

Myelodysplastic Syndromes

Version 3.2006

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NCCN Myelodysplastic Panel Members

- * Peter L. Greenberg, MD/Chair ‡
Stanford University Cancer Center
- * Maria R. Baer, MD † ‡
Roswell Park Cancer Institute
- * John M. Bennett, MD † †
Consultant
- * Clara D. Bloomfield, MD †
Arthur G. James Cancer Hospital &
Richard J. Solove Research Institute at
The Ohio State University
- * Carlos M. DeCastro, MD †
Duke Comprehensive Cancer Center
- * H. Joachim Deeg, MD † ‡
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance
- * Marcel Devetten, MD † ‡
UNMC Eppley Cancer Center at The
Nebraska Medical Center
- * Peter D. Emanuel, MD ‡
University of Alabama at Birmingham
Comprehensive Cancer Center
- * Harry P. Erba, MD, PhD † ‡
University of Michigan Comprehensive
Cancer Center
- * Eli Estey, MD ‡
The University of Texas M. D. Anderson
Cancer Center
- * James Foran, MD †
University of Alabama at Birmingham
Comprehensive Cancer Center
- * Steven D. Gore, MD † ‡
The Sidney Kimmel Comprehensive Cancer
Center at Johns Hopkins
- * Michael Millenson, MD † ‡
Fox Chase Cancer Center
- * Willis Navarro, MD † ‡
UCSF Comprehensive Cancer Center
- * Stephen D. Nimer, MD † ‡
Memorial Sloan-Kettering Cancer Center
- * Margaret R. O'Donnell, MD ‡
City of Hope Cancer Center
- * Hussain I. Saba, MD, PhD ‡
H. Lee Moffitt Cancer Center & Research
Institute at the University of South Florida
- * Kathy Spiers, MD
St. Jude Children's Research
Hospital/University of Tennessee Cancer
Institute
- * Richard M. Stone, MD ‡
Dana-Farber/Partners CancerCare
- * Martin S. Tallman, MD ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

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* Writing Committee Member
† Medical Oncology
‡ Hematology/Hematology Oncology
† Internal Medicine

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NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.

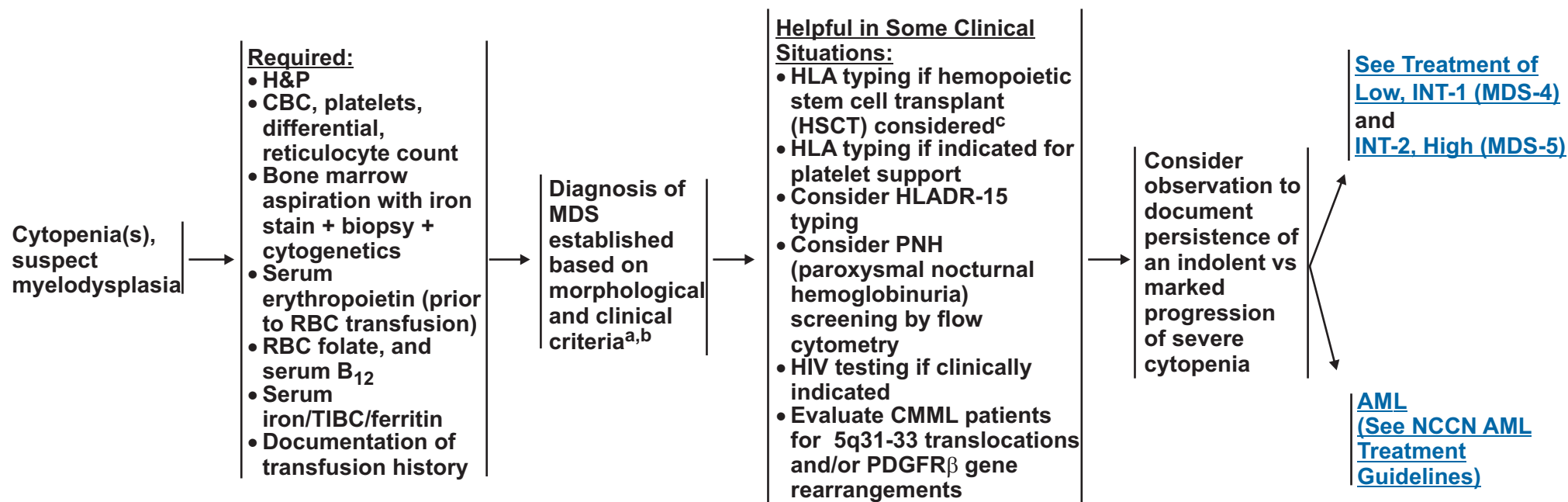
See [NCCN Categories of Consensus](#)

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INITIAL EVALUATION

CATEGORY



^aConfirm diagnosis of MDS according to FAB and WHO criteria for classification with application of IPSS. [See Classification Systems \(MDS-2 and 3\)](#). Percentage of marrow myeloblasts should be reported.

^bPatients with significant cytopenias and karyotypes t(8;21), t(15;17), and/or inv(16) or variants should be considered AML. [\(See NCCN AML Guidelines\)](#).

^cFamily HLA - evaluation to include all first-degree relatives; unrelated evaluation to include high resolution allele level typing for HLAA, B, C, DR, DQ.

