NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes


NCCN.org

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# NCCN Guidelines Version 1.2016 Panel Members

## Myelodysplastic Syndromes

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<thead>
<tr>
<th>Panel Member</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

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

NCCN Myelodysplastic Syndromes Panel Members

Summary of Guidelines Updates

Initial Evaluation (MDS-1)

Additional Testing and Classification (MDS-2)

2008 WHO Classification of MDS (MDS-3)

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) WHO Classification (MDS-4)

International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System (IPSS-R) (MDS-5)

WHO-Based Prognostic Scoring System (WPSS) (MDS-6)

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Prognostic Category Low, Intermediate-1 Treatment (MDS-9)

Prognostic Category Intermediate-2, High Treatment (MDS-11)

Evaluation of Related Anemia/Treatment of Symptomatic Anemia/Follow-up (MDS-12)

Recommendations for Flow Cytometry (MDS-A)

Supportive Care (MDS-B)

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Updates in Version 1.2016 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 2.2015 include:

**MDS-2**
- Modified footnote l: “Germline mutations of \textit{RUNX1} or \textit{GATA2} can be found in some families with inherited thrombocytopenia and MDS. Inherited bone marrow failure syndromes, like Fanconi anemia, dyskeratosis congenita (DKC), and disorders with mutations of telomerase complex genes, will demonstrate shortened telomere length. Telomere length can be measured by fluorescence in situ hybridization (FISH) assays using leukocyte samples.”

**MDS-3**
- Following Myelodysplastic syndrome, unclassified, under Blood, added “± 1% blasts”

**MDS-7**
- Following SF3B1, under Clinical Significance, removed “Frequently mutated in CLL (15%).”

**MDS-8**
- Added the following references:

**MDS-11**
- The flow chart was reorganized.
- Changed “donor available” to “donor stem cells available.”
- Added “Consider HCT or donor lymphocyte infusion (DLI)” to the algorithm.
- Added the following sentence to footnote tt: “In patients who have clinical benefit, continue treatment with hypomethylating agent as maintenance therapy.”
- Modified footnote vv, “Consider second transplant or DLI immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.”

**MDS-12**
- Modified footnote mm: “Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days or 28 days monthly for 2 to 4 months to assess response (See Discussion)...”

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INITIAL EVALUATION

Cytopenia(s), suspect myelodysplasia

Required:
- H&P
- Complete blood count (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)
- Red blood cell (RBC) folate, serum $B_{12}\text{d}$
- 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 (MDS-2)

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*aMDS is also suspected in the presence of acquired MDS-related cytogenetic abnormalities, and in the unexpected increase in blasts or dysplasia.

*b Confirm diagnosis of MDS according to WHO/NCCN criteria for classification with application of IPSS or IPSS-R. 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 Initial Evaluation in the Discussion).

*c Patients with significant cytopenias and karyotypes t(8;21), t(15;17), or inv(16) or variants should be considered to have AML. (See NCCN Guidelines for AML).

*dRBC folate is a more representative measure of folate stores and is the preferred test to serum folate. Serum methylmalonic acid testing is an accurate way to assess $B_{12}$ status.

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**ADDITIONAL TESTING**

**Helpful in Some Clinical Situations:**

- Consider flow cytometry (FCM) for MDS diagnostic aid\(^6\) to assess possible large granular lymphocyte (LGL) disease\(^f\) and to evaluate for paroxysmal nocturnal hemoglobinuria (PNH) clone\(^g\)
- Human leukocyte antigen (HLA) typing if hematopoietic cell transplant (HCT) candidate\(^h\)
- Consider HLA-DR15 typing\(^i\)
- HLA typing if indicated for platelet support
- HIV testing if clinically indicated
- Evaluate chronic myelomonocytic leukemia (CMML) patients for 5q31-33 translocations and/or \(PDGFR\beta\) gene rearrangements\(^j\)
- Consider molecular testing for recurrently mutated MDS genes in appropriate clinical contexts\(^k\)
- Consider additional genetic screening for patients with familial cytopenias, particularly for younger patients\(^l\)
- Consider evaluation of copper deficiency

\(^6\)See Recommendations for Flow Cytometry (MDS-A) and Discussion.

\(^f\)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 (ed 4th). Lyon: IARC; 2008:272-273.

\(^g\)FCM analysis of granulocytes and monocytes from blood with FLAER (fluorescent aerolysin) and at least one GPI-anchored protein to assess the presence of a PNH clone. Borowitz MJ, Craig FE, Diigiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry B Clin Cytom 2010;78:211-230.

\(^h\)Donors should be evaluated by high-resolution allele level typing for HLA-A, -B, -C, -DR, and -DQ. All full siblings should be evaluated for HLA match prior to unrelated donor match.

\(^i\)To assist determination of patient’s potential responsiveness to immunosuppressive therapy.

\(^j\)CMML patients with this abnormality may respond well to tyrosine kinase inhibitors (TKIs) such as imatinib mesylate.

\(^k\)Bone marrow or peripheral blood may be assayed for MDS-associated gene mutations. These can establish the presence of clonal hematopoiesis, which can help exclude benign causes of cytopenias in cases with non-diagnostic morphology, but do not establish a diagnosis of MDS in the absence of clinical diagnostic criteria (See Table MDS-7). Certain gene mutations (\(TP53\), \(ASXL1\), \(ETV6\), \(RUNX1\), and \(EZH2\)) can refine the prognosis of MDS in patients risk stratified by the IPSS or IPSS-R and may be helpful in patients predicted to have intermediate risk. Consider molecular testing for \(JAK2\) mutation in MDS patients with thrombocytosis. (See Table on MDS-7 and Discussion).

\(^l\)Germline mutations of \(RUNX1\) or \(GATA2\) can be found in some families with inherited thrombocytopenia and MDS. Inherited bone marrow failure syndromes, like Fanconi anemia, dyskeratosis congenita (DKC), and disorders with mutations of telomerase complex genes, will demonstrate shortened telomere length. 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\(^m,n\)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD)(^o)</td>
<td>Single or bcytopenia</td>
<td>Dysplasia in ≥10% of one cell line, &lt;5% blasts</td>
</tr>
<tr>
<td>Refractory anemia with ring 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, 5%–9% blasts, no Auer rods</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, 10%–19% blasts, ± Auer rods</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias, ±1% blasts</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)(^n)</td>
<td>Cytopenias, 5%–19% blasts</td>
<td>Multilineage dysplasia, 20%–30% blasts, ± Auer rods</td>
</tr>
</tbody>
</table>

\(^m\)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. IARC, Lyon, 2008.

\(^n\)In the 2008 WHO classification, RAEB-T patients with 20% to 30% blasts AND a stable clinical course for at least 2 months can be considered as either MDS or AML, (as previously classified by the FAB group, Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189-199) is classified as AML with myelodysplasia-related changes and may be more akin to MDS than AML. Refer to Arber DA, Bruning RD, Orazi A, et al. Acute myeloid leukaemia with myelodysplasia-related changes. In Chapter 6. Acute Myeloid Leukemia and Related Precursor Neoplasms, in Swerdlow S, Campo E, Harris NL, et al (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC, Lyon, 2008, pp 124-126.

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

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### CLASSIFICATION SYSTEMS FOR DE NOVO MDS (page 2 of 4)

**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 (CMML)-1</td>
<td>&gt;1x10⁹/L monocytes, &lt;5% blasts</td>
<td>Dysplasia in ≥1 hematopoietic line, &lt;10% blasts</td>
</tr>
<tr>
<td>CMML-2</td>
<td>&gt;1x10⁹/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;13x10⁹/L, neutrophil precursors &gt;10%, &lt;20% blasts, dysgranulopoiesis</td>
<td>Hypercellular, &lt;20% blasts</td>
</tr>
<tr>
<td>Juvenile myelomonocytic leukemia (JMML)</td>
<td>&gt;1x10⁹/L monocytes, &lt;20% blasts</td>
<td>&gt;1x10⁹/L monocytes</td>
</tr>
<tr>
<td>MDS/MPN, unclassifiable (&quot;Overlap syndrome&quot;)</td>
<td>Dysplasia + myeloproliferative features, No prior MDS or MPN</td>
<td>Dysplasia + myeloproliferative features</td>
</tr>
</tbody>
</table>

**AML with myelodysplasia-related changes**

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

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### International Prognostic Scoring System (IPSS)\(^x,y\)

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marrow blasts (%)(^z)</th>
<th>5-10</th>
<th>---</th>
<th>11-20</th>
<th>21-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype(^aa)</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Cytopenia(^bb)</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Revised International Prognostic Scoring System (IPSS-R\(^cc\))

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyto genetic(^dd)</th>
<th>Very good</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
<th>Very poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow blasts (%)(^z)</td>
<td>≤2</td>
<td>&gt;2-&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Survival and AML evolution

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

#### IPSS-R Risk category (% IPSS-R pop.)

<table>
<thead>
<tr>
<th>IPSS-R Risk category (% IPSS-R pop.)</th>
<th>Overall score</th>
<th>Median survival (y) in the absence of therapy</th>
<th>25% AML progression (y) in the absence of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY LOW (19)</td>
<td>≤1.5</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>LOW (38)</td>
<td>&gt;1.5-≤3.0</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>INT (20)</td>
<td>&gt;3.0-≤4.5</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>HIGH (13)</td>
<td>&gt;4.5-≤6.0</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>VERY HIGH (10)</td>
<td>&gt;6.0</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\(^x\)IPSS should be used for initial prognostic and planning purposes. WPSS permits dynamic estimation of prognosis at multiple time points during the course of MDS.


