are a group of heterogeneous bone marrow disorders characterized by a failure of hematopoiesis and an increased propensity for transformation to acute myeloid leukemia. Determining the prognosis of patients with MDS is essential for discerning the best therapy, which can vary from supportive care to allogeneic stem cell transplantation. The most widely used prognostic model in MDS is the International Prognostic Scoring System (IPSS), which estimates survival and risk of transformation to acute myeloid leukemia based on the percentage of blasts, karyotype, and number of cytopenias, but the IPSS has several limitations that preclude more widespread application. Over the past decade, several studies have reported on new prognostic factors for MDS, including transfusion dependency and DNA methylation abnormalities. More recently, two prognostic models for MDS that aim to overcome the limitations of the IPSS have been published. This review focuses on the most recent advances in this field, detailing current prognostic models and the more important risk factors in MDS.

Keywords Myelodysplastic syndrome · MDS · IPSS · WPSS · Prognosis

H. Kantarjian · G. Garcia-Manero · F. Ravandi (✉)
Department of Leukemia, University of Texas,
M.D. Anderson Cancer Center,
1515 Holcombe Boulevard, Unit 0428,
Houston, TX 77030, USA
e-mail: fravandi@mdanderson.org

F. P. S. Santos
Hematology Department, Hospital Israelita Albert Einstein,
São Paulo, Brazil

Introduction

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell disorders characterized by hematopoietic cell dysplasia, ineffective hematopoiesis, peripheral blood cytopenias, and an increased risk of transformation to acute myeloid leukemia (AML) [1]. MDS is more common in the elderly population, with a median age at diagnosis of 71 years [2]. The overall annual incidence of MDS is 3.27 cases per 100,000 persons, increasing to 20.05 cases per 100,000 persons in the population 70 to 79 years of age [3]. Known risk factors for developing MDS include exposure to radiation therapy, chemotherapy, or benzene; tobacco use; and other hematopoietic stem cell disorders, including aplastic anemia and inherited bone marrow (BM) failure syndromes such as Fanconi anemia [4, 5]. Current minimal diagnostic criteria for MDS require the presence of peripheral blood cytopenia in association with at least one of the following: 1) dysplasia in at least 10% of cells from one or various hematopoietic cell lineages (erythroid, neutrophilic, megakaryocytic) and/or >15% ring sideroblasts; 2) 5% to 19% myeloid blasts; 3) characteristic karyotypic abnormality [6]. Additionally, all hematopoietic and nonhematopoietic disorders that can cause cytopenias must be excluded before a diagnosis can be firmly made.

MDS is a very heterogeneous group of entities: some are indolent with prolonged survival, whereas others have an aggressive course similar to AML, with a median survival of less than 6 months [1]. This heterogeneity is related to differences in the biology of the disease and has important clinical implications, as patients with low-risk MDS are usually managed with growth factors and supportive care measures, while patients with high-risk disease receive aggressive treatments such as chemotherapy and allogeneic stem cell transplantation (SCT) [1]. Thus, estimating the

risk of death and transformation to AML of an individual patient with MDS is essential to indicate the proper treatment.

Ever since the French-American-British (FAB) classification of MDS in 1982 [7], several studies have proposed prognostic models in MDS with the objective of differentiating low-risk from high-risk patients [8, 9]. The International Prognostic Scoring System (IPSS) is the scoring model most often used for patients with MDS [10], but in more recent years, several studies have proposed alternative models that can overcome some of the limitations of the IPSS [11, 12••]. There is a continuous search for the ideal prognostic model in MDS. This review summarizes recent data in this field.

The International Prognostic Scoring System

The IPSS evaluated 816 patients with primary, untreated MDS and analyzed clinical and morphologic features that were associated with overall survival (OS) and risk of transformation to AML [10]. Variables significantly associated with these end points in the univariate analysis included FAB subtype, percentage of blasts, karyotype abnormalities, and number of cytopenias. The results of a Cox proportional hazards multivariate analysis confirmed that blast percentage, karyotype, and the number of cytopenias were associated with OS and risk of transformation to AML; a categoric prognostic model was developed, which could successfully predict outcome in these patients (Table 1) [10].