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CLASSIFICATION SYSTEMS (page 1 of 2)

FAB Classification of MDS^{d,e}

FAB subtype	% of Peripheral blasts	% of Bone marrow blasts
Refractory anemia (RA)	< 1	< 5
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5
Refractory anemia with excess blasts (RAEB)	< 5	5-20
Refractory anemia with excess blasts in transformation (RAEB-t)	< 5	21-30
Chronic myelomonocytic leukemia (CMML) (> 1,000 monocytes/mcL blood)	< 5-20	5-20

IPSS^{f,g,h}

Survival and AML evolution					
Prognostic variable	Score value				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%) ⁱ	< 5	5-10	---	11-20	21-30
Karotype ^j	Good	Intermediate	Poor		
Cytopenia ^k	0/1	2/3			

Risk category (% IPSS pop.)	Overall score	Median survival (y)	25% AML progression (y)
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

^dFAB = French-American-British classification system of MDS.

^eBennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982;51:189-199.

^fIPSS = International Prognostic Scoring System

^gGreenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088.

^hGreenberg P, Cox C, LeBeau M, et al: Erratum. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1998;91:1100.

ⁱPatients with 20-30 % blasts may be considered as MDS or AML.

^jCytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (≥ 3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML not MDS.]

^kCytopenias: neutrophil count <1,800/mcL, platelets < 100,000/mcL, Hb < 10g/dL.

[Continued on next page](#)

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CLASSIFICATION SYSTEMS (page 2 of 2)

WHO Classification of MDS^{l,m}

Subtype	Blood	Bone marrow
Refractory anemia (RA)	Anemia; no or rare blasts	Erythroid dysplasia only; < 5% blasts; < 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia); no or rare blasts; no Auer rods; < 1 x 10 ⁹ /L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; < 5% blasts; no Auer rods; < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia; no blasts	Erythroid dysplasia only; < 5 % blasts; ≥ 15 % ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia); no or rare blasts; no Auer rods; < 1 x 10 ⁹ /L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; < 5% blasts; no Auer rods; ≥ 15 % ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias; < 5% blasts; no Auer rods; < 1 x 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia; 5% to 9% blasts; no Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias; 5-19% blasts; Auer rods ±; < 1 x 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia 10% to 19% blasts; Auer rods ±
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias; no or rare blasts; no Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes; < 5% blasts; no Auer rods
MDS associated with isolated del(5q)	Anemia; < 5% blasts; platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei; < 5% blasts; no Auer rods; isolated del (5q)

^lWHO = World Health Organization classification system of MDS.

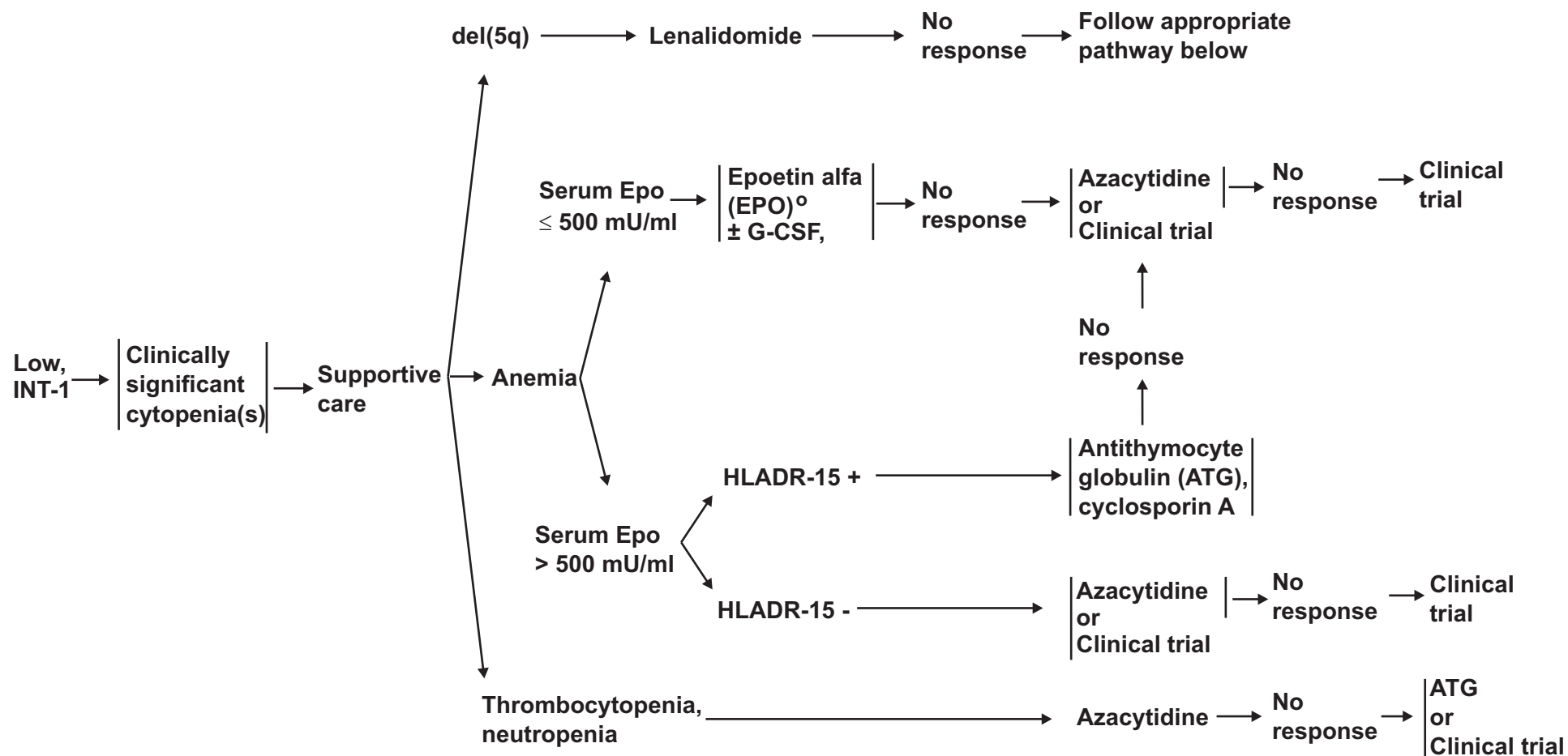
^mVardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2292-2302.