\(^z\)Patients with 20%-30% blasts may be considered to have MDS (FAB) or AML (WHO).

\(^aa\)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.]

\(^bb\)Cytopenias: neutrophil count <1,800/mcL, platelets <100,000/mcL, Hb <10g/dL.


\(^dd\)Cytogenetic risks: Very good = -Y, del(11q); Good = Normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = –7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor = Complex: >3 abnormalities.

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### WHO-Based Prognostic Scoring System (WPSS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO category</td>
<td></td>
<td>RCU, RARS, MDS with isolated deletion (5q)</td>
<td>RCMD</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype<strong>aa</strong></td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Severe anemia (hb &lt;9 g/dL in males or &lt;8 g/dL in females)</td>
<td>Absent</td>
<td>Present</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

**WPSS Risk**

<table>
<thead>
<tr>
<th>WPSS Risk</th>
<th>Sum of individual variable scores</th>
<th>Median survival (y) from diagnosis</th>
<th>Median time (y) to AML progression from diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>0</td>
<td>11.6</td>
<td>NR</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>9.3</td>
<td>14.7</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>5.7</td>
<td>7.8</td>
</tr>
<tr>
<td>High</td>
<td>3–4</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Very High</td>
<td>5–6</td>
<td>1.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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**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.]

## Frequent Mutations in MDS-Associated Genes Likely to Indicate Clonal Hematopoiesis

<table>
<thead>
<tr>
<th>Mutated Gene†</th>
<th>Typical Somatic Mutation Type and Locations§‡</th>
<th>Overall Incidence</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TET2</strong></td>
<td>Nonsense or Frameshift</td>
<td>20%–25%</td>
<td>Associated with normal karyotypes. More frequent in CMML (40%–60%).</td>
</tr>
<tr>
<td></td>
<td>Missense: any in codons 1134–1444 or 1842–1921</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DNMT3A</strong></td>
<td>Nonsense or Frameshift</td>
<td>12%–18%</td>
<td>Associated with a poor prognosis.</td>
</tr>
<tr>
<td></td>
<td>Missense: in codon R882</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Nonsense or Frameshift</td>
<td>8%–12%</td>
<td>Independently associated with a poor prognosis. More frequent with complex karyotypes (50%) and del(5q) (15%–20%). May predict resistance or relapse to lenalidomide.</td>
</tr>
<tr>
<td></td>
<td>Missense: any codon except P47S and P72R</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SF3B1</strong></td>
<td>Missense: E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, D781</td>
<td>18%–30%</td>
<td>Strongly associated with ring sideroblasts and more frequent in RARS (80%). Associated with a more favorable prognosis.</td>
</tr>
<tr>
<td><strong>SRSF2</strong></td>
<td>Missense: P95</td>
<td>10%–15%</td>
<td>More frequent in CMML (40%–50%) and associated with a poor prognosis.</td>
</tr>
<tr>
<td><strong>RUNX1</strong></td>
<td>Nonsense or Frameshift</td>
<td>10%–15%</td>
<td>Independently associated with a poor prognosis in MDS. May be familial in very rare cases.</td>
</tr>
<tr>
<td></td>
<td>Missense: any in codons 100–210</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EZH2</strong></td>
<td>Nonsense or Frameshift</td>
<td>5%–10%</td>
<td>Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).</td>
</tr>
<tr>
<td></td>
<td>Missense: any in codons 622–732 (except Y646)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NRAS</strong></td>
<td>Missense: G12, G13, Q61</td>
<td>5%–10%</td>
<td>Associated with a poor prognosis, particularly in patients predicted to have lower-risk MDS. More frequent in CMML and JMML (~15%).</td>
</tr>
<tr>
<td><strong>CBL</strong></td>
<td>Missense: any in codons 366-420</td>
<td>&lt;5%</td>
<td>More frequent in CMML (10%–20%) and JMML (15%).</td>
</tr>
<tr>
<td><strong>JAK2</strong></td>
<td>Missense: V617F</td>
<td>&lt;5%</td>
<td>More frequent in RARS-T (50%).</td>
</tr>
<tr>
<td><strong>SETBP1</strong></td>
<td>Missense: E858, D868, S869, G870, I871, D880</td>
<td>&lt;5%</td>
<td>Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).</td>
</tr>
<tr>
<td><strong>IDH1</strong></td>
<td>Missense: R132</td>
<td>&lt;5%</td>
<td>More frequent in AML.</td>
</tr>
<tr>
<td><strong>IDH2</strong></td>
<td>Missense: R140Q, R172</td>
<td>&lt;5%</td>
<td>More frequent in AML.</td>
</tr>
<tr>
<td><strong>ETV6</strong></td>
<td>Nonsense or Frameshift</td>
<td>&lt;5%</td>
<td>Independently associated with a poor prognosis.</td>
</tr>
</tbody>
</table>

---

**Table:** This table lists gene mutations likely to be somatic (acquired, not congenital/germline) and, therefore, indicative of clonal hematopoiesis. In the appropriate context (eg, cytopenias present without AML-defining criteria, no evidence of other malignancy), they could aid in the determination of diagnosis. However, no mutation is specific for MDS. There is insufficient evidence to support the use of somatic mutations as presumptive evidence of the disease when diagnostic criteria for MDS have not been met. Other disease-related mutations of the listed genes can occur in MDS, as can mutations in other genes, but these may have less certain significance (ie, possible germline variants or less specificity for MDS). Not all MDS patients will have a mutation in one of these genes.

- The specific mutations listed in this table are likely to be somatic if found in tumor material. Their absence in non-hematopoietic tissues would be required to prove that they are acquired. Several of the genes listed can have congenital mutations that are disease-related in rare cases (eg, RUNX1, TP53, CBL). Known gene polymorphisms frequent in the population should be excluded from DNA sequencing results as they are likely germline variants and not evidence of clonal hematopoiesis.

†Somatic mutations in several MDS-associated genes (eg, TET2, DNMT3A, TP53) can occur in non-disease states and no gene mutation is diagnostic of MDS. Mutations in several genes can occur in neoplasms other than MDS, including lymphoid malignancies such as CLL and ALL. Mutations should not be used as presumptive evidence of MDS when diagnostic criteria for MDS have not been met.

‡Mutation type definitions: **Nonsense** – a mutation that changes an amino acid codon into a premature stop codon. **Frameshift** – the insertion or deletion of DNA base pairs that changes the amino acid reading frame. **Missense** – a mutation that changes one amino acid codon into another (eg, K700E indicates that the lysine [K] at codon 700 was mutated to a glutamic acid [E]). If no new amino acid is specified for a codon in the table, then it may be mutated into one of several possible amino acids (eg, R882 indicates that the arginine [R] at position 882 can be mutated in more than one way).
### Frequent Mutations in MDS-Associated Genes Likely to Indicate Clonal Hematopoiesis

Data for the table are derived from references listed below and are discussed in the following reviews:


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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**PROGNOSTIC CATEGORY**

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

- Clinically significant cytopenia(s) or increased marrow blasts
- Symptomatic anemia
- Clinically relevant thrombocytopenia or neutropenia or increased marrow blasts
- del(5q) ± other cytogenetic abnormalities
- No del(5q) ± other cytogenetic abnormalities
- Serum EPO ≤500 mU/mL
- Serum EPO >500 mU/mL

### TREATMENT

- Supportive care as an adjunct to treatment
- Azacitidine/decitabine or Immunosuppressive therapy (IST) for select patients
- Disease progression/No response
- See MDS-10

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

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

---

**Presence of comorbidities should also be considered for evaluation of prognosis. See Comorbidity Indices in the Discussion.**

**Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. 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 the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.**

**See Supportive Care (MDS-B).**

**Patients generally ≤60 y, and ≤5% marrow blasts or those with hypocellular marrows, HLA-DR15 positivity, PNH clone positivity, or STAT-3 mutant cytotoxic T cell clones.**


**IPSS Intermediate-1, IPSS-R, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for hematopoietic stem cell transplant (HCT): Allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).**

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**MDS-9**
PROGNOSTIC CATEGORY

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

TREATMENT

**Symptomatic anemia with del(5q) ± other cytogenetic abnormalities**

- **Serum EPO ≤500 mU/mL**
  - Epoetin alfa (rHu EPO) ± G-CSF
  - **No response** or intolerance
  - Follow pathway below

- **Serum EPO >500 mU/mL**
  - **No response** or intolerance
  - Follow pathway below

**Symptomatic anemia with no del(5q)**

- **Good probability to respond to IST**
  - ATG, cyclosporin A

- **Poor probability to respond to IST**
  - Azacitidine/decitabine or Consider lenalidomide or Clinical trial

