Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hematopathies 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, the incidence rate of MDS is approximately 5 per 100,000 people per year.\(^1\)\(^2\) MDS is rare among children/adolescents and young adults, with an incidence rate of 0.2 per 100,000 people per year in those younger than 40 years; however, among individuals older than 70 years, the incidence rate increases to approximately 26 per 100,000 people, and increases further to 48 per 100,000 people among those aged 80 years and older.\(^1\)

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\(^\circledR\)) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines\(^\circledR\) is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network\(^\circledR\) (NCCN\(^\circledR\)) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. The full NCCN Guidelines for Myelodysplastic Syndromes are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Myelodysplastic Syndromes Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Myelodysplastic Syndromes Panel members can be found on page 874. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
Managing MDS is complicated by the generally advanced age of the patients (median age at diagnosis is 70–75 years), the attendant nonhematologic comorbidities, and the older patients’ relative inability to tolerate certain intensive forms of therapy. In addition, when the illness progresses to AML, these patients experience lower response rates to standard therapy than those with de novo AML.

The multidisciplinary panel of MDS experts for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) meets annually to update recommendations on standard approaches to the diagnosis and treatment of MDS in adults. These recommendations are based on a review of recent clinical evidence that has led to important advances in treatment or has yielded new information on biological factors that may have prognostic significance in MDS. A more complete version of the discussion text for the NCCN Guidelines for MDS is available at NCCN.org, which also includes pediatric MDS, molecular abnormalities in MDS, comorbidity indices, and management of iron overload.

**Diagnostic Classification**

Initial evaluation of patients with suspected MDS requires careful assessment of their peripheral blood smear and blood counts, their marrow morphology, the duration of their abnormal blood counts, other potential causes for their cytopenias, and concomitant illnesses. The NCCN Guidelines for MDS include the WHO classification system for diagnostic evaluations.

In 2008, a revision of the WHO classification...
INITIAL EVALUATION

Cytopenia(s), suspect myelodysplasia

Required:
- H&P
- CBC, platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping
- Serum erythropoietin (prior to RBC transfusion)
- RBC folate, serum B12
- Serum ferritin, iron, total iron-binding capacity (TIBC)
- Documentation of transfusion history
- TSH (thyroid stimulating hormone) to rule out hypothyroidism

Diagnosis of MDS established based on morphologic and clinical criteria

See Additional Testing: Helpful in Some Clinical Situations (facing page)

**MDS-1**

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**Notes:**
- MDS is also suspected in the presence of acquired MDS-related cytogenetic abnormalities and in the unexpected increase in blasts or dysplasia.
- Confirm diagnosis of MDS according to FAB or WHO criteria for classification with application of IPSS. See Classification Systems (MDS-3 and MDS-5).
- The percentage of marrow myeloblasts based on morphologic assessment (aspirate smears preferred) should be reported. Flow cytometric estimation of blast percentage should not be used as a substitute for morphology in this context. In expert hands, expanded flow cytometry may be a useful adjunct for diagnosis in difficult cases (see discussion).
- Patients with significant cytopenias and karyotypes t(8;21), t(15;17), and/or inv(16) or variants should be considered to have AML. (See NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Acute Myeloid Leukemia; to view the most recent version of these guidelines, visit NCCN.org).
Patients with significant cytopenias and karyotypes t(8;21), t(15;17), and/or inv(16) or variants should be considered to have AML. (See NCCN Clinical Guidelines for AML*)

To confirm diagnosis of MDS according to FAB or WHO criteria for classification of MDS is also suspected in the presence of acquired MDS-related cytogenetic abnormalities and unexpected increase in blasts or dysplasia.

**Practice Guidelines in Oncology [NCCN Guidelines] for AML** (See NCCN.org)

- **MDS**
  - Consider observation to document indolent course vs. marked progression of severe cytopenia or increase in blasts

**ADDITIONAL TESTING**

### Helpful in Some Clinical Situations:
- Consider flow cytometry (FCM) for MDS diagnostic aid to assess possible large granular lymphocytic (LGL) disease and to evaluate for PNH clone.
- HLA typing if hematopoietic stem cell transplant (HSCT) candidate.
- Consider HLA-DR15 typing.
- HLA typing if indicated for platelet support.
- HIV testing if clinically indicated.
- Evaluate CMML patients for 5q31-33 translocations and/or PDGFRβ gene rearrangements.
- Consider molecular testing for JAK2 mutation in patients with thrombocytosis.
- Consider additional genetic screening for patients with familial cytopenias, particularly for younger patients.
- Consider evaluation of copper deficiency.

### CLASSIFICATION

**MDS**

- See Classification Systems (MDS-3 and MDS-5)

**AML**

- (See NCCN Guidelines for AML*)

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*To view the most recent version of these guidelines, visit NCCN.org.

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**Footnotes:**

1. See Recommendations for Flow Cytometry (MDS-A; available online, in these guidelines, at NCCN.org) and discussion.
2. Marrow or peripheral blood cell FCM may be assayed and T-cell gene rearrangement studies may be conducted if LGLs are detected in the peripheral blood. Chan WC, Foucar K, Morice WG, Catovsky D. T-cell large granular lymphocytic leukemia. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC; 2008:272-273.
4. Family HLA: evaluation to include all full siblings; unrelated evaluation to include high-resolution allele level typing for HLA-A, -B, -C, -DR, and -DQ.
5. To assist determination of patient’s potential responsiveness to immunosuppressive therapy.
6. Consider evaluation of copper deficiency.
7. Marrow or peripheral blood cell FCM may be assayed and T-cell gene rearrangement studies may be conducted if LGLs are detected in the peripheral blood. Chan WC, Foucar K, Morice WG, Catovsky D. T-cell large granular lymphocytic leukemia. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC; 2008:272-273.
9. Family HLA: evaluation to include all full siblings; unrelated evaluation to include high-resolution allele level typing for HLA-A, -B, -C, -DR, and -DQ.
10. To assist determination of patient’s potential responsiveness to immunosuppressive therapy.
11. Consider additional genetic screening for patients with familial cytopenias, particularly for younger patients.
12. Consider evaluation of copper deficiency.
13. 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 fluorescence in situ hybridization (FISH) assays using leukocyte samples (see discussion).
CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 1 of 4)

2008 WHO Classification of MDS

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD) (^m)</td>
<td>Single or bicytopenia</td>
<td>Dysplasia in ≥10% of one cell line, &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia, no blasts</td>
<td>≥15% of erythroid precursors w/ring sideroblasts, erythroid dysplasia only, &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenia(s), &lt;1 x 10^9/L monocytes</td>
<td>Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, ± 15% ring sideroblasts, &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenia(s), ≤2%-4% blasts, &lt;1 x 10^9/L monocytes</td>
<td>Unilineage or multilineage dysplasia, No Auer rods, 5%-9% blasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenia(s), 5%-19% blasts, &lt;1 x 10^9/L monocytes</td>
<td>Unilineage or multilineage dysplasia Auer rods, ± 10%-19% blasts</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias</td>
<td>Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, &lt;5% blasts</td>
</tr>
<tr>
<td>MDS associated with isolated del(5q)</td>
<td>Anemia, platelets normal or increased</td>
<td>Unilineage erythroid dysplasia, isolated del(5q), &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts in transformation (RAEB-T) (^j)</td>
<td>Cytopenias, 5%-19% blasts</td>
<td>Multilineage dysplasia, Auer rods ±, 20%-30% blasts</td>
</tr>
</tbody>
</table>

\(^k\)Refer to Table 5.01 (p. 89) of 2008 WHO Classification: Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue. Lyon, France: IARC; 2008.


\(^m\)This category encompasses refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS, unclassified.

MDS-3
### CLASSIFICATION SYSTEMS FOR DE NOVO MDS

#### Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) WHO Classification

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelomonocytic leukemia-1 (CMML-1)</td>
<td>&gt;1 x 10⁹/L monocytes, &lt;5% blasts</td>
<td>Dysplasia in ≥1 hematopoietic line, &lt;10% blasts</td>
</tr>
<tr>
<td>CMML-2</td>
<td>&gt;1 x 10⁹/L monocytes, 5%-19% blasts or Auer rods</td>
<td>Dysplasia in ≥1 hematopoietic line, 10%-19% blasts or Auer rods</td>
</tr>
<tr>
<td>Atypical chronic myeloid leukemia (CML), BCR-ABL1-negative</td>
<td>WBC &gt;13 x 10⁹/L, neutrophil precursors &gt;10%, &lt;20% blasts</td>
<td>Hypercellular, &lt;20% blasts</td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukemia (JMML)</td>
<td>&gt;1 x 10⁹/L monocytes, &lt;20% blasts&lt;sup&gt;o&lt;/sup&gt;</td>
<td>&gt;1 x 10⁹/L monocytes,</td>
</tr>
<tr>
<td>MDS/MPN, unclassifiable ('overlap syndrome')</td>
<td>Dysplasia + myeloproliferative features&lt;sup&gt;o&lt;/sup&gt;, No prior MDS or MPN</td>
<td>Dysplasia + myeloproliferative features</td>
</tr>
</tbody>
</table>

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**Notes:**

- <sup>o</sup>Refer to Tables 4.01 (p. 76), 4.02 (p. 80), 4.03 (p. 82), and 4.04 (p. 85) of 2008 WHO Classification: Orazi A, Bennett JM, Germing U, et al., Myelodysplastic/myeloproliferative neoplasms. In: Swerdlow S, Campo E, Harris NL, et al., eds. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: IARC Press, 2008:76-86.