Note: All recommendations are category 2A unless otherwise indicated.

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IPSS CATEGORYⁿ

TREATMENT



ⁿSee IPSS Classification System (MDS-2).

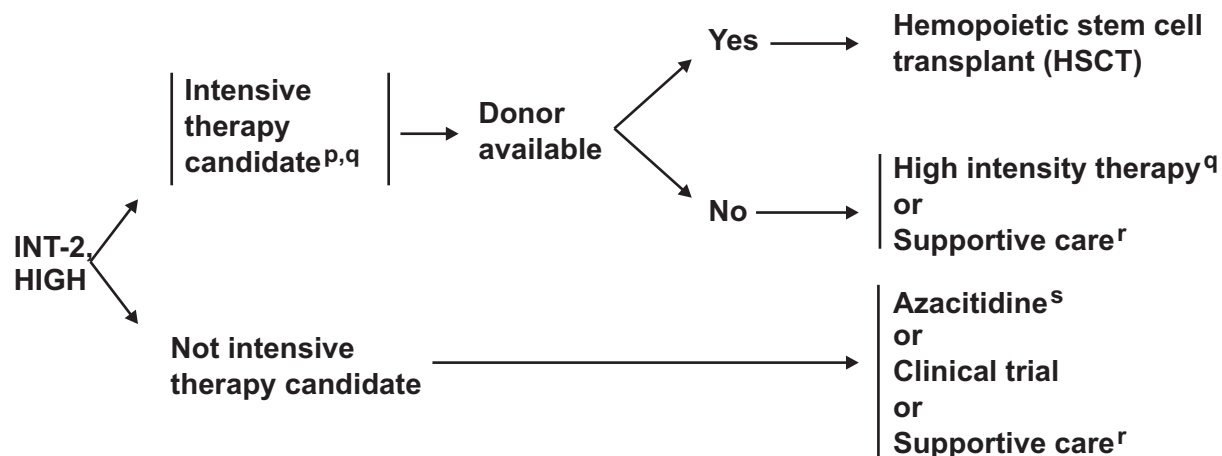
^oThe use of darbepoetin alfa is currently under active investigation.

**Progressive Disease -
See INT-2, HIGH (MDS-5)**

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IPSS CATEGORYⁿ

TREATMENT



ⁿ See [IPSS Classification System \(MDS-2\)](#).

^p Based on age, performance status and absence of major comorbid medical conditions that would preclude high dose therapy.

^r See [Supportive Care \(MDS-A\)](#).

^s The use of decitabine is under active investigation for this purpose.

^qHigh-Intensity Therapy:

- Clinical Trials (preferred)
 - › Investigational therapy preferred.
 - › Standard induction therapy if investigational protocol unavailable or as a bridge to HSCT. (See text for more detail)
 - › Hemopoietic stem cell transplant (HSCT):
 - allogeneic-matched sibling including standard and (experimental) reduced intensity preparative approaches or matched unrelated donor (MUD)

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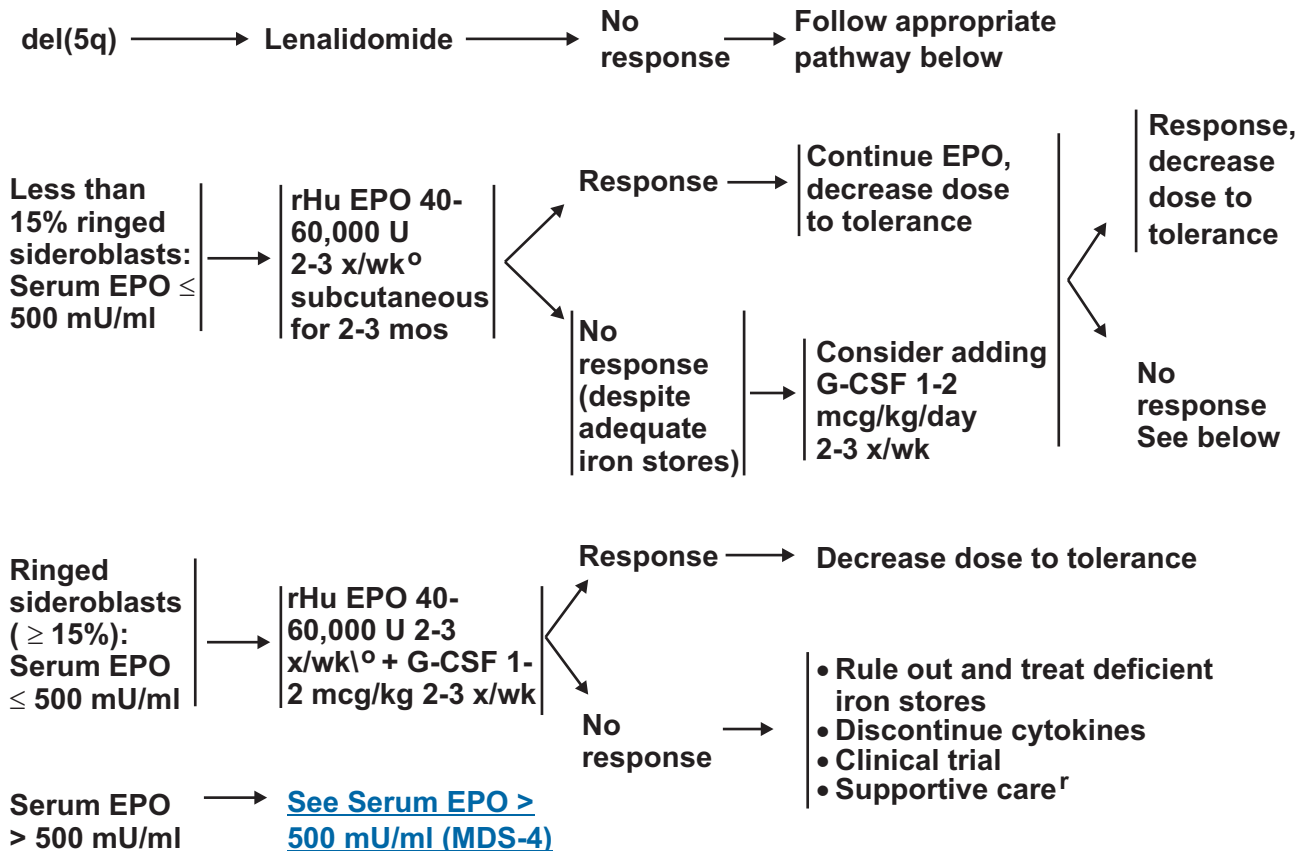
EVALUATION OF RELATED ANEMIA

