



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Myelodysplastic Syndromes

Version 2.2011

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Specialties Index

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Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical_trials/physician.html](#)

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

See [NCCN Categories of Evidence and Consensus](#)

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Updates in Version 2.2011 of the NCCN Guidelines from Version 1.2011 include:

[Discussion](#)

The Discussion section has been updated to correspond with the revised algorithm.

Updates in Version 1.2011 of the NCCN Guidelines from Version 1.2010 include:

[MDS-1](#)

- Under the initial evaluation, changed serum ferritin ± iron, TIBC. The recommendation now states serum ferritin, iron, TIBC.
- Under helpful in some clinical situations, added a new bullet: "Consider evaluation of copper deficiency."
- Footnote "a" was changed to: Confirm diagnosis of MDS according to FAB "or" WHO criteria for classification with application of IPSS. [See Classification Systems \(MDS-2 and MDS-4\)](#). Percentage of marrow myeloblasts should be reported.

[MDS-4](#)

- Added the WHO-Based Prognostic Scoring System (WPSS) for MDS as a Category 2B recommendation.
- Modified footnote "p": "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."
- Footnote "u" is new to the page: "RBC transfusion requirement = having ≥ 1 RBC transfusion every 8 weeks over a 4 month period."

[MDS-6](#)

- Modified footnote "c": "Azacytidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability."

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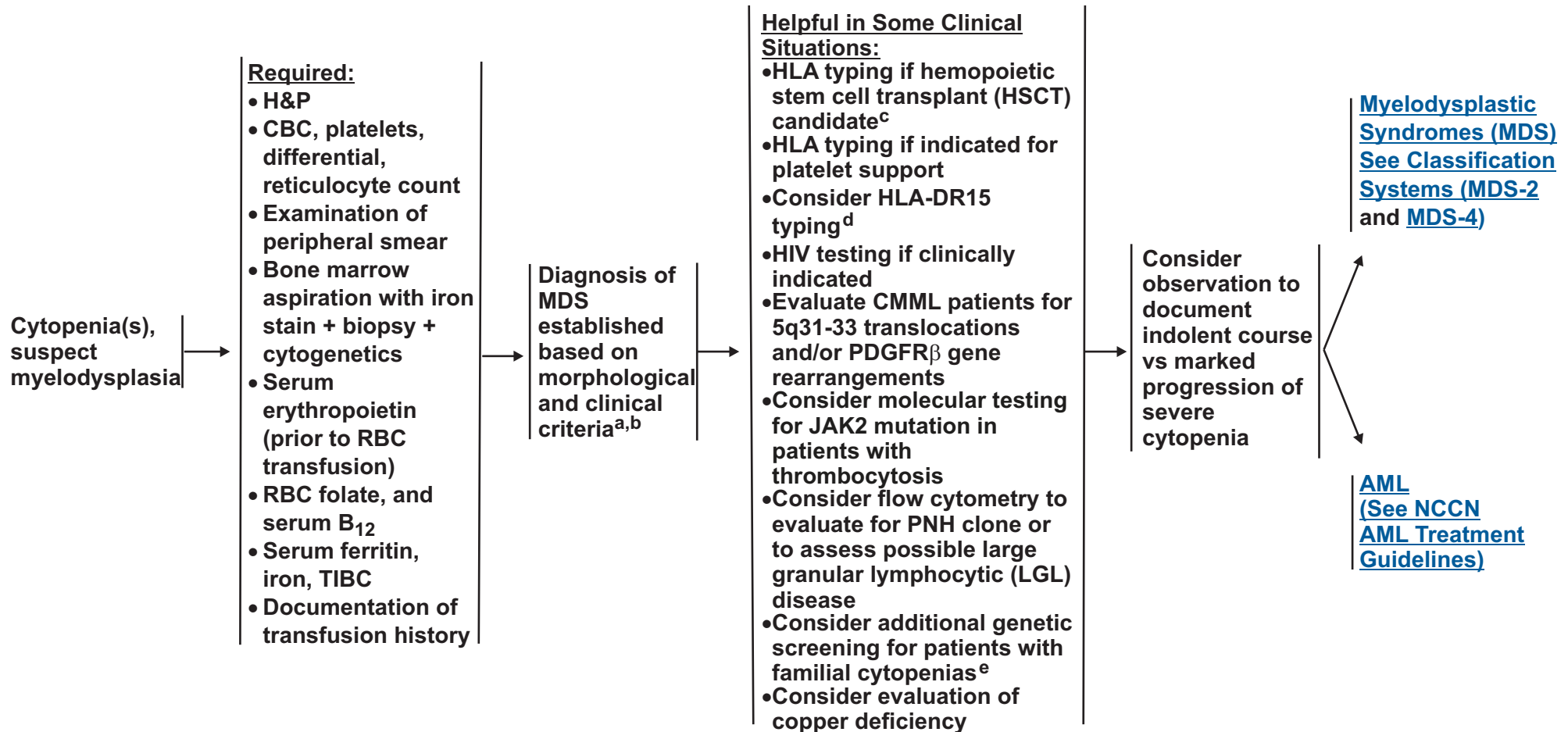


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Myelodysplastic Syndromes

INITIAL EVALUATION

CLASSIFICATION



^aConfirm diagnosis of MDS according to FAB or WHO criteria for classification with application of IPSS. [See Classification Systems \(MDS-2 and MDS-4\)](#). 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 full siblings; unrelated evaluation to include high resolution allele level typing for HLAA, B, C, DR, DQ.

^dTo aid the evaluation for improved response to immunosuppressive therapy.

^eTo assess possible Fanconi anemia or dyskeratosis congenita.