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

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

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### PROGNOSTIC CATEGORY


### TREATMENT

<table>
<thead>
<tr>
<th>Donor stem cell source available:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

**Transplant candidate**

<table>
<thead>
<tr>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

#### Allo-HCT
- **or** Azacitidine/decitabine followed by HCT
- **or** High-intensity chemotherapy followed by HCT

#### Consider HCT or donor lymphocyte infusion (DLI)
- **or** Azacitidine/decitabine
- **or** Clinical trial

#### Response
- **Continue**
- **No response**

#### No response
- **Clinical trial**
- **Supportive care**

---

**Presence of comorbidities should also be considered for evaluation of prognosis. See Comorbidity Indices in the Discussion.**

**Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. 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.**

---


**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 can be used to decrease marrow blasts to an acceptable level prior to transplant.**

**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 HCT.**

**HCT: Allogeneic-matched sibling including standard and reduced-intensity preparative approaches or MUD.**

**While the response rates are similar for both drugs, survival benefit from a phase III randomized trial is reported for azacitidine and not for decitabine. Azacitidine or decitabine therapy should be continued for at least 4 to 6 cycles to assess response to these agents. In patients who have clinical benefit, continue treatment with hypomethylating agent as maintenance therapy.**

**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 HCT.

**Consider second transplant or DLI immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.**

---

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### 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-DR 15 typing
- Rule out coexisting causes

### TREATMENT OF SYMPTOMATIC ANEMIA

1. **Serum EPO ≤500 mU/mL**
   - Ring sideroblasts <15%
   - **Lenalidomide**
   - **Response**
     - Continue lenalidomide, decrease dose to tolerance
   - **No response**
     - **See IPSS: Low/Intermediate-1**
     - **WPSS: Very Low, Low, Intermediate (MDS-10)**

2. **Serum EPO >500 mU/mL**
   - **See Serum EPO >500 mU/mL (MDS-10)**

### FOLLOW-UP

- **Response**
  - Continue EPO, decrease dose to tolerance
  - Consider adding G-CSF
  - **No response**
  - Decrease dose to tolerance

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
RECOMMENDATIONS FOR FLOW CYTOMETRY

Initial Evaluation [See MDS-1]

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

- Clinical monitoring
- Psychosocial support ([See NCCN Guidelines for Survivorship](#))
- Quality-of-life assessment
- Transfusions:
  - RBC transfusions (leuko-reduced) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mm$^3$. Irradiated products are suggested for transplant candidates.
  - Cytomegalovirus (CMV)-negative or leuko-reduced blood products are recommended whenever possible for CMV-negative transplant candidates.
- Antibiotics are recommended for bacterial infections, but no routine prophylaxis is recommended except in patients with recurrent infections.
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.
- Iron chelation:
  - If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for LOW/INT-1 and for potential transplant patients. For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL$^3$ ([See Discussion](#)).
  - Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox.
- Cytokines:
  - EPO: [See Anemia Pathway (MDS-12)](#)
  - G-CSF or GM-CSF:
    - Not recommended for routine infection prophylaxis.
    - Consider use if recurrent or resistant infections in neutropenic patient.
    - Combine with EPO for anemia when indicated. [See Anemia Pathway (MDS-12)](#).
    - Platelet count should be monitored.

---

1.[See NCCN Guidelines for Supportive Care](#).
2.Avoid transfusions for arbitrary hemoglobin thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke. In situations where transfusions are necessary, transfuse the minimum units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin level. Hicks L, Bering H, Carson K, et al. The ASH Choosing Wisely campaign: five hematologic tests and treatments to question. Blood. 2013;122:3879-3883.
3.Clinical trials in MDS are currently ongoing with oral chelating agents.
Discussion

NCCN Categories of Evidence and Consensus

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

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

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

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with relatively heterogeneous spectrums of presentation. The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In the general population, the incidence rate of MDS is approximately 4.8 per 100,000 people per year.\(^1\) 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 of age. However, among individuals between the ages of 70 and 79, the incidence rate increases to 29.6 per 100,000 people, and the rate increases further to 55.8 per 100,000 people among those 80 years of age and older.\(^1\)

Managing MDS is complicated by the generally advanced age of the patients (median age at diagnosis, 70–75 years),\(^2\) the attendant non-hematologic comorbidities, and the relative inability of older patients to tolerate certain intensive forms of therapy. In addition, when the illness progresses into AML, these patients experience lower response rates to standard therapy than patients with de novo AML.\(^3\)

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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Myelodysplastic Syndromes, an electronic search of the PubMed database was performed to obtain key literature published between June 1, 2014 and March 1, 2015, using the following search term: myelodysplastic syndromes. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.\(^4\)

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 28 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.
Diagnostic Classification

The initial evaluation of patients with suspected MDS requires careful assessment of the peripheral blood smear and blood counts, marrow morphology, duration of abnormal blood counts, other potential causes of cytopenias, and concomitant illnesses. The NCCN Guidelines for MDS include the WHO classification system for diagnostic evaluations. The French-American-British (FAB) classification is discussed below to provide a historical overview of the diagnostic classification system utilized in MDS.

The FAB classification initially categorized patients for the diagnostic evaluation of MDS. Dysplastic changes in at least two of the three hematopoietic cell lineages have been used by most histopathologists to diagnose MDS. These changes include megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in the early myeloid and erythroid precursors, and dysmorphic megakaryocytes. Patients with MDS are classified as having one of five subtypes of disease: refractory anemia (RA); RA with ring sideroblasts (RARS); RA with excess of blasts (RAEB); RAEB in transformation (RAEB-t); and chronic myelomonocytic leukemia (CMML). MDS are generally indolent, with patients' blood counts remaining relatively stable over at least several months.

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

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

In 2001, WHO proposed an alternative classification for MDS that was modified from the FAB definitions. In contrast to the FAB classification that required dysplasia in at least two lineages for the diagnosis of MDS, the WHO guidelines include unilineage dysplasia for the diagnosis of RA and RARS provided that other causes of the dysplasia are absent and the dysplasia persists for at least 6 months. To establish the diagnosis of MDS, careful morphologic review and correlation with the patient's clinical features are important, because a number of medications and viral infections (including HIV infection) can cause morphologic changes in marrow cells that are similar to MDS.

In 2008, a revision of the WHO classification incorporated new scientific and clinical information and refined diagnostic criteria for previously described neoplasms; it also introduced newly recognized disease entities. A new subtype in the MDS classification is refractory cytopenia with unilineage dysplasia (RCUD), which includes: RA (unilineage erythroid dysplasia), refractory neutropenia (RN) (unilineage dysgranulopoiesis), and refractory thrombocytopenia (RT) (unilineage dysmegakaryocytopoiesis). RN and RT were previously classified as MDS unclassifiable. 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; RARS; 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 of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) includes CMML (CMML-1 and CMML-2); atypical CML, BCR-ABL1 negative; and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features; the MDS/MPN unclassifiable group is also included in this category. The distinction between CMML-1 and CMML-2 is based on the percentage of blasts plus monocytes in the peripheral blood and bone marrow. CMML had been categorized by FAB as MDS and by the International MDS Risk Analysis Workshop (IMRAW) as proliferative type, termed myeloproliferative disorder (MPD) (white blood cell [WBC] counts \( \geq 12,000/mm^3 \)), or non-proliferative type, termed dysplastic MDS. 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 \( \geq 450 \times 10^9/L \)), is included in the MDS/MPN unclassifiable group. The morphology of RARS-T is characterized by RARS features (no blasts in the peripheral blood, dysplastic erythroid proliferation, ring sideroblasts \( \geq 15% \) of erythroid precursors, and <5% blasts in marrow) with proliferation of large atypical megakaryocytes similar to those seen in essential thrombocythemia or primary myelofibrosis; up to 60% of RARS-T cases have the JAK2 V617F mutation or MPL W515K/L mutation.

The 2001 WHO classification excludes RAEB-t patients from MDS by reducing the blast percentage to 20% or more, rather than the previous cut-off of 30% or more. However, MDS are not only related to blast quantitation, but they also possess a differing pace of disease related to distinctive biologic features when compared with de novo AML. In addition, therapeutic responses generally differ between these two patient groups.

The current 2008 WHO classifications have helped clarify the clinical differences between the FAB RAEB-t patients and AML. The 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 that have 20% to 29% marrow blasts, especially patients considered RAEB-t by the FAB classification, may behave in a manner more similar to MDS than to AML.