TREATMENT OF SYMPTOMATIC ANEMIA

FOLLOW-UP

- H&P
- CBC, platelets, differential, reticulocyte count
- Bone marrow aspiration with iron stain + biopsy + cytogenetics
- Serum EPO level
- Consider HLA-DR 15 typing
- Rule out coexisting causes

- Treat coexisting causes
- Replace iron, folate, B₁₂ if needed
- RBC transfusions (leuko-reduced)
- Supportive care^r



Growth Factors

- Use 20,000-40,000 U/mL EPO vial
- Multidose G-CSF refrigerated vials

^oThe use of darbepoetin alfa is currently under active investigation.

^rSee [Supportive Care \(MDS-A\)](#).

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SUPPORTIVE CARE¹

- **Observation:**
 - ▶ 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
- **Antibiotics for bacterial infections**
- **Aminocaproic 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, strongly consider daily chelation with deferoxamine SC or deferasirox orally to decrease iron overload, particularly for LOW/INT-1 patients²
- **Cytokines:**
 - ▶ EPO [See Anemia pathway \(MDS-6\)](#)
 - ▶ 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 \(MDS-6\)](#)
 - * Platelet count should be monitored

¹[See NCCN Supportive Care Guidelines.](#)

²Clinical trials in MDS are currently ongoing with oral chelating agents.

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SUMMARY OF GUIDELINES UPDATES

Highlights of major changes in the 2006 version of the NCCN Myelodysplastic Syndromes guidelines from the 1.2005 version include:

- The NCCN MDS panel modified pages [MDS-2](#) and [MDS-3](#) to include 3 classification systems:
 - French-American-British classification system of MDS (FAB)
 - International Prognostic Scoring System (IPSS)
 - World Health Organization classification system of MDS (WHO).
- The use of lenalidomide for patients with del(5q) has recently been approved by the FDA and added to the guideline on pages [MDS-4](#) and [MDS-6](#).
- Supportive care for MDS page [MDS-A](#) has been updated. The category 2B recommendation for irradiated products for transplant candidates has been removed.
- [MDS-A](#) Deferasirox/ICL670 has recently been approved by the FDA for treatment of iron overload. The NCCN MDS panel members recommend consideration of chelation with deferoxamine SC or deferasirox/ICL670 orally to decrease iron overload .

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NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

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 patients' 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 age 70, the incidence increases between 22 and 45 per 100,000 and increasing further with age.

Managing MDS is complicated by the generally advanced age of the patients (median ages range from 65 to 70 years old), the attendant non-hematologic comorbidities, and the older patients' relative inability to tolerate certain intensive forms of therapy. In addition,

when the illness progresses into AML, these patients experience lower response rates to standard therapy than patients with de novo AML.¹

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 ([MDS-1](#)). The French-American-British (FAB) classification initially categorized patients for the diagnostic evaluation of MDS.² Dysplastic changes in at least two of the three 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.³ Patients with MDS are classified as having one of five subtypes of disease: refractory anemia (RA); RA with ringed sideroblasts (RARS); RA with excess of blasts (RAEB); RAEB in transformation (RAEB-T); and chronic myelomonocytic leukemia (CMML). MDS are generally indolent, with patients' blood counts remaining relatively stable over at least several months ([MDS-2](#)).

With a moderate degree of variability, RAEB patients (those with 5% to 20% marrow blasts) and those with RAEB-T (20% to 30% marrow blasts) generally have a relatively poor prognosis, with a median survival ranging from 5 to 12 months. In contrast, RA patients (fewer than 5% blasts) or RARS patients (fewer than 5% blasts plus more than 15% ringed sideroblasts) have a median survival of approximately 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.

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

Chronic myelomonocytic leukemia is categorized as MDS, although it often has the characteristics of a myeloproliferative disorder. Some groups have separated these patients into proliferative or non-proliferative/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.

