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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Myelodysplastic Syndromes**

Version 1.2012

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## [NCCN Guidelines Panel Disclosures](#)

### [NCCN Myelodysplastic Syndromes Panel Members](#)

### [Summary of Guidelines Updates](#)

### [Initial Evaluation \(MDS-1\)](#)

### [The French-American-British \(FAB\) \(MDS-3\)](#)

### [World Health Organization \(WHO\) Classification for de Novo MDS \(MDS-3\)](#)

### [International Prognostic Scoring System \(IPSS\) and](#)

### [WHO-Based Prognostic Scoring System \(WPSS\) for MDS \(MDS-5\)](#)

### [Treatment of LOW INT-1 \(MDS-6\)](#)

### [Treatment of INT-2, HIGH \(MDS-8\)](#)

### [Evaluation and Treatment of Related Anemia \(MDS-9\)](#)

### [Recommendations for Flow Cytometry \(MDS-A\)](#)

### [Supportive Care for MDS \(MDS-B\)](#)

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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 1.2012 of the NCCN Guidelines from Version 2.2011 include:****MDS-1**

- After 'Cytopenia(s), suspect myelodysplasia': added a footnote "MDS also suspected in the presence of acquired MDS-related cytogenetic abnormalities, unexpected increase in blasts or dysplasia."
- Under 'Initial Evaluation' 'Required': 4th bullet, for 'cytogenetics', clarified this as 'cytogenetics by standard karyotyping.'
- Added bullet "TSH (thyroid stimulating hormone) to rule out hypothyroidism."
- Under 'Helpful in Some Clinical Situations' : 7th bullet, added footnote following 'PNH clone'
- After 'Consider observation to document indolent vs marked progression of severe cytopenia', added 'or increase in blasts'.
- Under footnote 'a': replaced the second sentence with: "Percentage of marrow myeloblasts, based upon morphologic assessment, should be reported. Flow cytometric estimation of blast percentage should not be used as a substitute for morphology in this context."

**MDS-2**

- Added a footnote "FCM with anti-CD55 and -59 used to assess the presence of PNH clone to assist determination of patient's potential responsiveness to immunosuppressive therapy."
- Added footnote "To assist determination of patient's potential responsiveness to immunosuppressive therapy."
- Added a footnote "CMML patients with this abnormality may respond well to tyrosine kinase inhibitors (TKIs) such as imatinib mesylate."
- Added a footnote "To assess possible Fanconi anemia or dyskeratosis congenita (DKC). Shortened telomere length has been associated with diseases of bone marrow failure, including inherited disorders such as DKC, particularly in the presence of mutations in the telomerase complex genes. Telomere length can be measured by FISH assays using leukocyte samples."

**MDS-5**

- Replaced both of the WPSS tables with Table 2 from the recently published version of the refined WHO-based Prognostic Scoring System (WPSS) based on the following reference:
  - ▶ Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO-based Prognostic Scoring System (WPSS). *Haematologica* 2011. Severe anemia has substituted for RBC transfusion dependence.

**MDS-6**

- Added a footnote after "PROGNOSTIC CATEGORY" at the top, "Presence of comorbidities should also be considered for evaluation of prognosis (See references 59-64 in the Discussion section)." This was also added to MDS-7 and MDS-8.
- After "Symptomatic anemia", the initial branch modified 'del(5q) ± other cytogenetic abnormalities' versus 'no del(5q)'; then, after 'no del(5q)', included the branches for stratification by serum Epo. Changed "Thrombocytopenia/neutropenia" to "Clinically relevant thrombocytopenia/neutropenia."

**MDS-7**

- After the branch for "Serum Epo ≤500 mU/mL "Epoetin alfa...." "No response": deleted the current entry after "No response" and instead, placed an arrow from "No response" to "Good probability to respond to IST".
- Moved footnote to after "... +/- G-CSF"
- Added a footnote on "Lenalidomide": 'Except for patients with low neutrophil counts or low platelet counts.'
- Added a footnote: "Both equine and rabbit ATG have been used in patients with MDS."

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# NCCN Guidelines® Version 1.2012 Updates Myelodysplastic Syndromes

[NCCN Guidelines Index](#)  
[MDS Table of Contents](#)  
[Discussion](#)

Updates in Version 1.2012 of the NCCN Guidelines from Version 2.2011 include:

## [MDS-9](#)

- Changed “ringed sideroblasts” to “ring sideroblasts”.
- Added footnote: “In some institutions, darbepoetin alfa has been administered using doses up to 500 mcg weekly; also, note that darbepoetin alfa 300 mcg every other week is equivalent to 150 mcg weekly.”

## [MDS-A](#)

- Recommendations for Flow Cytometry - this page is new to the guidelines

## [MDS-B](#)

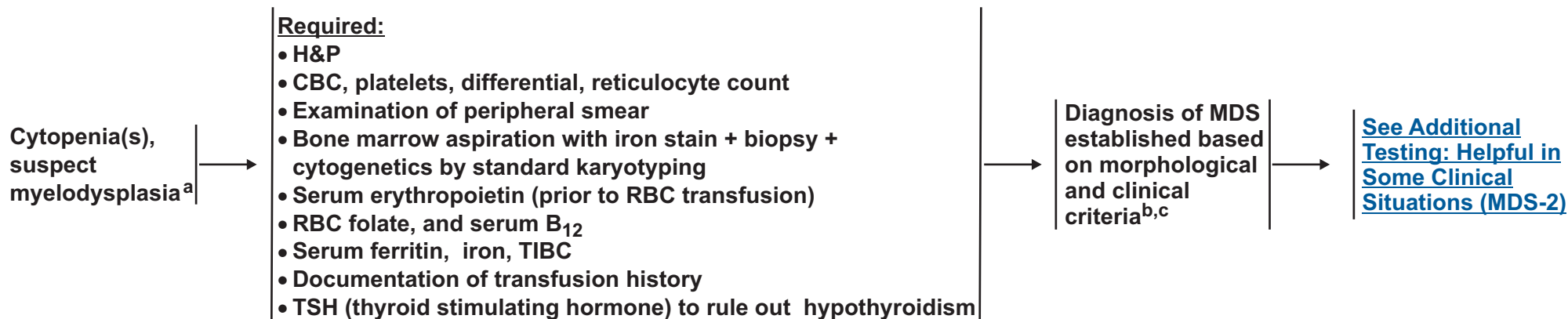
- After “Antibiotics for bacterial infections”, added “but no routine prophylaxis except in patients with recurrent infections”.
- Added: “RBC transfusions (leuko-reduced) for symptomatic anemia, platelet transfusions for thrombocytopenic bleeding; however, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count  $<10,000/\text{mm}^3$ .”

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**INITIAL EVALUATION**



<sup>a</sup>MDS also suspected in the presence of acquired MDS-related cytogenetic abnormalities, unexpected increase in blasts or dysplasia.

<sup>b</sup>Confirm diagnosis of MDS according to FAB or WHO criteria for classification with application of IPSS. [See Classification Systems \(MDS-3 and MDS-5\)](#). Percentage of marrow myeloblasts based upon morphologic assessment, should be reported. Flow cytometric estimation of blast percentage should not be used as a substitute for morphology in this context.