The decision to treat patients who have 20% to 30% marrow blasts with intensive AML therapy is thus complex and should be individualized. The clinician should consider such factors as age, antecedent factors, cytogenetics, comorbidities, pace of disease, performance status, and the patient’s goal for treatment. However, as indicated in the algorithm (see 2008 WHO Classification of MDS on page MDS-3), RAEB-t patients with 20% to 30% blasts AND a stable clinical course for at least 2 months can be considered as either MDS or AML. Patients who have previously been included in and benefitted...
from therapeutic trials for MDS should continue to be eligible for MDS-type therapy. Thus, the MDS Panel recommends using the WHO classification with the caveat that the RAEB-t patient subgroup be considered as either MDS or AML. This recommendation is further supported by the results from several validation studies and analyses. A recent report provides biologic evidence indicating that patients with splicing factor (SF) mutations among the RAEB, RAEB-t with a low blast count (LBC) AML (ie, those with 20%–29% marrow blasts), and some AML categories had similar clinical phenotypes, including lower blast counts, older age, lower WBC counts, and higher erythroblast counts in bone marrow compared with SF-unmutated cases, indicating that SF-mutated cases comprised a distinct entity among MDS/AML. These data suggest that SF-mutant RAEB/AML-LBC constitutes a related disorder overriding the artificial separation between AML and MDS.

AML evolving from MDS (AML-MDS) is often more resistant to standard cytotoxic chemotherapy than is de novo AML, which arises without antecedent hematologic disorder. High-risk MDS, AML-MDS, and some elderly patients with AML may have a more indolent clinical course in terms of short-term progression compared with patients who have standard presentations of de novo AML. Therefore, treating patients with a standard presentation of de novo AML should be done on a separate protocol than the one for patients with indolent MDS (see NCCN Guidelines for Acute Myeloid Leukemia).

To assist in providing consistency in the diagnostic guidelines of MDS, an International Consensus Working Group recommended that minimal diagnostic criteria for this disease include two 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 and/or cytopenia. In addition, the diagnosis of MDS requires at least one of three MDS-related (decisive) criteria: 1) dysplasia (≥10% in one or more of the three major bone marrow lineages); 2) a blast cell count of 5% to 19%; and 3) a specific MDS-associated karyotype [eg, del(5q), del(20q), +8, or -7/del(7q)]. Furthermore, several co-criteria may help confirm the diagnosis of MDS. These co-criteria include flow cytometry studies, bone marrow histology and immunohistochemistry, or molecular marker analysis (to detect or exclude abnormal CD34 antigen expression, fibrosis, dysplastic megakaryocytes, atypical localization of immature progenitors, and myeloid clonality).

Initial Evaluation

Several types of evaluations are needed to determine the clinical status of patients with MDS. Understanding clinical status is necessary for determining diagnostic and prognostic categorization and deciding treatment options. Clinical history should include the timing, severity, and tempo of abnormal cytopenias; prior infections or bleeding episodes; and number of transfusions. Concomitant medications and comorbid conditions require careful assessment. Because MDS are relatively indolent disorders, blood count stability is used to distinguish MDS from evolving AML. Other possible causes of 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 a biopsy are needed to evaluate the degree and relative proportions of hematopoietic cell maturation abnormalities, percentage of marrow blasts, marrow cellularity, presence or absence of ring sideroblasts (and
presence of iron per se), and fibrosis. Cytogenetics for bone marrow samples (by standard karyotyping methods) should be obtained, because they are of major prognostic importance.

Other useful laboratory screening tests include serum erythropoietin (sEpo), vitamin B₁₂, red blood cell (RBC) folate levels, and serum ferritin. RBC folate and serum folate levels should not be considered equivalent and RBC folate is preferred. RBC folate levels are more indicative of folate stores, whereas serum folate levels are reflective of recent nutrition. However, if RBC folate cannot be evaluated, serum folate should be considered as an alternative, though clinicians should be advised of the limitations. Serum ferritin levels may be nonspecific, particularly in the face of inflammatory conditions such as rheumatoid arthritis. Therefore, in such cases, obtaining the serum iron levels and total iron-binding capacity along with serum ferritin may be helpful. As hypothyroidism and other thyroid disorders can lead to anemia, patients should also be evaluated for levels of thyroid-stimulating hormone.²⁷

If patients require platelet transfusions for severe thrombocytopenia, human leukocyte antigen (HLA) typing (A and B) may be helpful. For hematopoietic cell transplant (HCT) candidates, cytomegalovirus (CMV) status and full HLA typing (A, B, C, DR, and DQ) of the patient and potential donors are needed. Flow cytometry for assessing the percentage of blast cells in the bone marrow (as measured by the expression of CD34 on the cell surface), and HIV screening, if clinically indicated, may also be valuable in some clinical situations. It should be emphasized, however, that estimates of blast percentage by flow cytometry do not provide the same prognostic information as the blast percentage derived from morphologic evaluation. Accordingly, flow cytometry data should not be used in lieu of the determination of morphologic blast percentage by an experienced hematopathologist.

The screening for paroxysmal nocturnal hemoglobinuria (PNH), HLA-DR15 positivity, or STAT-3 mutant cytotoxic T-cell clones is potentially useful for determining which patients may be more responsive to immunosuppressive therapy (IST), particularly young patients with normal cytogenetics and hypoplastic MDS²⁸⁻³¹ (see Prognostic Stratification in the Discussion). PNH is a rare acquired hematopoietic stem cell disorder arising from mutations in the PIGA gene resulting in defective synthesis of the glycosphatidylinositol (GPI) anchor. This, in turn, leads to a deficiency of proteins that are normally linked to the cell membrane of blood cells via a GPI anchor.³²⁻³⁴ Deficiency in GPI-anchored proteins such as those involved in complement inhibition (eg, CD55, CD59) leads to complement sensitivity of RBCs and subsequent hemolysis.³² Flow cytometry is the established method for detecting GPI-anchor-deficient cells for the diagnosis of PNH. Fluorescent aerolysin (FLAER), a protein that specifically binds to GPI anchors, has been shown to be a highly specific and reliable marker for detecting GPI-anchor-deficient clones among granulocytes or monocytes.³⁵ For evaluation of PNH clonogenicity, it is recommended that multiparameter flow cytometry analysis of granulocytes and monocytes using FLAER, and at least one GPI-anchored protein, be conducted.³²,³⁵ It should be emphasized that although evidence for a minor PNH clone may be present in about 20% of patients with MDS, there is usually no evidence for PNH-related hemolysis in these patients.

It is suggested that detection of HLA-DR15 positivity reflects a T-cell-mediated immune mechanism affecting bone marrow failure. In a retrospective study, HLA-DR15 was detected at a frequency of 46% in MDS-RA patients compared to 21% in the control population (P < .001); this association was not seen in the MDS-RAEB and MDS-RARS groups.²⁹ Furthermore, HLA-DR15 positivity showed a
significantly higher response to IST ($P = .003$) as measured by univariate analysis.

Cases of patients with myelodysplastic features and clonal expansion of large granular lymphocytes (LGLs) have been reported. In one of these studies, 3 out of 9 patients responded to IST as indicated by improved blood counts. Although patients with both MDS and LGL did not respond as well as LGL patients (33% vs. 66%; $P = .01$), the presence of the T-cell clone may reflect a target for IST. A second study reported improved outcomes in 61 MDS patients with LGL clonogenicity receiving anti-thymocyte globulin (ATG). Moreover, the MDS-RA subtype was determined as a favorable predictor of response compared to non-MDS-RA patients (OR, 0.15; 95% CI, 0.04–0.59; $P = .005$).

There have been reports that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS. Copper deficiency is an etiology of anemia, neutropenia, and bone marrow dysplasia that may be under-recognized. There are rare patients with clinical presentation consistent with MDS that may be deficient in copper and for whom copper supplementation may resolve hematologic abnormalities. Copper and ceruloplasmin level assessments should be considered as part of the initial diagnostic workup in patients suspected of having low-risk MDS, especially those with gastrointestinal (GI) disorders and neuropathy. Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors, prior GI surgery, a history of vitamin B$_{12}$ deficiency, and a history of zinc supplementation.

Bone marrow biopsy staining for reticulin is helpful for evaluating the presence and degree of bone marrow fibrosis. Increased reticulin fibers in the marrow at diagnosis are seen in approximately 5% to 10% of MDS cases. MDS with fibrosis (MDS-F) is not considered a distinct subtype of MDS but rather is relegated to the unclassifiable category in the most recent WHO classification. MDS-F patients frequently present with severe pancytopenia; decreased survival in these patients has been reported.

In addition to basic flow cytometric evaluation at presentation for characterization of blasts and evaluation of lymphoid populations, expanded flow cytometry may be a useful adjunct for diagnosis of MDS in difficult cases. In expert hands (both in terms of technical sophistication and interpretation), flow cytometry may demonstrate abnormal differentiation patterns or aberrant antigen expression in myeloid or progenitor cells, which may help confirm a diagnosis of MDS, exclude differential diagnostic possibilities, and, in some patients, provide prognostic information. Flow analysis should use appropriate antibody combinations with four fluorescence channel instrumentation. Multiple aberrancies should be present for the diagnosis of MDS, as single aberrancies are not infrequent in normal populations. For follow-up studies, antibody combinations may be tailored to detect specific abnormalities implicated in the initial evaluation. While aberrancies have also been described in erythroid cells, most flow cytometry laboratories do not provide erythroid analysis.