Recently, the World Health Organization (WHO) proposed a new classification for MDS⁴⁻⁶ ([MDS-3](#)). This report suggests modifying the FAB definitions of MDS. Although most prior data require at least two-line dysplasia for the diagnosis of MDS, the WHO guidelines accept unilineage dysplasia for the diagnosis of RA and RARS provided that other causes of the dysplasia are absent and the dysplasia 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 a number of medications and viral infections (including HIV infection) may cause morphologic changes in marrow cells similar to MDS.^{1,7}

Other categories within the WHO proposal include refractory cytopenia with multilineage dysplasia (RCMD), separating RAEB patients into those with less than 10% marrow blasts and those with 10% or more marrow blasts, 5q minus syndrome, and MDS unclassified (with or without ringed sideroblasts). The category MDS/MPD has been proposed for patients who previously have been classified as having CMML. The MDS/MPD category includes CMML, atypical CML, and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features. CMML had been categorized by FAB as MDS; by the International MDS Risk Analysis Workshop (IMRAW) as proliferative type (WBC12,000/mm³) (a myeloproliferative disorder (MPD) or non-proliferative type (dysplastic MDS)).⁸ The 5q- syndrome, recognized by WHO as a separate MDS category, includes patients with an isolated 5q31-33 deletion and marrow showing <5% blasts, often with thrombocytosis.⁴⁻⁶ This disorder generally has a relatively good prognosis.⁹

The WHO panel also suggests excluding RAEBT patients from MDS (proposing that AML should now include patients with 20% or more marrow blasts, rather than the previously used 30% or more cutoff). However, MDS are not only related to blast quantitation, but also possess a differing pace of disease related to distinctive biologic features that differ from de novo AML.^{10,11} In addition, therapeutic responses may differ between these two patient groups.

The decision to treat patients having marrow blasts in the range of 20% to 30% with intensive AML therapy is thus complex and should be individualized. The clinician should consider such factors as age, antecedent factors, cytogenetics, comorbidities, pace of disease, and performance status. To aid this approach and given the long-standing experience with the FAB categorization, the NCCN MDS

panel members currently endorse reporting and using **both** the FAB and the WHO classification systems. Thus, RAEBT patients may be considered as either MDS or AML. Recent studies have provided conflicting evidence regarding the use of the WHO proposals,^{12,13} and further evaluation of this classification system is ongoing.

Information from the International MDS Risk Analysis Workshop (IMRAW) with its IPSS diagnostic classification provides data indicating that patients in IPSS Int-2 and High categories are relatively high-risk, whereas Low and Int-1 patients are in relatively low risk prognostic categories⁸ ([MDS-2](#)).

AML evolving from MDS (AML-MDS) is often more resistant to standard cytotoxic chemotherapy than is de novo AML, which arises without antecedent hematologic disorder. High-risk MDS, 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 protocols for treating patients with standard presentation of de novo AML and for these other patient groups (such as MDS-AML, elderly AML, and high-risk MDS groups) seem appropriate. Clinical trials (investigational therapy) are preferable for the latter patient groups.

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 also require careful evaluation ([MDS-1](#)).

In addition to establishing current blood and reticulocyte counts, clinicians need a peripheral blood smear evaluation to determine the degree of dysplasia and, thus, potentially dysfunctional cells. Bone marrow aspiration and biopsy are needed to calculate 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 (EPO), vitamin B₁₂, iron, ferritin, and red blood cell folate levels. 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 CMV status and full HLA typing (A, B, C, DR, DQ) of the patient and potential donors are needed. Bone marrow flow cytometry for CD34 (blast cells are usually CD34+), paroxysmal nocturnal hemoglobinuria (PNH) screening (peripheral blood), and HIV screening, if clinically indicated, may also be valuable in some clinical situations. The screening for 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^{14,15} (see [Prognostic Stratification](#) below).

Determination of PDGFR gene rearrangements in CMML/MPD patients with 5q31-33 translocations is helpful for evaluating these patients ([MDS-1](#)). The activation of the gene encoding a receptor

tyrosine kinase for platelet-derived growth factor receptor beta (PDGFR) has been shown in some of these patients.^{16,17} Recent data have indicated that MPD/CMML patients with such PDGFR fusion genes may respond well to treatment with Imatinib mesylate.^{18,19}

Recent flow cytometric studies suggest the potential utility of this methodology for characterizing MDS marrow blast cells and as an aid for assessing prognosis of these patients.^{20,21} However, due to the non-standardized nature of these analyses, further investigations are warranted prior to suggesting their routine use.

Prognostic Stratification

Despite its value for diagnostic categorization of patients with MDS, the prognostic limitations of the FAB classification have become apparent with quite 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% to 20%) and CMML (1% to 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.²²

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW ([MDS-2](#)).^{8,9} 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.^{8,22} FAB morphologic criteria were used to establish the diagnoses of MDS.

In addition, relative stability of peripheral blood counts for 4 to 6 weeks were needed to exclude other possible etiologies for the cytopenias, such as drugs, other diseases, or incipient evolution to AML. CMML was subdivided into proliferative and non-proliferative subtypes. Patients with proliferative type CMML (those with white blood cell counts less than 12,000/mcL) were excluded from this analysis.⁸ Patients with non-proliferative CMML (with white blood cell counts of 12,000/mcL or more as well as other features of MDS) were included in the analysis.²³

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 divisible into four 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 (ANC) below 1,800/mcL, and platelet count below 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 (three or more 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, the vast majority 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 generated⁸ ([MDS-2](#)). By combining the risk scores for the three major variables, patients were stratified into four 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 four 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.⁸

Therapeutic Options

The patient's IPSS risk category is used in planning therapeutic options because it provides a risk-based patient evaluation. In addition, the patient's age and performance status are critical determinants because they have a major influence on the patient's ability to tolerate certain intensive treatments.