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Myelodysplastic Syndromes

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

2008 WHO^h Classification of MDSⁱ

FAB^f Classification of MDS^g

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	5-20

Subtype	Blood	Bone marrow
Refractory cytopenia with unilineage dysplasia (RCUD) ^j	Single or bicytopenia	Dysplasia in ≥ 10 % of one cell line, < 5% blasts
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	≥ 15 % of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, < 5 % blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s), < 1 x 10 ⁹ /L monocytes	Dysplasia in ≥ 10 % of cells in ≥ 2 hematopoietic lineages, ± 15 % ring sideroblasts, < 5 % blasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s), ≤ 2-4 % blasts, < 1 x 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia, No Auer rods, 5 % to 9 % blasts
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s), 5-19 % blasts, < 1 x 10 ⁹ /L monocytes	Unilineage or multilineage dysplasia Auer rods ±, 10 % to 19 % blasts
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	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

[Continued on next page](#)

^fFAB = French-American-British.

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

^hWHO = World Health Organization.

ⁱFrom Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue. IARC, Lyon, 2008.

^jThis category encompasses refractory anemia (RA), Refractory Neutropenia (RN) and Refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS Unclassified.

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

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) WHO Classification^k

Subtype	Blood	Marrow
Chronic myelomonocytic leukemia-1 (CMML-1)	>1x10⁹/L monocytes, <5% blasts	Dysplasia in ≥1 hematopoietic line, <10% blasts
CMML-2	>1x10⁹/L monocytes, 5-19% blasts or Auer rods	Dysplasia in ≥1 hematopoietic line, 10-19% blasts or Auer rods
Atypical chronic myeloid leukemia (CML), Bcr-Abl 1 negative	WBC 13x10⁹/L, neutrophil precursors >10%, <20% blasts	Hypercellular, <20% blasts
Juvenile myelomonocytic leukemia (JMML)	>1x10⁹/L monocytes, <20% blasts^l	>1x10⁹/L monocytes, <20% blasts^l
MDS/MPN, unclassifiable ('Overlap syndrome')	Dysplasia + myeloproliferative features^m, No prior MDS or MPN	Dysplasia + myeloproliferative features

Acute myeloid leukemia with myelodysplasia-related changesⁿ

WHO Classification^o

- 1. AML post MDS or MDS/MPN**
- 2. AML with an MDS-related cytogenetic abnormality**
- 3. AML with multilineage dysplasia**

[Continued on next page](#)

^kOrazi A, Bennet JM, Germing U, et al, Myelodysplastic/Myeloproliferative Neoplasms, Chapter 4, in Swerdlow S, Campo E, Harris NL, et al. (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 76-86.

^lPh negative plus ≥ 2 features: Hb F, PB immature myeloid cells, WBC >10x10⁹/L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro.

^mFor example, thrombocytosis, leukocytosis, splenomegaly.

ⁿGreater 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 to overt AML.

^oArber DA, Brunning RD, Orazi A, et al. Acute myeloid leukaemia with myelodysplasia-related changes, In Chapter 6, Acute Myeloid Leukemia and Related Precursor Neoplasms, in Swerdlow S, Campo E, Harris NL, et al. (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 124-126.

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Myelodysplastic Syndromes

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

International Prognostic Scoring System (IPSS)^{P,Q}

Survival and AML evolution					
Prognostic variable	Score value				
	0	0.5	1.0	1.5	2.0
Marrow blasts (%) ^r	< 5	5-10	---	11-20	21-30
Karyotype ^s	Good	Intermediate	Poor		
Cytopenia ^t	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

^PIPSS 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.

^QGreenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088; Erratum. Blood 1998;91:1100. © the American Society of Hematology.

^rPatients with 20-30% blasts may be considered as MDS (FAB) or AML (WHO).

WHO-Based Prognostic Scoring System (WPSS) for MDS^P (Category 2B)

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

RA = refractory anemia RARS = refractory anemia with ringed sideroblasts RCMD = refractory cytopenia with multilineage dysplasia RCMD-RS = refractory cytopenia with multilineage dysplasia and ringed sideroblasts RAEB-1 = refractory anemia with excess of blasts-1 RAEB-2 = refractory anemia with excess of blasts-2.

WPSS for MDS groups related to survival and AML progression			
WPSS Risk Groups/Score	Overall Survival (months, median)	AML Progression (probability)	
		2 years	5 years
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, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25(23):3503-3510. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

^sCytogenetics: 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.]

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

^uRBC transfusion requirement = having ≥ 1 RBC transfusion every 8 weeks over a 4 month period.