The European LeukemiaNET developed a flow cytometric score based on the reproducible parameters of CD34 and CD45 markers to aid in the diagnosis of MDS. The scoring system was developed using multicenter retrospective data from patients with low-grade MDS (defined as <5% marrow blasts; n=417) and patients with non-clonal cytopenias as controls (n=380). This patient population was selected because low-grade MDS often lack specific diagnostic markers (eg, ring sideroblasts, clonal cytogenetic abnormalities) and, therefore, may be difficult to diagnose based on morphology alone. Bone marrow samples
from patients with MDS compared with samples from patients with non-clonal cytopenias showed different flow cytometric patterns, including: 1) increased CD34+ myeloblast-related cluster size (defined by a wider distribution of CD45 expression and greater side scatter characteristics [SSC]); 2) decreased CD34+ B-progenitor cluster size (defined by a relatively low CD45 expression and low SSC); 3) aberrant myeloblast CD45 expression (based on the lymphocyte to myeloblast CD45 ratio); and 4) a decreased granulocyte SSC value (based on the granulocyte to lymphocyte SSC ratio). These four parameters were included in a logistic regression model and a weighted score (derived from regression coefficients) was assigned to each 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 diagnosis. Using this flow cytometric score in the learning cohort, a correct diagnosis of MDS was made with 70% sensitivity and 93% specificity. Among MDS patients without specific markers of dysplasia, 65% were correctly identified. The positive predictive and negative predictive values were 92% and 74%, respectively. These outcomes were confirmed in the validation cohort, which showed 69% sensitivity and 92% specificity. This flow cytometric scoring system demonstrated a high diagnostic power in differentiating low-grade MDS from non-clonal cytopenias, and may be particularly useful in establishing a diagnosis in situations where traditional diagnostic methods are indeterminate. Further independent validation studies are warranted to determine the utility of this method.

Because of the associated expense, the requirement for both technical and interpretational expertise, and the 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 LGL disease, as indicated by LGLs present in the peripheral blood. 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. Telomere length can be measured by fluorescence in situ hybridization (FISH) assays using leukocyte (or leukocyte subset) samples. 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 one cause of a relatively rare autosomal-dominant familial platelet disorder that predisposes these patients to myeloid malignancies. In affected families with the RUNX1 lesions, the incidence of MDS/AML is high, ranging from 20% to 60% in which the median age of onset is 33 years. This familial platelet disorder is characterized by the presence of thrombocytopenia, and a tendency for mild-to-moderate bleeding generally presents from childhood; however, some affected individuals may not display these clinical characteristics. 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. Identification of Fanconi anemia is clinically important, because it is associated with chromosomal fragility that results in variability of disease response to hypomethylating agents. 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.\(^6\) Recently, heritable mutations in \(GATA2\) were identified in families with highly penetrant, early-onset MDS and/or AML.\(^6\) 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 HCT.\(^6\) More importantly, family members may not be eligible as donors for allogeneic HCT.

Determination of platelet-derived growth factor receptor beta (\(PDGFR\beta\)) gene rearrangements is helpful for evaluating CMML/MPD patients with 5q31-33 translocations. The activation of this gene encoding a receptor tyrosine kinase for \(PDGFR\beta\) has been identified in some of these patients.\(^6\) Data have shown that CMML/MPD patients with \(PDGFR\beta\) fusion genes may respond well to treatment with the tyrosine kinase inhibitor imatinib mesylate.\(^6\)

Recurrent mutations in several genes can be found in MDS bone marrow and blood cells that may be clinically useful in specific contexts. For example, mutations in SF genes are much more common in patients with MDS, RARS, and CMML compared to other myeloid neoplasms. Approximately 40% of MDS patients will carry a mutation in one of the three most frequently mutated SFs: \(SF3B1\), \(SRSF2\), and \(U2AF1\).\(^7\) A typical mutation in one of these genes indicates the presence of clonally derived hematopoiesis and may help determine diagnosis in the appropriate clinical context.

Mutations of \(SF3B1\) are associated with the presence of ring sideroblasts and are highly prevalent in patients with RARS or RARS-T (>80%).\(^7\) Mutations of \(JAK2\) are found in 50% of RARS-T, though it is much rarer in other subtypes. Mutations of \(SRSF2\) are enriched in patients with CMML, although it not unique to this subtype. Patients with JMML will often have mutations in one of the tyrosine kinase signaling genes such as \(PTPN11\), \(NF1\), \(NRAS\), \(KRAS\), or \(CBL\).\(^7\) In many cases, these mutations are congenital and part of a larger syndrome.

Typical mutations in other genes (see Table on page MDS-7) can also establish the presence of clonal hematopoiesis, but they are less specific for disease subtype. Of note, several mutated genes associated with MDS (eg, \(TET2\), \(DNMT3A\), \(SF3B1\), \(EZH2\), \(NRAS\), \(BRAF\), \(TP53\)) can be mutated in other neoplasms, including lymphoid malignancies. Rare patients can have dual diagnoses (eg, MDS and chronic lymphocytic leukemia), which can confound the interpretation of sequencing results. Therefore, the presence of mutations must be interpreted in an appropriate clinical context consistent with MDS. Acquired mutations of \(TET2\) and \(DNMT3A\) are frequent in MDS but have also been identified in older persons with clonal hematopoiesis and normal blood counts. Whether mutations of these or other genes are predictive of MDS in patients with cytopenias who do not meet morphologic diagnostic criteria for MDS is not known. Therefore, somatic mutations should not be used as presumptive evidence of MDS in the absence of other diagnostic features. Patients with cytopenias who lack bone marrow findings diagnostic of MDS can have somatic mutations indicative of clonal hematopoiesis, but the clinical outcomes for these patients are not known. The mere presence of a mutation is not a substitute for the pathologic diagnosis of MDS and should not be used as the sole indication for treatment. Mutations in some non-MDS genes may indicate the presence of neoplasms that can mimic MDS. These include \(CALR\) mutations associated with primary myelofibrosis, \(CSF3R\) mutations associated with atypical CML and chronic neutrophilic leukemia, and \(STAT3\) mutations associated with LGL leukemia.
Flow cytometric studies suggest the potential utility of this methodology for both characterizing MDS marrow blast cells and aiding in the assessment of prognosis.\textsuperscript{75,76} However, due to the non-standardized nature of these analyses, further investigations are warranted prior to suggesting their routine use.

**Pediatric MDS**

Several differences exist between adult and childhood myelodysplasia. MDS and myelodysplasia are quite rare in children, occurring in 1 to 4 cases per million per year with a median age of 6.8 years.\textsuperscript{77-79} MDS in children is strongly associated with congenital disorders.\textsuperscript{80} Genetic syndromes are evident in 50\% of cases, including Down syndrome,\textsuperscript{81-83} trisomy 8 syndrome,\textsuperscript{84} Fanconi anemia,\textsuperscript{85,86} congenital neutropenia (Kostmann syndrome),\textsuperscript{87,88} Diamond-Blackfan anemia,\textsuperscript{89} Shwachman-Diamond syndrome,\textsuperscript{90} DC,\textsuperscript{91} neurofibromatosis type 1,\textsuperscript{92} Bloom syndrome,\textsuperscript{93,94} Noonan syndrome,\textsuperscript{95} and Dubowitz syndrome.\textsuperscript{96} Prior exposure to cytotoxic therapy (eg, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors),\textsuperscript{97-100} and radiation\textsuperscript{101,102} increases the risk for MDS.

The 2008 WHO classification separates pediatric MPDs into three groups: MDS (refractory cytopenia of childhood [RCC], RAEB, RAEB-t, or AML with MDS-related changes); myelodysplastic/myeloproliferative disease (JMML); and Down syndrome disease (transient abnormal myelopoiesis and myeloid leukemia of Down syndrome).\textsuperscript{11} RCC is the most common subtype of MDS found in children, accounting for approximately 50\% of cases.\textsuperscript{79} Abnormal karyotypes are found in 30\% to 50\% of children with MDS,\textsuperscript{103} most common are numerical anomalies with fewer than 10\% showing structural abnormalities. Monosomy 7 is the most common cytogenetic abnormality, occurring in 30\% of cases,\textsuperscript{104,105} followed by trisomy 8\textsuperscript{106,107} and trisomy 21.\textsuperscript{108} The del(5q) abnormality is rarely seen in children.\textsuperscript{109} Clinically, isolated RAs are uncommon in children. Thrombocytopenia and/or neutropenia, often accompanied by hypocellular marrow, is a common presentation. Fetal hemoglobin levels are frequently elevated.

Differential diagnoses include aplastic anemia (AA) and AML. Compared to AA, children with MDS have a significantly elevated mean corpuscular volume; clonal hematopoiesis is confirmatory. Higher expression of p53, lower expression of survivin, or the presence MDS-related cytogenetic abnormalities can also help differentiate MDS from AA.\textsuperscript{110} Compared with AML, low WBC count, multi-lineage dysplasia, and clonal hematopoiesis with numerical, rather than structural, cytogenetic abnormalities suggest MDS. A bone marrow blast count of less than 20\% also suggests MDS, but biological features are more important than a strict blast cut-off value. Monosomy 7 strongly suggests MDS. When patients present with AML, the marrow frequently shows dysplastic features, but this does not necessarily indicate that the AML arose after MDS. Indeed, criteria for the diagnosis of MDS in a patient who presents with AML are stringent.\textsuperscript{111} Dysplasia in bone marrow cells may also be due to other etiologies including infection (eg, Parvo virus,\textsuperscript{112,113} herpes viruses,\textsuperscript{114} HIV), deficiencies of B\textsubscript{12} and copper,\textsuperscript{115} drug therapy, and chronic disease.\textsuperscript{116} Congenital dyserythropoietic anemia and Pearson syndrome should also be excluded.

