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## Myelodysplastic Syndromes:

### Clinical Practice Guidelines in Oncology

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### Keywords

NCCN Clinical Practice Guidelines; NCCN Guidelines; myelodysplastic syndromes; chronic myelomonocytic leukemia; refractory anemia; cytopenias; treatment

### Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with relatively heterogeneous spectrums of presentation. The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In the general population, MDS occur in 5 per 100,000 people. However, among individuals older than 70 years, the incidence increases to between 22 and 45 per 100,000 and increases further with age.

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#### Disclosures for the NCCN Guidelines Panel for Myelodysplastic Syndromes

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Individual disclosures for the NCCN Guidelines for Myelodysplastic Syndromes panel members can be found on page 56. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at [www.NCCN.org](http://www.NCCN.org).)

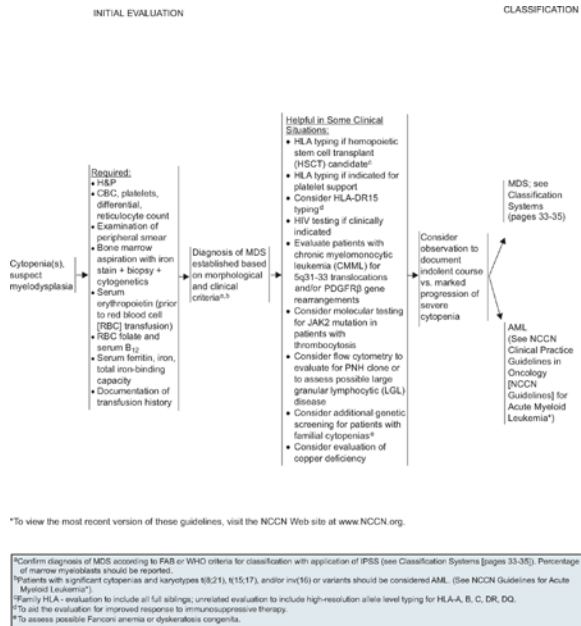
These guidelines are also available on the Internet. For the latest update, please visit [www.NCCN.org](http://www.NCCN.org).

Managing MDS is complicated by the generally advanced age of the patients (median ages, 65–70 years), attendant nonhematologic comorbidities, and relative inability to tolerate certain intensive forms of therapy among older patients. In addition, when the illness progresses to AML, these patients experience lower response rates to standard therapy than those with de novo AML.<sup>1</sup>

### Diagnostic Classification

Initial evaluation of patients with suspected MDS requires careful assessment of their peripheral blood smear and blood counts, marrow morphology, duration of their abnormal blood counts, other potential causes for their cytopenias, and concomitant illnesses. The French-American-British (FAB) classification initially categorized patients for the diagnostic evaluation of MDS.<sup>2</sup> Dysplastic changes in at least 2 of the 3 hematopoietic cell lines have been used by most histopathologists to diagnose MDS. These changes include megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in the early myeloid and erythroid precursors, and dysmorphic megakaryocytes.<sup>3</sup> Patients with MDS are classified as having 1 of 5 subtypes of disease: refractory anemia (RA); RA with ringed sideroblasts (RARS); RA with excess of blasts (RAEB); RAEB in transformation (RAEB-T); or chronic myelomonocytic leukemia (CMML). MDS are generally indolent, with patients' blood counts remaining relatively stable over at least several months.

With a moderate degree of variability, patients with RAEB (5%–20% marrow blasts) and those with RAEB-T (20%–30% marrow blasts) generally have a relatively poor prognosis, with a median survival of 5 to 12 months. In contrast, patients with RA (< 5% blasts) or those with RARS (< 5% blasts plus > 15% ringed sideroblasts) have a median survival of 3 to 6 years. The proportion of these individuals whose disease transforms to AML ranges from 5% to 15% in the low-risk RA/RARS group to 40% to 50% in the relatively high-risk RAEB/RAEB-T group. The FAB classification categorizes patients with more than 30% marrow blasts as having AML.



CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 1 of 3)

FAB <sup>1</sup> Classification of MDS <sup>2</sup>			2008 WHO <sup>3</sup> Classification of MDS <sup>4</sup>		
FAB Subtype	% of Peripheral Blasts	% of Bone Marrow Blasts	Subtype	Blood	Bone Marrow
Refractory anemia (RA)	< 1	< 5	Refractory cytopenia with multilineage dysplasia (RCUD) <sup>5</sup>	Single or bicytopenia	Dysplasia in ≥ 10% of one cell line, < 5% blasts
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5	Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	≥ 15% of erythroid precursors with ring sideroblasts, erythroid dysplasia only, < 5% blasts
Refractory anemia with excess blasts (RAEB)	< 5	5-20	Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s), < 1 x 10 <sup>9</sup> /L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 hematopoietic lineages, ≥ 15% ring sideroblasts, < 5% blasts
Refractory anemia with excess blasts in transformation (RAEB-T)	> 5	21-30	Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s), ≤ 2%-4% blasts, < 1 x 10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia, no Auer rods, 5%-9% blasts
CMML (> 1000 monocytes/mL blood)	< 5	5-20	Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s), 5%-19% blasts, < 1 x 10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia, Auer rods, ≥ 10%-19% blasts
			MDS, unclassified (MDS-U)	Cytopenia(s)	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
			MDS associated with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), < 5% blasts

<sup>1</sup>FAB = French-American-British.  
<sup>2</sup>Rivetti JM, Côtévik D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982;51:189-199.  
<sup>3</sup>WHO = World Health Organization.  
<sup>4</sup>Bruning R, Orazi A, Germing U, et al. Myelodysplastic syndromes. In: Swerdlow S, Campo E, Harris NL, et al., eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue*, 4th ed. Lyon, France: IARC Press; 2008:88-103.  
<sup>5</sup>This category encompasses refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS Unclassified.

CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 2 of 3)

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) WHO Classification<sup>1</sup>

Subtype	Blood	Bone Marrow
CMML-1	> 1 x 10 <sup>9</sup> /L monocytes, < 5% blasts	Dysplasia in ≥ 1 hematopoietic line, < 10% blasts
CMML-2	> 1 x 10 <sup>9</sup> /L monocytes, 5%-19% blasts or Auer rods	Dysplasia in ≥ 1 hematopoietic line, 10%-19% blasts, or Auer rods
Atypical chronic myeloid leukemia (aMCL), Bcr-Abl 1 negative	WBC 13 x 10 <sup>9</sup> /L, neutrophil precursors > 10%, < 20% blasts	Hypercellular, < 20% blasts
Juvenile myelomonocytic leukemia (JMML)	> 1 x 10 <sup>9</sup> /L monocytes, < 20% blasts <sup>2</sup>	> 1 x 10 <sup>9</sup> /L monocytes, < 20% blasts <sup>2</sup>
MDS/MPN, unclassifiable ("Overlap syndrome")	Dysplasia + myeloproliferative features, <sup>3</sup> no prior MDS or MPN	Dysplasia + myeloproliferative features

AML with myelodysplasia-related changes<sup>4</sup>  
 WHO Classification<sup>5</sup>  
 1. AML post MDS or MDS/MPN  
 2. AML with an MDS-related cytogenetic abnormality  
 3. AML with multilineage dysplasia

<sup>1</sup>Orazi A, Bennett JM, Germing U, et al. Myelodysplastic/myeloproliferative neoplasms. In: Swerdlow S, Campo E, Harris NL, et al., eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th ed. Lyon, France: IARC Press; 2008:79-86.  
<sup>2</sup>Phi-negative plus ≥ 2 features: Hb F, FB immature myeloid cells, WBC >10x10<sup>9</sup>/L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro.  
<sup>3</sup>For example, thrombocytosis, leukocytosis, splenomegaly.  
<sup>4</sup>> Greater than 20% blasts in PB or marrow. Some cases with 20%-29% blasts, especially if arising from MDS, may be slowly progressive and may behave more similar to MDS (RAEB-T by FAB classification) than overt AML.  
<sup>5</sup>After DA, Bruning RD, Orazi A, et al. Acute myeloid leukemia with myelodysplasia-related changes. In: Swerdlow S, Campo E, Harris NL, et al., eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th ed. Lyon, France: IARC Press; 2008:124-126.

CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 3 of 3)

International Prognostic Scoring System (IPSS)<sup>1,2,4</sup>

Survival and AML Evolution		Score Value				
Prognostic variable		0	0.5	1.0	1.5	2.0
Marrow blasts (%)	< 5	5-10	—	11-20	21-30	
Karyotype <sup>3</sup>	Good	Intermediate	Poor			
Cytopenia <sup>4</sup>	0 / 1	2 / 3				

Risk Category (% IPSS pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥ 2.5	0.4	0.2

WHO-Based Prognostic Scoring System (WPSS) for MDS<sup>5</sup> (category 2B)

Parameter	Score			
	0	1	2	3
WHO category	RA, RARS, Sq-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype <sup>6</sup>	Good	Intermediate	Poor	—
RBC transfusion requirement <sup>7</sup>	No	Regular	—	—

Abbreviations: 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.

WPSS Risk Groups/Score	Overall Survival (mo, median)	AML Progression 2 y (Probability)	5 y (Probability)
Very low/0	141	0.03	0.03
Low/1	66	0.06	0.14
Intermediate/2	48	0.21	0.33
High/3-4	26	0.38	0.54
Very high/5	9	0.80	0.84

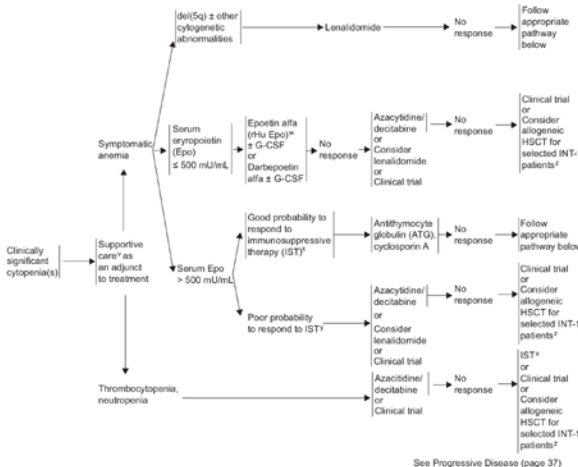
Modified from Malcovati L, Germing U, Kuentgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol* 2007;25:3503-3510. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

IPSS should be used for initial prognostic and planning purposes. The WHO classification-based prognostic scoring system (WPSS) permits dynamic estimation of prognosis at multiple time points during the course of MDS.  
<sup>1</sup>Greenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079-2086. *Erratum in: Blood* 1998;91:1100. © The American Society of Hematology.  
<sup>2</sup>Patients with 20%-30% blasts may be considered as MDS (RAE) or AML (WHO).  
<sup>3</sup>Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. (This excludes karyotypes (k(21), inv(16), and t(8;21)), which are considered to be AML, not MDS.)  
<sup>4</sup>Cytopenias: neutrophil count < 1800/mcL, platelets < 100,000/mcL, Hb < 10 g/dL.  
<sup>5</sup>RBC transfusion requirement = having ≥ 1 RBC transfusion every 8 wk over a 4-mo period.

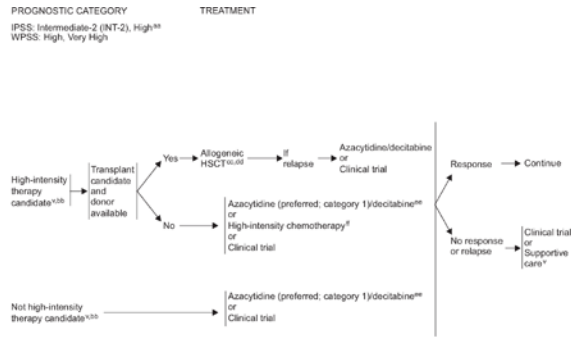
PROGNOSTIC CATEGORY

IPSS: Low/Intermediate-1 (INT-1)  
 WPSS: Very Low, Low, Intermediate

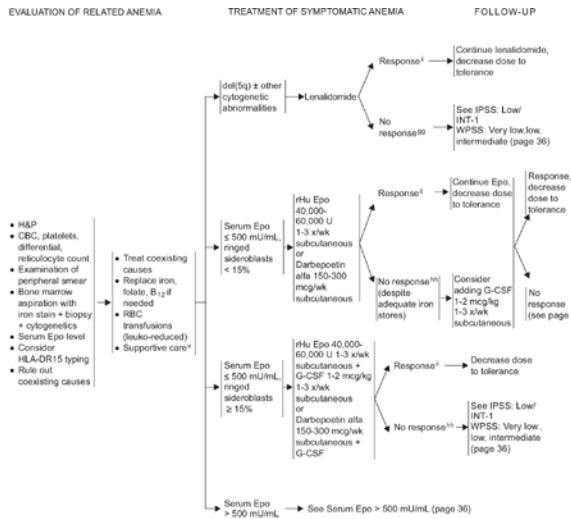
TREATMENT



\*See Supportive Care (page 39).  
 \*\*See dosing of hemopoietic cytokines (page 38).  
 †Particularly low/INT-1 patients aged ≤ 60 y or those with hypocellular marrow, HLA-DR15, or PNH clone positivity.  
 ‡Patients have features listed in footnote x.  
 §INT-1 patients with severe cytopenias would also be considered candidates for HSCT: allogeneic-matched sibling transplant, including standard and reduced-intensity preparative approaches or matched unrelated donor.



<sup>102</sup>See Supportive Care (page 36).  
<sup>103</sup>INT-1 patients with severe cytopenias unresponsive to standard therapy would also be considered candidates for allogeneic HSCT.  
<sup>104</sup>Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.  
<sup>105</sup>Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability.  
<sup>106</sup>HSCT: allogeneic-matched sibling, including standard and reduced-intensity preparative approaches or matched unrelated donor.  
<sup>107</sup>While the response rates are similar for both drugs, survival benefit from a phase II randomized trial is reported for azacitidine and not for decitabine.  
<sup>108</sup>High-intensity chemotherapy  
 Clinical trials with investigational therapy (preferred)  
 Standard induction therapy if investigational protocol unavailable or as a bridge to HSCT.



<sup>109</sup>See Supportive Care (transf page).  
<sup>110</sup>Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 3-4 mL of treatment.  
<sup>111</sup>Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 6-8 mL of treatment.  
<sup>112</sup>Target hemoglobin up to 12 g/dL.

SUPPORTIVE CARE<sup>1</sup>

- Clinical monitoring
- Psychosocial support
- Quality-of-life assessment
- Transfusions:
  - RBC transfusions (leuko-reduced) for symptomatic anemia, platelet transfusions for thrombocytopenic bleeding, irradiated products suggested for transplant candidates
  - Cytomegalovirus (CMV)-negative blood products are recommended whenever possible for CMV-negative transplant candidates
- Antibiotics for bacterial infections
- Antinoplastic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia
- Iron chelation:
  - If > 20-30 RBC transfusions received, consider daily chelation with deferasamine subcutaneously or deferasirox orally to decrease iron overload, particularly for Low/INT-1 and for potential transplant patients. For patients with serum ferritin levels > 2500 ng/mL, with the goal of decreasing ferritin levels to < 1000 ng/mL<sup>2</sup>
- Cytokines:
  - Epo: see Anemia pathway (previous page)
  - G-CSF or GM-CSF
    - Not recommended for routine infection prophylaxis
    - Consider use if recurrent or resistant infections in neutropenic patient
    - Combine with Epo for anemia when indicated; see Anemia Pathway (previous page)
    - Platelet count should be monitored

<sup>1</sup>See NCCN Guidelines for Supportive Care; to view the most recent version of all guidelines, visit the NCCN Web site at [www.nccn.org](http://www.nccn.org).  
<sup>2</sup>Clinical trials in MDS are currently ongoing with oral chelating agents.

In a study evaluating time-to-disease evolution, 25% of patients with RAEB and 55% of those with RAEB-T underwent transformation to AML at 1 year, whereas 35% of those with RAEB and 65% of those with RAEB-T underwent transformation to AML at 2 years.<sup>1</sup> In contrast, the incidence of transformation for RA was 5% at 1 year and 10% at 2 years. None of the patients with RARS developed leukemia within 2 years.