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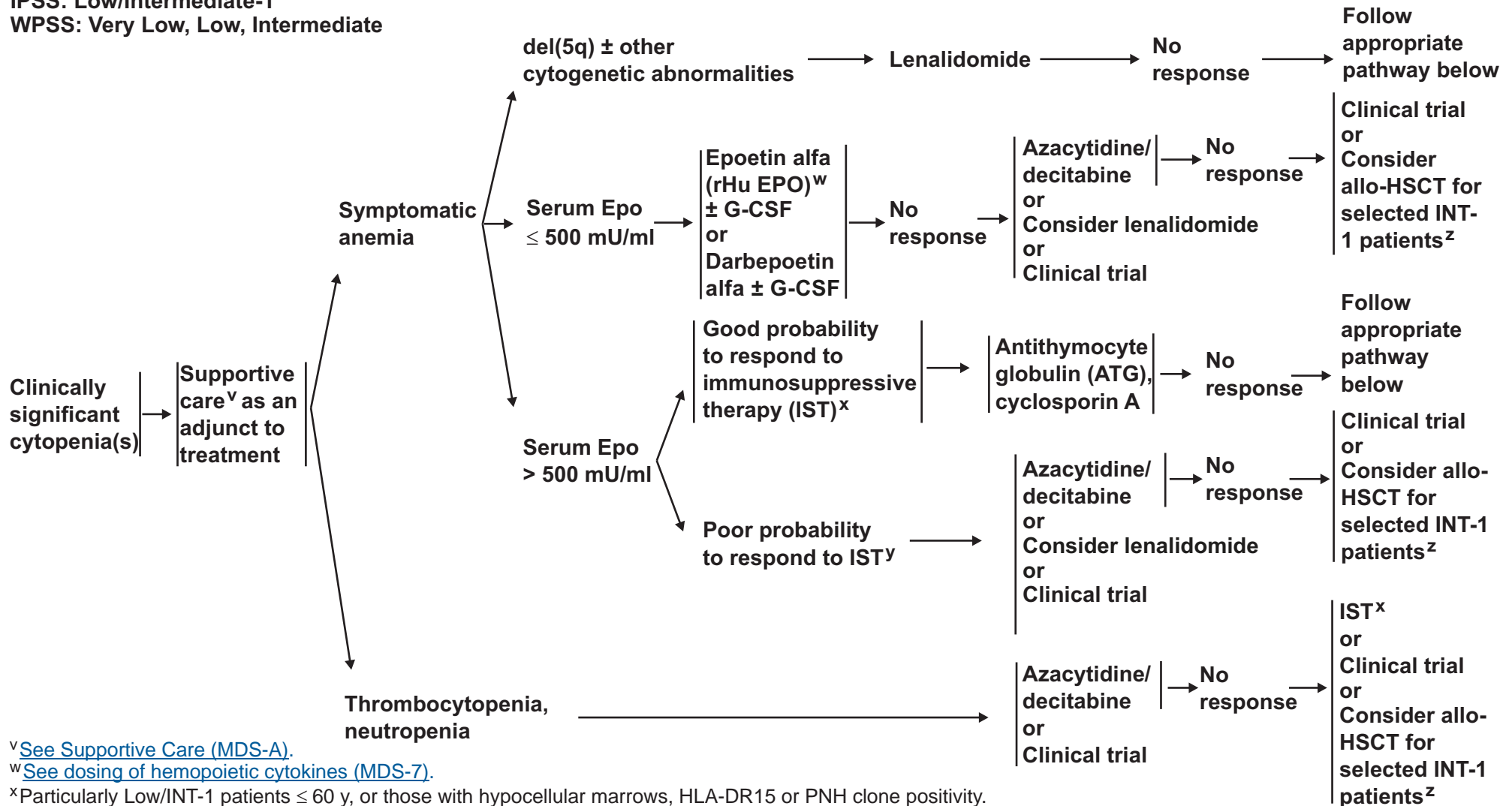
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Myelodysplastic Syndromes

PROGNOSTIC CATEGORY

IPSS: Low/Intermediate-1
WPSS: Very Low, Low, Intermediate

TREATMENT



^v See Supportive Care (MDS-A).

^w See dosing of hemopoietic cytokines (MDS-7).

^x Particularly Low/INT-1 patients ≤ 60 y, or those with hypocellular marrows, HLA-DR15 or PNH clone positivity.

^y Patients lack features listed in footnote x.

^z INT-1 patients with severe cytopenias would also be considered candidates for HSCT (hemopoietic stem cell transplant): Allogeneic-matched sibling transplant including standard and reduced intensity preparative approaches or matched unrelated donor.

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[See Progressive Disease- \(MDS-6\)](#)



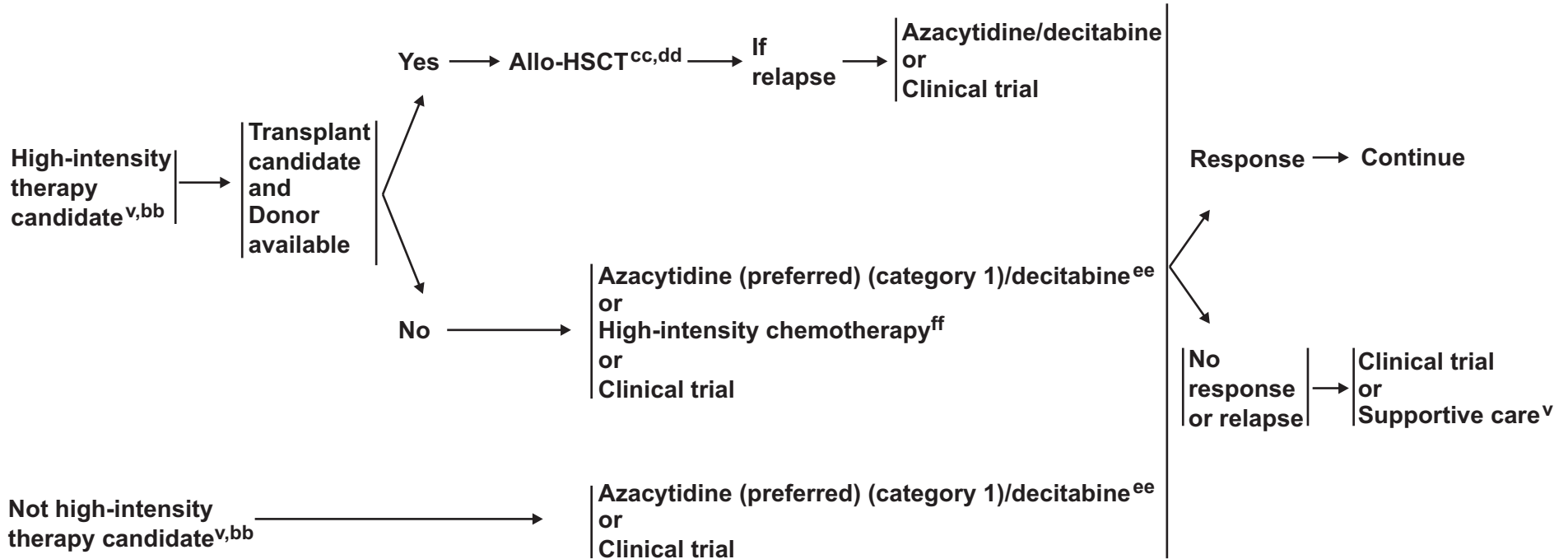
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Myelodysplastic Syndromes