- <sup>p</sup>Ph-negative plus ≥2 features: Hb F, PB immature myeloid cells, WBC >10 x 10⁹/L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro.


- <sup>q</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 similarly to MDS (RAEB-T by FAB classification) than to overt AML.


Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
### WHO-Based Prognostic Scoring System (WPSS)\(^x\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>WHO category</td>
<td>RCUD, RARS, MDS with isolated deletion (5q)</td>
</tr>
<tr>
<td>Karyotype(^y)</td>
<td>Good</td>
</tr>
<tr>
<td>Severe anemia (hemoglobin &lt;9 g/dL in men or &lt;8 g/dL in women)</td>
<td>Absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WPSS risk</th>
<th>Sum of individual variable scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>3-4</td>
</tr>
<tr>
<td>Very high</td>
<td>5-6</td>
</tr>
</tbody>
</table>

\(^x\)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 and not MDS.]

PROGNOSTIC CATEGORY

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

TREATMENT

- Symptomatic anemia
  - Supportive care as an adjunct to treatment

- Clinically relevant cytopenia(s) or increased marrow blasts
  - See facing page

- No del(5q) ± other cytogenetic abnormalities
  - Serum EPO >500 mU/mL
    - See facing page

- Clinically relevant thrombocytopenia or neutropenia or increased marrow blasts
  - Azacitidine/decitabine or Immunosuppressive therapy (IST)
    - Disease progression/No response
      - Clinical trial
      - Consider allo-HSCT for selected IPSS Intermediate-1 patients

a Presumption of comorbidities should also be considered for evaluation of prognosis (see references 128-133 in the discussion).
b IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending on additional prognostic factors, such as age, performance status, serum ferritin levels, and serum LDH levels. If patients initially are managed as lower risk but fail to respond, move to higher risk management strategies.
cc See Supportive Care (MDS-B; available online, in these guidelines, at NCCN.org).
ee Patients generally aged ≥60 y, and with ≥5% marrow blasts, or those with hypocellular marrows, HLA-DR15 positivity, or PNH clone positivity.
ff IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT (hematopoietic stem cell transplant): allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).
Myelodysplastic Syndromes, Version 2.2014

PROGNOSTIC CATEGORY

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

TREATMENT

- del(5q) ± other cytogenetic abnormalities (for symptomatic anemia only)
  - Serum EPO ≥500 mU/mL
    - Epoetin alfa (rHu EPO) ± G-CSF
      - No response
      - Good probability to respond to IST
        - Antithymocyte globulin (ATG)
        - No response
        - Follow appropriate pathway below
  - Symptomatic anemia with no del(5q)
    - Serum EPO >500 mU/mL
      - Poor probability to respond to IST
        - Azacitidine/decitabine
        - No response
        - Consider lenalidomide or clinical trial
  - Following pathway below

- Patients aged ≥60 y, or those with hypocellular marrows, HLA-DR15 positivity, or PNH clone positivity.
- Presence of comorbidities should also be considered for evaluation of prognosis (see references 128-133 in the discussion).
- IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT (hematopoietic stem cell transplant); allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).
- Except for patients with low neutrophil counts or low platelet counts.
- Recommended initial dose is: 10 mg/d for 21 out of 28 days monthly for 2-4 months to assess response (see discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≥500 mU/mL.
- See dosing of hematopoietic cytokines (MDS-10).
- Patients lack features listed in footnote “dd”.
- Both equine and rabbit ATG have been used in patients with MDS (see discussion).
PROGNOSTIC CATEGORY\textsuperscript{aa}

<table>
<thead>
<tr>
<th>IPSS: Intermediate-2, High\textsuperscript{ee}</th>
<th>IPSS-R: Intermediate,\textsuperscript{kk} High, Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPSS: High, Very High</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT

- **Yes**
  - Transplant candidate
  - Donor available
  - Allo-HSCT\textsuperscript{mm,nn}
  - If relapse
  - Azacitidine/decitabine\textsuperscript{oo} or Clinical trial

- **No**
  - Azacitidine (preferred) (category 1)/decitabine\textsuperscript{oo} or High-intensity chemotherapy\textsuperscript{pp} or Clinical trial

- **Response\textsuperscript{dd}**
  - Continue

- **No response\textsuperscript{dd}**
  - Clinical trial or Supportive care\textsuperscript{cc}


\textsuperscript{pp}High-intensity chemotherapy:
- Clinical trials with investigational therapy (preferred), or
- Standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HSCT.

\textsuperscript{oo}Azacitidine (preferred) (category 1)/decitabine

\textsuperscript{ab}Presence of comorbidities should also be considered for evaluation of prognosis (see references 128-133 in the discussion).

\textsuperscript{cc}See Supportive Care (MDS-B; available online, in these guidelines, at NCCN.org).


\textsuperscript{ee}IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT: allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).

\textsuperscript{kk}IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending on additional prognostic factors, such as age, performance status, serum ferritin levels, and serum LDH levels.

\textsuperscript{mm}Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant, or bridging therapy should be used to decrease marrow blasts to an acceptable level before transplant. Transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).

\textsuperscript{nn}Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability. However, these agents should not be used to delay available HSCT.

\textsuperscript{oo}Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability. However, these agents should not be used to delay available HSCT.

\textsuperscript{pp}High-intensity chemotherapy:
- Clinical trials with investigational therapy (preferred), or
- Standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HSCT.

MDS-9

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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EVALUATION OF RELATED ANEMIA

- H&P
- CBC, platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics
- Serum EPO level
- Consider HLA-DR15 typing
- Rule out coexisting causes

<table>
<thead>
<tr>
<th>Serum EPO ≤500 mU/mL</th>
<th>Serum EPO &gt;500 mU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring sideroblasts &lt;15%</td>
<td>Ring sideroblasts ≥15%</td>
</tr>
<tr>
<td>lenalidomide</td>
<td>See Serum EPO &gt;500 mU/mL (MDS-8)</td>
</tr>
</tbody>
</table>

TREATMENT OF SYMPTOMATIC ANEMIA

- Treat coexisting causes
- Replace iron, folate, B12 if needed
- RBC transfusions (leukoreduced)
- Supportive care

<table>
<thead>
<tr>
<th>Serum EPO ≤500 mU/mL</th>
<th>Serum EPO &gt;500 mU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring sideroblasts</td>
<td></td>
</tr>
<tr>
<td>≤15%</td>
<td>≥15%</td>
</tr>
<tr>
<td>rHu EPO 40,000-60,000 U 1-3 x/wk subcutaneous or Darbepoetin alfa 150-300 mcg/wk subcutaneous</td>
<td></td>
</tr>
<tr>
<td>rHu EPO 40,000-60,000 U 1-3 x/wk subcutaneous + G-CSF 1-2 mcg/kg 1-3 x/wk subcutaneous or Darbepoetin alfa 150-300 mcg/wk subcutaneous + G-CSF</td>
<td></td>
</tr>
<tr>
<td>Response&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Decrease response&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Continue EPO, decrease dose to tolerance</td>
<td>Decrease dose to tolerance</td>
</tr>
</tbody>
</table>

FOLLOW-UP

- Continue lenalidomide, decrease dose to tolerance
- See IPSS: Low/Intermediate-1 WPSS: Very Low, Low, Intermediate (MDS-8)
- See IPSS: Low/Intermediate-1 WPSS: Very Low, Low, Intermediate (MDS-8)
- Response, decrease dose to tolerance
- No response (See MDS-8)
- Target hemoglobin range 10-12 g/dL; not to exceed 12 g/dL.
- Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 6-8 weeks of treatment.

**cc** See Supportive Care (MDS-8; available online, in these guidelines, at NCCN.org).

<sup>®</sup> Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days monthly for 2-4 months to assess response (see discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤500 mU/mL.

<sup>®</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>®</sup> Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 3-4 months of treatment.

<sup>®</sup> Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 6-8 weeks of treatment.

MDS-10

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incorporated new scientific and clinical information and refined diagnostic criteria for previously described neoplasms; it also introduced newly recognized disease entities. A new subtype in the MDS classification is refractory cytopenia with unilineage dysplasia (RCUD), which includes refractory anemia (RA; unilineage erythroid dysplasia), refractory neutropenia (RN; unilineage dysgranulopoiesis), and refractory thrombocytopenia (RT; unilineage dysmegakaryocytepoiesis). RN and RT were previously classified as MDS unclassifiable. 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.

Other categories within the WHO classification include refractory cytopenia with multilineage dysplasia (RCMD) with or without ring sideroblasts, RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB) cases separated into those with less than 10% marrow blasts (RAEB-1), and those with 10% or more marrow blasts (RAEB-2), 5q deletion [del(5q)] syndrome, and MDS unclassified (with MDS cytogenetics, with or without unilineage dysplasia). The del(5q) syndrome, recognized by WHO as a separate MDS category, includes patients with an isolated 5q31–33 deletion and marrow showing less than 5% blasts, often with thrombocytosis. This disorder generally has a relatively good prognosis and is highly responsive to lenalidomide therapy.