CMML is categorized by the FAB as MDS, although it often has the characteristics of a myeloproliferative disorder. Some groups have separated these patients into proliferative or nonproliferative/dysplastic subtypes, with prognosis mostly depending on the proportion of marrow blasts. Patients with the dysplastic form are classified within the FAB subtypes based on their percent marrow blasts. Within the RAEB and CMML subgroups, an increased proportion of marrow blasts has negative prognostic significance.

In 2001, the WHO proposed a classification for MDS.<sup>4-6</sup> The report suggested modifying the FAB definitions of MDS. Although most prior data require at least 2-line dysplasia for diagnosing MDS, the WHO guidelines accept unilineage dysplasia for diagnosing RA and RARS, provided that other causes of the dysplasia are absent and it persists for at least 6 months. To establish the diagnosis of MDS, careful morphologic review and correlation with the patient’s clinical features are important, because several medications and viral infections (including HIV infection) may cause morphologic changes in marrow cells similar to MDS.<sup>1,7</sup>

In 2008, a revision of the WHO classification incorporated new scientific and clinical information, refined diagnostic criteria for previously described neoplasms, and introduced newly recognized disease entities.<sup>8</sup> A new subtype in the MDS classification is refractory cytopenia with unilineage dysplasia, which includes RA (unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), and refractory thrombocytopenia (RT; unilineage dysmegakaryocytopoiesis). Refractory neutropenia and RT were previously classified as *MDS unclassifiable*.<sup>9</sup> A review article in the *Blood* discusses the major changes and the rationale behind the changes in the 2008 WHO classification of MDS and AML evolving from MDS.<sup>10</sup>

Other categories within the WHO classification include refractory cytopenia with multilineage dysplasia with or without ring sideroblasts, separating patients with RAEB into those with fewer than 10% marrow blasts (RAEB-1) and those with 10% or more marrow blasts (RAEB-2), 5q minus (del(5q)) syndrome, and MDS unclassified (with MDS cytogenetics, with or without unilineage dysplasia). The del(5q) syndrome, recognized by WHO as a separate MDS category, includes patients with an isolated 5q31–33 deletion and marrow showing less than 5% blasts, often with thrombocytosis.<sup>4–6</sup> This disorder generally has a relatively good prognosis<sup>11</sup> and is highly responsive to lenalidomide therapy.<sup>12</sup>

The MDS/myeloproliferative neoplasms (MPN) category includes CMML (CMML-1 and -2); atypical CML, BCR-ABL1–negative; and juvenile myelomonocytic leukemia as disorders having overlapping dysplastic and proliferative features, and the MDS/MPN unclassifiable group.<sup>13</sup> The distinction between CMML-1 and CMML-2 is based on the percentage of blasts plus monocytes in peripheral blood and bone marrow. CMML had been categorized by FAB as MDS, and by the International MDS Risk Analysis Workshop (IMRAW) as proliferative type (white blood cell [WBC] count  $\geq 12,000/\text{mm}^3$ ; a myeloproliferative disorder [MPD]) or nonproliferative type (dysplastic MDS).<sup>11</sup>

The WHO classification excludes patients with RAEB-T from MDS (proposing that AML should now include patients with  $\geq 20\%$  marrow blasts, rather than the previously used 30% cutoff). However, MDS not only are related to blast quantitation but also possess a differing pace of disease related to distinctive biologic features that differ from de novo AML.<sup>14,15</sup> Additionally, therapeutic responses generally differ between these patient groups.

Therefore, the decision to treat patients who have 20% to 30% marrow blasts with intensive AML therapy is complex and should be individualized. Factors such as age, antecedent factors, cytogenetics, comorbidities, pace of disease, and performance status should be considered. To aid this approach, and given the longstanding experience with the FAB categorization, the panel currently endorses reporting using both the FAB and WHO classification systems. Thus, patients with RAEB-T may be considered as having either MDS or AML. Studies have provided evidence supportive of the use of the WHO proposals.<sup>16,17</sup>

The 2008 WHO classifications have helped clarify the clinical differences between the patients having FAB-classified RAEB-T and those with AML.<sup>18</sup> The current WHO classification lists the entity “AML with myelodysplasia-related changes,” which encompasses patients with AML post-MDS, AML with multilineage dysplasia, and AML with MDS-associated cytogenetic abnormalities.<sup>18</sup> According to this classification, some patients with AML with myelodysplasia-related changes having 20% to 29% marrow blasts, especially those arising from MDS, and considered RAEB-T by the FAB classification, may have disease features that behave more similar to MDS than to AML.

AML evolving from MDS (AML-MDS) is often more resistant to standard cytotoxic chemotherapy than de novo AML, which arises without antecedent hematologic disorder. Patients with high-risk MDS or AML-MDS, and some elderly patients with AML may have a more indolent course in terms of short-term progression compared with patients with standard presentations of de novo AML. Separate treatment protocols for patients with standard presentation of de novo AML and for other patient groups, such as those with MDS-AML, elderly AML, and high-risk MDS, seem appropriate (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Acute Myeloid Leukemia; to view the most recent version of these guidelines, visit the NCCN Web site at [www.NCCN.org](http://www.NCCN.org)).

To help provide consistency in diagnostic guidelines of MDS, an International Consensus Working Group recommended that minimal diagnostic criteria for this disease include



required diagnostic prerequisites: stable cytopenia (for at least 6 months unless accompanied by a specific karyotype or bilineage dysplasia, in which case only 2 months are needed) and the exclusion of other potential disorders as a primary reason for dysplasia and/or cytopenia. In addition, the diagnosis of MDS requires at least 1 of 3 MDS-related (decisive) criteria: 1) dysplasia (≥ 10% in ≥ 1 of the 3 major bone marrow lineages), 2) a blast cell count of 5% to 19%, and 3) a specific MDS-associated karyotype, such as del(5q), del(20q), +8, or -7/del(7q). Furthermore, several co-criteria help confirm the diagnosis of MDS, including studies with flow cytometry, bone marrow histology and immunohistochemistry, or molecular markers (to detect or exclude abnormal CD34 antigenic expression, fibrosis, dysplastic megakaryocytes, atypical localization of immature progenitors, and myeloid clonality).<sup>19</sup>

## Initial Evaluation

Several types of evaluations are needed to determine the clinical status of patients with MDS. Understanding clinical status is necessary for determining diagnostic and prognostic categorization and deciding treatment options. Clinical history should include the timing, severity, and tempo of abnormal cytopenias; prior infections or bleeding episodes; and number of transfusions. Concomitant medications and comorbid conditions require careful assessment. Because MDS are relatively indolent disorders, blood count stability is used to distinguish MDS from evolving AML. Other possible causes for patients' cytopenias should also be carefully evaluated.

In addition to establishing current blood and reticulocyte counts, clinicians need to evaluate a peripheral blood smear to determine the degree of dysplasia and, thus, potentially dysfunctional cells. Bone marrow aspiration with Prussian blue stain for iron and biopsy are needed to evaluate the degree of hematopoietic cell maturation abnormalities and relative proportions, percentage of marrow blasts, marrow cellularity, presence or absence of ringed sideroblasts (and presence of iron per se), and fibrosis. Marrow cytogenetics should be obtained because they are of major importance for prognosis.

Other useful screening laboratory studies include serum erythropoietin (sEpo), vitamin B<sub>12</sub>, red blood cell (RBC) folate levels, and serum ferritin. Serum ferritin levels may be nonspecific, particularly in the presence of inflammatory conditions such as rheumatoid arthritis, and therefore obtaining the serum iron levels and total iron binding capacity along with serum ferritin may be helpful.