PROGNOSTIC CATEGORY

IPSS: Intermediate-2, High^{aa}
WPSS: High, Very High

TREATMENT



^vSee Supportive Care (MDS-A).

^{aa}INT-1 patients with severe cytopenias unresponsive to standard therapy would also be considered candidates for allogeneic hemopoietic stem cell transplant (allo-HSCT).

^{bb}Based on age, performance status, major comorbid conditions, psychosocial status, patient preference and availability of caregiver.

^{cc}Azacytidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability.

^{dd}Hemopoietic stem cell transplant (HSCT): Allogeneic-matched sibling including standard and reduced intensity preparative approaches or matched unrelated donor (MUD).

^{ee}While the response rates are similar for both drugs, survival benefit from a Phase III randomized trial is reported for azacytidine and not for decitabine.

^{ff}High-intensity chemotherapy:

Clinical trials with investigational therapy (preferred)

Standard induction therapy if investigational protocol unavailable or as a bridge to HSCT.

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Myelodysplastic Syndromes

EVALUATION OF RELATED ANEMIA

TREATMENT OF SYMPTOMATIC ANEMIA

FOLLOW-UP

- H&P
- CBC, platelets, differential, reticulocyte count
- Examination of peripheral smear
- 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^v

del(5q) ± other cytogenetic abnormalities

→ Lenalidomide

Responseⁱⁱ

No response⁹⁹

Continue lenalidomide decrease dose to tolerance

[See IPSS: Low/Intermediate-1 WPSS: Very Low, Low, Intermediate \(MDS-5\)](#)

**Serum EPO ≤ 500 mU/ml
Less than 15% ringed sideroblasts**

→ rHu EPO 40,000 - 60,000 U 1-3 x/wk subcutaneous or Darbepoetin alfa 150-300 mcg/wk subcutaneous

Responseⁱⁱ

No response^{hh} (despite adequate iron stores)

Continue EPO, decrease dose to tolerance

Consider adding G-CSF 1-2 mcg/kg 1-3 x/wk subcutaneous

Response, decrease dose to tolerance

No response [See \(MDS-5\)](#)

**Serum EPO ≤ 500 mU/ml
Ringed sideroblasts ≥ 15%**

→ rHu EPO 40,000 - 60,000 U 1-3 x/wk subcutaneous + G-CSF 1-2 mcg/kg 1-3 x/wk subcutaneous or Darbepoetin alfa 150-300 mcg/wk subcutaneous + G-CSF

Responseⁱⁱ

No response^{hh}

Decrease dose to tolerance

[See IPSS: Low/Intermediate-1 WPSS: Very Low, Low, Intermediate \(MDS-5\)](#)

Serum EPO > 500 mU/ml

→ [See Serum EPO > 500 mU/ml \(MDS-5\)](#)

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

⁹⁹Lack of 1.5 gm/dl rise in Hb or decreased RBC transfusion requirement by 3-4 months of treatment.

^{hh}Lack of 1.5 gm/dl rise in Hb or decreased RBC transfusion requirement by 6-8 weeks of treatment.

ⁱⁱTarget hemoglobin up to 12gm/dl.

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SUPPORTIVE CARE¹

- **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**
 - **CMV negative blood products are recommended whenever possible for CMV negative 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, consider daily chelation with deferoxamine SC 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, aim to decrease ferritin levels to < 1000ng/ml.²
- **Cytokines:**
 - **EPO See Anemia pathway ([MDS-7](#))**
 - **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 \(MDS-7\)](#)
 - ◊ **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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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

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 increases 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. 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.

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 by the FAB 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.

In 2001, the World Health Organization (WHO) proposed a classification for MDS.⁴⁻⁶ The report suggested 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}

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

Other categories within the WHO classification include refractory cytopenia with multilineage dysplasia (RCMD) with or without ring sideroblasts, separating RAEB patients into those with less 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 <5% blasts, often with thrombocytosis.⁴⁻⁶ This disorder generally has a relatively good prognosis¹¹ and is highly responsive to lenalidomide therapy.¹²

The category myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN), includes CMML (CMML-1 and CMML-2); atypical CML, BCR-ABL1 negative; and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features, and the MDS/MPN unclassifiable group.¹³ 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; by the International MDS Risk Analysis Workshop

(IMRAW) as proliferative type (WBC $\geq 12,000/\text{mm}^3$) (a myeloproliferative disorder (MPD) or non-proliferative type (dysplastic MDS)).¹¹

The WHO classification excludes RAEB-T 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.^{14, 15} In addition, therapeutic responses generally 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, RAEB-T patients may be considered as either MDS or AML. Studies have provided evidence supportive of the use of the WHO proposals.^{16, 17}

The 2008 WHO classifications have helped clarify the clinical differences between the FAB RAEB-T patients and AML.¹⁸ 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.¹⁸ According to the 2008 WHO classification, some patients with AML with myelodysplasia-related changes having 20-29% marrow blasts, especially those arising from MDS, considered RAEB-T

by the FAB classification, may behave in a manner more similar to MDS than to AML.