If the patient was only recently evaluated, determining the relative stability of the patient's blood counts over several months is very important to assess whether the patient's disease progresses, including incipient transformation to AML. In addition, this assessment permits determination of other possible etiologies 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 ([MDS-4](#), [MDS-5](#)). In evaluating results of therapeutic trials the panel found it important for studies to use the standardized International Working Group (IWG) response criteria.^{24,25}

For the MDS therapeutic algorithm, all patients should receive relevant supportive care ([MDS-4](#), [MDS-A](#)). Following that, the panel has pro-

posed initially stratifying patients with clinically significant cytopenia(s) into two major risk groups: (1) relatively low risk patients who are in the IPSS Low, Intermediate-1 category, and (2) higher risk patients in the IPSS Intermediate-2/ High categories. Per IWG criteria, for patients in the lower risk group, the major therapeutic aim would be hematologic improvement, whereas for those in the higher risk group alteration of the disease natural history is viewed as paramount. Cytogenetic and quality of life responses were also important parameters to assess.

Supportive Care

Currently, the standard of care in the community for MDS is supportive care ([MDS-A](#), and [NCCN Supportive Care Guidelines](#)). This entails observation, clinical monitoring, psychosocial support, and quality-of-life (QOL) assessment. Major efforts should be directed toward addressing the relevant QOL domains (eg, physical, functional, emotional, spiritual, social) which adversely effect the patient. Supportive care should include red blood cell transfusions for symptomatic anemia as needed (generally leukocyte-reduced) or platelet transfusions for severe thrombocytopenia or thrombocytopenic bleeding. There was non-uniform consensus among the panel members based on differing institutional policies regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agrees that all directed-donor products and transfused products for potential stem cell transplant patients should be irradiated. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.

Management of Iron Overload

For relatively low-risk patients with excessive iron accumulation resulting from the number of red blood cell transfusions received, iron chelation therapy should be instituted.²⁶

Although the specific therapies patients receive may alleviate RBC transfusion need, a substantial proportion of MDS patients may not respond to these treatments and may develop iron overload as well as its consequences.²⁷ Thus, effective treatment of such transfusional siderosis in MDS patients is quite germane. Studies in patients requiring relatively large numbers of RBC transfusions (eg, thalassemia and MDS) have demonstrated the pathophysiology and adverse effects of chronic iron overload on hepatic, cardiac and endocrine function. Increased non-transferrin bound iron (NTBI), 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.^{28,29}

Reversal of some of the consequences of iron overload in MDS and other iron overload states (eg, thalassemia) by iron chelation therapy have been shown in patients in whom most effective chelation occurred.^{24,28} This included transfusion independence, in a portion of a small group of carefully studied MDS patients who had undergone effective DFO chelation for 1-4 years.³⁰ In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.³¹ Data have shown decreased survival for RBC transfusion dependent low risk patients compared to those patients not requiring transfusions.³² Such findings have major implications for altering the morbidity of MDS patients, particularly those with pre-existing cardiac or hepatic dysfunction.

Thus, the use of DFO for such patients is highly recommended. This is generally administered for patients who have previously received 20-30 units of RBCs, for whom ongoing RBC transfusions are anticipated and for those with serum ferritin levels >2,500 mcg/L. This treatment is predominantly used for patients with relatively

lower risk MDS, whose clinical course suggests ongoing chronic RBC transfusion need, and for those with concurrent cardiac or hepatic dysfunction. Monitoring serum ferritin may be useful, aiming to decrease ferritin levels to <1,000 mcg/L. It is recognized that such measurements, though useful, are less precise than SQUID (Superconducting Quantum Interference Device) or the more recent development of specific measurement of hepatic MRI evaluations of hepatic iron content.^{33,34} Treatment with DFO is generally given as 1-2 gm by overnight subcutaneous (sc) infusion 5-7 nights weekly. An alternate form of administration has been the use of 1-2 gm bid sc bolus administration. Due to the short half-life of the DFO, IV bolus administration is generally not useful for chronic iron overload. Careful monitoring of eye, ear and renal function is needed for patients treated with DFO. However, it is understood that due to the logistical difficulties of chronic lengthy sc infusions of DFO in the generally elderly MDS patients who also have a variety of comorbidities, such therapy is often begun late and with limited enthusiasm, both by patient and physician. For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored.

The current clinical availability of two oral iron chelators deferiprone, L1³⁵ and deferasirox/ICL670^{36,37} now provides potentially useful drugs for more readily treating this iron overload state.

Deferasirox/ICL670 has just been approved by the FDA for treatment of iron overload. The NCCN MDS panel members recommend to strongly consider chelation with deferoxamine SC or deferasirox/ICL670 orally to decrease iron overload ([MDS-A](#)). Clinical trials in MDS are ongoing with oral iron chelating agents.

Hematopoietic cytokine support should be considered for refractory symptomatic cytopenias.³⁸ For example, recombinant human

granulocyte colony stimulating factor (G-CSF) or granulocyte-monocyte CSF (GM-CSF) treatment could be considered for neutropenic MDS patients with recurrent or resistant bacterial infections. The use of recombinant human erythropoietin to treat symptomatic anemia is discussed under [MDS-4](#) and “[Evaluation and Treatment of Related Anemia](#)”.

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, supportive care or occasional hospitalization (for example, for treatment of infections) may be needed after certain of these treatments.