If patients require platelet transfusions for severe thrombocytopenia, human leukocyte antigen (HLA) typing (A, B) may be helpful. For hematopoietic stem cell transplant (HSCT) candidates, the patient's cytomegalovirus (CMV) status and the full HLA typing (A, B, C, DR, and DQ) of the patient and potential donors are needed. Bone marrow flow cytometry for assessing the percentage of CD34+ cells (blast cells are usually CD34+) and HIV screening, if clinically indicated, may also be valuable in some clinical situations. However, estimates of blast percentage derived from flow cytometry do not provide the same prognostic information as that derived from morphologic evaluation. Accordingly, data from flow cytometry should not be used in lieu of the determination of morphologic blast percentage by an experienced hematopathologist. The screening for paroxysmal nocturnal hemoglobinuria (PNH) and HLA-DR15 is potentially useful for determining which patients may be more responsive to immunosuppressive therapy, particularly in young patients with normal cytogenetics and hypoplastic MDS<sup>20,21</sup> (see Prognostic Stratification, opposite column).

Bone marrow biopsy staining for reticulin is helpful for evaluating the presence and degree of bone marrow fibrosis. Flow cytometry studies should be used to determine the presence



of a PNH clone or to assess the possibility of large granular lymphocytic disease. Review of peripheral smear is important to determine the presence of large granular lymphocytic disease.

Additional genetic screening should be considered for patients with familial cytopenias, because it will help evaluate for Fanconi's anemia or dyskeratosis congenita. In addition, this information is of clinical importance because familial MDS is associated with chromosomal fragility, and therefore these patients may have a different response to hypomethylating agents and, more importantly, family members may not be eligible as donors for allogeneic HSCT.

Determining platelet-derived growth factor receptor beta (PDGFRb) gene rearrangements in patients with CMML/MPD with 5q3133 translocations is helpful for evaluation. The activation of this gene encoding a receptor tyrosine kinase for PDG-FRb has been shown in some of these patients.<sup>22,23</sup> Data have indicated that patients with CMML/MPD with these PDGFRb fusion genes may respond well to treatment with imatinib mesylate.<sup>24,25</sup>

The frequency of activating mutations of the tyrosine kinase known as Janus Kinase 2 (JAK2) in MDS and de novo AML is lower compared with myeloproliferative disorders.<sup>26</sup> If thrombocytosis is encountered in patients with MDS, screening for JAK2 mutations may be helpful; a positive result is consistent with the presence of a myeloproliferative component of the disease.<sup>27</sup>

Recent flow cytometric studies suggest the potential efficacy of this methodology for characterizing MDS marrow blast cells and as an aid for assessing prognosis.<sup>28,29</sup> However, because of the nonstandardized nature of these analyses, further investigations are warranted before their routine use can be recommended.

Reports have shown that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.<sup>30-32</sup> Thus, in certain instances assessment of copper and ceruloplasmin levels may be indicated as part of the initial diagnostic workup of suspected MDS. Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,<sup>30-32</sup> prior gastrointestinal surgery,<sup>30,31</sup> and a history of vitamin B<sub>12</sub> deficiency.<sup>31,33</sup>

## Prognostic Stratification

Despite its value for diagnostic categorization of patients with MDS, the prognostic limitations of the FAB classification have become apparent, with variable clinical outcomes within the FAB subgroups. The morphologic features contributing to this variability include the wide range of marrow blast percentages for patients with RAEB (5%–20%) and CMML (1%–20%); lack of inclusion of critical biologic determinants, such as marrow cytogenetics; and the degree and number of morbidity-associated cytopenias. These well-perceived problems for categorizing patients with MDS have led to the development of additional risk-based stratification systems.<sup>34</sup>

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW.<sup>11</sup> Compared with previously used systems, the risk-based IPSS has markedly improved prognostic stratification of MDS cases. In this analysis, cytogenetic, morphologic, and clinical data were combined and collated from a relatively large group of MDS cases that had been included in previously reported prognostic studies.<sup>11,34</sup> FAB morphologic criteria were used to establish the diagnoses of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible causes for the cytopenias, such as drugs, other diseases, or incipient evolution

to AML. CMML was subdivided into proliferative and nonproliferative subtypes. Patients with proliferative-type CMML (WBC > 12,000/mcL) were excluded from this analysis,<sup>11</sup> whereas those with nonproliferative CMML (WBC ≤ 12,000/mcL and other features of MDS) were included.<sup>35</sup>

Significant independent variables for determining outcome for both survival and AML evolution were found to be marrow blast percentage, number of cytopenias, and cytogenetic subgroup (good, intermediate, poor). Patients with the chromosome anomalies t(8;21) or inv16 are considered to have AML and not MDS, regardless of the blast count. Age was also a critical variable for survival, although not for AML evolution. The percentage of marrow blasts was divided into 4 categories: 1) less than 5%, 2) 5% to 10%, 3) 11% to 20%, and 4) 21% to 30%.

Cytopenias were defined for the IPSS as having hemoglobin level less than 10 g/dL, an absolute neutrophil count less than 1800/mcL, and platelet count less than 100,000/mcL. Patients with normal marrow karyotypes, del(5q) alone, del(20q) alone, and -Y alone had relatively good prognoses (70%), whereas patients with complex abnormalities (≥ 3 chromosome anomalies) or chromosome 7 anomalies had relatively poor prognoses (16%). The remaining patients were intermediate in outcome (14%). Of the patients in the “complex” category, most had chromosome 5 or 7 abnormalities in addition to other anomalies.

To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroup, and number of cytopenias) were generated.<sup>11</sup> By combining the risk scores for the 3 major variables, patients were stratified into 4 distinctive risk groups in terms of both survival and AML evolution: low, intermediate-1 (INT-1), intermediate-2 (INT-2), and high.

When either cytopenias or cytogenetic subtypes were omitted from the classification, discrimination among the 4 subgroups was much less precise. Both for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods, including the FAB system.<sup>11</sup>

Recent data indicate that additional clinical variables are additive to the IPSS regarding prognosis for patients with MDS. The WHO prognostic scoring system (WPSS) incorporates the WHO-based morphologic categories, the IPSS cytogenetic categories, and patients' need or lack of dependence on RBC transfusion.<sup>36</sup> This system showed that the requirement for RBC transfusions is a negative prognostic factor for patients in the lower-risk MDS categories. In addition, depth of anemia per se has additive and negative prognostic import for the intermediate IPSS categories.<sup>37</sup> Compared with the 4 groups defined by the IPSS, the WPSS classifies patients into 5 risk groups differing in both survival and risk for AML: very low, low, intermediate, high, and very high. After an initial report by Malcovati et al.<sup>36</sup> regarding the usefulness of WPSS, other studies have confirmed the findings.<sup>38–41</sup> However, whether the WPSS offers an improvement over the IPSS is a matter of ongoing debate. Based on the current available data, the panel included the WPSS in the current version of the treatment algorithm with a category 2B designation.

## Therapeutic Options

The patient's IPSS risk category is used in planning therapeutic options because it provides a risk-based patient evaluation (category 2A). In addition, age and performance status are critical determinants because they have a major influence on the patient's ability to tolerate certain intensive treatments. The WPSS provides dynamic estimation of prognosis at any time during the course of MDS.

In patients who were only recently evaluated, determining the relative stability of their blood counts over several months is important to assess disease progression, including incipient transformation to AML. In addition, this assessment permits determination of other possible causes for cytopenias. The patient's preference for a specific approach is also important in deciding treatment options. The therapeutic options for MDS include supportive care, low-intensity therapy, high-intensity therapy, and/or clinical trial. In evaluating results of therapeutic trials, the panel found it important for studies to use the standardized International Working Group (IWG) response criteria.<sup>42,43</sup>

For the MDS therapeutic algorithm, all patients should undergo relevant supportive care. After that, the panel has proposed initially stratifying patients with clinically significant cytopenias into 2 major risk groups: 1) relatively lower-risk patients (who are in the IPSS low and INT-1 categories, or WPSS very low, low, and intermediate categories); and 2) higher-risk patients (who are in the IPSS INT-2 and high categories, or WPSS high and very high categories). Per IWG response criteria, for patients in the lower-risk group, the major therapeutic goal would be hematologic improvement, whereas alteration of the disease natural history is viewed as paramount for those in the higher risk group. Cytogenetic and quality-of-life responses are also important parameters to assess. The algorithms outline management of primary MDS only. Most patients with therapy-related MDS have poorer prognoses than those with primary MDS, including a substantial proportion with poor-risk cytogenetics. These patients are generally managed as having higher-risk disease.