The IPSS is by far the best-known and most-used scoring model in MDS and has served to guide treatment decisions and the design of clinical trials for patients with this disease [13, 14]. However, the IPSS has several limitations that preclude its more widespread application. First, it excluded from the analysis patients with secondary MDS (i.e., therapy-related myeloid disorder [t-MDS]), who comprise 20% to 30% of patients with MDS and are usually associated with worse survival [5, 12••]. Patients with chronic myelomonocytic leukemia (CMML) who presented with a white blood cell (WBC) count of 12×10^9/L or higher were also excluded, as their disease was considered to be closer to myeloproliferative neoplasms than to MDS. However, several clinical studies in patients with MDS also include cases of CMML regardless of WBC count, and drugs that are approved for MDS (e.g., decitabine) may also be highly active in CMML [15]. Patients who were previously treated were not included in the IPSS classification, and the model was valid only at the time of diagnosis. MDS is dynamic, however, so a prognostic model that is also dynamic and can predict outcome when the features of a patient's disease change during the clinical course is highly desirable.

Risk Factors in Myelodysplastic Syndromes

In the 13 years since the publication of the IPSS, several studies of prognostic factors in MDS have been published. These reports either refined well-known prognostic criteria such as morphology and karyotype or described new

Table 1 International Prognostic Scoring System (IPSS) prognostic model for myelodysplastic syndromes

Variable	Points				
	0	0.5	1.0	1.5	2.0
Bone Marrow Blasts (%)	< 5	5-10	-	11-20	21-30
Cytopenias[a]	0/1	2/3	-	-	-
Karyotype[b]	Good	Intermediate	Poor	-	-

Risk Group	IPSS Score	25% AML Evolution (yr)	Overall Survival (yr)
Low	0	9.4	5.7
Intermediate-1	0.5-1.0	3.3	3.5
Intermediate-2	1.5-2.0	1.1	1.2
High	2.5-3.5	0.2	0.4

Legends - a- Hb < 10 g/dL; Absolute Neutrophil Count < $1.8x10^9$/L; Platelet Count < $100x10^9$/L; b- Good: Normal, del(5q), del(20q), -Y; Intermediate: all others; Poor: complex (> 3 abnormalities), chromosome 7 abnormalities

factors like DNA methylation patterns or transfusion dependency. A comprehensive review of all known risk factors in MDS is beyond the scope of this article, and we will focus only on the most important ones.

Bone Marrow Morphology

Morphologic evaluation of marrow findings is an important tool for classifying and predicting prognosis in patients with MDS [16]. Classically, the most important morphologic feature with prognostic relevance has been the percentage of blasts in a 500-cell manual count of a BM aspirate smear [10]. The importance of blasts was shown in the FAB classification, which roughly divides MDS into two subtypes: low-risk with less than 5% blasts (refractory anemia [RA], refractory anemia with ring sideroblasts [RARS]) versus high-risk with 5% or more of blasts (refractory anemia with excess blasts [RAEB], refractory anemia with excess blasts in transformation [RAEB-t]) [7]. The IPSS model also uses blast percentage as the sole morphologic marker for prognosis [10].

Neither the FAB classification nor the IPSS model recognizes that the presence of multilineage dysplasia in the absence of increased blasts defines a distinct subtype of MDS with worse survival. Before publication of the World Health Organization (WHO) classification, Rosati et al. [17] reported on 18 patients with refractory cytopenias and multilineage dysplasia (RCMD). These patients had more profound cytopenias than patients having RA or RARS and a higher percentage of abnormal karyotype (49% vs. 7%) [17]. Median survival with RCMD (24 months) was intermediate between survival with RA/RARS (108 months) and survival with RAEB (18 months). Other reports have confirmed the impact of severe dysplasia on the outcome of patients with MDS [18, 19].

The 3rd edition of the WHO classification of hematopoietic neoplasms added the category of RCMD to the roster of MDS subtypes [16]. In a recent publication, Malcovati et al. [20] compared the outcomes of 467 patients with MDS reclassified according to the WHO classification. Patients with RCMD with or without ring sideroblasts (RS) had significantly inferior survival compared with patients having RA/RARS (median OS, 49 months vs. 108 months; $P<0.001$) [20], confirming that multilineage dysplasia is associated with worse survival than unilineage involvement.