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

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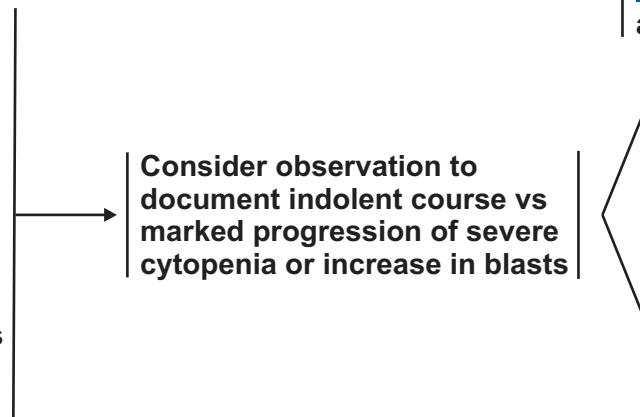


**ADDITIONAL TESTING**

**CLASSIFICATION**

**Helpful in Some Clinical Situations:**

- Consider flow cytometry (FCM) for MDS diagnostic aid,<sup>d</sup> to assess possible large granular lymphocytic (LGL) disease,<sup>e</sup> and to evaluate for PNH clone<sup>f</sup>
- HLA typing if hemopoietic stem cell transplant (HSCT) candidate<sup>g</sup>
- Consider HLA-DR15 typing<sup>h</sup>
- HLA typing if indicated for platelet support
- HIV testing if clinically indicated
- Evaluate CMML patients for 5q31-33 translocations and/or PDGFR $\beta$  gene rearrangements<sup>i</sup>
- Consider molecular testing for JAK2 mutation in patients with thrombocytosis
- Consider additional genetic screening for patients with familial cytopenias<sup>j</sup>
- Consider evaluation of copper deficiency



**Myelodysplastic syndromes (MDS)**  
[See Classification Systems \(MDS-3 and MDS-5\)](#)

**AML**  
[\(See NCCN AML Treatment Guidelines\)](#)

<sup>d</sup>[See Recommendations for Flow Cytometry \(MDS-A\) and Discussion.](#)

<sup>e</sup>Marrow or peripheral blood cell FCM may be assayed for this plus T-cell gene rearrangement studies if LGLs are detected in the peripheral blood.

<sup>f</sup>FCM with anti-CD55 and -59 used to assess the presence of PNH clone to assist determination of patient's potential responsiveness to immunosuppressive therapy.

<sup>g</sup>Family HLA - evaluation to include all full siblings; unrelated evaluation to include high resolution allele level typing for HLAA, B, C, DR, DQ.

<sup>h</sup>To assist determination of patient's potential responsiveness to immunosuppressive therapy.

<sup>i</sup>CMML patients with this abnormality may respond well to tyrosine kinase inhibitors (TKIs) such as imatinib mesylate.

<sup>j</sup>To assess possible Fanconi anemia or dyskeratosis congenita (DKC). Shortened telomere length has been associated with diseases of bone marrow failure, including inherited disorders such as DKC, particularly in the presence of mutations in the telomerase complex genes. Telomere length can be measured by FISH assays using leukocyte samples.

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# NCCN Guidelines® Version 1.2012

## Myelodysplastic Syndromes

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

2008 WHO<sup>m</sup> Classification of MDS<sup>n</sup>

### FAB<sup>k</sup> Classification of MDS<sup>l</sup>

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) <sup>o</sup>	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 <sup>9</sup> /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 <sup>9</sup> /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 <sup>9</sup> /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](#)

<sup>k</sup>FAB = French-American-British.

<sup>l</sup>Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982;51:189-199.

<sup>m</sup>WHO = World Health Organization.

<sup>n</sup> From Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue. IARC, Lyon, 2008.

<sup>o</sup> This category encompasses refractory anemia (RA), Refractory Neutropenia (RN) and Refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS Unclassified.

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

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

Subtype	Blood	Marrow
<b>Chronic myelomonocytic leukemia-1 (CMML-1)</b>	<b>&gt;1x10<sup>9</sup>/L monocytes, &lt;5% blasts</b>	<b>Dysplasia in ≥1 hematopoietic line, &lt;10% blasts</b>
<b>CMML-2</b>	<b>&gt;1x10<sup>9</sup>/L monocytes, 5-19% blasts or Auer rods</b>	<b>Dysplasia in ≥1 hematopoietic line, 10-19% blasts or Auer rods</b>
<b>Atypical chronic myeloid leukemia (CML), Bcr-Abl 1 negative</b>	<b>WBC 13x10<sup>9</sup>/L, neutrophil precursors &gt;10%, &lt;20% blasts</b>	<b>Hypercellular, &lt;20% blasts</b>
<b>Juvenile myelomonocytic leukemia (JMML)</b>	<b>&gt;1x10<sup>9</sup>/L monocytes, &lt;20% blasts<sup>Q</sup></b>	<b>&gt;1x10<sup>9</sup>/L monocytes, &lt;20% blasts<sup>Q</sup></b>
<b>MDS/MPN, unclassifiable ('Overlap syndrome')</b>	<b>Dysplasia + myeloproliferative features<sup>r</sup>, No prior MDS or MPN</b>	<b>Dysplasia + myeloproliferative features</b>

**Acute myeloid leukemia with myelodysplasia-related changes<sup>S</sup>**

**WHO Classification<sup>t</sup>**

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

[Continued on next page](#)

<sup>P</sup>Orazi 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.

<sup>Q</sup>Ph negative plus ≥ 2 features: Hb F, PB immature myeloid cells, WBC >10x10<sup>9</sup>/L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro.

<sup>r</sup>For example, thrombocytosis, leukocytosis, splenomegaly.

<sup>S</sup>Greater than 20% blasts in PB or marrow. Some cases with 20-29% blasts, especially if arising from MDS, may be slowly progressive and may behave more similar to MDS (RAEB-t by FAB classification) than to overt AML.

<sup>t</sup>Arber 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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**CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 3 of 3)**

**International Prognostic Scoring System (IPSS)<sup>u,v</sup>**

Survival and AML evolution					
	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%) <sup>w</sup>	< 5	5-10	---	11-20	21-30
Karyotype <sup>x</sup>	Good	Intermediate	Poor		
Cytopenia <sup>y</sup>	0/1	2/3			

Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥ 2.5	0.4	0.2

**WHO-based Prognostic Scoring System (WPSS)<sup>z</sup>**

Variable	Variable scores			
	0	1	2	3
WHO category	RCUD, RARS, MDS with isolated deletion (5q)	RCMD	RAEB-1	RAEB-2
Karyotype <sup>x</sup>	Good	Intermediate	Poor	---
Severe anemia (hb <9 g/dL in males or <8 g/d/L in females)	Absent	Present	---	---

WPSS Risk	Sum of individual variable scores
Very low	0
Low	1
Intermediate	2
High	3-4
Very high	5-6

<sup>u</sup>IPSS should be used for initial prognostic and planning purposes. The WHO classification-based prognostic scoring system (WPSS) permits dynamic estimation of prognosis at multiple time points during the course of MDS.

<sup>v</sup>Greenberg 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.

<sup>w</sup>Patients with 20-30% blasts may be considered as MDS (FAB) or AML (WHO).

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

<sup>y</sup>Cytopenias: neutrophil count <1,800/mcL, platelets < 100,000/mcL, Hb < 10g/dL.