### Supportive Care

Currently, the standard of care in the community for MDS includes supportive care (see page 39 and the NCCN Guidelines for Supportive Care; to view the most recent version of all guidelines, visit the NCCN Web site at [www.NCCN.org](http://www.NCCN.org)). This entails observation, clinical monitoring, psychosocial support, and quality-of-life assessment. Major efforts should be directed toward addressing the relevant quality-of-life domains (e.g., physical, functional, emotional, spiritual, social) that adversely affect patients. Supportive care should include RBC transfusions for symptomatic anemia as needed (generally leukocyte-reduced) or platelet transfusions for severe thrombocytopenia or thrombocytopenic bleeding. The panel reached nonuniform consensus based on differing institutional policies regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agreed that all directed-donor and transfused products for potential stem cell transplant patients should be irradiated. Additionally, CMV-negative blood products are recommended whenever possible for CMV-negative recipients. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.

Hematopoietic cytokine support should be considered for refractory symptomatic cytopenias.<sup>44</sup> For example, recombinant human granulocyte colony stimulating factor (G-CSF) or granulocyte-monocyte CSF (GM-CSF) treatment could be considered for neutropenic patients with MDS with recurrent or resistant bacterial infections. The use of recombinant human erythropoietin to treat symptomatic anemia is discussed in Evaluation and Treatment of Related Anemia (see page 49).

**Management of Iron Overload**—RBC transfusions are a key component of the supportive care for patients with MDS. Although specific therapies may alleviate the need for an RBC transfusion, a substantial proportion of patients may not experience response to these treatments and may develop iron overload and its consequences.<sup>45</sup> Thus, effective treatment of transfusional siderosis in patients with MDS is germane.

Studies in patients requiring relatively large numbers of RBC transfusions (e.g., those with thalassemia and MDS) have shown the pathophysiology and adverse effects of chronic iron overload on hepatic, cardiac, and endocrine function. Increased non-transferrin-bound iron levels, generated when plasma iron exceeds transferrin's binding capacity, combines with oxygen to form hydroxyl and oxygen radicals. These toxic elements cause lipid peroxidation and cell membrane, protein, DNA, and organ damage.<sup>46,47</sup>

Although limited, retrospective evidence suggests that organ dysfunction can result from iron overload in patients with MDS.<sup>48,49</sup> Retrospective data suggest that transfusional iron overload might be a contributor of increased mortality and morbidity in early-stage MDS.<sup>50</sup> The WPSS has shown that RBC transfusion requirement is a negative prognostic factor for patients with MDS.<sup>36</sup>

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The panel recommends monitoring serum ferritin levels and number of RBC transfusions received to assess iron overload as a practical means to determine iron stores. Monitoring serum ferritin may be useful, with the goal of decreasing ferritin levels to less than 1000 mcg/L. Experts recognize that these measurements, although useful, are less precise than SQUID (Superconducting Quantum Interference Device) or the more recent development of specific measurement of hepatic iron content using MRI.<sup>51,52</sup>

Reversal of some of the consequences of iron overload in MDS and other iron overload states (e.g., thalassemia) using iron chelation therapy has been shown in patients in whom the most effective chelation occurred.<sup>43,47</sup> This included transfusion independence in a portion of a small group of carefully studied patients with MDS who had undergone effective deferoxamine chelation for 1 to 4 years.<sup>53</sup> In addition, improvement in cardiac iron content was shown in these patients after chelation.<sup>36,54</sup> These findings have major implications for altering the morbidity of patients with MDS, particularly those with preexisting cardiac or hepatic dysfunction.

The current clinical availability of 2 oral iron chelators in the United States,<sup>55</sup> deferoxamine and deferasirox,<sup>56,57</sup> now provides potentially useful drugs to more readily treat this iron overload state. Although not available in the United States, a third chelating agent, deferiprone, is licensed in Europe for the treatment of iron overload in patients with thalassemia when deferoxamine is inadequate or contraindicated.<sup>58</sup>

Clinical trials in MDS are ongoing with oral iron chelating agents to determine whether iron chelation alters the natural history of patients with MDS who are transfusion-dependent. A recent NCCN task force report titled *Transfusion and Iron Overload in Patients with Myelodysplastic Syndromes* presents the available evidence regarding iron chelation in patients with MDS.<sup>59</sup>

The panel recommends considering chelation with deferoxamine SC or deferasirox/ICL670 orally once daily to decrease iron overload in patients with low or INT-1 risk disease who have received or are anticipated to receive greater than 20 RBC transfusions, for whom ongoing RBC transfusions are anticipated, and for those with serum ferritin levels greater than 2500 ng/mL, with the goal of decreasing ferritin levels to less than 1000 ng/mL.

Recently a black box warning by the FDA and Novartis was added to deferasirox. After postmarketing use of deferasirox, cases of acute renal failure or hepatic failure were reported, some with a fatal outcome. Most of the reported fatalities occurred in patients with multiple comorbidities and in advanced stages of their hematologic disorders. Additionally, there were postmarketing reports of cytopenias, including agranulocytosis, neutropenia, and

thrombocytopenia, and of gastrointestinal bleeding in patients treated with deferasirox, with some patients dying. The relationship of these episodes to treatment with deferasirox has not yet been established. However, the panel recommends closely monitoring patients on deferasirox therapy, including measuring their serum creatinine and/or creatinine clearance and performing liver function tests before initiation of therapy and regularly thereafter.

### Low-Intensity Therapy

Low-intensity therapy includes the use of low-intensity chemotherapy or biologic response modifiers. Although this type of treatment is mainly provided in the outpatient setting, certain treatments may require supportive care or occasional hospitalization afterwards (e.g., to treat infections).

### Hypomethylating Agents

As a form of relatively low-intensity chemotherapy, the DNA methyltransferase inhibitor (DMTI) hypomethylating agents 5-azacytidine (AzaC) and decitabine (5-aza-2 - deoxycytidine) have been shown in randomized phase III trials to decrease the risk of leukemic transformation and, in a portion of the patients, improve survival.<sup>60,61</sup> For AzaC, hematologic responses occurred in 60% of patients in the azacitidine arm (7% complete response, 16% partial response, 37% improved) compared with an overall 5% response rate in those receiving supportive care. Additionally, the time to progression to AML or death was improved in those who received AzaC earlier in the course of disease, suggesting that the drug prolonged the duration of stable disease. Subsequently Silverman et al.<sup>62</sup> provided a summary of 3 studies of AzaC in a total of 306 patients with high-risk MDS. In this analysis, which included patients receiving either subcutaneous or intravenous delivery of the drug (75 mg/m<sup>2</sup>/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of patients treated with AzaC, partial remissions were rare, and 23% to 36% of patients had hematologic improvement. Of the responses, 90% were seen by cycle 6 and the median number of cycles to first response was 3. The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. Data from a randomized trial for higher-risk MDS show that AzaC is superior to conventional care (standard chemotherapy or supportive care) regarding overall survival.<sup>63</sup> Patients randomized to AzaC enjoyed a superior median survival (24 vs. 15 months) compared with those in the control arm, thus providing support for the use of this agent in higher-risk disease.

AzaC therapy should be considered for treating patients with progressing or relatively high-risk MDS. The drug is generally administered at a dose of 75 mg/m<sup>2</sup>/d subcutaneously for 7 days monthly for at least 4 to 6 courses. Treatment courses may need to be extended further or may be used as a bridging therapy to more definitive therapy (e.g., HSCT for patients whose marrow blast counts require lowering before that procedure). This drug is FDA-approved for treating patients with MDS.