Other morphologic features that indicate a worse prognosis include BM fibrosis and aggregates or clusters of CD34+ cells [21–23]. Increased marrow fibrosis has long been reported in BM biopsies from patients with MDS. More recently, one large series confirmed that patients with hyperfibrotic MDS (grade 2–3 BM fibrosis) have shorter leukemia-free survival and OS [21]. The effect was independent from other variables and from the IPSS and WHO classification-based Prognostic Scoring System (WPSS) criteria [21]. In practical terms, the finding of grade 2 to 3 BM fibrosis had the equivalent effect of shifting patients one category up in the IPSS and WPSS risk scores. Other series have confirmed the poor prognosis of these patients [24].

Abnormal localization of immature precursors (ALIP) in the central portion of the BM has been described in core BM biopsies of patients with MDS, being more common in RAEB and associated with poor outcome [23]. Immunohistochemistry studies have revealed that these aggregates are composed of CD34+ cells and represent clusters of blast cells [22]. All BM biopsies of patients with MDS should be evaluated for the presence of CD34+ clusters, as these patients have an increased risk of transformation to AML [21].

Cytogenetics

Karyotype has emerged as one of the most important prognostic factors in MDS. Chromosomal abnormalities are found in approximately 50% of patients with de novo MDS, and in 80% to 92% of patients with therapy-related MDS [25]. Balanced chromosomal translocations commonly found in AML—t(8;21), t(15;17)—are uncommon in MDS, which is more frequently characterized by gains and losses of chromosomal material and unbalanced translocations. Some of the most common cytogenetic abnormalities in MDS include del(5q) (6%), -7/del(7q) (2%), +8 (4.5%), del(20q) (1.7%), and -Y (2%) [25, 26]. Additionally, the 2001 WHO classification defines one subtype of MDS based on the karyotype (5q- syndrome), and it is expected that future updates of this classification will include more cytogenetically defined entities [16].

Regarding prognosis, the IPSS classified karyotype into three risk groups: good [diploid, del(20q), del(5q), -Y], intermediate (neither good or poor), and poor (chromosome 7 abnormalities and complex karyotypes) [10]. However, more recent studies using larger databases of patients with MDS have revealed that some rare chromosomal abnormalities that would normally be classified as intermediate have distinct prognostic significance, such as del(12p) (median survival 108 months) and +19 (median survival 19.8 months) [25]. Another limitation of the IPSS is that it underestimates the prognostic impact of karyotype relative to the percentage of blast cells. In an analysis of 3169 patients with MDS from Europe and the United States, Cox proportional hazards regression revealed that the relative hazard ratio (HR) for OS was 3.88 for complex karyotype with chromosome 5/7 abnormalities and 2.09 for sole -7/del (7q), whereas the HR for elevated blasts was 1.5 for 5% to 10% blasts, 1.64 for 11% to 20% blasts, and 1.81 for greater than 20% blasts. However the IPSS gives only 1.0

point for a poor-risk karyotype but 1.5 points for 11% to 20% blasts and 2.0 points for 20% to 29% blasts [27]. Thus, a revision of the cytogenetic grouping of the IPSS is needed, with reclassification of the risk group of specific chromosomal abnormalities and an increase in the impact of karyotype relative to the blast percentage. Recent publications analyzing large datasets of patients with MDS have provided revised cytogenetic classifications that predict survival outcomes more effectively than the IPSS; these may serve as a framework for future prognostic models [25, 26].

Even though G-banding metaphase cytogenetics is the standard method for evaluating karyotype in MDS, recent reports using techniques with higher resolution (comparative genomic hybridization [CGH] array; single nucleotide polymorphism [SNP] array) have revealed a wealth of additional chromosomal abnormalities in patients with MDS, characterized by microscopic gains and losses of chromosomal material and copy number–neutral loss of heterozygosity (CNN-LOH) due to uniparental disomy (UPD), even in patients with diploid karyotype by metaphase cytogenetics [28]. In one study, the investigators analyzed the genome of CD34+ cells from 174 patients with myeloid malignancies (including 74 patients with MDS) with 250 K SNP arrays [28]. Chromosomal defects were detected in 78% of patients with MDS, compared with 59% of patients by standard metaphase cytogenetics. UPD was found in 20% of MDS cases. SNP arrays detected new lesions in 62% of patients with normal cytogenetics. Importantly, the detection of new chromosomal lesions by SNP arrays affected survival: among patients with IPSS Int-1 MDS, median survival was 9 months for those with SNP-array abnormalities versus 28 months for those without abnormalities. Future prognostic models in MDS should incorporate new technologies for detecting chromosomal defects, as doing so may lead to increased recognition of poor-risk patients.