The category myelodysplastic/myeloproliferative neoplasms (MDS/MPN), includes chronic myelomonocytic leukemia-1 and -2 (CMML-1 and CMML-2); atypical chronic myelogenous leukemia (CML), BCR-ABL1–negative; and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features, and the MDS/MPN unclassifiable group. The distinction between CMML-1 and CMML-2 is based on the percentage of blasts plus monocytosis in peripheral blood and bone marrow. CMML had been categorized by French-American-British (FAB) classification as MDS, and by the International MDS Risk Analysis Workshop (IMRAW) as proliferative type (WBC count ≥12,000/mm³; a myeloproliferative disorder [MPD]) or nonproliferative type (dysplastic MDS). The MDS/MPN unclassifiable group includes the provisional entity, RARS associated with marked thrombocytosis (RARS-T), which includes cases that present with clinical and morphologic features consistent with MDS, and thrombocytosis (platelet counts ≥450 × 10⁹/L). The morphology of RARS-T is characterized by RARS features (no blasts in peripheral blood, dysplastic erythroid proliferation, ring sideroblasts ≥15% of erythroid precursors, and <5% blasts in marrow), with proliferation of large atypical megakaryocytes similar to those seen in essential thrombocytopenia or primary myelofibrosis; up to 60% of RARS-T cases have the JAK2 V617F mutation or MPL W515K/L mutation.

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

The 2008 WHO classifications have helped clarify the clinical differences between the patients with FAB RAEB-T and those with AML. 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. According to the 2008 WHO classification, some patients with AML with myelodysplasia-related changes having 20% to 29% marrow blasts, especially those arising from MDS (considered RAEB-T by the FAB classification), may have disease that behaves more similar to MDS than to AML.

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 factors such as age, antecedent factors, cytogenetics, comorbidities, pace of disease, performance status, and patient’s goal for treatment. The NCCN MDS Panel currently endorses reporting and using the WHO classification system. However, as indicated in the algorithm (see MDS-3, page 842), patients with RAEB-T (with 20%–30% blasts AND a stable clinical course for at least 2 months) should be considered as either MDS or AML. These patients were previously included in and benefited from many therapeutic trials for MDS, and should continue to be eligible for MDS-type
therapy. Thus, the NCCN MDS Panel recommends using the WHO classification but having the RAEB-T subgroup considered as either MDS or AML. Studies have provided evidence supporting the use of the WHO proposals.17-21

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. Patients with high-risk MDS or AML-MDS, and some elderly patients with AML may have a more indolent course in terms of short-term progression compared with patients with standard presentations of de novo AML. Separate protocols for treating patients with a standard presentation of de novo AML and these other presentations seem appropriate (see NCCN Guidelines for Acute Myeloid Leukemia; to view the most recent version of these guidelines, visit NCCN.org).

To help provide consistency in diagnostic guidelines of MDS, an international consensus working group recommended that minimal diagnostic criteria for this disease include required diagnostic prerequisites: stable cytopenia (for at least 6 months unless accompanied by a specific karyotype or bilineage dysplasia, in which case only 2 months of stable cytopenias are needed) and the exclusion of other potential disorders as a primary reason for dysplasia or and cytopenia. In addition, the diagnosis of MDS requires at least 1 of 3 MDS-related (decisive) criteria: 1) dysplasia (≥10% in ≥1 of the 3 major bone marrow lineages), 2) a blast cell count of 5% to 19%, and 3) a specific MDS-associated karyotype, such as del(5q), del(20q), +8, or −7/del(7q). Furthermore, several co-criteria help confirm the diagnosis of MDS, including studies with flow cytometry, bone marrow histology and immunohistochemistry, or molecular markers (to detect or exclude abnormal CD34 antigenic expression, fibrosis, dysplastic megakaryocytes, atypical localization of immature progenitors, and myeloid clonality).22

Initial Evaluation

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

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

Other useful screening laboratory studies include serum erythropoietin (sEpo), vitamin B12, red blood cell (RBC) folate levels, and serum ferritin. Serum ferritin levels may be nonspecific, particularly in the face of inflammatory conditions such as rheumatoid arthritis, and therefore obtaining the serum iron levels and total iron binding capacity along with serum ferritin may be helpful. Because hypothyroidism and other thyroid disorders can lead to anemia, patients should also be evaluated for levels of thyroid-stimulating hormone.23

If patients require platelet transfusions for severe thrombocytopenia, HLA typing (A, B) may be helpful. For hematopoietic stem cell transplant (HSCT) candidates, the cytomegalovirus (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 percentage of CD34+ cells (blast cells are usually CD34+), and HIV screening if clinically indicated, may also be valuable in some clinical situations. However, estimates of blast percentage derived from flow cytometry do not provide the same prognostic information as that derived from morphologic evaluation. Accordingly, data from flow cytometry should not be used in lieu of the determination of morphologic blast percentage by an experienced hematopathologist. The screening for paroxysmal nocturnal hemoglobinuria (PNH) and HLA-DR15 is potentially useful for determining
which patients may be more responsive to immuno-
suppressive therapy, particularly in young patients
with normal cytogenetics and hypocellular MDS24,25
(see “Prognostic Stratification,” facing page). PNH
is a rare acquired hematopoietic stem cell disorder
arising from mutations in the PIGA gene, resulting
in defective synthesis of the glycolipid phosphatidylinosi-
tol (GPI) anchor, which in turn leads to deficiency
of proteins that are normally linked to the cell mem-
brane of blood cells via a GPI anchor.26 Deficiency
in GPI-anchored proteins such as those involved in
complement inhibition (eg, CD-55, CD-59) leads to
complement sensitivity of RBCs and subsequent he-
molysis.26 Flow cytometry is the established method
for detecting GPI anchor–deficient cells for the di-
agnosis of PNH. Recent data show that fluorescent
aerolysin (FLAER), a protein that specifically binds
to GPI anchors, was a reliable marker for detecting
GPI anchor–deficient clones among granulocytes or
monocytes, with high sensitivity.29 For evaluation of
PNH clone, multiparameter flow cytometry analysis
of granulocytes and monocytes using FLAER and at
least one GPI-anchored protein are recommended.26,29
Although evidence for a minor PNH clone may be
present in approximately 20% of patients with MDS,
usually no evidence of PNH-related hemolysis is seen
in these patients.

Bone marrow biopsy staining for reticulin is
helpful for evaluating the presence and degree of
bone marrow fibrosis.

Discrete from basic flow cytometric evaluation at
presentation for characterizing blasts and evaluating
lymphoid populations, expanded flow cytometry may
be a useful adjunct for diagnosing MDS in difficult
cases. In expert hands (both in terms of technical so-
phistication and interpretation), flow cytometry may
demonstrate abnormal differentiation patterns or
aberrant antigen expression in myeloid or progeni-
tor cells, which may help confirm diagnosis of MDS,
exclude differential diagnostic possibilities, and, in
some patients, provide prognostic information.30–34
To achieve these purposes, the flow analysis should
use appropriate antibody combinations with 4-chan-
nel fluorescence instrumentation.30–34 Multiple aber-
rancies have also been described in erythroid cells,
erthroid analysis is not provided by most flow cy-
tometry laboratories. The European LeukemiaNET
recently developed a flow cytometric score based on
reproducible parameters using CD34 and CD45 as
markers to help diagnose MDS.35 The scoring system
was developed using multicenter retrospective data
from patients with low-grade MDS (defined as <5%
marrow blasts; n=417) and those with nonclonal
cytopenias as controls (n=380). This population of
patients was chosen for the study because low-grade
MDS often lack specific diagnostic markers (eg, ring
sideroblasts, clonal cytogenetic abnormalities), and
therefore may be difficult to diagnose based on mor-
phology alone. Bone marrow samples from patients
with MDS showed different flow cytometric patterns
compared with samples from patients with nonclonal
cytopenias with regard to the following: increased
CD34+ myeloblast-related cluster size (defined by
wider distribution of CD45 expression and greater
side scatter characteristics [SSC]), decreased CD34+
B-progenitor cluster size (defined by relatively low
CD45 expression and low SSC), aberrant myeloblast
CD45 expression (based on lymphocyte-to-myelo-
blast CD45 ratio), and decreased granulocyte SSC
value (based on granulocyte-to-lymphocyte SSC ra-
tio).35 These 4 parameters were included in a logis-
tic regression model, and a weighted score (derived
from regression coefficients) was assigned to each pa-
parameter; the sum of the scores provided the overall
flow cytometric score for each sample, with a score of
2 or higher defined as the threshold for MDS diagno-
asis.35 Using this flow cytometric score in the learning
cohort, a correct diagnosis of MDS was made with
70% sensitivity and 93% specificity. Among patients
with MDS with no specific markers of dysplasia, 65%
were correctly identified. The positive and negative
predictive values were 92% and 74%, respectively.
These outcomes were confirmed in the validation
cohort, which showed 69% sensitivity and 92% spec-
ificity.35 This flow cytometric scoring system
demonstrated high diagnostic power in differentiat-
ing low-grade MDS from nonclonal cytopenias, and
may be particularly useful in establishing a diagnosis
when traditional diagnostic methods are indeter-
minate. Further independent validation studies are
warranted to determine the utility of this method.