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. See [NCCN Acute Myeloid Leukemia Guidelines](#).

To assist in providing 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 of stable cytopenias are needed) and the exclusion of other potential disorders as a primary reason for dysplasia or/and cytopenia. In addition to these two diagnostic prerequisites, the diagnosis MDS requires at least one of three MDS-related (decisive) criteria: i) dysplasia ($\geq 10\%$ in one or more of the three major bone marrow lineages), ii) a blast cell count of 5-19%, and iii) a specific MDS-associated karyotype, e.g. del(5q), del(20q), +8, or -7/del(7q). Further, several co-criteria help confirm the diagnosis of MDS. These co-criteria include 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 (ALIP), myeloid clonality].¹⁹

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.

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 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 B₁₂, red blood cell folate levels, and serum ferritin. Serum ferritin levels may be nonspecific, particularly in the face of inflammatory conditions such as rheumatoid arthritis. Therefore, in such cases, obtaining the serum iron levels and total iron binding capacity (TIBC) 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

CMV status and full HLA typing (A, B, C, DR, and DQ) of the patient and potential donors are needed. Bone marrow flow cytometry for assessing the % of CD34+ cells (blast cells are usually CD34+), and HIV screening, if clinically indicated, may also be valuable in some clinical situations. Please note, however, that estimates of blast percentage by flow cytometry do not provide the same prognostic information as the blast percentage 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^{20, 21} (see Prognostic Stratification below).

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 (LGL) disease. Review of peripheral smear to determine the presence of LGL is important in this regard.

Additional genetic screening should be considered for patients with familial cytopenias. This will help in evaluating for Fanconi's anemia or dyskeratosis congenita. In addition, this information is of clinical importance as familial MDS is associated with chromosomal fragility and therefore these patients may respond differently to hypomethylating agents and, more importantly, family members may not be eligible as donors for allogeneic hematopoietic stem cell transplant.

Determination of PDGFR β gene rearrangements in CMML/MPD patients with 5q31-33 translocations is helpful for evaluating these patients. The activation of this gene encoding a receptor tyrosine kinase for platelet-derived growth factor receptor beta (PDGFR β) has been shown in some of these patients.^{22, 23} Data have indicated that MPD/CMML patients with such PDGFR β fusion genes may respond well to treatment with imatinib mesylate.^{24, 25}

The frequency of activating mutations of the tyrosine kinase known as Janus Kinase 2 (JAK2) in MDS and *de novo* AML is lower compared to myeloproliferative disorders.²⁶ If one encounters thrombocytosis in patients with MDS, screening for JAK2 mutations may be helpful. A positive test for JAK2 mutation is consistent with presence of a myeloproliferative component of their disorder.²⁷

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.^{28, 29} However, due to the non-standardized nature of these analyses, further investigations are warranted prior to suggesting their routine use.

There have been reports that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.³⁰⁻³² Thus, assessment of copper and ceruloplasmin levels may be indicated as part of the initial diagnostic workup of suspected MDS in certain instances. Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,³⁰⁻³² prior gastrointestinal surgery,^{30, 31} and a history of vitamin B12 deficiency.^{31, 33}

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.³⁴

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW.¹¹ 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.^{11, 34} 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 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 greater than 12,000/mcL) were excluded from this analysis.¹¹ Patients with non-proliferative CMML (with white blood cell counts of 12,000/mcL or less as well as other features of MDS) were included in the analysis.³⁵

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 generated.¹¹ 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.¹¹

Recent data have indicated that additional clinical variables are additive to the IPSS regarding prognosis for MDS patients. The WHO prognostic scoring system (WPSS) incorporates the WHO-based morphologic categories, the IPSS cytogenetic categories and the

patients' need or lack of RBC transfusion dependence.³⁶ This system demonstrated 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.³⁷ As compared with the four groups defined by the IPSS, the WPSS classifies patients into five risk groups differing in both survival and risk of AML. The five risk groups are: Very low, Low, Intermediate, High, and Very high. Following initial report of the usefulness of WPSS by Malcovati et al³⁶ there have been confirmatory studies.³⁸⁻⁴¹ However, there is an ongoing debate whether the WPSS offers an improvement over the IPSS. Based on the current available data, the NCCN MDS Panel has 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 initial planning therapeutic options because it provides a risk-based patient evaluation (category 2A). 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. The WPSS provides dynamic estimation of prognosis at any time during the course of MDS.

If the patient was only recently evaluated, determining the relative stability of the patient's blood counts over several months is 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. In

evaluating results of therapeutic trials the panel found it important for studies to use the standardized International Working Group (IWG) response criteria.^{42, 43}

For the MDS therapeutic algorithm, all patients should receive relevant supportive care. Following that, the panel has proposed initially stratifying patients with clinically significant cytopenia(s) into two major risk groups: (1) relatively lower-risk patients (who are in the IPSS Low, Intermediate-1 category, or WPSS Very Low, Low, and Intermediate); and (2) higher-risk patients (who are in the IPSS Intermediate-2/ High categories or WPSS High, Very High categories). Per IWG response 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 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 Supportive Care section in the Guidelines 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 (e.g., physical, functional, emotional, spiritual, social) which adversely affect 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 agreed that all directed-donor products 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.⁴⁴ 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 “Evaluation and Treatment of Related Anemia”.