Transfusion Dependency

The development of transfusion-dependent anemia has been associated with worse survival in patients with MDS [12••, 20]. One Italian study analyzed 467 patients with de novo MDS and demonstrated that development of transfusion dependency, number of transfused units of red blood cells (RBCs), and rate of RBC transfusion were associated with worse OS and leukemia-free survival in both univariate and multivariate analysis [20]. The effect was more relevant in patients without an increase in the percentage of blasts (RA, RARS, RCMD, 5q- syndrome). Development of iron overload (defined by a ferritin serum level >1,000 ng/mL) was also associated with worse survival. Other studies have confirmed the impact that transfusion dependency has on the outcome of patients with MDS [12••, 29].

It is still unknown why transfusion dependency affects survival in these patients. It could be a marker for a more aggressive disease phenotype, it could be related to the deleterious effect of iron overload, or both. In patients with MDS, the clinical impact of iron overload appears to be more relevant in patients with low-risk disease, and transfusion-dependent patients with iron overload (ferritin >1,000 ng/mL) have a higher rate of death due to cardiac complications [20, 30]. However, published studies of T2* MRI failed to demonstrate an increase in myocardial iron content in most transfusion-dependent patients with MDS [31]. It could be that the development of cardiac iron overload requires a greater extent of transfusion dependency, as in one report only patients with a history of transfusion of more than 100 units of RBCs had signs of cardiac iron overload on MRI [31]. Additionally, it is possible that iron has other subtle effects on the outcomes of patients with MDS. Some studies have suggested that increased iron body stores are associated with increased infections, particularly fungal infections [32]. Iron overload may also contribute to leukemic evolution. Sanz et al. [29] reported that iron overload was an independent factor for leukemia-free survival in patients with MDS (HR, 6.6), and the effect was independent of the presence of transfusion dependency. In one retrospective report, iron chelation in patients with MDS was associated with improvement in OS and in the rate of leukemic transformation [33]. Ongoing randomized trials evaluating iron chelators in this disease may shed further light on this issue.

Age and Comorbidities

Older age is generally associated with a worse outcome in several types of cancer, including MDS [12••]. The reasons why older patients fare worse are probably more related to the performance status of the patient and the presence of comorbidities rather than to chronologic age per se. It can be difficult to assess the impact of comorbidities on survival; to that end, standardized comorbidities scores have been developed, including the Charlson Comorbidity Index (CCI) and the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI), based on the CCI [34]. MDS is a disease of the elderly, but the impact of comorbidities on survival has been systematically investigated only recently. Most prognostic models (e.g., IPSS, WPSS) do not account for age and the presence of other diseases. Wang et al. [35] reported on 1708 patients with MDS diagnosed in the United States in 2001 and 2002, of whom 51% had identified comorbidities. In a multivariable regression analysis, the CCI significantly reflected survival: the HR was 1.19 for a CCI of 1 to 2 and 1.77 for a CCI of 3 or higher. Two other studies retrospectively evaluated the impact of the CCI and the HCT-CI in patients with MDS

and concluded that increased comorbidities, as assessed by the HCT-CI, were independently associated with poor survival [36, 37]. Recently, Della Porta et al. [30] developed a specific comorbidity score to be applied to patients with MDS (MDS-CI), based on data from 840 patients. Relevant comorbidities included cardiac disease (2 points), moderate to severe liver disease (1 point), severe pulmonary disease (1 point), renal disease (1 point), and the presence of solid tumors (1 point). The MDS-CI was able to predict survival in a validation cohort of 504 patients, with a 2-year rate of nonleukemic deaths of 24% for patients with a low MDS-CI score (0 points), 42% with an intermediate score (1–2 points), and 61% with a high score (> 2 points).