Because of the associated expense, requirements
for both technical and interpretational expertise,
and need for greater consensus on specific antibody combinations and procedures that are most informative and cost-effective, flow cytometric assays should be performed by experienced laboratories and used in general practice only when diagnosis is uncertain with traditional approaches (eg, blood counts, morphology, cytogenetics, increased blasts). Flow cytometry studies may also be used to assess the possibility of large granular lymphocytic (LGL) disease, if relevant as indicated by LGLs being present in the peripheral blood.36

Additional genetic screening should be considered for patients with familial cytopenias, which will help evaluate for Fanconi 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.37,38 Telomere length can be measured by fluorescence in situ hybridization assays using leukocyte (or leukocyte subset) samples.37,39 Other genetic lesions, such as those occurring in the RUNX1 or GATA2 gene, have been implicated in familial cases of MDS and other myeloid malignancies. Lesions within the RUNX1 gene (mutations, deletions, or translocations) have been identified as a cause of a relatively rare autosomal dominant familial platelet disorder that predisposes to myeloid malignancies.40,41 In affected families with the RUNX1 lesions, the incidence of MDS/AML is high, ranging from 20% to 60%; the median age of onset is 33 years.42 This familial platelet disorder is characterized by the presence of thrombocytopenia, and a tendency for mild to moderate bleeding generally present from childhood; however, some affected individuals may not display these clinical characteristics.42 Different types of genetic lesions in RUNX1 account for the variable phenotypes associated with familial platelet disorder between different families. Cryptic genetic lesions in RUNX1 have been reported in some patients with Fanconi anemia and MDS/AML.43 The GATA2 gene codes for a transcription factor involved in gene regulation during the development and differentiation of hematopoietic cells, and its expression was shown to correlate with severe dysplasia in patients with primary MDS.44 Recently, heritable mutations in GATA2 were identified in families with highly penetrant early-onset MDS and/or AML.45 The mutations showed an autosomal dominant pattern of inheritance, and affected individuals with this familial form of MDS/AML had poor outcomes in the absence of allogeneic stem cell transplant.45 Identification of familial MDS is of clinical importance because it is associated with chromosomal fragility, and these patients may therefore respond differently to hypomethylating agents; more importantly, family members may not be eligible as donors for allogeneic HSCT.

Determination of platelet-derived growth factor receptor beta (PDGFRβ) gene rearrangements is helpful for evaluating patients with CMML/MPD 5q31–33 translocations. The activation of this gene encoding a receptor tyrosine kinase for PDGFRβ has been shown in some of these patients.46,47 Data have indicated that patients with CMML/MPD with these PDGFRβ fusion genes may respond well to treatment with the tyrosine kinase inhibitor imatinib mesylate.48–50

The frequency of activating mutations of the tyrosine kinase known as Janus kinase 2 (JAK2) in MDS and de novo AML is lower compared with that in myeloproliferative disorders.51 If thrombocytosis is encountered in patients with MDS, screening for JAK2 mutations may be helpful; a positive result is consistent with the presence of a myeloproliferative component of this disorder.52

Recent flow cytometric studies suggest the potential efficacy of this methodology for characterizing MDS marrow blast cells and as an aid for assessing prognosis.53,54 However, because of the nonstandardized nature of these analyses, further investigations are warranted before their routine use can be suggested.

Reports have shown that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.55–57 Thus, in certain instances, assessment of copper and ceruloplasmin levels may be indicated as part of the initial diagnostic workup of suspected MDS. Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,55–57 prior gastrointestinal surgery,55,56 and a history of vitamin B12 deficiency.56,58

Prognostic Stratification

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

Prognostic Scoring Systems
The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW. 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. FAB morphologic criteria were used to establish the diagnoses of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible causes for the cytopenias, such as drugs, other diseases, or incipient evolution to AML. CMML was subdivided into proliferative and nonproliferative subtypes. Patients with proliferative-type CMML (WBC >12,000/mcL) were excluded from this analysis. Patients with nonproliferative CMML (WBC ≤12,000/mcL and other features of MDS) were included in the analysis.

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

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

To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroup, and number of cytopenias) were generated. Through combining the risk scores for the 3 major variables, patients were stratified into 4 distinctive risk groups in terms of both survival and AML evolution: low, intermediate-1 (INT-1), intermediate-2 (INT-2), and high. When either cytopenias or cytogenetic subtypes were omitted from the classification, discrimination among the 4 subgroups was much less precise. Both for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods, including the FAB system.

Recent data have indicated that additional clinical variables are additive to the IPSS regarding prognosis for patients with MDS. The WHO classification-based prognostic scoring system (WPSS) incorporates the WHO morphologic categories, IPSS cytogenetic categories, and patients’ need or lack of dependence on RBC transfusion. This system showed that the requirement for RBC transfusions is a negative prognostic factor for patients in the lower-risk MDS categories. In addition, depth of anemia per se has additive and negative prognostic import for the intermediate IPSS categories. Compared with the 4 groups defined by the IPSS, the WPSS classifies patients into 5 risk groups, differing in both survival and risk of AML: very low, low, intermediate, high, and very high. Malcovati et al initially reported on the usefulness of WPSS, and subsequent studies have confirmed the findings.

The initial WPSS was recently 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 based on transfusion dependency is replaced by the presence (or absence) of severe anemia, defined as hemoglobin levels less than 9 g/dL for men and less than 8 g/dL for women. This approach allows for an objective assessment of anemia, while maintaining the prognostic implications of the 5 risk categories defined in the original WPSS (as mentioned earlier). Currently,
whether the WPSS offers an improvement over the IPSS is a matter of ongoing debate. Based on the current available data, the NCCN MDS Panel included the WPSS in the current version of the treatment algorithm with a category 2B designation.

Most recently, a revised IPSS (IPSS-R) was developed that also defines 5 risk groups (very low, low, intermediate, high, and very high) versus the 4 groups defined in the initial IPSS.\(^6\) The IPSS-R, which was derived from an analysis of a large dataset from multiple international institutions, refined the original IPSS by incorporating the following into the prognostic model: more detailed cytogenetic subgroups, separate subgroups within the “marrow blasts less than 5%” group, and depth of cytopenias defined, with cutoffs for hemoglobin, platelet, and neutrophil counts. In the IPSS-R, the cytogenetic subgroups comprise 5 risk groups (vs 3 in the original IPSS) based on the recently published cytogenetic scoring system for MDS.\(^6\) Other parameters including age, performance status, serum ferritin, lactate dehydrogenase (LDH), and \(\beta_2\)-microglobulin provided additional prognostic information for survival outcomes but not for AML evolution; age as an additional factor was more prognostic among lower-risk versus higher-risk groups.\(^6\) The predictive value of the IPSS-R was recently validated in several independent studies based on registry data, including in studies that evaluated outcomes for patients treated with hypomethylating agents.\(^6\)-\(^9\) In a multiregional study of registry data of patients with MDS from Italy (N=646), significant differences in outcomes among the IPSS-R risk categories were found for overall survival, AML evolution, and progression-free survival (latter defined as leukemic evolution or death from any cause).\(^2\) Notably, in this cohort, the predictive power (based on Harrell’s C statistics) of IPSS-R was found to be greater than IPSS, WPSS, and refined WPSS for the 3 outcome measures mentioned earlier. The investigators acknowledged the short follow-up (median, 17 months) of the study cohort.\(^2\) In a retrospective analysis of data from patients with lower-risk MDS (IPSS low or INT-1) in a large multicenter registry (N=2410) from Spain, the IPSS-R could identify 3 risk categories (very low, low, intermediate) within the IPSS low-risk group, with none of the patients categorized as IPSS-R high or very high.\(^3\) Within the IPSS INT-1 risk group, the IPSS-R further stratified patients into 4 risk categories (very low, low, intermediate, high), but with only 1 patient categorized as very high risk. The IPSS-R was significantly predictive of survival outcomes in both the subgroups of IPSS low and INT-1. Within the IPSS low-risk group, median survival based on the IPSS-R risk categories was 118.8 months for very low, 65.9 months for low, and 58.9 months for intermediate (P<.001). Within the IPSS INT-1 risk group, median survival based on the IPSS-R risk categories was 113.7 months for very low, 60.3 months for low, 30.5 months for intermediate, and 21.2 months for high risk (P<.001).\(^3\) In addition, within the IPSS INT-1 risk group (but not for IPSS low-risk), IPSS-R was significantly predictive of the 3-year rate of AML evolution.\(^2\) Thus, in this analysis, the IPSS-R seemed to provide prognostic refinement within the IPSS INT-1 group, with a large proportion of patients (511 of 1096 those with IPSS INT-1) identified as having poorer prognosis (median survival, 21–30 months). This study also applied the refined WPSS to further stratify the IPSS low and INT-1 risk groups, and was able to identify a group of patients (refined WPSS high-risk group) within the IPSS INT-1 group who had poorer prognosis (185 of 1096 IPSS INT-1 patients; median survival 24.1 months). However, the IPSS-R identified a larger proportion of patients with poor-risk IPSS INT-1 than the refined WPSS (47% vs 17%).\(^3\) Outcomes of risk stratification using the MD Anderson Lower-Risk Prognostic Scoring System are discussed in the following paragraph. In a retrospective database analysis of patients with MDS from a single institution (N=1029), median overall survivals according to IPSS-R risk categories was 82 months for very-low, 57 months for low, 41 months for intermediate, 24 months for high, and 14 months for very-high risk groups (P<.005).\(^2\) The median follow-up in this study was 68 months. IPSS-R was also predictive of survival outcomes among the patients who underwent therapy with hypomethylating agents (n=618). A significant survival benefit with hypomethylating agents was shown only for the group of patients with very-high-risk IPSS-R (median 16 vs 7 months with no hypomethylating therapy; P<.005). In addition, significantly longer overall survival with allogeneic HSCT was only observed for patients with high (median, 42 vs 21 months without HSCT; P=.004) and very high (median, 31 vs 12 months without HSCT; P<.005) risks.\(^2\) The IPSS-R may therefore provide a
tool for therapeutic decision-making, although prospective studies are needed to confirm these findings. Further evaluation is warranted and ongoing regarding the utility of the IPSS-R in both the settings of clinical trials and routine clinical practice.