Management of Iron Overload

RBC transfusions are a key component of the supportive care for MDS patients. 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.⁴⁵ Thus, effective treatment of such transfusional siderosis in MDS patients is quite germane.

Studies in patients requiring relatively large numbers of RBC transfusions (e.g., 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) 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.^{46, 47}

Although limited, there is retrospective evidence suggesting that organ dysfunction can result from iron overload in patients with MDS.^{48, 49}

Retrospective data suggest that transfusional iron overload might be a contributor of increased mortality and morbidity in early stage MDS.⁵⁰

The WPSS has shown that requirement for RBC transfusions is a negative prognostic factor for patients with MDS.³⁶

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The NCCN panel members recommend monitoring serum ferritin levels and number of RBC transfusions received to assess iron overload as practical means to determine iron stores. 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.^{51, 52}

Reversal of some of the consequences of iron overload in MDS and other iron overload states (e.g., thalassemia) by iron chelation therapy have been shown in patients in whom the most effective chelation occurred.^{43, 47} This included transfusion independence, in a portion of a small group of carefully studied MDS patients who had undergone effective deferoxamine chelation for 1-4 years.⁵³ In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.^{54 36} Such findings have major implications for altering the morbidity of MDS patients, particularly those with pre-existing cardiac or hepatic dysfunction.

The current clinical availability of two oral iron chelators in the U.S,⁵⁵ deferoxamine and deferasirox^{56, 57} now provides potentially useful drugs for more readily treating this iron overload state. A third chelating agent, deferiprone is not available in the US. In Europe, deferiprone is licensed for treatment of iron overload in patients with β -thalassemia when deferasirox is inadequate or contraindicated.⁵⁸

Clinical trials in MDS are ongoing with oral iron chelating agents to address the question 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 MDS", discusses in detail the available evidence regarding iron chelation in patients with MDS.⁵⁹

The NCCN MDS panel members recommend considering chelation with deferoxamine SC or deferasirox/ICL670 orally once daily to decrease iron overload in low or intermediate-1 patients 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 > 2500 ng/mL, aiming to decrease ferritin levels to <1,000 ng/ml.

Recently a 'black box' warning by the FDA and Novartis was added to deferasirox. Following post-marketing use of deferasirox, there were case reports of acute renal failure, or hepatic failure, some with a fatal outcome. Most of the fatalities reported were in patients with multiple co-morbidities and who were in advanced stages of their hematological disorders. Additionally, there were post-marketing reports of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia and GI bleeding in patients treated with deferasirox where some of the patients died. The relationship of these episodes to treatment with deferasirox has not yet been established. However, it is

recommended to closely monitor patients on deferasirox therapy including measurement of serum creatinine and/or creatinine clearance and liver function tests prior to 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, supportive care or occasional hospitalization (for example, for treatment of infections) may be needed after certain of these treatments.

Hypo-methylating Agents

As a form of relatively low-intensity chemotherapy, the DNA methyl transferase inhibitor (DMTI) hypo-methylating 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, to improve survival.^{60, 61} 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 and colleagues provided a summary of three studies of AzaC in a total of 306 patients with high risk MDS.⁶² In this analysis, which included patients receiving either subcutaneous or intravenous delivery of the drug (75 mg/m²/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of AzaC treated patients; partial remissions were rare; 23% to 36% of patients had hematologic improvement. Ninety percent of the

responses were seen by cycle 6 and the median number of cycles to first response was three. The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. Data from a randomized trial for higher risk MDS demonstrates that AzaC is superior to conventional care (standard chemotherapy or supportive care) regarding overall survival.⁶³ Patients randomized to AzaC enjoyed a superior median survival (24 vs. 15 months) compared with those on control arm, thus providing support for the use of this agent in higher risk disease.

AzaC 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 SubQ x7 days monthly for at least 4-6 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 prior to that procedure). This drug has been approved by the FDA for treatment of MDS patients.

Similarly, the other DMTI hypomethylating agent, decitabine, given intravenously and administered with a regimen which required hospitalization of patients, has also shown encouraging results for the therapy of patients with higher risk MDS. As 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,^{64, 65} with an overall response rate of 49%, and 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.^{66, 67}

The results of a Phase III randomized trial of decitabine [15mg/m² IV infusion over 3 hours every 8 hours (i.e., 45mg/m²/day) on 3

consecutive days every 6 wks for up to 10 cycles] vs. supportive care in adult primary and secondary MDS patients 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.^{60, 66} Overall response rates (CR + PR) were 17% with an additional 13% having hematologic improvement. The probability of progression to AML or death was 1.68-fold greater for SC patients than for those receiving decitabine. Based on this study and three supportive Phase II trials,⁶⁸ the drug has also been approved by the FDA for treating MDS patients.

Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated.⁶⁹ In 2007 Kantarjian and colleagues provided an update of their results in 115 patients with higher risk MDS using alternative and lower dose decitabine treatment regimens.⁷⁰ Patients received 1 of 3 different schedules of decitabine, including both subcutaneous and IV administration and received a mean of 7 courses of therapy. Responses were improved with this longer duration of therapy. Overall, 80 patients (70%) responded with 40 patients (35%) achieving a complete response and 40 (35%) achieving a partial response. The median remission duration was 20 months, and the median survival was 22 months. Kantarjian and colleagues also compared the three different schedules of decitabine in a randomized study of 95 patients with MDS or CMML, receiving either 20 mg/m² intravenously daily for 5 days; 20 mg/m² subcutaneously daily for 5 days; or 10 mg/m² intravenously daily for 10 days.⁷¹ The 5-day intravenous schedule was considered the optimal schedule; the complete response rate in this arm was 39%, compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day intravenous arm (P < 0.05).