Gene Mutations

Besides chromosomal defects, somatic gene mutations are also responsible for the pathogenesis of MDS. Compared with AML, relatively few gene mutations have been described in patients with MDS. Some of the more commonly mutated genes in MDS include *RUNX1* (also known as *AML1*), *TP53*, *TET2*, *ASXL1*, and *JAK2*.

The gene encoding the transcription factor *RUNX1*, located at chromosome 21q22, can harbor mutations in patients with MDS [38]. Mutations of *RUNX1* in MDS can occur in any portion of the gene but seem to cluster in the DNA binding domain and have been described in 14% of patients with MDS [38]. They are more frequent in patients with therapy-related MDS, and frequently occur in conjunction with chromosome 7 abnormalities [38]. Clinically, the finding of *RUNX1* mutations in patients with MDS is associated with survival much poorer than for patients without *RUNX1* mutations, but their independent impact on prognosis has not yet been shown [38].

The cell cycle checkpoint gene *TP53* has been found to be mutated in roughly 13% of patients with MDS and is associated with a very poor outcome [39]. The prognostic value of *TP53* mutations is independent of the IPSS, and these mutations are usually seen in patients with advanced MDS with complex karyotypes [39, 40].

TET2 mutations are found in roughly 20% of patients with MDS [41]. *TET2* and family members *TET1* and *TET3* encode enzymes responsible for catalyzing the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, which may be one of the enzymes responsible for DNA demethylation [42]. Mutations that can involve the *TET2* gene include missense, nonsense, and frameshift mutations, and they seem to occur all over the gene [41]. Kosmider et al. [41] analyzed 99 MDS patients and reported that the presence of *TET2* mutations was associated with improved outcome: 5-year OS was 76.9% versus 18.3% for patients without mutations (P=0.005), and 3-year leukemia-free survival was 89.3% versus 69.7% for patients without mutations (P=0.03). However, in another series of 355 patients with MDS and CMML, the presence of *TET2* mutations had no impact on survival [43]. More studies are needed to clarify the influence of *TET2* in MDS evolution.

DNA Methylation Abnormalities

Epigenetic abnormalities, including aberrant DNA methylation and histone covalent modification, are found in cancer cells and contribute to the malignant phenotype by suppressing expression of tumor suppressor genes and genes related to cellular differentiation. In MDS, abnormalities of DNA methylation have been described, and whole genome studies revealed that MDS and secondary AML are characterized by greater DNA methylation than in normal cells and de novo AML [44]. Recently, Shen et al. [45••] reported on the methylation profile of 10 different genes in 317 patients with MDS, the majority of whom were treated with hypomethylating agents (decitabine, azacitidine). The methylation levels of individual genes were combined to obtain a methylation score. Patients characterized as having a high methylation score had worse OS (12.3 months vs. 17.5 months; P=0.04) and progression-free survival (6.4 months vs. 14.9 months; P=0.01). In multivariate analysis, the methylation score was independent of the IPSS score.

Recent Prognostic Models in MDS

WHO Classification–Based Prognostic Scoring System

The WPSS model is a dynamic prognostic model that can be applied both at diagnosis and at any time during disease progression [11]. The learning cohort for the model consisted of 426 patients with MDS treated at the University of Pavia in Italy. Patients with CMML and t-MDS were excluded. In a previous report, the same group demonstrated that the most important variables affecting survival were WHO subtype, karyotype, and transfusion dependency [20]. Accordingly, multivariable Cox regression analysis for OS and risk of AML was performed with these three variables included as time-dependent continuous variables. Cytogenetic abnormalities were grouped as per the IPSS criteria. WHO subtypes were grouped into RA/RARS/del(5q), RCMD/RCMD-RS, RAEB-I, and RAEB-II. These three variables were used to define the WPSS prognostic system (Table 2). Patients were effectively divided into five risk groups: very low (0 points), low (1 point), intermediate (2 points), high (3–4 points), and very high (5–6 points). The WPSS efficiently differentiated these five groups regarding survival and

Table 2 WHO Classification–Based Prognostic Scoring System (WPSS) prognostic model for myelodysplastic syndromes

Variable	Points			
	0	1	2	3
WHO Subtype	RA, RARS, del (5q)	RCMD, RCMD-RS	RAEB-I	RAEB-II
Karyotype[a]	Good	Intermediate	Poor	-
Transfusion Dependency[b]	No	Yes		