The Lower-Risk Prognostic Scoring System (LR-PSS) developed by investigators at MD Anderson Cancer Center is another prognostic model used in the evaluation of MDS, and was designed to help identify patients with lower-risk disease (IPSS low or INT-1) who may have poor prognosis. The prognostic model was developed using clinical and laboratory data from patients with IPSS low (n=250) and INT-1 (n=606) MDS. Factors associated with decreased survival were identified and a prognostic model constructed based on results of multivariate Cox regression analysis. The final model included the following factors that were independent predictors for survival outcomes: unfavorable cytogenetics, older age (≥60 years), decreased hemoglobin (<10 g/dL), decreased platelet counts (<50 × 10^9/L or 50–200 × 10^9/L), and higher percentage of bone marrow blasts (≥4%). Important to note, however, is that the cytogenetic categories in this system were derived from the previously defined IPSS categories rather than from the more-refined IPSS-R. Each of these factors were given a weighted score, and the sum of the scores (ranging from 0–7 points) were used to generate 3 risk categories; a score of 0 to 2 points was assigned to category 1, a score of 3 or 4 was category 2, and a score of 5 to 7 was category 3. Using this scoring system, median survival was 80.3 months for category 1, 26.6 months for category 2, and 14.2 months for category 3; the 4-year survival rates were 65%, 33%, and 7%, respectively. The scoring system allowed for further stratification into these 3 risk categories for both the subgroup of patients with IPSS low-risk and IPSS INT-1 risk disease. The LR-PSS could therefore be a useful tool to identify patients with lower risk disease who may have poorer prognosis and may require earlier treatment. The prognostic value of the LR-PSS has been validated in several independent studies. In a retrospective analysis of data from lower risk MDS (IPSS Low or INT-1) patients in the multicenter Spanish registry (N=2410), the LR-PSS was able to further stratify these lower risk patients into 3 risk categories. The LR-PSS was significantly predictive of survival outcomes in the subgroups of patients with IPSS low and INT-1 risk. Within the IPSS low-risk group, median survival using the LR-PSS risk categories was 130.3 months for category 1 (low-risk), 69.7 months for category 2 (intermediate-risk), and 58.4 months for category 3 (high-risk; P<.001); the corresponding median survival values for the patients with IPSS INT-1 risk were 115.2, 51.3, and 24.1 months, respectively (P<.001). The LR-PSS identified an important proportion of patients (334 of 1096 patients; 30.5%) within the IPSS INT-1 risk group who had poorer prognosis (median survival 24 months). In addition, within the IPSS INT-1 risk group (but not for IPSS low-risk), LR-PSS was significantly predictive of the rate of AML evolution at 3 years. In another analysis using data from a cohort of patients with lower-risk MDS from 2 centers (N=664), median survival according to the LR-PSS risk categories was 91.4 months for category 1, 35.6 months for category 2, and 22 months for category 3. Using data from the same cohort of patients, median survival according to the IPSS-R risk groups was 91.4 months for IPSS-R very good, 35.9 months for good, and 27.8 months for the combined intermediate/high/very-high risk groups. Both of these prognostic scoring systems were significantly predictive of survival outcomes. The predictive power (based on Harrell’s C statistics) of LR-PSS and IPSS-R was 0.64 and 0.63, respectively.

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. In patients who were only recently evaluated, determining the relative stability of the patient’s blood counts over several months is important to assess disease progression, including incipient transformation to AML. In addition, this assessment permits determination of other possible causes for cytopenias. The patient’s preference for a specific approach is also important in deciding treatment options. The therapeutic options for MDS include supportive care, low-intensity therapy, high-intensity therapy,
and/or 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.79–81

For the MDS therapeutic algorithm, all patients should undergo relevant supportive care. After that, the panel has proposed initially stratifying patients with clinically significant cytopenias into 2 major risk groups: 1) relatively lower-risk patients (who are in the IPSS low and INT-1 category; IPSS-R very low, low, and intermediate categories; or WPSS very low, low, and intermediate categories); and 2) higher-risk patients (who are in the IPSS INT-2/high categories; IPSS-R intermediate, high, very high categories; or WPSS high, very high categories). Patients in the IPSS-R intermediate category may be managed as very low/low risk or high/very high risk depending on evaluation of additional prognostic factors, such as age, performance status, serum ferritin levels, and serum LDH levels.67 In addition, patients with intermediate-risk whose disease does not respond to therapy for lower-risk disease would be eligible to receive therapy for higher-risk MDS.

Based on IWG response criteria, hematologic improvement is the major therapeutic aim for patients in the lower-risk group, whereas alteration of the disease natural history is viewed as paramount for those in the higher risk group. Cytogenetic response and quality-of-life (QOL) 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 MDS-B [available online, in these guidelines, at NCCN.org] and appropriate NCCN Guidelines for Supportive Care; see list of NCCN Guidelines for Supportive Care, available online, at NCCN.org). This entails observation, clinical monitoring, psychosocial support, and QOL assessment. Major efforts should be directed toward addressing the relevant QOL domains (eg, physical, functional, emotional, spiritual, social) that adversely affect the patient. Supportive care should include RBC 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. Based on differing institutional policies, the panel reached nonuniform consensus regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agreed that all directed-donor and transfused products for potential stem cell transplant patients should be irradiated. Additionally, CMV-negative blood products are recommended whenever possible for CMV-negative recipients. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding episodes refractory to platelet transfusions or for profound thrombocytopenia.

Hematopoietic Cytokines

Hematopoietic cytokine support should be considered for refractory symptomatic cytopenias.82 For example, recombinant human granulocyte colony-stimulating factor (G-CSF) or granulocyte-monocyte colony-stimulating factor (GM-CSF) treatment could be considered for neutropenic patients with MDS with recurrent or resistant bacterial infections.

Erythropoiesis-stimulating agents (ESAs), such as recombinant human erythropoietin (Epo) or darbepoetin, with or without G-CSF, have been evaluated for the treatment of symptomatic anemia in patients with MDS.83–85 In a phase II study in patients with MDS (RA, RARS and RAEB; N=50), Epo combined with G-CSF (n=47 evaluable) resulted in hematologic response in 38% of patients (complete response in 21%).83 Epo and G-CSF seemed to have synergistic activity. Lower serum Epo levels (<500 mU/mL) and lower pretreatment RBC transfusion requirement (<2 units per month) were associated with higher response rate; response rates were not significantly different across IPSS risk groups.83 Median survival (N=71, including patients from a prior study) was 26 months. Among patients with low-risk IPSS, median survival had not been reached at 5 years, and the 5-year survival rate was 68%. Median survivals among INT-1 and INT-2 risk groups were 27 and 14 months, respectively. AML progression occurred in 28% of patients overall during the observation period; the frequencies of AML progression in the low-, INT-1, INT-2, and high-risk groups were...
12%, 21%, 45%, and 100%, respectively. Among responding patients who received maintenance treatment with Epo and G-CSF, the median duration of response was 24 months. A subsequent analysis of long-term outcomes with Epo combined with G-CSF (given 12–18 weeks, followed by maintenance in responders) in patients with MDS (n=121; patients from 3 phase II Nordic trials) reported a hematologic response rate of 39%, with a median duration of response of 23 months. Long-term outcomes of these patients were compared with outcomes from untreated patients (n=237) as controls. Based on multivariate Cox regression analysis, treatment with Epo plus G-CSF was associated with significantly improved survival outcomes (hazard ratio, 0.61; 95% CI, 0.44–0.83; P=.002). An exploratory analysis revealed that the association between treatment and survival was significant only for the IPSS low-risk group. In addition, the survival benefit with treatment was observed only in patients requiring fewer than 2 units of RBC transfusions per month. No significant association was found between treatment and frequency of AML progression. Similar findings were reported in a study from the French group, which analyzed outcomes with ESAs (epoetin or darbepoetin), with or without G-CSF, in patients with MDS with anemia (N=403). Based on IWG 2000 criteria, the hematologic response rate was 62%, with a median duration of response of 20 months. Based on IWG 2006 criteria, the corresponding results were 50% and 24 months, respectively. IPSS low/INT-1 risk was associated with significantly higher response rates and longer response durations. In a comparison of outcomes (in the subset of low/INT-1 risk with anemia) between treated patients (n=284) and a historical cohort of untreated patients (n=225), multivariate analysis showed a significant association between treatment with ESAs and survival outcomes. The frequency of AML progression was similar between the cohorts. In a phase II study evaluating darbepoetin (given every 2 weeks for 12 weeks), with or without G-CSF (added at 12 weeks in nonresponders), in patients with MDS with lower-risk IPSS with anemia (and with serum Epo levels <500 mU/mL), hematologic response rate was 48% at 12 weeks and 56% at 24 weeks. Median duration of response was not reached, with a median follow-up of 52 months. The 3-year cumulative incidence of AML progression was 14.5% and the 3-year survival rate was 70%. This study also showed improvements in QOL parameters among responding patients. Collectively, these studies suggest that ESAs may provide clinical benefit in patients with lower-risk MDS with symptomatic anemia. Limited data are available on the effectiveness of ESAs in the treatment of anemia in lower-risk patients with del(5q). Epo has been shown to promote the growth of cytokytopenically normal cells isolated from patients with del(5q), while having minimal proliferative effects on MDS progenitor cells from these patients in vitro. Retrospective studies from the French group reported hematologic response rates of 46% to 64%, with a median duration of response of 11 months (and mean duration of 13–14 months) among patients with del(5q) treated with ESAs, with or without G-CSF. Duration of response in these patients was significantly decreased compared with that in patients without del(5q) (mean duration, 25–27 months). Based on multivariate analysis, del(5q) was a significant predictor of shorter response duration with treatment. The use of ESAs to treat symptomatic anemia is discussed further in “Therapy for Lower Risk Patients” and “Evaluation and Treatment of Related Anemia” on pages 863 and 865, respectively.