Similarly, the other DMTI hypomethylating agent, decitabine, given intravenously and administered with a regimen that required hospitalization, has also shown encouraging results in patients with higher-risk MDS. Because the treatment regimen was generally associated with low-intensity-type toxicities, it is also considered to be low intensity therapy. The drug has shown cytogenetic conversion in approximately 30% of patients,<sup>64,65</sup> with an overall response rate of 49% and a 64% response rate in patients with a high-risk IPSS score. The results of these studies were substantially similar to those for AzaC.<sup>66,67</sup>

The results of a phase III randomized trial of decitabine (15 mg/m<sup>2</sup> intravenous infusion over 3 hours every 8 hours [i.e., 45 mg/m<sup>2</sup>/d] on 3 consecutive days every 6 weeks for up to 10 cycles) versus supportive care in adult patients with primary and secondary MDS with



IPSS INT-1– (31%), INT-2– (44%) and high- (26%) risk disease indicated higher response rates, remission duration, time to AML progression, and survival benefit in patients with INT-2– and high-risk subtypes.<sup>60,66</sup> Overall response rates (complete plus partial responses) were 17%, with an additional 13% having hematologic improvement. The probability of progression to AML or death was 1.68-fold greater for patients receiving supportive care than for those receiving decitabine. Based on this study and 3 supportive phase II trials,<sup>68</sup> the FDA also approved this drug for treating patients with MDS.

Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated.<sup>69</sup> In 2007, Kantarjian et al.<sup>70</sup> provided an update of their results in 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens. Patients received 1 of 3 different schedules of decitabine, including both subcutaneous and intravenous administration, and received a mean of 7 courses of therapy. Responses were improved with this longer duration of therapy. Overall, 80 patients (70%) experienced response, with 40 (35%) experiencing a complete response and 40 (35%) a partial response. The median remission duration was 20 months and the median survival 22 months.

Kantarjian et al.<sup>71</sup> also compared the 3 different schedules of decitabine in a randomized study, with 95 patients with MDS or CMML receiving either 20 mg/m<sup>2</sup> intravenously daily for 5 days; 20 mg/m<sup>2</sup> subcutaneously daily for 5 days; or 10 mg/m<sup>2</sup> intravenously daily for 10 days. The 5-day intravenous schedule was considered the optimal schedule, with a complete response rate of 39% compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day intravenous arm ( $P < .05$ ).

Currently, azacytidine and decitabine are considered therapeutically relatively similar, although the improved survival of higher-risk patients treated with AzaC compared with control patients in a phase III trial supports the preferred use of AzaC in this setting. “Failure to respond to hypomethylating agents” is considered if a lack of complete response, partial response, or hematologic improvement is seen; frank progression to AML occurs, in particular with loss of control (proliferation) of peripheral counts; or excess toxicity precludes continuation of therapy. The minimum number of courses before considering the treatment a failure should be 4 to 6 courses.

Because data have predominantly indicated altered natural history and decreased evolution to AML in patients who experience response to treatment, the major candidates for these drugs are patients with IPSS INT-2– or high-risk MDS, such as:

- Those who are not candidates for high-intensity therapy.
- Those who are potential candidates for allogeneic HSCT but for whom delay in receipt of that procedure is anticipated (e.g., because of time needed to further reduce the blast count, improve the patient’s performance status, or identify a donor). In these circumstances, the drugs may be used as bridging therapy for that procedure.
- Those who experience relapse after allogeneic HSCT.

### **Biologic Response Modifiers and Immunosuppressive Therapy**

Available non-chemotherapy, low-intensity agents (biologic response modifiers) include antithymocyte globulin (ATG), cyclosporine, thalidomide, lenalidomide, anti-tumor necrosis factor receptor fusion protein, and vitamin D analogues, all of which have shown some efficacy in phase I and II trials.<sup>1,72–77</sup>

Use of anti-immune-type therapy with ATG with or without cyclosporine<sup>74,75</sup> has been shown in several studies to be most efficacious in patients with MDS with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a PNH clone.<sup>20,21</sup> The NIH group updated their analysis of 129 patients treated with immunosuppressive therapy involving ATG and cyclosporine alone or in combination.<sup>78</sup> This study showed markedly improved response rates in younger (age < 60 years) and INT-1–risk patients and those with high response probability characteristics as indicated by their prior criteria (HLA-DR15+, age, and number of transfusions).<sup>78</sup>

Encouraging data have been presented for treating patients with lower-risk MDS with lenalidomide.<sup>12,79</sup> Beneficial results have been particularly evident for patients with del(5q) chromosomal abnormalities.<sup>12,79,80</sup> In a multicenter phase II trial of lenalidomide, given at a dose of 10 mg/d for 21 days every 4 weeks or 10 mg daily to 148 patients with MDS with del(5q) and RBC transfusion–dependent anemia, with or without additional cytogenetic abnormalities, the response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained. RBC transfusion independence (assessed at 24 weeks) occurred in 66% of patients with IPSS low/INT-1 compared with 52% of patients with higher-risk disease.<sup>12</sup> Cytogenetic responses occurred in 76% of patients; 55% had a complete cytogenetic response. However, common adverse events occurred (in ~50% of patients) that required treatment interruption or dose reduction because of potentially serious but generally transient neutropenia and/or thrombocytopenia. Thus, careful monitoring of patients' blood counts during treatment is mandatory when using this agent, particularly in those with renal dysfunction (from the drug's renal route of excretion). The FDA recently approved lenalidomide for treating patients with MDS with del(5q).

A phase II study evaluated lenalidomide treatment in 214 transfusion-dependent patients with low- or INT-1–risk MDS without del(5q).<sup>81</sup> Results showed 26% of the non-del(5q) patients (56 of 214) experienced transfusion independence after a median of 4.8 weeks of treatment. Transfusion independence continued for a median duration of 41 weeks, and the median rise in hemoglobin was 3.2 g/dL (range, 1.0–9.8 g/dL) for these patients. A 50% or greater reduction in transfusion requirement was noted in an additional 37 patients (17%), yielding an overall rate of hematologic improvement of 43%. The most common grade 3/4 adverse events were neutropenia (30%) and thrombocytopenia (25%). Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents in patients with MDS without del(5q). The panel recommends that lenalidomide be considered for treatment of symptomatically anemic non-del(5q) patients whose anemia did not respond to initial therapy.

### High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy or HSCT.<sup>1,82</sup> Although these approaches have the potential to change the natural history of the disease, they also have an attendant greater risk of regimen-related morbidity and mortality. The panel recommends giving these treatments in the context of clinical trials. Recent comparative studies have not shown benefit between several different intensive chemotherapy regimens (including idarubicin-, cytarabine-, fludarabine-, and topotecan-based regimens) in MDS.<sup>83</sup>

A high degree of multidrug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS,<sup>84</sup> with decreased responses and shorter response durations associated with many standard regimens of induction chemotherapy. Thus, chemotherapeutic agents used to treat “resistant-type” AML, and agents that modulate this resistance, are now being evaluated for treating patients with advanced MDS. Although several studies using multidrug resistance modulators were positive in this setting,<sup>85,86</sup>



others were not.<sup>87</sup> Further clinical trials evaluating other multidrug resistance modulators are ongoing.

Allogeneic HSCT from an HLA-matched sibling donor is a preferred approach for treating a portion of patients with MDS, particularly those with high-risk disease.<sup>88–96</sup> Matched nonmyeloablative transplant regimens<sup>97,98</sup> and matched unrelated donor stem cell transplants<sup>99–101</sup> are becoming options at some centers to treat these patients. In certain investigative settings, autologous bone marrow or peripheral blood stem cell transplantation is being considered.<sup>102</sup> Whether transplants should be performed before or after patients experience remission following induction chemotherapy has not been established.<sup>103</sup> Comparative clinical trials are needed to determine these points.

## Recommended Treatment Approaches

### Therapy for Lower-Risk Patients (IPSS Low, INT-1 or WPSS Very Low, Low, and Intermediate)

Regarding the algorithm for therapeutic options for lower-risk patients with clinically significant cytopenias, the panel recommends stratifying these patients into several groups. Those with del(5q) chromosomal abnormalities and symptomatic anemia should receive lenalidomide. Other patients with symptomatic anemia are categorized based on levels of sEpo. Those with levels of 500 mU/mL or less should be treated with recombinant human erythropoietin or darbepoetin with or without G-CSF (see Evaluation and Treatment of Related Anemia, opposite page). Non-responders should be considered for treatment with azacytidine or decitabine or for lenalidomide therapy. In addition, these patients or nonresponders to this therapy could be considered for participation in a clinical trial with other relevant agents, or for allogeneic HSCT (see Allogeneic HSCT, opposite column).