Currently, azacytidine and decitabine are considered to be therapeutically relatively similar, although the improved survival of higher risk patients treated with AzaC compared to control patients in a Phase III trial as indicated above supports the preferred use of AzaC in this setting. 'Failure to respond to hypomethylating agents' is considered if there is lack of CR, PR, hematologic improvement or frank progression to AML, in particular with loss of control (proliferation) of peripheral counts, or excess toxicity that precludes continuation of therapy. The minimum number of courses prior to considering the treatment a failure should be 4-6 courses.

As data have predominantly indicated altered natural history and decreased evolution to AML in responders, the major candidates for these drugs are MDS patients with IPSS Intermediate-2 or High risk disease. Such candidates include the following:

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

Biologic Response Modifiers and Immunosuppressive 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, 72-77}

Use of anti-immune type therapy with ATG with or without cyclosporine^{74, 75} 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.^{20, 21} The NIH group has updated their analysis of 129 patients treated with immunosuppressive therapy (IST). The patients were treated with antithymocyte globulin (ATG) and cyclosporine alone or in combination.⁷⁸ This study demonstrated markedly improved response rates in younger (≤ 60 years old) and intermediate 1 patients as well as in those with high response probability characteristics as indicated by their prior criteria (HLADR15+, age and number of transfusions).⁷⁸

Encouraging data have been presented for treating lower risk MDS patients with lenalidomide.^{12, 79} Beneficial results have been particularly evident for patients with del(5q) chromosomal abnormalities.^{12, 79, 80} In a multicenter phase II trial of lenalidomide, given at a dose of 10 mg/day for 21 days every 4 weeks or 10 mg daily in 148 anemic RBC transfusion-dependent MDS patients with del(5q), with or without additional cytogenetic abnormalities. The response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1 to 49) 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.¹² 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).

A phase II study evaluated lenalidomide treatment in 214 transfusion-dependent patients with low or INT-1-risk MDS without the 5q- deletion.⁸¹ Results showed 26% of the non-(del) 5q patients (56 of 214) achieved transfusion independence (TI) after a median of 4.8 weeks of treatment. TI continued for a median duration of 41 weeks. The median rise in hemoglobin was 3.2 g/dL (range 1.0 to 9.8 g/dL) for those achieving TI. A $\geq 50\%$ 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 for non-del(5q) MDS patients. The NCCN MDS panel members recommend 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.^{1, 82} 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 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.⁸³

A high degree of multi-drug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS,⁸⁴ 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,^{85, 86} others were not.⁸⁷ Further clinical trials evaluating other multi-drug resistance modulators are ongoing.

Allogeneic HSCT from a HLA-matched sibling donor is a preferred approach for treating a portion of patients with MDS, particularly those with high-risk disease.⁸⁸⁻⁹⁶ Matched non-myeloablative transplant regimens^{97, 98} and matched unrelated donor stem-cell transplants⁹⁹⁻¹⁰¹ 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.¹⁰² Whether transplants should be performed before or after patients achieve remission after induction chemotherapy has not been established.¹⁰³ Comparative clinical trials are needed to determine these points.

Recommended Treatment Approaches

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

Regarding the algorithm for therapeutic options for the lower risk patients with clinically significant cytopenias, the NCCN 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 on the basis of their levels of serum erythropoietin (sEpo). Those with levels ≤ 500 mU/ml should be treated with recombinant human Epo (Epo) or darbepoetin with or without granulocyte colony

stimulating factor (G-CSF) (see section on Evaluation and Treatment of Related Anemia below). Non-responders should be considered for treatment with azacytidine or decitabine or for lenalidomide therapy. In addition, such patients or non-responders to this therapy could be considered for participation in a clinical trial with other relevant agents, or for allogeneic HSCT (see section on Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) below).

Anemic patients with sEpo level >500 should be evaluated to determine whether they have a good probability of responding to immunosuppressive therapy. The most appropriate candidates include those who are either ≤ 60 years old (with IPSS Low or INT-1 MDS or with WPSS Very low, Low or Intermediate), are HLA-DR15 positive, have a PNH positive clone, or have hypoplastic MDS. Immunosuppressive therapy consists of anti-thymoglobulin or cyclosporine. Non-responders to immunosuppressive therapy would be considered for treatment with azacytidine, decitabine, or a clinical trial. Patients with sEpo levels >500 who have a low probability of responding to immunosuppressive therapy should be considered for treatment with azacytidine, decitabine, or lenalidomide. Others or non-responders to that therapy could be considered for a clinical trial or for allogeneic hematopoietic stem cell transplantation. Patients with other serious cytopenias (particularly clinically severe thrombocytopenia) should be considered for treatment with azacytidine or decitabine or a clinical trial. Such patients, if they do not respond to this treatment, should be considered for treatment with immunosuppressive therapy, a clinical trial, or for allogeneic hematopoietic stem cell transplantation.