Severe thrombocytopenia is associated with increased risks for bleeding events, and is currently managed with platelet transfusions. The mechanism of thrombocytopenia in patients with MDS may be attributed to decreased platelet production (possibly related to regulatory pathways involving the production and/or metabolism of endogenous thrombopoietin [TPO]) and increased destruction of bone marrow megakaryocytes or circulating platelets. Endogenous TPO levels have been reported to be increased among patients with MDS compared with those of healthy individuals. At the same time, TPO receptor (c-mpl) sites per platelet seem to be decreased among patients with MDS compared with healthy subjects. Among patients with MDS, those with RA seemed to have the highest TPO levels compared with those with RAEB or RAEB-T, whereas the number of TPO receptor sites remained similar across subtypes.

In addition, studies have reported that high endogenous TPO levels correlated with decreased platelet counts in patients with RA, but not in patients with RAEB or RAEB-T. This observation suggests that the regulatory pathway for endogenous...
TPO may be further disrupted in patients with RAEB or RAEB-T, potentially because of overexpression of TPO receptors in blasts that may lead to inadequate TPO response. Several studies are investigating the role of the thrombopoietin receptor agonist romiplostim in the treatment of thrombocytopenia in patients with lower-risk MDS. Phase I/II studies with romiplostim showed promising rates of platelet response (46%–65%) in patients with lower-risk MDS. Recent randomized placebo-controlled studies in patients treated for lower-risk MDS have reported beneficial effects of romiplostim in terms of decreased bleeding events and reduced needs for platelet transfusions in patients receiving hypomethylating agents, and decreased frequency of dose reductions or delays in those receiving lenalidomide therapy. Eltrombopag is another thrombopoietin receptor agonist that has been shown to increase normal megakaryopoiesis in vitro in bone marrow cells isolated from patients with MDS. Ongoing phase I and II clinical trials are investigating the activity and safety of this agent in the treatment of thrombocytopenia in patients with MDS. Concerns for potential proliferation of leukemic blasts in response to exogenous TPO were raised in early in vitro studies in the past, particularly for patients with high-risk MDS. Results from ongoing clinical trials with the TPO mimetics mentioned earlier will help to elucidate the risks for leukemic transformations in patients with MDS. Neither romiplostim nor eltrombopag is currently approved for use in patients with MDS.

Low-Intensity Therapy

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

Hypomethylating Agents

As a form of relatively low-intensity chemotherapy, randomized phase III trials have shown that the DNA methyltransferase inhibitor (DMTI) hypomethylating agents 5-azacytidine (AzaC) and decitabine (5-aza-2′-deoxycytidine) decrease the risk of leukemic transformation, and, in a portion of the patients, improve survival. In one trial comparing 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 those receiving supportive care. The median time to AML progression or death was significantly prolonged with AzaC compared with supportive care (21 vs 13 months; P=.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 et al provided a summary of 3 studies of AzaC in a total of 306 patients with high-risk MDS. In this analysis, which included patients receiving either subcutaneous or intravenous delivery of the drug (75 mg/m²/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of patients treated with AzaC, partial remissions were rare, and 23% to 36% of patients had hematologic improvement. Of the responses, 90% were seen by cycle 6 and the median number of cycles to first response was 3. The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. Results from a phase III randomized trial in patients (N=358) with higher-risk MDS (IPSS INT-1, 5%; INT-2, 41%; high-risk, 47%) showed that AzaC was superior to conventional care (standard chemotherapy or supportive care) in terms of overall survival. 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=.0001), thus providing support for the use of this agent in patients with higher-risk disease. AzaC therapy should be considered for treating patients with MDS with progressing or relatively high-risk disease. It is FDA-approved for the treatment of patients with MDS and is generally administered at a dose of 75 mg/m²/d subcutaneously for 7 days every 28 days for at least 4 to 6 courses. Treatment courses may need to be extended further or may be used as a bridging therapy to more definitive therapy (eg, HSCT for patients whose marrow blast counts require lowering before that procedure). Although the optimal duration of therapy with AzaC has not been defined, some data suggest that continuation of AzaC beyond first response may improve
remission quality. Secondary analysis from the aforementioned phase III randomized trial of AzaC in patients with higher-risk MDS\textsuperscript{101} showed that among patients responding to AzaC, response quality was improved in 48% with continued therapy; although most responding patients achieved a first response by 6 cycles of therapy, up to 12 cycles was required for most responders to attain a best response.\textsuperscript{106} In this study, the median number of cycles from first response to best response was 3 to 3.5 cycles, and responding patients received a median of 8 additional cycles (range, 0–27 cycles) beyond first response.\textsuperscript{106} An alternative 5-day schedule of AzaC has been evaluated, both as a subcutaneous regimen (including the 5-2-2 schedule [75 mg/m\textsuperscript{2}/d subcutaneously for 5 days followed by 2 days of no treatment, then 75 mg/m\textsuperscript{2}/d for 2 days, every 28 days] and the 5-day schedule [75 mg/m\textsuperscript{2}/d subcutaneously for 5 days every 28 days]) and as an intravenous regimen (75 mg/m\textsuperscript{2}/d intravenously for 5 days every 28 days).\textsuperscript{108} Although response rates with the 5-day regimens seemed to be similar to those for the approved 7-day dosing schedule,\textsuperscript{107,108} survival benefit with AzaC has only been shown using the 7-day schedule.

Similarly, the other DMTI hypomethylating agent, decitabine, given intravenously and administered with a regimen that requires hospitalization, has also shown encouraging results in patients with higher-risk MDS. Because the treatment regimen was generally associated with low-intensity–type toxicities, it is also considered to be “low-intensity therapy.” In earlier phase II studies, the drug resulted in cytogenetic conversion in approximately 30% of patients,\textsuperscript{109} with an overall response rate of 49% and a 64% response rate in patients with a high-risk IPSS score.\textsuperscript{110} The results of these studies were similar to those for AzaC.\textsuperscript{111,112}

The results of a phase III randomized trial of decitabine (15 mg/m\textsuperscript{2} intravenous infusion over 3 hours every 8 hours [ie, 45 mg/m\textsuperscript{2}/d] on 3 consecutive days every 6 weeks for up to 10 cycles) versus supportive care in adult patients (N=170) with primary and secondary MDS with IPSS INT-1 (31%), INT-2 (44%), and high-risk (26%) disease indicated higher response rates, longer remission duration, longer time to AML progression, and greater survival benefit in the INT-2 and high-risk groups.\textsuperscript{102,111} Overall response rate (complete response plus partial response) 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 patients receiving supportive care than for those receiving decitabine. Based on results of this study and 3 supportive phase II trials,\textsuperscript{111} the FDA also approved the drug for treating MDS.

In a recent phase III randomized trial, decitabine was compared with best supportive care in older patients aged 60 years or older (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.\textsuperscript{103} Median progression-free survival was significantly improved with decitabine compared with supportive care (6.6 vs 3.0 months; hazard ratio, 0.68; 95% CI, 0.52–0.88; \textit{P}=.004) and the risk of AML progression at 1 year was significantly reduced with decitabine (22% vs 33%; \textit{P}=.036). However, no significant differences were observed between decitabine and supportive care for the primary end point of overall survival (10.0 vs 8.5 months, respectively) or for median AML-free survival (8.8 vs 6.1 months, respectively).\textsuperscript{103} 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.\textsuperscript{103}

Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated. In 2007, Kantarjian et al\textsuperscript{114} provided an update of their results in 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens. Patients received 1 of 3 different schedules of decitabine, including both subcutaneous and intravenous administration, and a mean of 7 courses of therapy. Responses were improved with this longer duration of therapy. Overall, 80 patients (70%) experienced a response, with 40 patients (35%) experiencing a complete response and 40 (35%) a partial response. The median remission duration was 20 months and the median survival time was 22 months. Kantarjian et al\textsuperscript{115} also compared the 3 different
schedules of decitabine in a study randomizing 95 patients with MDS or CMML to either 20 mg/m²/d intravenously for 5 days; 20 mg/m²/d subcutaneously for 5 days; or 10 mg/m²/d intravenously for 10 days. The 5-day intravenous schedule was considered the optimal schedule, with a complete response rate in this arm of 39% compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day intravenous arm (P<.05).

Several retrospective studies have evaluated the role of cytoreductive therapy with hypomethylating agents before allogeneic HSCT (with both myeloablative and reduced-intensity conditioning regimens). Results suggest that hypomethylating agents may provide a feasible alternative to induction chemotherapy regimens before transplant, and may serve as a bridge to allogeneic HSCT.