Anemic patients with sEpo levels greater than 500 should be evaluated to determine whether they have a good probability of responding to immunosuppressive therapy. The most appropriate candidates include those who either are aged 60 years or younger (with IPSS low, INT-1 MDS or WPSS very low, low, or intermediate), are HLA-DR15–positive, have a PNH-positive clone, or have hypoplastic MDS. Immunosuppressive therapy consists of ATG or cyclosporine. Nonresponders to immunosuppressive therapy would be considered for treatment with azacytidine, decitabine, or a clinical trial. Patients with sEpo levels greater than 500 mU/mL who have a low probability of responding to immunosuppressive therapy should be considered for treatment with azacytidine, decitabine, or lenalidomide. Others or nonresponders to that therapy could be considered for a clinical trial or for allogeneic HSCT. Patients with other serious cytopenias (particularly clinically severe thrombocytopenia) should be considered for treatment with azacytidine or decitabine or a clinical trial. Patients who experience no response this treatment should be considered for treatment with immunosuppressive therapy, a clinical trial, or allogeneic HSCT.

Careful monitoring for disease progression and consideration of the patient's desires play major roles in the timing and decision to embark on treatment for lower- or higher-risk disease.

### Therapy for Higher-Risk Patients (IPSS INT-2, High or WPSS High, Very High)

Treatment for higher-risk patients depends on whether they are believed to be candidates for intensive therapy (e.g., allogeneic HSCT, intensive chemotherapy). Clinical features relevant for this determination include patient age, performance status, absence of major comorbid conditions, psychosocial status, patient preference, and availability of a suitable donor and caregiver. In addition, the patient's personal preference for type of therapy needs particular consideration. Supportive care should be provided for all patients.

## Intensive Therapy

**Allogeneic HSCT**—The potential for patients to undergo allogeneic HSCT depends on several factors, including patient age, performance status, major co-morbid conditions, psychosocial status, availability of a caregiver, IPSS or WPSS score, and availability of a suitable donor. For those who are transplant candidates, the first choice of donor has remained an HLA-matched sibling, although results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA haploidentical related donors, HSCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas the approach using reduced/low-intensity conditioning (RIC) for HSCT is generally the strategy in older individuals.<sup>104</sup>

To aid therapeutic decision-making regarding the timing and selection of patients for HSCT, a study compared outcomes in patients with MDS aged 60 years or younger who underwent HSCT from HLA-matched siblings with those in nontreated patients with MDS from the IMRAW/IPSS database. Using a Markov decision analysis, this investigation indicated that IPSS INT-2 and high-risk patients aged 60 years or younger had the highest life expectancy if transplantation occurred (from HLA-identical siblings) soon after diagnosis, whereas patients with IPSS low-risk MDS had the best outlook if HSCT was delayed until disease progression. Patients in the INT-1 risk group only had a slight gain in life expectancy if HSCT was delayed, and therefore decisions should probably be made on an individual basis in these patients (e.g., dependent on platelet or neutrophil counts).<sup>105</sup> A study published in 2008 retrospectively evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT.<sup>38</sup> The data suggest that lower-risk patients (based on WPSS risk score) do very well with allogeneic HSCT, with a 5-year overall survival of 80%. With increasing WPSS scores, the probability of 5-year survival after HSCT declined progressively to 65% (intermediate risk), 40% (high risk), and 15% (very high risk).<sup>38</sup>

Based on recent data regarding RIC for transplantation from 2 reported series<sup>106,107</sup> and 2 comprehensive reviews of this field,<sup>108,109</sup> patient age and disease status generally dictate the type of conditioning to be used. Patients older than 55 or 60 years, particularly if they have fewer than 10% marrow myeloblasts, would generally undergo HSCT after RIC; if the blast count is high, pre-HSCT debulking therapy is generally given. Younger patients, regardless of marrow blast burden, will generally receive high-dose conditioning. Variations on these approaches would be considered by the individual transplant physician based on these features and the specific regimen used at that center. Some general recommendations were presented recently in a review in *Blood*.<sup>110</sup>

## Intensive Chemotherapy

For patients eligible for intensive therapy lacking a stem cell donor, or those requiring reduction of marrow blast count, intensive induction chemotherapy should be considered.<sup>111</sup> Although the response rate and durability of this treatment is lower than for standard AML, this treatment (particularly in clinical trials with novel agents) could be beneficial in a portion of patients. For patients with a potential stem cell donor who require reduction of tumor burden (i.e., to decrease the marrow blast count), even a partial remission may be adequate to permit the HSCT. For this purpose, AzaC, decitabine, and participation in clinical trials are also available treatment options.

## Nonintensive Therapy

For higher-risk patients who are not candidates for intensive therapy, the use of AzaC, decitabine, or participation in a relevant clinical trial should be considered. Based on the recently published results of the phase III trial showing superior median survival in patients receiving AzaC compared with best supportive care, the panel made this a preferred category 1 recommendation compared with decitabine. Preliminary results of another recent trial comparing decitabine with supportive care in higher-risk patients failed to show a survival advantage, although response rates are similar to those reported previously for AzaC.<sup>112</sup> However, no trials have compared AzaC and decitabine directly.

For some patients eligible for HSCT therapy requiring a reduction in tumor burden, the use of AzaC or decitabine may be a bridge to usefully decrease the marrow blast count enough to permit the transplant.

## Supportive Care Only

For patients with adverse clinical features or disease progression despite therapy and absence of reasonable specific antitumor therapy, good supportive care should be maintained.

## Evaluation and Treatment of Related Anemia

Major morbidities of MDS include symptomatic anemia and its associated fatigue. Much progress has been made in improving the management of this anemia. However, along with giving specific treatment for anemia related to MDS, health care providers must identify and treat any coexisting causes of anemia.

Standard assessments should be performed to look for other causes of anemia, such as gastrointestinal bleeding, hemolysis, renal disease, and nutritional deficiency. If needed, iron, folate, or vitamin B<sub>12</sub> studies should be obtained and the cause of depletion corrected if possible. After excluding these causes and providing proper treatment for them, treatment for the MDS-related anemia should be considered further. Currently, the standard of care for symptomatic anemic patients is RBC transfusion support (using leukopoor products). If the patient is a potential HSCT candidate, the panel recommends that CMV-negative (if the patient is CMV-negative serologically) and irradiated transfused products be considered.

Anemia related to MDS generally presents as a hypoproliferative macrocytic anemia, often associated with suboptimal elevation of sEpo levels.<sup>1,113</sup> To determine FAB subtype, iron status, and the level of ring sideroblasts, bone marrow aspiration with iron stain, biopsy, and cytogenetics should be examined. Patients also should be considered for HLA-DR15 typing.

Individuals with symptomatic anemia and del(5q) with or without other cytogenetic abnormalities should receive a trial of lenalidomide. Those with normal cytogenetics, less than 15% marrow ringed sideroblasts, and sEpo levels of 500 mU/mL or less may respond to erythropoietin if relatively high doses of recombinant human erythropoietin are administered.<sup>44,114,115</sup> The required erythropoietin dose is 40,000 to 60,000 units given 1 to 3 times a week subcutaneously. Erythroid responses generally occur within 6 to 8 weeks of treatment.<sup>116-119</sup> A more prompt response may be obtained by starting at the higher dose; this dose is much higher than that needed to treat renal causes of anemia wherein marrow responsiveness would be relatively normal. If a response occurs, the recommendation is to continue this dose but attempt to decrease it to tolerance. The literature supports daily or 2- to 3-times-per-week dosing.