<sup>z</sup>Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). Severe anemia has substituted for RBC transfusion dependence. Obtained from Haematologica / the Hematology Journal 2011 <http://www.haematologica.org>

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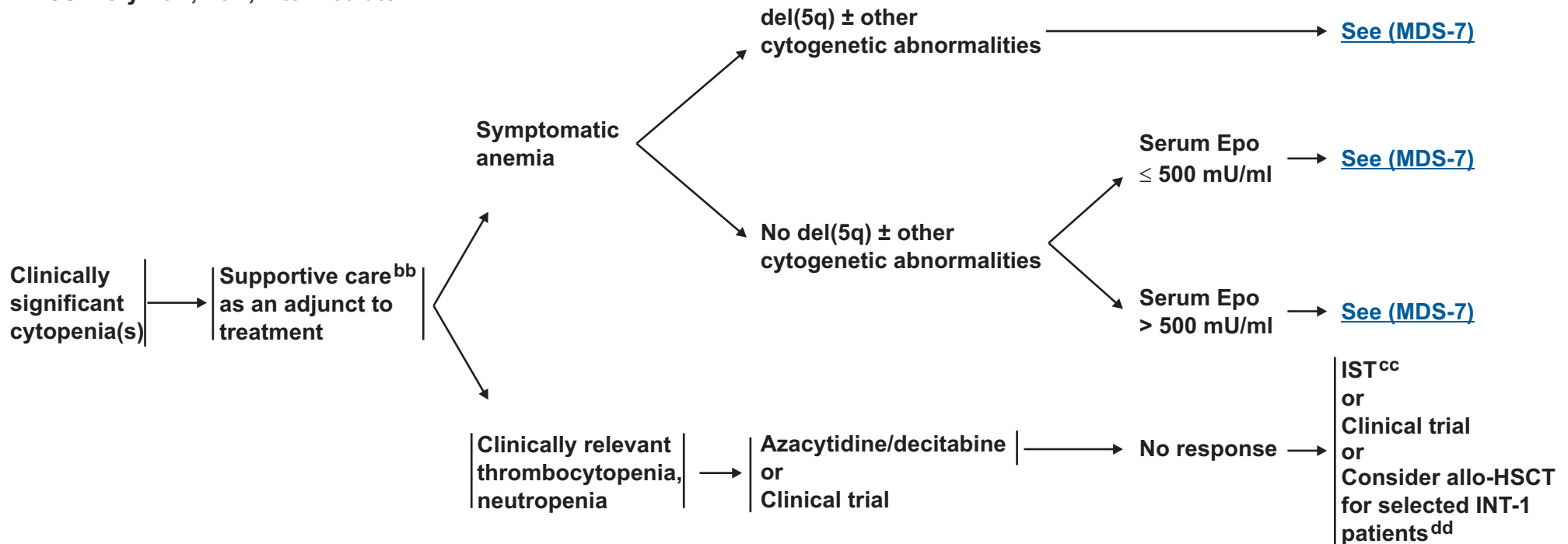
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**PROGNOSTIC CATEGORY<sup>aa</sup>**

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

**TREATMENT**



<sup>aa</sup>Presence of comorbidities should also be considered for evaluation of prognosis (See references 59-64 in the [Discussion section](#)).

<sup>bb</sup>[See Supportive Care \(MDS-B\)](#).

<sup>cc</sup>Patients ≤ 60 y, or those with hypocellular marrows, HLA-DR15 or PNH clone positivity.

<sup>dd</sup>INT-1 and WPSS INT 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.

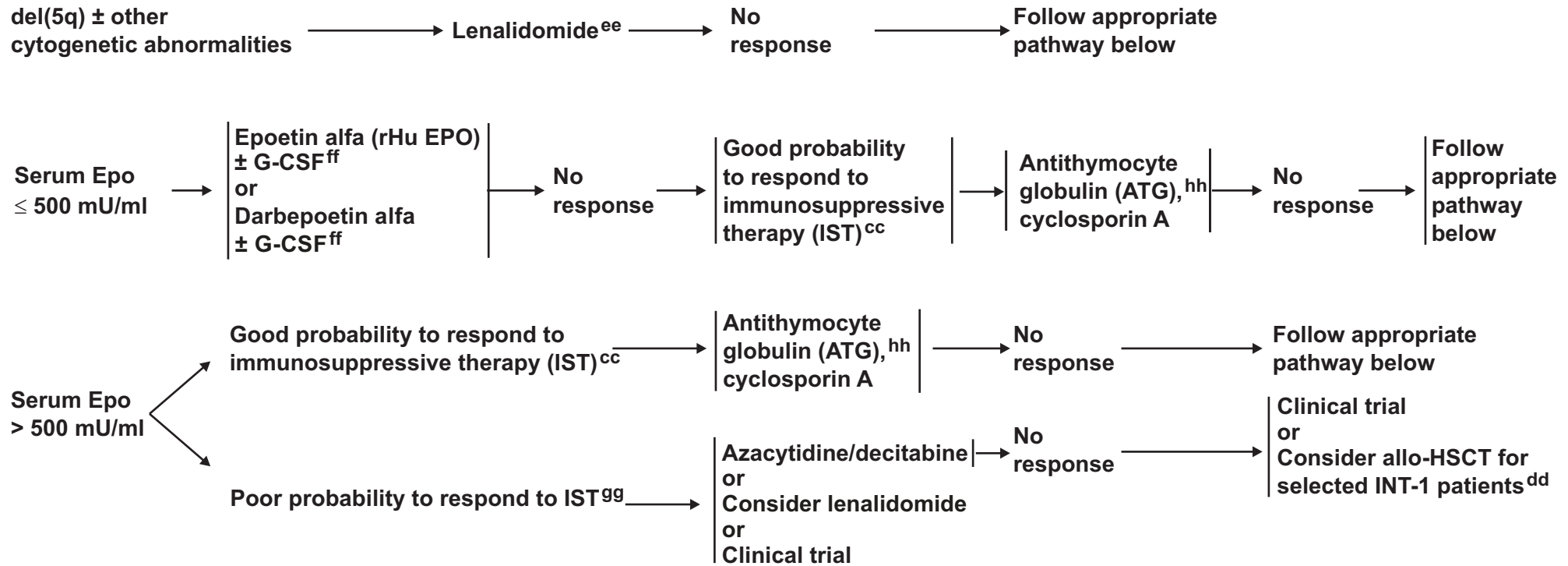
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**PROGNOSTIC CATEGORY<sup>aa</sup>**

**TREATMENT**

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



<sup>aa</sup>Presence of comorbidities should also be considered for evaluation of prognosis (See references 59-64 in the [Discussion section](#)).

<sup>cc</sup> Patients ≤ 60 y, or those with hypocellular marrows, HLA-DR15 or PNH clone positivity.

<sup>dd</sup>INT-1 and WPSS INT 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

<sup>ee</sup>Except for patients with low neutrophil counts or low platelet counts ([See Discussion](#)).

<sup>ff</sup>[See dosing of hemopoietic cytokines \(MDS-9\)](#).

<sup>gg</sup>Patients lack features listed in footnote cc.

<sup>hh</sup>Both equine and rabbit ATG have been used in patients with MDS ([See Discussion](#)).