Currently, AzaC and decitabine are considered to be therapeutically relatively similar, although the improved survival of higher-risk patients treated with AzaC compared with controls seen in a phase III trial, as indicated earlier, supports the preferred use of AzaC in this setting. “Failure to respond to hypomethylating agents” is considered if a lack of complete response, partial response, or hematologic improvement is seen; frank progression to AML occurs, particularly with loss of control (proliferation) of peripheral counts; or excess toxicity precludes continuation of therapy. The minimum number of courses before the treatment is considered a failure should be 4 to 6 courses. As discussed earlier, the optimal duration of therapy with hypomethylating agents has not been well defined and no consensus exists. The NCCN MDS Panel generally feels that treatment should be continued in the presence of an ongoing response and no toxicities, in which case modifications should be made to the dosing frequency for individual patients.

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

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

In addition, hypomethylating agents are appropriate options for patients with IPSS low- or INT-1-risk or IPSS-R very low- or low-risk disease without symptomatic anemia, or with symptomatic anemia and elevated serum Epo levels who are not expected to experience a response to (or who relapsed after) immunosuppressive therapy.

### Biologic Response Modifiers and Immunosuppressive Therapy

The currently available nonchemotherapy low-intensity agents (biologic response modifiers) include antithymocyte globulin (ATG), cyclosporine, thalidomide, lenalidomide, anti–tumor necrosis factor receptor fusion protein, and vitamin D analogues, all of which have shown some efficacy in phase I and II trials.

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

Both equine and rabbit ATG are available in the United States for immunosuppressive therapy. A randomized study from the NIH compared the activity of equine versus rabbit ATG, combined with cyclosporine, in previously untreated patients with severe aplastic anemia (N=120) who were not eligible for transplant. This study showed that in this patient population, rabbit ATG was inferior to
equimyeloid ATG, as shown by the lower 6-month hematologic response rate (primary end point, 37% vs 68%; \(P<.001\)) and higher number of deaths (14 vs 4 patients), resulting in decreased survival rates among patients treated with rabbit ATG. The 3-year survival rate was also significantly lower with rabbit ATG compared with equine ATG (76% vs 96%; \(P=.04\)).128 The 3-year cumulative incidence of relapse was not significantly different between treatment groups (11% vs 28%, respectively).127 Within the setting of MDS, however, only limited data are available regarding the comparative effectiveness of the 2 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.129

Lenalidomide (a thalidomide analog) is an immunomodulating agent that has shown activity in patients with lower-risk MDS.11,130 Beneficial results have been particularly evident for patients with del(5q) chromosomal abnormalities.11,130,131 In a multicenter phase II trial of lenalidomide, given at a dose of 10 mg/d for 21 days every 4 weeks or 10 mg/d to 148 patients with MDS with del(5q) and RBC transfusion–dependent anemia, with or without additional cytogenetic abnormalities, hematologic response was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained.11 RBC transfusion independence (assessed at 24 weeks) occurred in 67% of patients, and in 69% of those with IPSS low/INT-1 risk (n=120).11 Cytogenetic responses were achieved in 62 of 85 evaluable patients (73%); 45% had a complete cytogenetic response. The most common grade 3 or 4 adverse events included myelosuppression (neutropenia in 55%; thrombocytopenia in 44%), which often required treatment interruption or dose reduction. Thus, careful monitoring of blood counts during the treatment period is mandatory when using this agent, particularly in patients with renal dysfunction (because of the drug’s renal route of excretion). The FDA approved lenalidomide for treating patients with IPSS low-/INT-1–risk MDS with del(5q) and transfusion-dependent anemia, with or without additional cytogenetic abnormalities.

A recent randomized controlled phase III trial compared the activity of lenalidomide (5 mg/d for 28 days or 10 mg/d for 21 days of a 28-day cycle) versus placebo in 205 patients with lower-risk MDS (IPSS low- and INT-1 risks) with del(5q) and transfusion-dependent anemia.132 The primary end point of RBC transfusion independence for 26 weeks or more was achieved in a significantly greater proportion of patients treated with lenalidomide, 5 mg or 10 mg, versus those treated with placebo (43% vs 56% vs 6%, respectively; \(P<.001\) for both lenalidomide groups vs placebo). Among patients achieving RBC transfusion independence with lenalidomide, onset of erythroid response was rapid, with 86% of patients experiencing response onset within the first 2 cycles (49% in cycle 1).132 Among patients treated with lenalidomide with baseline serum Epo levels greater than 500 mU/mL, the 10-mg dose resulted in significantly higher rates of RBC transfusion independence compared with the 5-mg dose (76% vs 33%; \(P=.004\)). Cytogenetic response rates were significantly higher for the lenalidomide 5- or 10-mg arms compared with placebo (25% vs 50% vs 0%, respectively; \(P<.001\) for both lenalidomide groups vs placebo; \(P = \) not significant between the lenalidomide dose groups), and complete response rates were observed in 16% and 29% of patients in the lenalidomide 5- 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 or 4 adverse events were myelosuppression and deep vein thrombosis (DVT). Grade 3 or 4 neutropenia was reported in 74%, 75%, and 15% of patients in the lenalidomide 5 mg, 10 mg, and placebo arms, respectively; thrombocytopenia occurred in 33%, 41%, and 1.5%, respectively. Grade 3 or 4 DVT occurred in 4 patients (6%) in the lenalidomide 10-mg arm, and 1 patient each in the lenalidomide 5-mg (1%) and placebo (1.5%) arms.132

A recent comparative analysis evaluated outcomes with lenalidomide (based on data from the 2 aforementioned trials; n=295) compared with no treatment (based on data from untreated patients in a multicenter registry; n=125) in patients with IPSS low-/INT-1–risk MDS with del(5q) RBC transfusion–dependent anemia.133 Untreated patients from the registry had received best supportive care, including RBC transfusion, iron chelation therapy, and/or ESAs. The 2-year cumulative incidence of AML progression was 7% with lenalidomide and 12% in the untreated cohort; the corresponding 5-year rate was
23% and 20%, respectively. Thus, the median time to AML progression has not been reached in either cohort. Lenalidomide was not a significant factor for AML progression in either univariate or multivariate analyses. The 2-year overall survival probability was 90% with lenalidomide and 74% in the untreated cohort; the corresponding 5-year probability was 54% and 40.5%, respectively. The median overall survival was 5.2 and 3.8 years, respectively (P=.755; Kaplan-Meier plot with left truncation to adjust for differences in timing of study entry between cohorts).133 Based on multivariate analysis using Cox proportional hazard models (also with left truncation), lenalidomide was associated with significantly decreased risk of death compared with no treatment (hazard ratio, 0.597; 95% CI, 0.399–0.894; P=.012). Other independent factors associated with decreased risk of death were female sex, higher hemoglobin levels, and higher platelet counts. Conversely, independent factors associated with increased risk of death included older age and greater RBC transfusion burden.131

A phase II study evaluated lenalidomide treatment in 214 transfusion-dependent patients with low- or INT-1–risk MDS without the del(5q).134 Results showed 26% of the non-del(5q) patients (56 of 214) experienced transfusion independence after a median of 4.8 weeks of treatment. This transfusion independence continued for a median duration of 41 weeks, and the median rise in hemoglobin was 3.2 g/dL (range, 1.0–9.8 g/dL). A 50% greater reduction in transfusion requirement was noted in an additional 37 patients (17%), yielding an overall rate of hematologic improvement of 43%. The most common grade 3 or 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 patients with non-del(5q) MDS. The NCCN MDS Panel recommends lenalidomide be considered for treating non-del(5q) patients with symptomatic anemia that did not respond to initial therapy.

High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy, or HSCT.131,135 Although these approaches have the potential to change the natural history of the disease, they also have an attendant greater risk of regimen-related morbidity and mortality. The panel recommends giving these treatments in the context of clinical trials. Comparative studies have not shown benefit between the different intensive chemotherapy regimens (including idarubicin-, cytarabine-, fludarabine-, and topotecan-based regimens) in MDS.136

A high degree of multidrug resistance occurs in marrow hematopoietic precursors in patients with advanced MDS,137 with associated decreased responses and shorter response durations associated with many standard treatment regimens of induction chemotherapy. Thus, chemotherapeutic agents used to treat “resistant-type” AML and agents that modulate this resistance are now being evaluated for treating patients with advanced MDS. Although several studies using modulators of multidrug resistance showed positive results in this setting,138,139 others did not.140 Further clinical trials evaluating other modulators of multidrug resistance are ongoing.

Allogeneic HSCT from an HLA-matched sibling donor is a preferred approach for treating a select group of patients with MDS, particularly those with high-risk disease.141–146 Matched nonmyeloablative transplant regimens and matched unrelated donor stem cell transplants are becoming options at some centers to treat these patients.149–157 In certain investigative settings, autologous bone marrow or peripheral blood stem cell transplantation is being considered.158 Whether transplants should be performed before or after patients experience remission following induction chemotherapy has not been prospectively established.159 Comparative clinical trials are needed to determine these points.