Children with Down syndrome have an increased risk for developing leukemia (50-fold greater risk if younger than 5 years old), and are usually categorized as having acute megakaryoblastic leukemia (AMKL, M7).\textsuperscript{81,83,117,118} This commonly has a prodromal phase of cytopenia(s) similar to MDS and may be considered a spectrum of the same disease. Prognosis of patients with Down syndrome and AMKL is quite good with an 80\% cure rate when treated with intensive chemotherapy. HCT is not
indicated in first complete remission for these children. Newborns with Down syndrome can develop abnormal myelopoiesis with leukocytosis, circulating blasts, anemia, and thrombocytopenia, but this resolves spontaneously within weeks to months. Approximately 20% of children with Down syndrome, who have transient abnormal myelopoiesis, will subsequently develop AMKL. 82

There is a paucity of clinical trials due to the rarity and heterogeneity of MDS in children. The primary goal of treatment is generally a cure rather than palliation. HCT is the only curative option in childhood MDS with 3-year disease-free survival rates of approximately 50%. 119-121 Myeloablative therapy with busulfan, cyclophosphamide, and melphalan, followed by either matched family or matched unrelated donor allogeneic HCT is the treatment of choice for children with MDS. Other treatments such as chemotherapy, growth factors, and IST have a limited role. Prognosis for untreated MDS depends on the rate of progression to AML. The stage of the disease at the time of HCT strongly predicts outcome. 105

Patients with RCC have a median time to progression to advanced MDS of 1.7 years, but the time to progression is highly variable, depending on the underlying cause of MDS and standard prognostic factors. 122 Patients with JMML have a variable prognosis; some younger patients with favorable genetics and clinical features have resolution of JMML without treatment, while others progress rapidly despite allogeneic HCT. 123 Children diagnosed before the age of 2 years have the best prognosis. Poor prognostic features include high hemoglobin F, older age, and thrombocytopenia.

Pediatric AML or MDS with monosomy 7 has a poor prognosis with conventional therapies. A recent review of 16 patients with AML and MDS with monosomy 7 treated by two transplant programs from 1992 to 2003 (MDS, n=5; therapy-related MDS [t-MDS], n=3; AML, n=5; therapy-related AML [t-AML], n=3) reported a 2-year event-free survival of 69%. 124 Four of the 5 deaths occurred in patients transplanted with active leukemia. Seven of 8 MDS patients were alive without evidence of disease (6 in first complete remission, 1 in second complete remission, and 1 death due to complications). 124

Although MDS cases can occur in both the adult and pediatric populations, the treatment strategies and recommendations are not necessarily the same. The NCCN Guidelines for MDS focus on recommendations for the diagnosis, evaluation, and treatment of adult patients with MDS; therefore, the discussions that follow pertain to adult patients.

Prognostic Stratification

Despite its value for the diagnostic categorization of patients with MDS, the highly variable clinical outcomes within the FAB subgroups indicate a prognostic limitation to this method. 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. 125

Prognostic Scoring Systems

IPSS

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW. 14 Compared with previous classification systems, the risk-based IPSS has markedly improved
prognostic stratification of MDS cases. The IPSS was developed based on the combined cytogenetic, morphologic, and clinical data from a relatively large group of MDS cases included in previously reported prognostic studies. FAB morphologic criteria were used to establish the diagnosis of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible etiologies for the cytopenias, such as drugs, other diseases, or incipient evolution to AML. CMML was subdivided into proliferative and non-proliferative subtypes. Patients with proliferative-type CMML (those with WBC counts >12,000/mcL) were excluded from this analysis. Patients with non-proliferative CMML (with WBC counts of ≤12,000/mcL plus other features of MDS) were included.

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

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

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

**WPSS**

Data have indicated a benefit to the addition of other clinical variables to the IPSS to improve the accuracy of prognosis. The WHO classification-based prognostic scoring system (WPSS) incorporates the WHO morphologic categories, the IPSS cytogenetic categories, and the degree of RBC transfusion dependence. This system demonstrated that the requirement for RBC transfusions is a negative prognostic factor for patients in the lower-risk MDS categories. In addition, depth of anemia per se has additive and negative prognostic importance for the intermediate IPSS categories. As compared with the four groups defined by the IPSS, the WPSS classifies patients into five risk groups differing in both survival and risk of AML. The five risk groups are: Very Low, Low, Intermediate, High, and Very High. Following the initial report by Malcovati et al, there have been confirmatory studies demonstrating the usefulness of the WPSS. The initial WPSS has been refined to address the notion that the requirement for RBC transfusion may be somewhat subjective. In the refined WPSS, the
measure of the degree of anemia by transfusion dependency is replaced by the presence (or absence) of severe anemia, defined as hemoglobin levels less than 9 g/dL for males and less than 8 g/dL for females. This approach allows for an objective assessment of anemia, while maintaining the prognostic implications of the five risk categories defined in the original WPSS (as mentioned above).

**IPSS-R**

Most recently, a revised IPSS (IPSS-R) was developed that also defines five risk groups (Very Low, Low, Intermediate, High, and Very High) versus the four groups in the initial IPSS. 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 <5%” group, and a depth of cytopenias measurement defined with cut-offs for hemoglobin levels, platelet counts, and neutrophil counts. In the IPSS-R, the cytogenetic subgroups comprise five risk groups (vs. three in the original IPSS) based on the recently published cytogenetic scoring system for MDS. 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 groups compared with the higher-risk groups. The predictive value of the IPSS-R was validated in a number of independent studies based on registry data, including studies that evaluated outcomes for patients treated with hypomethylating agents.

In a multiregional study of MDS patient registry data from Italy (N=646), significant differences in outcomes among the IPSS-R risk categories were found for overall survival (OS), AML evolution, and progression-free survival (later defined as leukemic evolution or death from any cause). Notably, the predictive power (based on Harrell’s C statistics) of the IPSS-R was found to be greater than the IPSS, WPSS, and refined WPSS for the three outcome measures mentioned above. The investigators acknowledged the limitation of a short follow-up (median, 17 months) in the study cohort.

In a retrospective analysis of data from lower-risk MDS (IPSS Low or INT-1) patients in a large multicenter registry (N = 2410) in 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. Within the IPSS INT-1-risk group, the IPSS-R further stratified patients into 4 risk categories (Very Low, Low, Intermediate, High) 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 patients. 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). 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. Thus, in this analysis, the IPSS-R appeared to provide prognostic refinement within the IPSS INT-1 group, with a large proportion of patients (511 of 1096 IPSS INT-1 patients) 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,
However, the IPSS-R identified a larger proportion of poor-risk IPSS INT-1 patients than the refined WPSS (47% vs. 17%).

In a retrospective database analysis of MDS patients from a single institution (N = 1088), median OS according to IPSS-R risk categories was 90 months for Very-Low-, 54 months for Low-, 34 months for Intermediate-, 21 months for High- and 13 months for Very-High-risk groups (P < .005). The median follow-up in this study was 70 months. IPSS-R was also predictive of survival outcomes among the patients who received therapy with hypomethylating agents (n = 618). A significant survival benefit with 5-azacitidine (AzaC) was shown only for the groups of patients with Very-High- and High-risk IPSS-R compared to patients not receiving AzaC (median survival, 25 vs. 18 months; P < .028; median survival, 15 vs. 9 months; P = .005, respectively). In addition, significantly longer OS with allogeneic HCT was only observed for patients at High (median survival, 40 vs. 19 months without HCT; P < .005) and Very High (median survival, 31 vs. 12 months without HCT; P < .005) risk. The IPSS-R may therefore provide a tool for therapeutic decision-making.

A recent study applied the IPSS-R to a series of t-MDS and oligoblastic t-AML (ot-AML) patients. Although some IPSS-R cutpoints were suboptimal for t-MDS/ot-AML patients, the overall IPSS-R scores separated t-MDS/ot-AML patients into five risk groups, with each category showing statistical differences in OS as well as AML progression probability in t-MDS. These findings indicated that the major IPSS-R variables (bone marrow blast count, cytopenias, and cytogenetic data) remained powerful predictors in the therapy-related setting. However, compared to de novo MDS/oligoblastic AML, the median OS for each IPSS-R risk group of patients was shorter in t-MDS/ot-AML, particularly in the very-low- and low-risk groups. These differences likely reflect a number of factors, including different biology and clinical approaches (eg, treatment, primary disease and its therapies) between t-MDS/ot-AML and de novo disease. Early data from the MDS Clinical Research Consortium similarly demonstrates the improved prognostic value of the IPSS-r in 370 t-MDS patients compared to the IPSS, the global MD Anderson risk model, or the t-MDS MD Anderson model. Further studies are warranted to better evaluate the impact of specific therapies and more refined variables and their cutpoints for analysis of this heterogeneous group of patients.