As a form of relatively low-intensity chemotherapy, the hypomethylating agent 5-azacytidine has been shown in a randomized phase III trial to decrease the risk of leukemic transformation, to improve patients' quality of life, and, in a portion of the patients, to improve survival.³⁹ Hematologic responses occurred in 60% of patients in the azacitidine arm (7% complete response, 16% partial response, 37% improved). This therapy should be considered for treating MDS patients with progressing or relatively high-risk disease. The drug is generally administered at a dose of 75mg/m²/d sc x7 days monthly for 4-6 courses. Treatment courses may need to be extended further or may be used as a bridging therapy to more definitive therapy (eg, HSCT, for patients whose marrow blast counts require lowering prior to that procedure). This drug has been approved by the FDA for treatment of MDS patients. Decitabine, a closely related hypomethylating compound, generally required hospitalization of the patients. Thus, this drug will be considered below under High Intensity Therapy.

The non-chemotherapy low-intensity agents (biologic response modifiers), currently available, include: anti-thymocyte globulin (ATG), cyclosporine, thalidomide, lenalidomide, anti-TNF receptor fusion protein, and vitamin D analogues, all of which have shown some efficacy in phase I and phase II trials.^{1,40-46} Use of anti-immune type therapy with ATG with or without cyclosporin^{40,41} has been shown in several studies to be most efficacious in MDS patients with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a PNH clone.^{14,15}

Encouraging data have been presented for treating lower risk MDS patients with lenalidomide (initially known as CC5013).^{47,48} This drug has been particularly evident for patients with del(5q) chromosomal abnormalities. In a multicenter phase II trial of lenalidomide, given at a dose of 10 mg/day for 21 days or 10 mg/day, in 148 anemic RBC transfusion-dependent MDS patients with del(5q), with or without additional cytogenetic abnormalities, RBC transfusion independence (assessed at 24 weeks) occurred in 66% of patients with Low/Intermediate-1 compared with 52% of patients with higher risk disease.⁴⁸ Cytogenetic responses were achieved in 76% of patients; 55% had a complete cytogenetic response. However, along with these results were common adverse events (in ~50% of patients) that required treatment interruption or dose reduction for potentially serious but generally transient neutropenia and/or thrombocytopenia. Thus, careful monitoring of the patients' blood counts during the treatment period is mandatory when using this agent, particularly in patients with renal dysfunction (due to the drug's renal route of excretion). This drug has recently been approved by the FDA for treatment of MDS patients with del(5q). Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents for non-del(5q) MDS patients.

High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy, or hematopoietic stem cell transplantation (HSCT).^{1,49} Although these approaches have a greater chance of changing the natural history of the disease, they also have an attendant greater risk of regimen-related morbidity and mortality. The panel recommends that such treatments be given 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.⁵⁰

The hypomethylating agent decitabine (5-aza-2'-deoxycytidine), given intravenously and which generally required hospitalization of patients, has shown encouraging results for the therapy of patients with high-risk MDS, with approximately 30% of patients showing cytogenetic conversion.^{51,52} The overall response rate was 49%, with a 64% response rate in patients with a high-risk IPSS score. Comparison of results of these studies with those of 5-azacytidine showed a substantial level of similarity.^{53,54} Studies are warranted using decitabine subcutaneously and in lower dose to determine the drug's efficacy as a low intensity therapeutic option.

A high degree of multi-drug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS,⁵⁵ with associated decreased responses and shorter response durations with many standard treatment 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 multi-drug resistance modulators were positive in this setting,^{56,57} others were not.⁵⁸ Further clinical trials evaluating other multi-drug resistance modulators are ongoing.

Allogeneic hematopoietic stem cell transplant (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.⁵⁹⁻⁶⁷ Matched non-myeloablative transplant regimens^{68,69} and matched unrelated donor stem-cell transplants⁷⁰⁻⁷² 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.⁷³ Whether transplants should be performed before or after patients achieve remission after induction chemotherapy has not been established.⁷⁴ Comparative clinical trials are needed to determine these points.

Recommended Treatment Approaches

Therapy for Lower Risk patients (IPSS Low/Intermediate-1)

Regarding the algorithm for therapeutic options for the lower risk patients with clinically significant cytopenias, the panel recommended stratifying these patients into several groups ([MDS-4](#)). Those with del(5q) chromosomal abnormalities should receive lenalidomide. The remaining anemic patients with levels of serum erythropoietin (Epo) ≤ 500 should be treated with recombinant human Epo (Epo) without or with granulocyte colony stimulating factor (G-CSF) (see [Evaluation and Treatment of Related Anemia](#) below and [MDS-6](#)). Non-responders should be considered for treatment with azacytidine or for participation in a clinical trial with other relevant agents.

Anemic patients with sEpo level >500 should be evaluated for the presence of HLA-DR15. If positive, they should be considered for treatment with ATG +/- cyclosporine. Non-responders would be considered for treatment with azacytidine or clinical trial. Patients with sEpo levels >500 who are HLA-DR15-, should be considered for treatment with azacytidine or clinical trial. Patients with other serious

cytopenias (particularly clinically severe thrombocytopenia) should be considered for treatment with azacitidine. Such patients, if they do not respond to this treatment, should be considered for treatment with ATG or clinical trial.

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 ([MDS-5](#)).

Therapy for Higher Risk Patients (IPSS Intermediate-2/High)

Therapy for higher risk patients is dependant on whether or not they are felt to be candidates for Intensive therapy (eg, allogeneic HSCT or intensive chemotherapy) ([MDS-5](#)). Clinical features relevant for this determination include the patient's age, performance status and absence of major comorbid conditions. In addition, the patient's personal preference for type of therapy needs particular consideration. Supportive care ([MDS-A](#)) should be provided for all patients.