**Recommended Treatment Approaches**

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

Regarding the algorithm for therapeutic options for the lower-risk patients with clinically significant cytopenias or increased bone marrow blasts, the NCCN MDS Panel recommends stratifying these patients into several groups. Those with del(5q) chromosomal abnormalities and symptomatic anemia should receive lenalidomide. The recommended dose in this setting is 10 mg once daily for 21 days, every 28 days; response should be assessed 2 to 4 months after initiation of treatment. However, lenalidomide should be avoided in patients with clinically significant de-
crease in neutrophil counts or platelet counts; in the previously discussed phase III trial with lenalidomide in patients with del(5q), those with low neutrophils (<500/mcL) or platelet counts (<25,000/mcL) were excluded. An alternative option in patients with del(5q) and symptomatic anemia may include an initial trial of ESAs in patients who have serum Epo levels of 500 mU/mL or less.

Other patients with symptomatic anemia are categorized based on their serum Epo levels. Those with levels of 500 mU/mL or less should be treated with ESAs (recombinant human Epo or darbepoetin) with or without G-CSF (see “Evaluation and Treatment of Related Anemia,” facing page). Nonresponders should be considered for immunosuppressive therapy (with ATG or cyclosporine) if they have a high likelihood of experiencing a response to this therapy. In lower-risk MDS, the most appropriate candidates for immunosuppressive therapy include patients who are aged 60 years or younger, are HLA-DR15–positive, have a PNH-positive clone, or have 5% or less marrow blasts or hypocellular marrow. Alternatively, or in patients who experience no response to immunosuppressive therapy, treatment with AzaC, 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 “Allogeneic HSCT,” opposite column).

Patients with anemia whose serum Epo levels are greater than 500 mU/mL should be evaluated to determine whether they have a good probability of response to immunosuppressive therapy. Nonresponders to immunosuppressive therapy would be considered for treatment with AzaC, decitabine, or a clinical trial. Patients with serum Epo levels greater than 500 mU/mL who have a low probability of responding to immunosuppressive therapy should be considered for treatment with AzaC, decitabine, or lenalidomide. Others or nonresponders to these treatments could be considered for a clinical trial or for allogeneic HSCT. Patients without symptomatic anemia who have other clinically relevant cytopenias (particularly clinically severe thrombocytopenia) or increased bone marrow blasts should be considered for treatment with AzaC or decitabine, immunosuppressive therapy (if there is a good probability of responding to these agents), 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 = 0.003); 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. Patients who do not respond to hypomethylating agents should be considered for treatment with immunosuppressive therapy, a clinical trial, or allogeneic HSCT.

Careful monitoring for disease progression and consideration of patient 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 INT-2 and High; IPSS-R Intermediate, High, and Very High; or WPSS High and Very High)**

Treatment for higher-risk patients depends on whether they are believed to be candidates for intensive therapy (eg, 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 preference, and availability of a suitable donor and caregiver. In addition, the patient’s personal preference for type of therapy needs particular consideration. Supportive care should be provided for all patients.

**Intensive Therapy: Allogeneic HSCT:** The potential for patients to undergo allogeneic HSCT depends on several factors, including patient age, performance status, major comorbid conditions, psychosocial status, availability of a caregiver, IPSS or WPSS score, and the availability of a suitable donor. For patients who are transplant candidates, the first choice of donor has remained an HLA-matched sibling, although results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA haplidential 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-intensity conditioning (RIC) for HSCT is generally the strategy in older individuals.

To aid therapeutic decision-making regarding the timing and selection of patients for HSCT, a study compared outcomes with HLA-matched sib-
ling HSCT in patients with MDS aged 60 years or younger to the data in nontreated patients with MDS from the IMRWA/IPSS database.\textsuperscript{161} Using a Markov decision analysis, this investigation indicated that IPSS INT-2 and high-risk patients aged 60 years or younger had the highest life expectancy if they underwent transplantation (from HLA-identical siblings) soon after diagnosis, whereas patients with IPSS low-risk had the best outlook if HSCT was delayed until disease progression. Patients in the INT-1 risk group had only a slight gain in life expectancy if HSCT was delayed, and therefore decisions should probably be made on an individual basis in these patients (eg, dependent on platelet or neutrophil counts).\textsuperscript{167} A study published in 2008 retrospectively evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT.\textsuperscript{61} 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).\textsuperscript{61}

Based on data regarding RIC for transplantation from 2 reported series\textsuperscript{162,163} and 2 comprehensive reviews of this field,\textsuperscript{164,165} patient age and disease status generally dictate the type of conditioning to be used. Patients older than 55 or 60 years, particularly if they have fewer than 10% marrow myeloblasts, would generally undergo HSCT after RIC; if the blast count is high, pre-HSCT debulking therapy is generally given. Younger patients, regardless of marrow blast burden, will generally receive high-dose conditioning. Variations on these approaches would be considered by individual transplant physicians based on these features and the specific regimen used at their center. Some general recommendations are presented in the review article by Deeg and Sandmaier.\textsuperscript{166}

Intensive Chemotherapy: For patients eligible for intensive therapy but lacking a stem cell donor, or for those requiring marrow blast count reduction, intensive induction chemotherapy should be considered.\textsuperscript{167} 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 patients with a potential stem cell donor who require reduction of their tumor burden (ie, to decrease the marrow blast count), even a partial remission may be adequate to permit the HSCT. For this purpose, AzaC, decitabine, and participation in clinical trials are also considered valid treatment options.

Nonintensive Therapy: For higher-risk patients who are not candidates for intensive therapy, the use of AzaC or decitabine or enrollment in a relevant clinical trial should be considered. Based on the recently published results of the phase III trial showing superior median survival in patients receiving AzaC compared with best supportive care, the NCCN MDS Panel made this a preferred category 1 recommendation compared with decitabine. Results from another recent phase III trial comparing decitabine and supportive care in higher-risk patients failed to show a survival advantage, although response rates are similar to those reported previously for AzaC.\textsuperscript{103,168} However, no trials have compared AzaC head-to-head with decitabine.

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

Supportive Care Only: For patients with adverse clinical features or disease progression despite therapy and absence of reasonable specific antitumor therapy, 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, health care providers must identify and treat any coexisting causes of anemia.

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

Anemia related to MDS generally presents as a hypoproliferative macrocytic anemia, often associated with suboptimal elevation of serum Epo levels. To determine WHO 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 earlier.

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

Iron repletion must be verified before instituting 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. This is particularly evident for patients with 15% or more ringed sideroblasts in the marrow (and serum Epo level ≤500 mU/mL), because the very low response rates in this subgroup to Epo or darbepoetin alone are markedly enhanced when combined with G-CSF.

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in patients who are initially neutropenic or to double the neutrophil count in patients who are initially normal. For this purpose, an average of 1 to 2 mcg/kg subcutaneously is administered daily or 1 to 3 times per week. Darbepoetin alfa is a longer-acting form of Epo. Studies predominantly involving patients with lower-risk MDS have shown a substantial proportion of erythroid responses with the initial trials, showing response rates of 40% and 60% (combined major and minor responses using IWG response criteria). Results of clinical trials in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than those to epoetin.

These response rates may be partly from the dosage used (150–300 mcg/wk, subcutaneously) or to the fact that better-risk patients were enrolled in studies of darbepoetin than in those of 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 ESAs. They noted that increased mortality, possible tumor promotion, and thromboembolic events were observed in patients without MDS receiving ESAs when dosing targeted hemoglobin levels greater than 12 g/dL (study patients had chronic kidney failure; were receiving radiation therapy for various malignancies, including head and neck, advanced breast, lymphoid, or non–small cell lung cancers; had cancer but were not receiving chemotherapy; or were orthopedic surgery patients).
However, as indicated earlier, ESAs have been used safely in large numbers of adults with MDS and have become important for symptomatic improvement of the anemia caused by this disease, often with a decrease in RBC transfusion requirements. The NCCN MDS Panel recommendations for using 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 patients with MDS compared with either randomized or historical controls have shown no negative impact of this treatment on survival or AML evolution. In addition, results of the studies by Jadersten et al indicated improved survival in patients with low-risk MDS with low transfusion need treated with these agents. The study by Park et al further indicated improved survival and decreased AML progression of patients with IPSS low/INT-1 disease treated with Epo/G-CSF compared with the historical control IMRAW database patients. Thus, the data do not indicate a negative impact of these drugs for treatment of MDS. Given these data, the NCCN MDS Panel endorses and reiterates the prior recommendations for ESA use in the management of symptomatic anemia in MDS, with a target hemoglobin range of 10 to 12 g/dL; the target should not exceed 12 g/dL.

In July 2007, the Centers for Medicare & Medicaid Services 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 (ie, not restricting ESA use in MDS through the NCD). Thus, local Medicare contractors may continue to make reasonable and necessary determinations on uses of ESAs that are not determined by the NCD.

Clinical trials with other experimental agents that are reportedly capable of increasing hemoglobin levels should be explored in patients whose disease is 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 were recently approved by the FDA for treating specific subtypes of MDS: lenalidomide for patients with del(5q) cytogenetic abnormalities; AzaC and decitabine for treating patients with higher risk or nonresponsive MDS; and deferasirox for iron chelation of patients with iron overloaded MDS. However, because a substantial proportion of 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 managing thrombocytopenia in MDS needs further evaluation. In addition, further determination of the effects of these therapeutic interventions on patient QOL is important.

Progress toward improving management of MDS has occurred over the past few years, and more of these advances are anticipated using these guidelines as a framework for coordinating comparative clinical trials.

References


Myelodysplastic Syndromes


Myelodysplastic Syndromes


Myelodysplastic Syndromes


Myelodysplastic Syndromes


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The NCCN guidelines staff have no conflicts to disclose.