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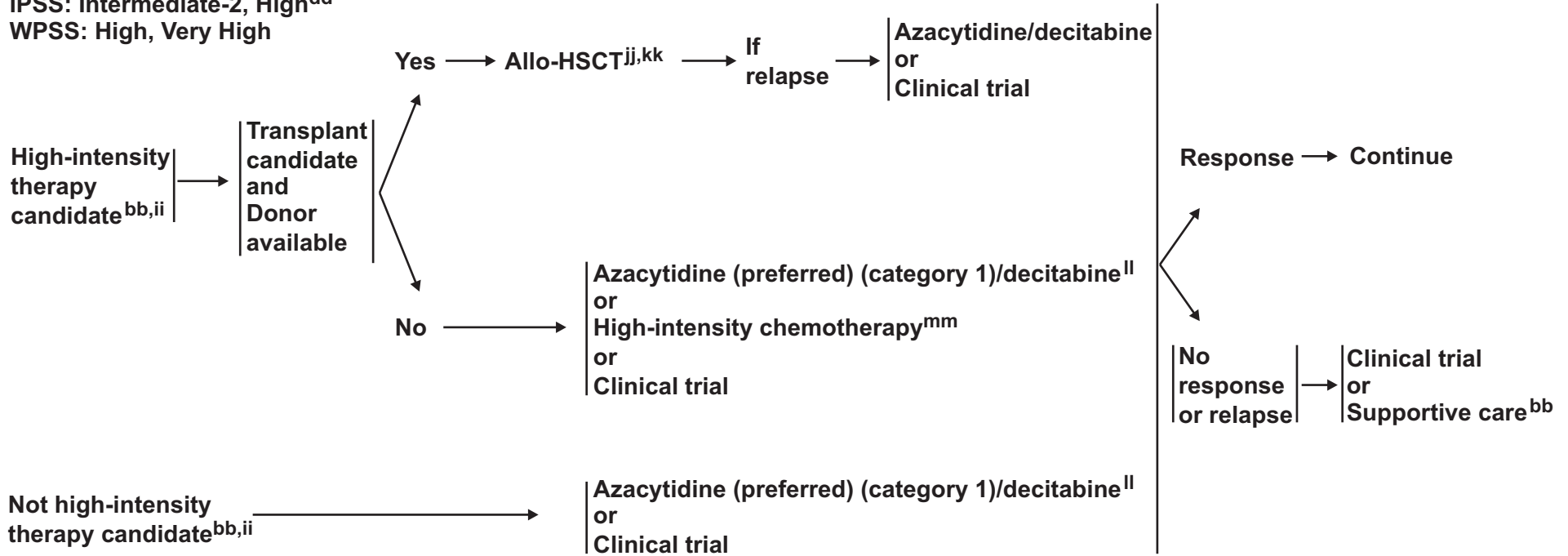
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**PROGNOSTIC CATEGORY<sup>aa</sup>**

**TREATMENT**

**IPSS: Intermediate-2, High<sup>dd</sup>**  
**WPSS: High, Very High**



<sup>aa</sup>Presence of comorbidities should also be considered for evaluation of prognosis (See references 59-64 in the [Discussion section](#)).

<sup>bb</sup>[See Supportive Care \(MDS-B\)](#).

<sup>dd</sup>INT-1 and WPSS INT 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.

<sup>ii</sup>Based on age, performance status, major comorbid conditions, psychosocial status, patient preference and availability of caregiver.

<sup>jj</sup>Azacytidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability.

<sup>kk</sup>Hemopoietic stem cell transplant (HSCT): Allogeneic-matched sibling including standard and reduced intensity preparative approaches or matched unrelated donor (MUD).

<sup>ll</sup>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.

<sup>mm</sup>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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# NCCN Guidelines® Version 1.2012

## 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<sup>bb</sup>

del(5q) ± other cytogenetic abnormalities

→ Lenalidomide

Response<sup>qq</sup> →

No response<sup>oo</sup> →

Continue lenalidomide decrease dose to tolerance

[See IPSS: Low/Intermediate-1](#)  
[WPSS: Very Low, Low, Intermediate \(MDS-7\)](#)

Serum EPO ≤ 500 mU/ml  
Ring sideroblast <15%

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

Response<sup>qq</sup> →

No response<sup>pp</sup> (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 \(MDS-7\)](#)

Serum EPO ≤ 500 mU/ml  
Ring 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<sup>nn</sup> 150-300 mcg/wk subcutaneous + G-CSF

Response<sup>qq</sup> →

No response<sup>pp</sup> →

Decrease dose to tolerance

[See IPSS: Low/Intermediate-1](#)  
[WPSS: Very Low, Low, Intermediate \(MDS-7\)](#)

Serum EPO >500 mU/ml

→ [See Serum EPO > 500 mU/ml \(MDS-7\)](#)

<sup>bb</sup> [See Supportive Care \(MDS-B\)](#).

<sup>nn</sup> In some institutions, darbepoetin alfa has been administered using doses up to 500 mcg weekly; also, note that darbepoetin alfa 300 mcg every other week is equivalent to 150 mcg weekly.

<sup>oo</sup> Lack of 1.5 gm/dl rise in Hb or decreased RBC transfusion requirement by 3-4 months of treatment. <sup>qq</sup> Target hemoglobin up to 12gm/dl.

<sup>pp</sup> Lack of 1.5 gm/dl rise in Hb or decreased RBC transfusion requirement by 6-8 weeks of treatment.

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## RECOMMENDATIONS FOR FLOW CYTOMETRY

### Initial Evaluation ([from MDS-1](#))

#### • Flow cytometry:

- ▶ Consideration should be given to obtain flow cytometry (FCM) testing at initial evaluation of MDS to include antibody combinations to characterize blasts and to identify abnormal lymphoid populations (such as increased hematogones, which may mimic blasts, leading to erroneous myeloblast quantitation). For example, a combination using anti-CD45, CD34, CD33, CD19, with forward scatter and side scatter) could be useful.
- ▶ It is understood that the blast percent for both diagnosis and risk stratification should be determined by morphologic assessment, not solely by flow cytometry. If blasts are increased and morphologic questions arise regarding their subtype (ie, myeloid or lymphoid), they should be characterized with a more elaborate panel of antibodies.
- ▶ In diagnostically difficult cases, an expanded panel of antibodies (to demonstrate abnormal differentiation patterns or aberrant antigen expression) may help confirm diagnosis of MDS. [See Discussion section](#)

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## SUPPORTIVE CARE<sup>1</sup>

- **Clinical monitoring**
- **Psychosocial support**
- **Quality-of-life assessment**
- **Transfusions:**
  - **RBC transfusions (leuko-reduced) for symptomatic anemia, platelet transfusions for thrombocytopenic bleeding; however, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mm<sup>3</sup>. Irradiated products are suggested for transplant candidates**
  - **CMV negative blood products are recommended whenever possible for CMV negative transplant candidates.**
- **Antibiotics for bacterial infections, but no routine prophylaxis except in patients with recurrent 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.<sup>2</sup>
- **Cytokines:**
  - **EPO See Anemia pathway ([MDS-9](#))**
  - **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 \(MDS-9\)](#)

- ◇ **Platelet count should be monitored**

<sup>1</sup>[See NCCN Supportive Care Guidelines.](#)

<sup>2</sup>Clinical trials in MDS are currently ongoing with oral chelating agents.