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 Intermediate-2, High or WPSS High, Very High)

Treatment for higher risk patients is dependent on whether they are felt to be candidates for intensive therapy (e.g., allogeneic HSCT or intensive chemotherapy). Clinical features relevant for this determination include the patient's age, performance status, absence of major comorbid conditions, psychosocial status, patient's 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 Hematopoietic Stem Cell Transplantation (HSCT)

The potential for patients to undergo allogeneic HSCT is dependent upon several factors including the patient's age, performance status, major comorbid conditions, psychosocial status, availability of a caregiver, IPSS or WPSS score and the availability of a suitable donor. For those patients who are transplant candidates the first choice of a donor has remained an HLA-matched sibling, although results with HLA matched unrelated donors (URD) 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.¹⁰⁴

To aid therapeutic decision-making regarding the timing and selection of MDS patients for HSCT, a study compared outcomes with HLA-matched sibling HSCT in MDS patients 60 years old or younger to the

data in non-treated MDS patients from the IMRAW/IPSS database. Using a Markov decision analysis, this investigation indicated that IPSS INT-2 and High risk patients 60 years old or younger had the highest life expectancy if transplanted (from HLA identical siblings) soon after diagnosis, whereas patients with IPSS low risk had the best outlook if HSCT was delayed until MDS progressed; for patients in the INT-1 risk group there was only a slight gain in life expectancy if HSCT was delayed, and in this group decisions should probably be made on an individual basis (e.g. dependent upon platelet or neutrophil counts).¹⁰⁵ A study published in 2008 retrospectively evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT.³⁸ 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).³⁸

Based on recent data regarding RIC for transplantation from two reported series^{106, 107} and two comprehensive reviews of this field,^{108, 109} patient age and disease status generally dictate the type of conditioning to be utilized. Patients older than 55 or 60 years, particularly if they have less 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 utilized at that center. Some general recommendations have been presented recently in a review in the journal *Blood*.¹¹⁰

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.¹¹¹ 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 (i.e., to decrease the marrow blast count), achievement of even a partial remission may be adequate to permit the HSCT. For this purpose, AzaC, decitabine, or participation in clinical trials, are also available treatment options.

Non-Intensive therapy

For higher risk patients who are not candidates for intensive therapy, the use of azacytidine, decitabine, or a relevant clinical trial should be considered. Based on the recently published results of the phase III trial showing superior median survival with azacytidine compared to best supportive care, the NCCN panel members have made this a preferred category 1 recommendation compared to decitabine. Preliminary results of another recent trial comparing decitabine to supportive care in higher risk patients failed to demonstrate a survival advantage although response rates are similar to those previously reported for AzaC.¹¹² However, it should be noted that no trials to date have compared azacytidine head-to-head with decitabine.

For some patients eligible for HSCT therapy, requiring a reduction in tumor burden, the use of azacytidine 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 anti-tumor 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, 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.^{1,113} 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 as indicated above.

Individuals having symptomatic anemia and del(5q) with or without other cytogenetic abnormalities should receive a trial of lenalidomide. Those with normal cytogenetics and 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.^{44, 114, 115} The Epo dose required is 40,000 - 60,000 units 1-3 times a week subcutaneously. Erythroid responses generally occur within 6 to 8 weeks of treatment.¹¹⁶⁻¹¹⁹ 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. The literature supports daily or 2-3 times per week dosing.

Iron repletion needs to be verified before instituting Epo 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.¹¹⁵⁻¹¹⁸ This is particularly evident for patients with $\geq 15\%$ ringed sideroblasts in the marrow (and serum Epo level ≤ 500 mU/mL) as the very low response rates in this subgroup to Epo or darbepoetin alone are markedly enhanced when combined with G-CSF.^{117, 118}

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 1-3 times a week.¹¹⁵⁻¹¹⁸ 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 trials or supportive care are also treatment 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.^{118, 120} Improved quality of life has been demonstrated in responding patients.¹²⁰ This cytokine treatment is not suggested for patients with endogenous serum Epo levels >500 mU/mL due to the very low erythroid response rate to these drugs in this patient population.

Darbepoetin alfa is a longer-acting form of Epo. 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).^{121, 122} Results of clinical trials in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than to epoetin.¹²¹⁻¹²⁴

These response rates may in part be due to the dosage used (150 to 300 mcg/kg/week subcutaneously) or to that fact that better risk patients were enrolled in studies of darbepoetin compared to epoetin. Features predictive of response have included relatively low basal serum Epo 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 non-MDS patients receiving ESAs when dosing has targeted hemoglobin levels >12 gm/dL (study patients had chronic kidney failure; were receiving radiation therapy for various malignancies, or including head and neck, advanced breast cancer, lymphoid or non-small cell lung cancer; were cancer patients not receiving chemotherapy; or were orthopedic surgery patients).

However, as indicated above, ESAs have been used safely in large numbers of adult MDS patients and have become important for symptomatic improvement of those affected by the anemia caused by this disease often with a decrease in RBC transfusion requirements. The NCCN MDS Practice Guidelines 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 Epo with or without G-CSF in MDS patients compared to either randomized controls¹²⁵ or historical controls^{126, 127} have shown no negative impact on survival or AML evolution of such treatment. In addition, results of the studies by Jadersten et al indicated improved survival in low risk MDS patients with low transfusion need treated with these agents.¹²⁶ The study by Park et al further indicated improved survival and decreased AML progression of IPSS Low/ INT-1 patients treated with Epo/G-CSF compared to the historical control IMRAW database patients.¹²⁷ Thus, these data do not indicate a negative impact of these drugs for treatment of MDS. Given these data, we endorse and re-iterate our prior recommendations for ESA use in the management of symptomatic anemia in MDS patients, but with a change in the target hemoglobin level—i.e., to aim for a target hemoglobin of ≤12gm/dl.

In July 2007, the Centers for Medicare and Medicaid Services (CMS) modified the scope of their decision regarding 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 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 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, azacytidine and decitabine for treating higher risk or non-responsive MDS patients, and deferasirox for iron chelation of iron overloaded MDS patients. However, as a substantial proportion of MDS patient subsets 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.^{116, 119, 120, 128, 129} 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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