Iron repletion must be verified before instituting erythropoietin or darbepoetin therapy. If no response occurs with these agents alone, the addition of G-CSF should be considered. Evidence suggests that G-CSF (and to a lesser extent GM-CSF) has synergistic erythropoietic activity when used in combination and markedly enhances the erythroid response rates.<sup>115–118</sup> This is particularly evident for patients with 15% or more ringed sideroblasts in the marrow (and sEpo level < 500 mU/mL), because the very low response rates in this subgroup to erythropoietin or darbepoetin alone are markedly enhanced when combined with G-CSF.<sup>117,118</sup>

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in initially neutropenic patients or to double the neutrophil count in those who are initially normal. For this purpose, an average of 1 to 2 mcg/kg is administered subcutaneously daily or 1 to 3 times a week.<sup>115–118</sup> Refrigerated multidose vials (withdrawing all contents at one time into separate syringes and leaving them in the refrigerator until used) permit more efficient use of G-CSF, decreasing its cost. Patients may be taught to self-administer the drug. Again, detection of erythroid responses generally occurs within 6 to 8 weeks of treatment. If no response occurs in this timeframe, this treatment should be considered a failure and discontinued. If treatment failure occurs, deficient iron stores should be ruled out and treated. Clinical trials or supportive care are also treatment options in these patients. A predictive and validated model has been developed for predicting erythroid responses to erythropoietin plus G-CSF, based on the patient's basal sEpo level and number of previous RBC transfusions.<sup>118,120</sup> Improved quality of life has been shown in patients experiencing response.<sup>120</sup> This cytokine treatment is not suggested for patients with endogenous sEpo levels greater than 500 mU/mL because of the very low erythroid response rate to these drugs.

Darbepoetin alfa is a longer-acting form of erythropoietin. Studies predominantly involving patients with lower-risk MDS have shown a substantial proportion of erythroid responses, with the initial trials showing response rates of 40% and 60% (combined major and minor responses using IWG response criteria).<sup>121,122</sup> Results of clinical trials in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than those to epoetin.<sup>121–124</sup> These response rates may be partly from the dosage used (150–300 mcg/week, subcutaneously) or because better-risk patients were enrolled in studies of darbepoetin compared with epoetin. Features predictive of response have included relatively low basal sEpo levels, low percentage of marrow blasts, and relatively few prior RBC transfusions.

In March 2007 and 2008, the FDA announced alerts and strengthened safety warnings for the use of erythropoiesis stimulating agents (ESAs). They noted that increased mortality, possible tumor promotion, and thromboembolic events were observed in patients without MDS receiving ESAs when dosing has targeted hemoglobin levels greater than 12 g/dL (study patients had chronic kidney failure; were undergoing radiation therapy for various malignancies, including head and neck, advanced breast, lymphoid, and non-small cell lung cancers; had cancer and were not undergoing chemotherapy; or were orthopedic surgery patients).

However, ESAs have been used safely in large numbers of adult patients with MDS and have become important for symptomatic improvement of those affected by anemia caused by this disease, often with a decrease in RBC transfusion requirements. The panel recommendations for use of ESAs in MDS have evolved from these and more recent data. In addition, studies assessing the long-term use of erythropoietin with or without G-CSF in patients with MDS compared with either randomized<sup>125</sup> or historical controls<sup>126,127</sup> have shown this treatment has no negative impact on survival or AML evolution. In addition,

results of the studies by Jadersten et al.<sup>126</sup> indicated improved survival in patients with low-risk MDS with low transfusion need treated with these agents. The study by Park et al.<sup>127</sup> further indicated improved survival and decreased AML progression in IPSS low/INT-1 patients treated with erythropoietin/G-CSF compared with the historical controls from the IMRAW database. Thus, these data do not indicate a negative impact of these drugs in the treatment of MDS. Given these data, the panel endorses and reiterates its prior recommendations for ESA use in the management of symptomatic anemia in patients with MDS, but with a change in the target hemoglobin level (i.e., with the goal of achieving a target hemoglobin of 12 g/dL).

In July 2007, the Centers for Medicare & Medicaid Services modified the scope of their decision regarding the use of ESAs in cancer and related neoplastic conditions to make no national coverage determination (NCD) on the use of ESAs in MDS (i.e., not restricting ESA use in MDS through the NCD). Thus, local Medicare contractors may continue to make reasonable and necessary determinations on uses of ESAs that are not determined by the NCD.

Clinical trials with other experimental agents that are reportedly capable of increasing hemoglobin levels should be explored in patients not experiencing response to standard therapy. These drugs should be used in the context of therapeutic approaches for the patient's underlying prognostic risk group.

## Summary

These suggested practice guidelines are based on extensive evaluation of the reviewed risk-based data and indicate useful current approaches for managing patients with MDS. Four drugs have recently been approved by the FDA for treating specific subtypes of MDS: lenalidomide for MDS patients with del(5q) cytogenetic abnormalities; azacitidine and decitabine for treating patients with higher-risk or nonresponsive MDS; and deferasirox for iron chelation of iron overloaded patients with MDS. However, because a substantial proportion of patient subsets with MDS lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents along with supportive care remain the hallmark of management for this disease. The role of thrombopoietic cytokines for management of thrombocytopenia in MDS needs further evaluation. In addition, further determination of the effects of these therapeutic interventions on the patient's quality of life is important.<sup>116,119,120,128,129</sup> Progress toward improving management of MDS has occurred over the past few years, and more advances are anticipated using these guidelines as a framework for coordination of comparative clinical trials.

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Table 1

## Individual Disclosures of the NCCN Myelodysplastic Syndromes Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Eyal Attar, MD	None	Celgene Corporation	None	None	12/4/09
John M. Bennett, MD	None	Novartis Pharmaceuticals Corporation	None	Celgene Corporation; and Johnson & Johnson	1/22/10
Clara D. Bloomfield, MD	None	None	None	None	9/28/09
Carlos M. De Castro, MD	Celgene Corporation; Cephalon, Inc.; and Pharmion Corporation	Alexion Pharmaceuticals, Inc.; Celgene Corporation; Janssen Pharmaceutica Products, LP; and Pharmion Corporation	None	None	7/7/09
H. Joachim Deeg, MD	None	None	None	None	12/8/09
James M. Foran, MD	Eisai Inc.; Genzyme Corporation; and Medarex, Inc.	Celgene Corporation; and Sunesis Pharmaceuticals, Inc.	None	None	2/9/10
Karin Gaensler, MD	None	None	None	None	9/21/10
Guillermo Garcia-Manero, MD	Celgene Corporation; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation	Merck & Co., Inc.; MGI PHARMA, INC.; Novartis Pharmaceuticals Corporation; and Pharmion Corporation	None	None	12/17/09
Steven D. Gore, MD	Celgene Corporation; and Johnson & Johnson	Celgene Corporation	Celgene Corporation	None	12/8/09
Peter L. Greenberg, MD	Amgen Inc.; Celgene Corporation; Eisai Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; and Onconova	Amgen Inc.; and Novartis Pharmaceuticals Corporation	None	None	4/23/10
David Head, MD	None	None	None	None	9/21/10
Rami Komrokji, MD	Celgene Corporation; Genentech, Inc.; Array Biopharma; and Onconova	Celgene Corporation; and Novartis Pharmaceuticals Corporation	None	None	1/8/10
Lori J. Maness, MD	None	None	None	None	10/28/09
Michael M. Millenson, MD	None	Amgen Inc.; Celgene Corporation; and GlaxoSmithKline	None	sanofi-aventis U.S.	12/8/09
Stephen D. Nimer, MD	None	None	None	None	12/28/09
Margaret R. O'Donnell, MD	National Cancer Institute	Anti-soma	None	None	5/24/10
Mark A. Schroeder, MD	None	None	None	None	6/4/10
Paul J. Shami, MD	Genzyme Corporation	Genzyme Corporation; Novartis Pharmaceuticals Corporation; and Novartis Pharmaceuticals Corporation	None	None	10/7/10

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Richard M. Stone, MD	Novartis Pharmaceuticals Corporation	Celgene Corporation; Cephalon, Inc.; Genzyme Corporation; and Merck & Co., Inc.	None	None	2/9/10
James E. Thompson, MD	None	None	None	None	4/28/10
Peter Westervelt, MD, PhD	None	Celgene Corporation; and Novartis Pharmaceuticals Corporation	None	None	10/6/09

The NCCN Guidelines staff have no conflicts to disclose.