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## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention 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 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.<sup>1</sup>

### Diagnostic Classification

Initial evaluation of patients with suspected MDS requires careful assessment of their peripheral blood smear and blood counts, marrow morphology, duration of their abnormal blood counts, other potential causes for their cytopenias and concomitant illnesses. The French-American-British (FAB) classification initially categorized patients for the diagnostic evaluation of MDS.<sup>2</sup> Dysplastic changes in at least 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.<sup>3</sup> 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.<sup>1</sup> 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 dependent 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.<sup>4-6</sup> The report suggested modifying the FAB definitions of MDS. Although most prior data require dysplasia in at least two lineages 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.<sup>1, 7</sup>

In 2008, a revision of the WHO classification incorporated new scientific and clinical information and refined diagnostic criteria for previously described neoplasms; it also introduced newly recognized disease entities.<sup>8</sup> 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.<sup>9</sup> A review article discusses the major changes and the rationale behind the changes in the 2008 WHO classification of MDS and AML evolving from MDS.<sup>10</sup>

Other categories within the WHO classification include refractory cytopenia with multilineage dysplasia (RCMD) with or without ring sideroblasts, separating RAEB cases 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.<sup>4-6</sup> This disorder generally has a relatively good prognosis<sup>11</sup> and is highly responsive to lenalidomide therapy.<sup>12</sup>

The 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.<sup>13</sup> The distinction between CMML-1 and CMML-2 is based on the percentage of blasts plus monocytes in peripheral blood and bone marrow. CMML had been categorized by FAB as MDS; 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)).<sup>11</sup>

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 cut-off of 30% or more). 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.<sup>14, 15</sup> 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.<sup>16-20</sup>

The 2008 WHO classifications have helped clarify the clinical differences between the FAB RAEB-T patients and AML.<sup>21</sup> The current WHO classification lists the entity 'AML with myelodysplasia-related changes', which encompasses patients with AML post-MDS, AML with multilineage dysplasia and AML with MDS-associated cytogenetic abnormalities.<sup>21</sup> 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 of 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).<sup>22</sup>





## Initial Evaluation

Several types of evaluations are needed to determine the clinical status of patients with MDS. Understanding clinical status is necessary for determining diagnostic and prognostic categorization and deciding treatment options. Clinical history should include the timing, severity, and tempo of abnormal cytopenias; prior infections or bleeding episodes; and number of transfusions. Concomitant medications and comorbid conditions require careful assessment. Because MDS are relatively indolent disorders, blood count stability is used to distinguish MDS from evolving AML. Other possible causes for patients' cytopenias 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. Cytogenetics for bone marrow samples (by standard karyotyping methods) should be obtained because they are of major importance for prognosis.

Other useful screening laboratory studies include serum erythropoietin (sEpo), vitamin B<sub>12</sub>, red blood cell 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. As hypothyroidism and other thyroid disorders can lead to anemia, patients should also be evaluated for levels of thyroid-stimulating hormone (TSH).<sup>23</sup>

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. It should be emphasized, 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<sup>24, 25</sup> (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.

Both the International and the European LeukemiaNet working groups of flow cytometry experts have proposed antibody combinations to define dysplasia as well as diagnostic and prognostic flow cytometry patterns.<sup>26, 27</sup> "In patients with suspected MDS, flow cytometry is potentially useful in detecting abnormal myeloid populations with aberrant antigen expression, and in excluding other possible causes of



cytopenias.<sup>26-29</sup> When flow cytometry is indicated, the initial study should use multiparameter analysis with at least four fluorescence channels, and contain reagent antibodies sufficient to accomplish the intended goals.<sup>27</sup> In patients with a previously characterized abnormal myeloid population, subsequent flow studies may be tailored to detect the abnormal population of interest when circumstances do not allow for a comprehensive flow study." The presence of multiple aberrancies has a higher predictive value for MDS than single aberrancies. Although several flow scoring systems have been validated that distinguish MDS from reactive/normal controls, flow cytometry analysis of MDS marrow is a complex issue and consensus has not yet been reached on specifically which parameters or inherent standardization procedures should be used.<sup>26</sup>

Additional genetic screening should be considered for patients with familial cytopenias, which will help evaluate for Fanconi's anemia or dyskeratosis congenita (DC). Shortened telomere length has been associated with diseases of bone marrow failure, including inherited disorders such as DC, particularly in the presence of mutations in the *DKC1*, *TERT* or *TERC* genes that encode for components of the telomere complex.<sup>30, 31</sup> Telomere length can be measured by FISH assays using leukocyte (or leukocyte subset) samples.<sup>30, 32</sup> Identification of familial MDS is of clinical importance because it is associated with chromosomal fragility and such patients may therefore respond differently to hypomethylating agents; more importantly, family members may not be eligible as donors for allogeneic hematopoietic stem cell transplant.

Determination of platelet-derived growth factor receptor beta (PDGFR $\beta$ ) gene rearrangements is helpful for evaluating CMML/MPD patients with 5q31-33 translocations. The activation of this gene encoding a receptor tyrosine kinase for PDGFR $\beta$  has been shown in some of these

patients.<sup>33, 34</sup> Data have indicated that MPD/CMML patients with such PDGFR $\beta$  fusion genes may respond well to treatment with the tyrosine kinase inhibitor imatinib mesylate.<sup>35-37</sup>

The frequency of activating mutations of the tyrosine kinase known as Janus Kinase 2 (JAK2) in MDS and *de novo* AML is lower compared to that in myeloproliferative disorders.<sup>38</sup> 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.<sup>39</sup>

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.<sup>40, 41</sup> 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.<sup>42-44</sup> 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,<sup>42-44</sup> prior gastrointestinal surgery,<sup>42, 43</sup> and a history of vitamin B12 deficiency.<sup>43, 45</sup>

## 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.<sup>46</sup>

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW.<sup>11</sup> Compared with previously used systems, the risk-based IPSS has markedly improved prognostic stratification of MDS cases. In this analysis, cytogenetic, morphologic, and clinical data were combined and collated from a relatively large group of MDS cases that had been included in previously reported prognostic studies.<sup>11, 46</sup> FAB morphologic criteria were used to establish the diagnoses of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible 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.<sup>11</sup> 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.<sup>47</sup>

Significant independent variables for determining outcome for both survival and AML evolution were found to be marrow blast percentage, number of cytopenias, and cytogenetic subgroup (good, intermediate, poor). Patients with the chromosome anomalies t(8;21) or inv16 are considered to have AML and not MDS, regardless of the blast count. Age was also a critical variable for survival, although not for AML evolution. The percentage of marrow blasts was 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.<sup>11</sup> 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.<sup>11</sup>

Recent data have indicated that additional clinical variables are additive to the IPSS regarding prognosis for MDS patients. The WHO-classification based prognostic scoring system (WPSS) incorporates the WHO morphologic categories, the IPSS cytogenetic categories and the patients' need or lack of RBC transfusion dependence.<sup>48</sup> 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





# NCCN Guidelines Version 1.2012

## Myelodysplastic Syndromes

prognostic import for the intermediate IPSS categories.<sup>49</sup> 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 al,<sup>48</sup> there have been confirmatory studies.<sup>50-52</sup> The initial WPSS has recently been refined to address the notion that the requirement for RBC transfusion may be somewhat subjective. In the refined WPSS, the measure of the degree of anemia by transfusion dependency is replaced by the presence (or absence) of severe anemia, defined as hemoglobin levels <9 g/dL for males and <8 g/dL for females.<sup>53</sup> This approach allows for an objective assessment of anemia, while maintaining the prognostic implications of the five risk categories defined in the original WPSS (as mentioned above).<sup>53</sup> At this time, there is still 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.