In addition to the reports above, other recent studies have confirmed the value of the IPSS-R in treated as well as untreated patients. Since more accurate risk stratification by the IPSS-R compared to the IPSS and WPSS has been demonstrated, the IPSS-R categorization is preferred, although other systems also have good value. It is understood that some ongoing studies are using the IPSS or WPSS. Thus, a transition period is expected before more uniform prognostic risk stratification is accepted by the field. Furthermore, for lower-risk patients the Lower-Risk Prognostic Scoring System (LR-PSS) is also prognostically useful (see Discussion below).

**LR-PSS**

The LR-PSS, developed by investigators at the 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) risk MDS. Factors associated with decreased survival were identified and a prognostic model was constructed based on the 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 (<200 × 10^9/L), and higher percentage of bone marrow blasts (≥4%). Importantly, 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 was given a weighted score, and the sum of the scores (range, 0–7 points) was 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 assigned to category 2, and a score of 5 to 7 was assigned to 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 IPSS Low-risk and IPSS INT-1-risk subgroups. The LR-PSS may be useful in identifying patients with lower-risk disease who have poorer prognosis and 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 both the subgroups of IPSS Low and INT-1 patients. Within the IPSS Low-risk group, median survival 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) using the LR-PSS–risk categories (P < .001); the corresponding median survival values within the IPSS INT-1-risk group using the LR-PSS–risk categories were 115.2 months, 51.3 months, and 24.1 months, respectively (P < .001). An important proportion of patients (334 of 1096 patients; 30.5%) within the IPSS INT-1–risk group were identified as having a poorer prognosis as indicated by their inclusion in the High-risk group (24.1 months). In addition, within the IPSS INT-1–risk group (but not for IPSS Low risk), the LR-PSS was significantly predictive of the rate of AML evolution at 3 years.

Data from a cohort of lower-risk MDS patients from two centers (N = 664) demonstrated a median survival according to the LR-PSS risk categories of 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 powers (based on Harrell’s C statistics) of LR-PSS and IPSS-R were 0.64 and 0.63, respectively.

Molecular Abnormalities in MDS

In recent years, several gene mutations have been identified among patients with MDS that may, in part, contribute to the clinical heterogeneity of the disease course, and thereby influence the prognosis of patients. Such gene mutations will be present in the majority of newly diagnosed patients, including most patients with normal cytogenetics. Several studies examining large numbers of MDS tumor samples have identified over 40 recurrently mutated genes with greater than 80% of patients harboring at least one mutation. The most frequently mutated genes were TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, TP53, U2AF1, EZH2, ZRSR2, STAG2, CBL, and NRAS, although no single mutated gene was found in more than a third of patients. Several of these gene mutations are associated with adverse clinical features such as complex karyotypes (TP53), excess bone marrow blast proportion (RUNX1, NRAS, and TP53), and severe thrombocytopenia (RUNX1, NRAS, and TP53).
Despite associations with clinical features considered by prognostic scoring systems, mutations in several genes hold independent prognostic value. Mutations of TP53, EZH2, ETV6, RUNX1, and ASXL1 have been shown to predict decreased OS in multivariable models adjusted for IPSS or IPSS-R risk groups in several studies of distinct cohorts. Within IPSS risk groups, a mutation in one or more of these genes identifies patients whose survival risk resembles that of patients in the next highest IPSS risk group (eg, the survival curve for INT-1–risk patients with an adverse gene mutation was similar to that of patients assigned to the INT-2–risk group by the IPSS). When applied to patients stratified by the IPSS-R, the presence of a mutation in one or more of these five genes was associated with shorter OS for patients in the Low- and Intermediate-risk groups. Thus, the combined analysis of these gene mutations and the IPSS or IPSS-R may improve upon the risk stratification provided by these prognostic models alone. Mutations of ASXL1 have also been shown to carry independent adverse prognostic significance in CMML. Other mutated genes have been associated with decreased OS, including DNMT3A, U2AF1, SRSF2, CBL, PRPF8, SETBP1, and KRAS. Only mutations of SF3B1 have been associated with a more favorable prognosis, but this may not be an independent risk factor. TET2 mutations have been shown to effect the response to hypomethylating agents. Patients with mutated TET2 had an 82% response rate to AzaC compared to 45% of patients with wildtype TET2 (P = .007). Response duration and OS were not statistically different. A recent study identified 39 genes that were mutated in 213 patients with MDS treated with AzaC or decitabine. A higher response to hypomethylating agents in patients with the TET2 mutation, albeit to a lesser degree, was seen (response rate, 55% vs. 44%; P = .14). This improved response was partially abrogated if ASXL1 mutations were also present (odds ratio, 3.65; P = .009). Mutations in TP53 and PTPN11 correlated with shorter OS but did not affect drug response. However, despite the predictive capabilities of these mutations, status of these molecular markers in patients should not preclude the use of hypomethylating agents nor be used to influence the selection of hypomethylating agents.

Mutations of TP53 are strongly associated with complex and monosomal karyotypes. However, approximately 50% of patients with a complex karyotype have no detectable TP53 abnormality and have an OS that is comparable to that of patients with non-complex karyotypes. Therefore, TP53 mutation status may be useful for refining the prognosis of these patients typically considered to have higher-risk disease. Patients with del(5q), either as an isolated abnormality or often as part of a complex karyotype, have a higher rate of concomitant TP53 mutations. These mutations are associated with diminished response or relapse after treatment with lenalidomide. In these cases, TP53 mutations may be secondary events and are often present in small subclones that can expand during treatment. More sensitive techniques may be required to identify the presence of subclonal, low-abundance TP53 mutations prior to treatment.

Mutations identified in peripheral blood samples can accurately reflect mutations detected in the bone marrow of patients with MDS when more sensitive sequencing techniques are used to detect them.

Comorbidity Indices

Patients with MDS predominantly comprise an elderly adult population, posing potential challenges in terms of treatment tolerability and outcomes due to the presence of comorbid conditions. About 50% of patients with newly diagnosed MDS present with one or more comorbidities, with cardiac disease and diabetes among the most...
frequently observed conditions.\textsuperscript{168-172} Assessment of the presence and degree of comorbidities using tools such as the Charlson Comorbidity Index (CCI) or the Hematopoietic Stem Cell Transplantation-Specific Comorbidity Index (HCT-CI) has demonstrated the significant prognostic influence of comorbidities on the survival outcome of patients with MDS.\textsuperscript{168,170-172} Recent studies have shown that comorbidity (as measured by HCT-CI or Adult Comorbidity Evaluation-27) was a significant prognostic factor for survival, independent of IPSS.\textsuperscript{169,172} In these studies, comorbidity indices provided additional prognostic information for survival outcomes in patients categorized as IPSS INT or High risk, but not for patients considered to have Low-risk disease. Interestingly, in another recent study, comorbidity (as measured by HCT-CI or CCI) was a significant predictor of OS and event-free survival in patients within the Low-risk or INT-1–risk groups, but not in the INT-2–risk or High-risk groups.\textsuperscript{170} Comorbidity has also been shown to provide additional risk stratification among WPSS risk categories (for Very Low-, Low- and Intermediate-risk groups but not for High- or Very-High-risk groups), prompting the development of a new MDS-specific comorbidities index that can be used in conjunction with WPSS for the assessment of prognosis.\textsuperscript{173} Improved risk stratification has also been demonstrated with the incorporation of the Myelodysplastic Syndromes Comorbidity Index with the IPSS-R.\textsuperscript{146} At this time, the NCCN MDS Panel makes no specific recommendations with regards to the optimal comorbidity index to be used for patients with MDS. However, a thorough evaluation of the presence and extent of comorbid conditions remains an important aspect of treatment decision-making and management of patients with MDS.

**Therapeutic Options**

The IPSS or IPSS-R risk categories are used in the initial planning of therapeutic options, because they provide a risk-based patient evaluation (category 2A). In addition, factors such as the patient’s age, performance status, and presence of comorbidities are critical determinants, because they have a major influence on the patient’s ability to tolerate certain intensive treatments. The WPSS provides dynamic estimation of prognosis at any time during the course of MDS.