Intensive therapy ([MDS-5](#))

Allogeneic Hematopoietic stem cell transplant (HSCT)

The potential for patients' receipt of an allogeneic HSCT (in addition to the patient's clinical characteristics, as above) is also dependent on whether a donor is available and if the patient's marrow blast count is sufficiently low (ie, <10 or 20% blasts for some institutions and specific protocols). For those patients with an available donor, preference is for a matched sibling donor, although data using matched-unrelated donors is nearly comparable in selected patients. Standard conditioning is used for relatively younger patients whereas the experimental approach using non-myeloablative transplant conditioning is preferable in older individuals.

To aid therapeutic decision-making regarding the timing and selection of MDS patients for HSCT, a recent study compared

allogeneic sibling matched HSCT data in MDS patients ≤60 years old to clinical outcomes to those of non-treated IMRAW/IPSS database MDS patients. Using Markov decision-making statistical analysis, this investigation indicated that transplant for INT-2 and High-risk patients ≤ 60 years old should proceed to transplant at diagnosis, whereas for those Low or INT-1 MDS patients, it would be beneficial to delay transplantation until disease progression.⁷⁵

Intensive chemotherapy

For patients eligible for intensive therapy lacking a stem cell donor, or for those in whom the marrow blast count requires reduction, consideration should be given to the use of intensive induction chemotherapy.⁷⁶ 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 the patients. For those patients with a potential stem cell donor who require reduction of their tumor burden (ie, to decrease the marrow blast count), achievement of even a partial remission may be adequate to permit the HSCT.

Non-Intensive therapy

For patients who are not candidates for intensive therapy, the use of azacitidine or a relevant clinical trial should be considered. As above for patients requiring a decrease in tumor burden prior to HSCT, for some patients eligible for such therapy, the use of azacitidine 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 anti-tumor therapy, good supportive care should be maintained ([MDS-A](#)).

Evaluation and Treatment of Related Anemia ([MDS-6](#))

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, the health care provider 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 B₁₂ studies should be obtained and the cause of depletion corrected if possible. After excluding these causes of the anemia and providing proper treatment for them, further consideration for treating the anemia related to MDS should be undertaken. Currently the standard of care for symptomatic anemic patients is red blood cell (RBC) transfusion support (using leuko-poor products). If the patient is a potential HSCT candidate, the panel recommends consideration of CMV negative (if the patient is CMV negative serologically) and irradiated transfused products.

Anemia related to MDS generally presents as a hypoproliferative macrocytic anemia, often associated with suboptimal elevation of serum Epo levels.^{1,77} To determine FAB subtype, iron status, and the level of ringed sideroblasts, bone marrow aspiration with iron stain, biopsy, and cytogenetics should be examined. Patient also should be considered for HLA-DR15 typing as indicated above.

Individuals with <15% marrow ringed sideroblasts and serum Epo level ≤500 mU/mL may respond to Epo if relatively high doses of recombinant human Epo are administered daily.^{38,78,79} The Epo dose required is 40-60,000 units 2-3 times a week subcutaneously. Erythroid responses generally occur within 6 to 8 weeks of treatment.⁸⁰⁻⁸³ A more prompt response may be obtained by starting at the

higher dose. This Epo 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. Although the literature supports daily dosing, this may not be logistically feasible. No data concerning weekly dosing are available as yet.

Iron repletion needs to be verified before instituting Epo therapy. If no response occurs with Epo 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 with Epo and markedly enhances the erythroid response rates.⁷⁹⁻⁸² This is particularly evident for patients with ≥15% ringed sideroblasts in the marrow (and serum Epo level ≤500 mU/mL) because the very low response rates in this subgroup to Epo alone are markedly enhanced when combined with G-CSF.^{81,82}

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 patients who are initially normal. For this purpose, an average of 1-2 mcg/kg subcutaneously is administered daily or 2-3 times a week.⁷⁹⁻⁸²

Refrigerated multi-dose 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 time frame, this treatment should be considered a failure and discontinued. If treatment failure occurs one should rule out and treat deficient iron stores. Clinical trial or supportive cares are also the options in this category of

patients. A predictive and validated model has been developed for predicting erythroid responses to Epo plus G-CSF, based on the patient's basal serum Epo level and number of previous RBC transfusions.^{81,84} Improved quality of life has been demonstrated in responding patients.⁸⁴ This cytokine treatment is not suggested for patients with endogenous serum Epo levels >500 mU/mL due to their very low erythroid response rate to these drugs.

Darbepoetin alfa, a recently developed longer-acting form of Epo, is currently under active investigation. Studies predominantly with patients having lower risk MDS have demonstrated 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).^{85,86} The different response rates may in part be due to the dosage used (150 and 300 mcg/week subcutaneously, respectively). Features predictive of response included relatively low basal serum Epo levels, low percentage of marrow blasts and relatively few prior RBC transfusions. Further studies with this drug in anemic MDS patients are warranted in order to confirm and extend these data.

Clinical trials with other experimental agents which are reportedly capable of increasing hemoglobin levels should be explored in patients not responding 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 the reviewed risk-based data and indicate useful current approaches for managing patients with MDS. Given the limited number of studies comparing different therapies in MDS, most of the

therapeutic drugs used to treat this disease should be assessed in the context of clinical trials. A number of clinical trials are ongoing assessing the efficacy of novel bio-specific agents in 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.^{80,83,84,87,88} Progress toward improving management of MDS has occurred over the past few years and more such advances are anticipated using these guidelines as a framework for coordination of comparative clinical trials.

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