In recent years, various gene mutations have been identified among patients with MDS, which may in part contribute to the clinical heterogeneity of the disease course, and thereby influence the prognosis of patients.<sup>54, 55</sup> Such gene mutations may be present in a substantial proportion of newly diagnosed patients, including in patients with normal cytogenetics. In a recent genetic study in samples from patients with MDS (N=439), at least one gene mutations was identified in 52% of samples and multiple gene mutations were found in 18% of samples.<sup>55</sup> The most frequently occurring genetic lesions were mutations in the *TET2*, *ASXL1*, *RUNX1*, *TP53*, *EZH2*, *NRAS*, *JAK2*, *ETV6*, *CBL*, and *IDH2* genes. Mutations in *TET2* is among the most common genetic lesions reported in patients with MDS (about 20% of

cases), and appears to confer a more favorable prognosis compared to cases without *TET2* mutations.<sup>55, 56</sup> In the present analysis, the presence of *TET2* mutations was found to be associated with normal karyotype and a median survival similar to that of the overall patient cohort.<sup>55</sup> Mutations in *ASXL1* is another relatively common lesion in patients with MDS (about 15% of cases) and as also reported in another recent study, is associated with significantly shorter overall survival.<sup>55, 57</sup> Mutations in *TP53* were associated with complex karyotype and chromosome 17 abnormalities. Importantly, *TP53* mutations were associated with the worse prognosis with respect to survival outcomes, which confirms earlier reports of the significant negative prognostic impact of *TP53* mutations in MDS.<sup>55, 58</sup> In this analysis, mutations in *TP53*, *RUNX1*, or *NRAS* were significantly associated with severe thrombocytopenia and elevated blast percentages.<sup>55</sup> Among the frequently occurring genetic lesions mentioned above, mutations in *TP53*, *EZH2*, *ETV6*, *RUNX1*, and *ASXL1* were found to be significant independent predictors of decreased overall survival in a multivariable regression model that also included age and IPSS risk groups as variables.<sup>55</sup> When these five poor-risk gene mutations were integrated into the survival analysis by IPSS categories, the presence of a mutation was shown to shift the survival curve of the IPSS risk category to resemble that of the next highest IPSS risk level (e.g., survival plot for low-risk IPSS group with a gene mutation was similar to that for INT-1 risk).<sup>55</sup> Thus, the combined analysis of the gene mutational status and IPSS may improve upon the risk stratification provided by assessment of IPSS alone. It is clear that evaluation of genetic and molecular abnormalities play an increasingly important role in determining the overall prognosis of patients with MDS.



Given that patients with MDS predominantly comprise an elderly adult population, the presence of comorbid conditions pose potential challenges in terms of treatment tolerability and outcomes. About 50% of patients with newly diagnosed MDS present with one or more comorbidities, with cardiac disease and diabetes being among the most frequently observed conditions.<sup>59-63</sup> Assessment of the presence and degree of comorbidities using tools such as the Charlson Comorbidity Index (CCI) or the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) has demonstrated the significant prognostic influence of comorbidities on the survival outcome of patients with MDS.<sup>59, 61-63</sup> Recent studies have shown that comorbidity (as measured by HCT-CI or ACE-27) was a significant prognostic factor for survival, independent of IPSS<sup>60, 63</sup>; in these studies, comorbidity indices provided additional prognostic information for survival outcomes in patients categorized as IPSS INT or High risk, but not for patients considered to have Low-risk disease. Interestingly, in another recent study, comorbidity (as measured by HCT-CI or CCI) was a significant predictor of overall and event-free survival in patients within the Low-risk or INT-1-risk groups, but not in the INT-2- or High-risk groups.<sup>61</sup> Comorbidity has also been shown to provide additional risk stratification among WPSS risk categories (for very low-, low- and intermediate-risk groups but not for high- or very high-risk groups), prompting the development of a new MDS-specific comorbidities index that can be used in conjunction with WPSS for assessment of prognosis.<sup>64</sup> At this time, the NCCN MDS Panel makes no specific recommendations with regards to the optimal comorbidity index to be used for patients with MDS. However, a thorough evaluation of the presence and extent of comorbid conditions remains an important aspect of treatment decision-making and management of patients with MDS.

## Therapeutic Options

The patient's IPSS risk category is used in initial planning of therapeutic options because it provides a risk-based patient evaluation (category 2A). In addition, factors such as the patient's age, performance status, and presence of comorbidities 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 participation in a clinical trial. In evaluating results of therapeutic trials, the panel found it important for studies to use the standardized International Working Group (IWG) response criteria.<sup>65, 66</sup>

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 categories); and (2) higher-risk patients (who are in the IPSS Intermediate-2/ High categories or WPSS High, Very High categories). Based upon IWG response criteria, the major therapeutic aim for patients in the lower risk group would be hematologic improvement, whereas for those in the higher risk group, alteration of the disease natural history is viewed as paramount. Cytogenetic response and



quality of life parameters are also important outcomes 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 management 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 bleeding events; however, platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of 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 episodes refractory to platelet transfusions or for profound thrombocytopenia.

Hematopoietic cytokine support should be considered for refractory symptomatic cytopenias.<sup>67</sup> 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.<sup>68</sup> Thus, effective treatment of such transfusional siderosis in MDS patients is necessary.

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.<sup>69, 70</sup>

Although limited, there is evidence suggesting that organ dysfunction can result from iron overload in patients with MDS.<sup>71-73</sup> Retrospective data suggest that transfusional iron overload might be a contributor of increased mortality and morbidity in early stage MDS.<sup>74</sup> The WPSS has shown that requirement for RBC transfusions is a negative prognostic factor for patients with MDS.<sup>48</sup>

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 iron content using MRI.<sup>75, 76</sup>

Reversal of some of the consequences of iron overload in MDS and other iron overload states (e.g., thalassemia) by iron chelation therapy has been shown in patients in whom the most effective chelation occurred.<sup>66, 70</sup> 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.<sup>77</sup> In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.<sup>78</sup> Such findings have major implications for altering the morbidity of MDS patients, particularly those with pre-existing cardiac or hepatic dysfunction.

The availability of iron chelators such as deferoxamine<sup>79</sup> and deferasirox<sup>80-82</sup> provides potentially useful drugs to more readily treat this iron overload state. Deferoxamine (given as intramuscular or subcutaneous injections) is indicated for the treatment of chronic iron overload due to transfusion-dependent anemias.<sup>79</sup> Deferasirox (given orally) is indicated for the treatment of chronic iron overload due to blood transfusions.<sup>80</sup> This agent has been evaluated in multiple phase II clinical trials in patients with transfusion-dependent MDS.<sup>83-86</sup> A large multicenter phase III randomized controlled trial is currently underway to evaluate outcomes with deferasirox compared with placebo in patients with MDS; the primary endpoint of this ongoing study is event-free survival (registered at [clinicaltrials.gov](http://clinicaltrials.gov); NCT00940602). The prescribing information for deferasirox contains a black-box warning

pertaining to increased risks for renal or hepatic impairment/failure and gastrointestinal bleeding in certain patient populations, including in patients with high-risk MDS. Deferasirox is contraindicated in patients with high-risk MDS. A third oral chelating agent, deferiprone, was recently approved (October 2011) in the U.S. for the treatment of patients with transfusional iron overload due to thalassemia when current chelation therapy is inadequate.<sup>87</sup> Controversy remains with regards to the use of this agent, however, as the FDA approval was based on results from a retrospective analysis of existing data pooled from previous safety and efficacy studies of deferiprone in patients with transfusion-related iron overload refractory to existing chelation therapy. The prescribing information for deferiprone contains a black-box warning pertaining to risks for agranulocytosis, which can lead to serious infections and death.<sup>87</sup>

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.<sup>88</sup>

The NCCN Guidelines panel recommends 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 <1000 ng/ml.

As mentioned above, a black-box warning by the FDA and Novartis was added to the prescribing information for 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 types of these treatments.