Risk Group	Points	Median Overall Survival (mo)[c]	% Evolution to AML at 2 years[c]
Very Low	0	103-141	0-3%
Low	1	66-72	6-11%
Intermediate	2	40-48	21-28%
High	3-4	21-26	38-52%
Very High	5-6	9-12	79-80%

Legends - a- Good: Normal, del(5q), del(20q), -Y; Intermediate: all others; Poor: complex (> 3 abnormalities), chromosome 7 abnormalities; b- having at least one transfusion every 8 weeks over a period of 4 months; c- values are given for both learning and validation cohort

time to AML (Table 2). The score was validated in a cohort of 739 German patients. Furthermore, comparison with age-adjusted mortality of the Italian population revealed that patients in all risk categories of the WPSS except for very low risk had higher mortality than the general population. A later report confirmed that the WPSS predicted survival and probability of relapse in patients who underwent allogeneic SCT [46].

M.D. Anderson Cancer Center Prognostic Model

Kantarjian et al. [12••] proposed a new prognostic model that accounts for variables not originally included in the IPSS. A total of 1915 patients with MDS were divided into a training cohort (958 patients) and validation cohort (957 patients). Patients with prior treatment for MDS, secondary MDS, and CMML were included. By Cox proportional hazards multivariable regression, the following covariates were associated with OS: older age, poor performance status, higher percentage of BM blasts, chromosome 7 abnormalities, complex karyotype, thrombocytopenia, leukocytosis, and prior transfusions. Based on these factors, the authors proposed a new risk model for MDS (Table 3). Patients were grouped into four risk categories, similar to the IPSS: low (0–4 points), intermediate-1 (5–6 points), intermediate-2 (7–8 points), and high (≥ 9 points). The M. D. Anderson model can be applied at any time during the disease course, and it includes all patients with MDS, regardless of previous treatment. The new model was able to predict survival within each subgroup of the IPSS, demonstrating that it added prognostic power to the IPSS. Conversely, the IPSS could not discriminate survival within the four risk groups of the new model. Subgroup analysis revealed that the model was valid in patients with less than 20% blasts and in patients with CMML. An independent validation of the M.D. Anderson model compared it against the WPSS and the IPSS. Among 1,074 patients who could be classified by all three prognostic groups, the M.D. Anderson model best identified the lowest-risk patients, and it could be applied to a broader group of patients [47].

Other Models

More recently, several reports have been published that describe prognostic models applied to specific subsets of

Table 3 M.D. Anderson prognostic model for myelodysplastic syndromes

Prognostic Factor	Points
Performance Status ™ 2	2
Age, years	
• 60-64	1
• ™ 65	2
Platelets, x10^9/L	
• < 30	3
• 30-49	2
• 50-199	1
Hemoglobin 12 g/dL	2
Bone Marrow Blasts, %	
• 5-10	1
• 11-29	2
White Blood Cell Count > 20x10^9/L	2
Karyotype: Chromosome 7 abnormality or complex ™ 3 abnormalities	3
Prior Transfusion, yes	1

Score	Median OS, Months
Low (0-4 points)	54
Intermediate-1 (5-6 points)	25
Intermediate-2 (7-8 points)	14
High (™ 9 points)	6

OS overall survival

(*Data from* Kantarjian et al. [12••].)

patients with MDS. Garcia-Manero et al. [48•] analyzed the outcomes of 856 patients with low/Int-1 risk MDS by the IPSS. They identified five variables (platelet count, percentage of blasts, age, hemoglobin, and karyotype) that were used to built a model that predicted survival among patients with low-risk MDS. Survival ranged from 80.3 months in the lowest-risk group to 14.2 months in the high-risk group, similar to patients with Int-2 risk in the M.D. Anderson model. Similar prognostic models analyzing patients with t-MDS and hypoplastic MDS were recently presented [49, 50]. Overall, these studies indicate that the current version of the IPSS is suboptimal, as it is possible to identify patients with very different outcomes among each IPSS category. Ideally, there should be no need for independent prognostic models for each subgroup of patients with MDS, unless clinical and biologic evidence indicates that the entity being studied has a different biology and pathophysiology.