### Hypo-methylating Agents

As a form of relatively low-intensity chemotherapy, the DNA methyl transferase inhibitor (DMTI) hypomethylating agents 5-azacytidine (AzaC) and decitabine (5-aza-2'-deoxycytidine) have been shown in randomized phase III trials to decrease the risk of leukemic transformation, and, in a portion of the patients, to improve survival.<sup>89-92</sup> In a phase III trial that compared AzaC with supportive care in patients with MDS (N=191; previously untreated in 83%; all IPSS risk groups), hematologic responses occurred in 60% of patients in the AzaC arm (7% complete response, 16% partial response, 37% hematologic improvement) compared with a 5% hematologic improvement (and no responses) in patients receiving supportive care.<sup>92</sup> The median time to

AML progression or death was significantly prolonged with AzaC compared with supportive care (21 vs. 13 months;  $P=0.007$ ). Additionally, the time to progression to AML or death was improved in patients 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.<sup>93</sup> In this analysis, which included patients receiving either subcutaneous or intravenous delivery of the drug (75 mg/m<sup>2</sup>/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of 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.<sup>93</sup> The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. Results from a recent phase III randomized trial in patients (N=358) with higher risk MDS (IPSS INT-1, 5%; INT-2, 41%; High-risk, 47%) demonstrated that AzaC was superior to conventional care (standard chemotherapy or supportive care) regarding overall survival.<sup>89</sup> AzaC was associated with a significantly longer median survival compared with conventional care (24.5 vs. 15 months; hazard ratio=0.58, 95% CI 0.43-0.77;  $P=0.0001$ ), thus providing support for the use of this agent in patients with 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/m<sup>2</sup>/day subcutaneously for 7 days every 28 days 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 DMT1 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'. In earlier phase II studies, the drug resulted in cytogenetic conversion in approximately 30% of patients,<sup>94</sup> with an overall response rate of 49%, and a 64% response rate in patients with a high-risk IPSS score.<sup>95</sup> Comparison of results of these studies with those of AzaC showed similarity.<sup>96, 97</sup>

The results of a phase III randomized trial of decitabine (15mg/m<sup>2</sup> IV infusion over 3 hours every 8 hours [i.e., 45mg/m<sup>2</sup>/day] on 3 consecutive days every 6 weeks for up to 10 cycles) compared with supportive care in adult patients (N=170) with primary and secondary MDS with IPSS INT-1 (31%), INT-2 (44%) and High (26%) risk disease indicated higher response rates, remission duration, time to AML progression and survival benefit in the INT-2 and High risk groups.<sup>90, 96</sup> Overall response rate (CR + PR) with decitabine was 17%, with an additional 13% having hematologic improvement; the median duration of response was 10 months. The probability of progression to AML or death was 1.68-fold greater for supportive care patients than for those receiving decitabine. Based on this study and three supportive phase II trials,<sup>98</sup> the drug has also been approved by the FDA for treating MDS patients.

In a recent phase III randomized trial, decitabine was compared with best supportive care in older patients age ≥60 years (N=233; median age 70 years, range 60-90 years) with higher risk MDS (IPSS INT-1, 7%; INT-2, 55%; High-risk, 38%) not eligible for intensive therapy.<sup>91</sup> Median progression-free survival (PFS) was significantly improved with decitabine compared with supportive care (6.6 vs.3 months; hazard

ratio=0.68, 95% CI 0.52-0.88; *P*=0.004) and the risk of AML progression at 1 year was significantly reduced with decitabine (22% vs. 33%; *P*=0.036). However, no significant differences were observed between decitabine and supportive care for the primary endpoint of overall survival (10 vs. 8.5 months, respectively) or for median AML-free survival (8.8 vs. 6.1 months, respectively).<sup>91</sup> In the decitabine arm, complete and partial responses were observed in 13% and 6% of patients, respectively, with hematologic improvement in an additional 15%; in the supportive care arm, hematologic improvement was seen in 2% of patients (with no hematologic responses). In addition, decitabine was associated with significant improvements in patient-reported QOL measures (as assessed by the EORTC QOL Questionnaire C30) for the dimensions of fatigue and physical functioning.<sup>91</sup>

Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated. 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.<sup>99</sup> 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 time 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/m<sup>2</sup> intravenously daily for 5 days; 20 mg/m<sup>2</sup> subcutaneously daily for 5 days; or 10 mg/m<sup>2</sup> intravenously daily for 10 days.<sup>100</sup> 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, AzaC 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 for 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<sup>1, 101-106</sup>

Use of anti-immune type therapy with ATG with or without cyclosporine<sup>103, 104</sup> 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.<sup>24, 25</sup> Researchers from the NIH have updated their analysis of 129 patients treated with immunosuppressive therapy (IST). The patients were treated with equine antithymocyte globulin (ATG) and cyclosporine alone or in combination.<sup>107</sup> This study demonstrated markedly improved response rates in younger ( $\leq 60$  years old) and IPSS INT-1 patients as well as in those with high response probability characteristics as indicated by their prior criteria (HLADR15+, age and number of transfusions).<sup>107</sup> Both equine and rabbit ATG are available in the U.S. for IST. Recently, a randomized study from the NIH compared the activity of equine versus rabbit ATG, combined with cyclosporin, in previously untreated patients with severe aplastic anemia (N=120) who were not eligible for transplant.<sup>108</sup> This study demonstrated that in this patient population, rabbit ATG was inferior to equine ATG as shown by the lower 3-month hematologic response rate (33 vs. 62%;  $P=0.0017$ ) and higher number of deaths (14 vs. 3 patients) resulting in decreased survival rates among patients treated with rabbit ATG.<sup>108</sup> Within the setting of MDS, however, only limited data are available regarding the comparative effectiveness of the two ATG formulations. In a relatively small phase II study in patients with MDS (N=35; primarily RA subtype), both equine and rabbit ATG were shown to be feasible and active.<sup>109</sup>

Encouraging data have been presented for treating lower risk MDS patients with lenalidomide.<sup>12, 110</sup> Beneficial results have been particularly evident for patients with del(5q) chromosomal





abnormalities.<sup>12, 110, 111</sup> In a multicenter phase II trial of lenalidomide (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, response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1 to 49) and sustained.<sup>12</sup> RBC transfusion independence (assessed at 24 weeks) occurred in 66% of patients with IPSS Low/INT-1 compared with 52% of patients with higher risk disease.<sup>12</sup> Cytogenetic responses 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 been approved by the FDA for treatment of MDS patients with del(5q).

A recent phase III randomized controlled trial compared the activity of lenalidomide 5 mg versus lenalidomide 10 mg (given daily for 21 consecutive days, every 28 days, for both dose groups) versus placebo, in RBC-transfusion-dependent patients (N=205) with lower risk MDS (IPSS Low- and INT-1 risks) with (del)5q.<sup>112</sup> The primary endpoint was RBC-transfusion independence (TI) for ≥26 weeks, which was achieved in a significantly greater proportion of patients treated with lenalidomide 5 mg or 10 mg versus placebo (43 vs. 56 vs. 6%, respectively;  $P<0.001$  for both lenalidomide groups vs. placebo). Among patients achieving RBC-TI with lenalidomide, onset of erythroid response was rapid, with 86% of patients experiencing response onset within the first two cycles (49% in Cycle 1).<sup>112</sup> Among lenalidomide-treated patients with baseline sEpo levels >500 mU/mL, the 10 mg

dose resulted in significantly higher rates of RBC-TI compared with the 5 mg dose (76 vs. 33%;  $P=0.004$ ). Cytogenetic response rates were significantly higher for the lenalidomide 5 mg or 10 mg arms compared with placebo (25 vs. 50 vs. 0%, respectively;  $P<0.001$  for both lenalidomide groups vs. placebo;  $P=NS$  between lenalidomide dose groups); complete response rates were observed in 16% and 29% of patients in the lenalidomide 5 mg and 10 mg arms, respectively. Median time to AML progression has not yet been reached in the lenalidomide treatment arms. No significant differences were observed in median overall survival between the lenalidomide 5 mg, 10 mg, and placebo groups (35.5 vs. 44.5 vs. 42 months, respectively). The most common grade 3-4 adverse events were myelosuppression and deep vein thrombosis (DVT). Grade 3-4 neutropenia was reported in 74%, 75%, and 15% of patients in the lenalidomide 5 mg, 10 mg, and placebo arms, respectively; grade 3-4 thrombocytopenia occurred in 33%, 41%, and 1.5%, respectively. Four patients (6%) in the lenalidomide 10 mg experienced grade 3-4 DVT while one patient each in the 5 mg and placebo arms had grade 3-4 DVT.<sup>112</sup>