Conclusions

At the present time, there are two new prognostic models for MDS in addition to the IPSS. Both try to correct deficiencies of the IPSS and incorporate new risk factors that have been described in the past decade. However, they still have limitations: the WPSS excludes certain groups of patients, and the M.D. Anderson model did not include the WHO subtypes in the analysis. Currently, a revised version of the IPSS is being developed. Future prognostic models should ideally include most important variables in the analysis to truly discern which have independent significance. Clinically useful risk factors ideally should have consistent effect across different populations of patients with MDS, should be reproducible among different centers, and should be widely available (i.e., not limited to research centers). Additionally, it is important to remember that prognostic models can be affected by treatment, which may

change the prognostic value of a previous known risk factor. As our knowledge of the pathophysiology of MDS and its treatment evolves, we can expect that our search for better prognostic models in this disease will continue.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med 2009, 361:1872–85.
2. Sekeres MA, Schoonen WM, Kantarjian H, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst 2008, 100:1542–51.
3. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001–2004, using data from the NAACCR and SEER programs. Blood 2008, 112:45–52.
4. Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol 2010, 150:179–88.
5. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 2003, 102:43–52.
6. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference. Leuk Res 2007, 31:727–36.
7. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982, 51:189–99.
8. Mufti GJ, Stevens JR, Oscier DG, et al. Myelodysplastic syndromes: a scoring system with prognostic significance. Br J Haematol 1985, 59:425–33.
9. Sanz GF, Sanz MA, Vallespi T, et al. Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: a multivariate analysis of prognostic factors in 370 patients. Blood 1989, 74:395–408.
10. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997, 89:2079–88.
11. 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, 25:3503–10.
12. •• Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. Cancer 2008, 113:1351–61. *This study of a large group of patients with MDS defines a prognostic scoring system that includes patients with prior therapy, secondary MDS, and CMML with leukocytosis.*
13. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009, 10:223–32.
14. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer 2006, 106:1794–803.
15. Aribi A, Borthakur G, Ravandi F, et al. Activity of decitabine, a hypomethylating agent, in chronic myelomonocytic leukemia. Cancer 2007, 109:713–7.
16. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001.
17. Rosati S, Mick R, Xu F, et al. Refractory cytopenia with multilineage dysplasia: further characterization of an 'unclassifiable' myelodysplastic syndrome. Leukemia 1996, 10:20–6.
18. Matsuda A, Jinnai I, Yagasaki F, et al. Refractory anemia with severe dysplasia: clinical significance of morphological features in refractory anemia. Leukemia 1998, 12:482–5.
19. Dunkley SM, Manoharan A, Kwan YL. Myelodysplastic syndromes: prognostic significance of multilineage dysplasia in patients with refractory anemia or refractory anemia with ringed sideroblasts. Blood 2002, 99:3870–1; author reply 1.
20. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005, 23:7594–603.
21. Della Porta MG, Malcovati L, Boveri E, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. J Clin Oncol 2009, 27:754–62.
22. Oriani A, Annaloro C, Soligo D, et al. Bone marrow histology and CD34 immunostaining in the prognostic evaluation of primary myelodysplastic syndromes. Br J Haematol 1996, 92:360–4.
23. Tricot G, De Wolf-Peeters C, Vlietinck R, Verwilghen RL. Bone marrow histology in myelodysplastic syndromes. II. Prognostic value of abnormal localization of immature precursors in MDS. Br J Haematol 1984, 58:217–25.
24. Buesche G, Teoman H, Wilczak W, et al. Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. Leukemia 2008, 22:313–22.
25. Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood 2007, 110:4385–95.
26. Schanz J, Tuechler H, Sole F, et al. Cytogenetic risk features in MDS—Update and present state [abstract]. Blood 2009, 114: Abstract 2772.
27. Schanz J, Estey EH, Steidl C, et al. Multivariate analysis suggests that the prognostic impact of poor cytogenetics is potentially under-estimated in the IPSS [abstract]. Blood 2007, 110:Abstract 248.
28. Gondek LP, Tiu R, O'Keefe CL, et al. Chromosomal lesions and uniparental disomy detected by SNP arrays in MDS, MDS/MPD, and MDS-derived AML. Blood 2008, 111:1534–42.
29. Sanz G, Nomdedeu B, Such E, et al. Independent impact of iron overload and transfusion dependency on survival and leukemic evolution in patients with myelodysplastic syndrome [abstract]. Blood 2008, 112:Abstract 640.
30. Della Porta MG, Malcovati L, Travaglino E, et al. a prognostic model for predicting the impact of comorbidities on survival of patients with myelodysplastic syndromes [abstract]. Blood 2007, 110:Abstract 2453.
31. Di Tucci AA, Matta G, Deplano S, et al. Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion

dependent patients with acquired anemias. Haematologica 2008, 93:1385–8.
32. Mattiuzzi G, Amin HM, Kantarjian H, et al. Baseline serum ferritin predicts rate of infection in patients with acute myelogenous leukemia and high-risk myelodysplastic syndrome [abstract]. Blood 2009, 114:Abstract 1611.
33. Leitch HA, Wong DHC, Leger CS, et al. Improved leukemia-free and overall survival in patients with myelodysplastic syndrome receiving iron chelation therapy: a subgroup analysis [abstract]. Blood 2007, 110:Abstract 1469.
34. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005, 106:2912–9.
35. Wang R, Gross CP, Halene S, Ma X. Comorbidities and survival in a large cohort of patients with newly diagnosed myelodysplastic syndromes. Leuk Res 2009, 33:1594–8.
36. Sperr WR, Wimazal F, Kundi M, et al. Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian MDS Study Group. Ann Oncol 2010, 21:114–9.
37. Zipperer E, Pelz D, Nachtkamp K, et al. The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. Haematologica 2009, 94:729–32.
38. Harada H, Harada Y, Niimi H, et al. High incidence of somatic mutations in the AML1/RUNX1 gene in myelodysplastic syndrome and low blast percentage myeloid leukemia with myelodysplasia. Blood 2004, 103:2316–24.
39. Kita-Sasai Y, Horiike S, Misawa S, et al. International prognostic scoring system and TP53 mutations are independent prognostic indicators for patients with myelodysplastic syndrome. Br J Haematol 2001, 115:309–12.
40. Kaneko H, Misawa S, Horiike S, et al. TP53 mutations emerge at early phase of myelodysplastic syndrome and are associated with complex chromosomal abnormalities. Blood 1995, 85:2189–93.
41. Kosmider O, Gelsi-Boyer V, Cheok M, et al. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). Blood 2009, 114:3285–91.
42. Ito S, D'Alessio AC, Taranova OV, et al. Role of Tet proteins in 5mC to 5hmC conversion, ES-cell self-renewal and inner cell mass specification. Nature 2010, 466:1129–33.
43. Smith AE, Mohamedali AM, Kulasekararaj A, et al. Next-generation sequencing of the TET2 gene in 355 MDS and CMML patients reveals low abundance mutant clones with early origins, but indicates no definite prognostic value. Blood 2010 Aug 6 (Epub ahead of print).
44. Figueroa ME, Skrabanek L, Li Y, et al. MDS and secondary AML display unique patterns and abundance of aberrant DNA methylation. Blood 2009, 114:3448–58.
45. •• Shen L, Kantarjian H, Guo Y, et al. DNA methylation predicts survival and response to therapy in patients with myelodysplastic syndromes. J Clin Oncol 2010, 28:605–13. *This important study examines the role of gene promoter CpG island methylation in patients with MDS treated with the hypomethylating agent decitabine and correlates it with the response and outcome.*
46. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood 2008, 112:895–902.
47. Hugo SE, Bundrick SC, Hanson CA, Steensma DP. Independent validation of the MD Anderson Cancer Center risk model for myelodysplastic syndromes (MDS), and comparison to the International Prognostic Scoring System (IPSS) and the World Health Organization-Based Prognostic Scoring System (WPSS) [abstract]. Blood 2009, 114:Abstract 3814.
48. • Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia 2008, 22:538–43. *This study examines the potential prognostic factors for the outcome of patients with lower-risk disease.*
49. Kim H, Jabbour E, Kadia T, et al. A prognostic model of therapy-related myelodysplastic syndrome [abstract]. Blood 2009, 114: Abstract 3796.
50. Tong WG, Kadia T, Borthakur G, et al. Prognostic factors and survival in patients with hypocellular myelodysplastic syndrome: development of a disease specific prognostic score [abstract]. Blood 2009, 114:Abstract 3819.