A phase II study evaluated lenalidomide treatment in transfusion-dependent patients (N=214) with low or INT-1-risk MDS without the 5q deletion.<sup>113</sup> Results showed 26% of the non-del(5q) patients (56 of 214) achieved 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 ≥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 Guidelines panel recommends lenalidomide be considered for treatment of symptomatically anemic non-del(5q) patients whose anemia did not respond to initial therapy.

### High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy, or HSCT.<sup>1, 114</sup> Although these approaches have the potential to change the natural history of the disease, they also have an attendant greater risk of regimen-related morbidity and mortality. The panel recommends that such treatments be given in the context of clinical trials. Recent comparative studies have not shown benefit between the different intensive chemotherapy regimens (including idarubicin-, cytarabine-, fludarabine-, and topotecan-based regimens) in MDS.<sup>115</sup>

A high degree of multi-drug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS,<sup>116</sup> with associated decreased responses and shorter response durations with many standard treatment regimens use for 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,<sup>117, 118</sup> others were not.<sup>119</sup> Further clinical trials evaluating other multi-drug resistance modulators are ongoing.

Allogeneic HSCT from an HLA-matched sibling donor is a preferred approach for treating a selected group of patients with MDS, particularly those with high-risk disease.<sup>120-127</sup> Matched non-myeloablative transplant regimens<sup>128, 129</sup> and matched unrelated donor stem-cell transplants<sup>130-132</sup> are becoming options at some centers to treat these patients. In certain investigative settings, autologous bone marrow or peripheral blood stem cell transplantation is being considered.<sup>133</sup>

Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been established.<sup>134</sup> 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 Guidelines panel recommends stratifying these patients into several groups. Those with del(5q) chromosomal abnormalities and symptomatic anemia should receive lenalidomide. However, lenalidomide should be avoided in patients with clinically significant decrease in neutrophil counts or platelet counts; in the previously discussed phase III trial with lenalidomide in patients with del(5q), patients with low neutrophils (<500/mcL) or platelet counts (<25,000/mcL) were excluded from the study.<sup>112</sup> 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 IST (with anti-thymoglobulin or cyclosporine) if there is a high likelihood of response to such therapy. The most appropriate candidates for IST 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. Alternatively, or in the case of non-response to IST, treatment with AzaC or decitabine or lenalidomide should be considered. Patients with no response to hypomethylating agents or lenalidomide in this setting



should 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 mU/mL should be evaluated to determine whether they have a good probability of responding to IST. Non-responders to IST would be considered for treatment with AzaC, decitabine, or a clinical trial. Patients with sEpo levels >500 mU/mL who have a low probability of responding to IST should be considered for treatment with AzaC, decitabine, or lenalidomide. Others or non-responders to these treatments 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 AzaC or decitabine or a clinical trial. Data from the phase III randomized trial of AzaC compared with conventional care showed significantly higher rates of major platelet improvement with AzaC compared with conventional care (33 vs.14%;  $P=0.0003$ ); it should be noted, however, that the rates for major neutrophil improvements were similar between AzaC and the control arm (19 vs.18%), and that the study was conducted in patients with higher risk MDS.<sup>89</sup> Patients who do not respond to hypomethylating agents should be considered for treatment with IST, a clinical trial, or for allogeneic HSCT.

Careful monitoring for disease progression and consideration of the patient's preferences 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 have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA haploidentical related donors, HSCT has become a viable option for many patients. High dose conditioning is typically used for younger patients, whereas the approach using reduced/low intensity conditioning (RIC) for HSCT is generally the strategy in older individuals.<sup>135</sup>

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.<sup>136</sup> 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).<sup>136</sup> A study published in 2008 retrospectively evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT.<sup>50</sup> The data suggest that lower risk patients (based on WPSS risk score) do very well with allogeneic HSCT, with a 5-year overall survival of 80%. With increasing WPSS scores, the probability of 5-year survival after HSCT declined progressively to 65% (intermediate risk), 40% (high risk), and 15% (very high risk).<sup>50</sup>

Based on recent data regarding RIC for transplantation from two reported series<sup>137, 138</sup> and two comprehensive reviews of this field,<sup>139, 140</sup> 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 article.<sup>141</sup>

#### *Intensive chemotherapy*

For patients eligible for intensive therapy but 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.<sup>142</sup> Although the response rate and durability of this treatment is lower than for standard AML, this treatment (particularly in

clinical trials with novel agents) could be beneficial in a portion of 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 considered valid treatment options.

#### ***Non-Intensive therapy***

For higher risk patients who are not candidates for intensive therapy, the use of AzaC, 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 AzaC compared to best supportive care, the NCCN Guidelines panel has made this a preferred category 1 recommendation compared with decitabine. Results from another recent phase III 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.<sup>91, 143</sup> However, it should be noted that no trials to date have compared AzaC head-to-head with decitabine.

For some patients eligible for HSCT therapy who require a reduction in tumor burden, the use of azacytidine or decitabine may be a bridge to sufficiently 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, adequate supportive care should be maintained.



### Evaluation and Treatment of Related Anemia

Major morbidities of MDS include symptomatic anemia and 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 B<sub>12</sub> 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.<sup>1, 144</sup> To determine FAB subtype, iron status, and the level of ring sideroblasts, bone marrow aspiration with iron stain, biopsy, and cytogenetics should be examined. Patients should also 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.<sup>67, 145,</sup>

<sup>146</sup> 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.<sup>147-150</sup> 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.<sup>146-149</sup> This is particularly evident for patients with ≥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.<sup>148, 149</sup>

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in initially neutropenic patients or to double the neutrophil count in 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.<sup>146-149</sup> G-CSF is available in single use vials or prefilled syringes containing either 300 mcg or 480 mcg and requires refrigeration. 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, treatment should be considered a failure and discontinued. In the case of treatment failure, one should rule out and treat deficient iron stores. Clinical trials or supportive care are also treatment options in this category of patients. A validated decision 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.<sup>149, 151</sup> Improved quality of life has been demonstrated in responding patients.<sup>151</sup> 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).<sup>152, 153</sup> Results of clinical trials in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than to epoetin.<sup>152-155</sup>

These response rates may in part be due to the dosage used (150 to 300 mcg/ 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 g/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 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 controls<sup>156</sup> or historical controls<sup>157, 158</sup> have shown no negative impact of such treatment on survival or AML evolution. 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.<sup>157</sup> 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.<sup>158</sup> 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 ≤12 g/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 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.<sup>147, 150, 151, 159, 160</sup> 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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# NCCN Guidelines Version 1.2012

## Myelodysplastic Syndromes

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