If the patient was only recently evaluated, determining the relative stability of the patient’s blood counts over several months is important to assess whether the disease progresses, including incipient transformation to AML. In addition, this assessment permits determination of other possible etiologies for cytopenias. The patient’s preference for a specific approach is also important in deciding treatment options. The therapeutic options for MDS include supportive care, low-intensity therapy, high-intensity therapy, and/or participation in a clinical trial. In evaluating results of therapeutic trials, the panel found it important for studies to use the standardized International Working Group (IWG) response criteria.\textsuperscript{174-176}

For the MDS therapeutic algorithm, all patients should receive relevant supportive care. Following that, the MDS panel has proposed initially stratifying patients with clinically significant cytopenia(s) into two major risk groups: 1) relatively lower-risk patients (who are in the IPSS Low, Intermediate-1 category; 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 Intermediate-2, High categories; IPSS-R Intermediate, High, Very High categories; or WPSS High, Very High categories). Patients who fall under the IPSS-R Intermediate category may be managed as either of the two risk groups depending on evaluation of additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels.\textsuperscript{133} In addition, Intermediate-risk patients 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, the major therapeutic aim for patients in the lower-risk group would be hematologic improvement, whereas for those in the higher-risk group, alteration of the disease natural history is viewed as paramount. Cytogenetic response and quality-of-life (QOL) parameters are also important outcomes to assess. The algorithms outline management of primary MDS only. Most patients with t-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 for MDS management includes supportive care (see **Supportive Care** on page MDS-B and the [NCCN Guidelines for Supportive Care](https://www.nccn.org/professionals/physician_gls/pdf/supportive.pdf)). 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), which 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. Both the number of transfusions as well as the number of packed RBCs per transfusion should be kept to a minimum in non-cardiac patients and in patients anticipated to be heavily transfused. The NCCN Guidelines Panel is in agreement with the recent American Society of Hematology (ASH) Choosing Wisely® Initiative addressing hematologic tests and treatments. There was non-uniform consensus among the panel members based on differing institutional policies regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agreed that all directed-donor products and transfused products for potential HCT patients should be irradiated. Additionally, CMV-negative blood products are recommended whenever possible for CMV-negative recipients. In the absence of CMV-negative blood, leuko-reduced blood may be used. 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. For example, recombinant human granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) treatment could be considered for neutropenic MDS patients with recurrent or resistant bacterial infections.

Erythropoiesis-stimulating agents (ESAs) such as recombinant human erythropoietin (rHu Epo) or darbepoetin, with or without G-CSF, have been evaluated in the treatment of symptomatic anemia in patients with MDS. 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 a hematologic response in 38% of patients (complete response [CR], 21%). Epo and G-CSF appeared to have synergistic activity. Lower sEpo levels (<500 mU/mL) and a lower pretreatment RBC transfusion requirement (<2 units per month) were associated with a higher response rate; response rates were not significantly different across IPSS risk groups. Median survival including patients from a prior study was 26 months (N = 71). Among patients with Low-risk IPSS, median survival had not been reached at 5 years; the 5-year survival rate was 68%. Median survival among the INT-1- and INT-2–risk groups...
was 27 months and 14 months, respectively. AML progression occurred in 28% of patients overall during the observation period. The frequency of AML progression in the Low-, INT-1-, INT-2-, and High-risk groups were 12%, 21%, 45%, and 100%, respectively. Among patients with responding disease who received maintenance treatment with Epo and G-CSF, the median duration of response was 24 months.\(^\text{179}\)

A subsequent combined analysis from three phase II Nordic trials (n = 121) on the long-term outcomes with Epo plus G-CSF (given for 12–18 weeks and followed by maintenance in responders) in patients with MDS reported a hematologic response rate of 39% with a median duration of response of 23 months.\(^\text{180}\) Long-term outcomes 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 [HR], 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 the treatment and frequency of AML progression.\(^\text{180}\)

Similar findings were reported in a study from the French myelodysplasia group, which analyzed outcomes with ESAs (epoetin or darbepoetin), with or without G-CSF, in MDS patients with anemia (N = 403).\(^\text{183}\) Based on the IWG 2000 criteria, the hematologic response rate was 62% with a median duration of 20 months; the corresponding results from the IWG 2006 criteria 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 Low/INT-1-risk subset 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.\(^\text{183}\) In a phase II study that evaluated darbepoeitin (given every 2 weeks for 12 weeks), with or without G-CSF (added at 12 weeks in non-responders), patients in the lower-risk IPSS group with anemia (and sEpo levels <500 mU/mL) had hematologic response rates of 48% at 12 weeks and 56% at 24 weeks.\(^\text{181}\) Median duration of response was not reached at the 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 patients with responding disease.\(^\text{181}\)

Collectively, these studies suggest that ESAs may provide clinical benefit to patients in the lower-risk group 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 cytogenetically normal cells isolated from patients with del(5q), while having minimal proliferative effects on MDS progenitor cells from these patients \textit{in vitro}.\(^\text{184}\) Retrospective studies from the French group reported hematologic response rates between 46% and 64%, with a median response duration of 11 months (mean duration, 13–14 months) among patients with del(5q) treated with ESAs, with or without G-CSF.\(^\text{182,183}\) Duration of response in these patients was significantly decreased compared with patients without del(5q) (mean duration, 25–27 months).\(^\text{182}\) Based on multivariate analysis, del(5q) was a significant predictor of a shorter response duration with treatment (see \textit{Prognostic Category Low, Intermediate-1 Treatment} on page MDS-9).\(^\text{183}\)

\textbf{Management of Thrombocytopenia}

Severe thrombocytopenia is associated with an increased risk 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]) as well as increased destruction of bone marrow megakaryocytes or circulating platelets. Increased endogenous TPO levels have been reported among patients with MDS compared with healthy individuals. At the same time, TPO receptor sites per platelet appear to be decreased among patients with MDS compared with healthy subjects. The RA subgroup appeared to have the highest TPO levels compared with RAEB or RAEB-t patients, while the number of TPO receptor sites remained similar across subtypes. This observation suggests that the regulatory pathway for endogenous TPO may be further disrupted in patients with RAEB or RAEB-t, potentially due to overexpression of TPO receptors in blasts that may lead to an inadequate TPO response.

A number of studies are investigating the role of the TPO 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. Randomized placebo-controlled studies in patients treated for lower-risk MDS have reported beneficial effects of romiplostim in terms of decreased bleeding events, reduced need for platelet transfusions in patients receiving hypomethylating agents, and decreased frequency of dose reductions or delays in patients receiving lenalidomide therapy. A model to predict response to romiplostim indicated that lower-risk MDS, lower baseline TPO levels (<500 pg/mL), and limited platelet transfusion history had the greatest effect on subsequent platelet response to romiplostim.

Eltrombopag is another TPO 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 for the treatment of thrombocytopenia in patients with MDS. Concerns for potential proliferation of leukemic blasts in response to exogenous TPO have been raised in earlier in vitro studies, particularly for high-risk MDS cases. Results from ongoing clinical trials with the TPO mimetics will help to elucidate the risks for leukemic transformations in patients with MDS. It should be noted that neither romiplostim nor eltrombopag are currently approved for use in patients with MDS.

Management of Iron Overload

RBC transfusions are a key component in the supportive care of MDS patients. Although the specific therapies patients receive may alleviate RBC transfusion need, a substantial proportion of MDS patients may not respond to these treatments and may develop iron overload and its consequences. Thus, effective treatment of transfusional siderosis in MDS patients may be necessary.

Studies in patients requiring relatively large numbers of RBC transfusions (eg, thalassemia, MDS) have demonstrated the pathophysiology and adverse effects of chronic iron overload on hepatic, cardiac, and endocrine function. Increased non-transferrin-bound iron, generated when plasma iron exceeds transferrin binding capacity, combines with oxygen to form hydroxyl and oxygen radicals. These toxic elements cause lipid peroxidation and cell membrane, protein, DNA, and organ damage.
Although limited, there is evidence suggesting that organ dysfunction can result from iron overload in patients with MDS.\(^{201-203}\) Retrospective data suggest that transfusional iron overload might be a contributor of increased mortality and morbidity in early-stage MDS.\(^{204}\) The WPSS has shown that the requirement for RBC transfusion is a negative prognostic factor for patients with MDS.\(^{127}\) In a meta-analysis including 8 observational studies, patients receiving iron chelation therapy had a longer median survival time compared to patients who did not receive therapy. The mean difference in median OS was 61.2 months, further supporting the need to control transfusional iron overload.\(^{205}\) However, prospective studies are required to substantiate the value of iron chelation in these patients.

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The NCCN Panel Members recommend monitoring serum ferritin levels and number of RBC transfusions received as a practical means to determine iron stores and assess iron overload. Monitoring serum ferritin may be useful, aiming to decrease ferritin levels to less than 1000 mcg/L. It is recognized that such measurements, though useful, are less precise than SQUID (Superconducting Quantum Interference Device), or more recently T2* MRI, to provide a specific measurement of hepatic iron content.\(^{206,207}\)

Reversal of some of the consequences of iron overload in MDS and other iron overload states by iron chelation therapy has been shown in patients in whom the most effective chelation occurred.\(^{176,200}\) This included transfusion independence (TI) in a subset of the small group of MDS patients who had undergone effective deferoxamine chelation for 1 to 4 years.\(^{208}\) In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.\(^{209}\) Such findings have major implications for altering the morbidity of MDS patients, particularly those with pre-existing cardiac or hepatic dysfunction.

The availability of iron chelators, such as deferoxamine\(^{210}\) and deferasirox,\(^{211-213}\) provide potentially useful drugs to more readily treat iron overload. Deferoxamine (given as intramuscular or subcutaneous [SC] injections) is indicated for the treatment of chronic iron overload due to transfusion-dependent (TD) anemias.\(^{210}\) Deferasirox (given orally) is indicated for the treatment of chronic iron overload due to blood transfusions.\(^{211}\) Deferasirox has been evaluated in multiple phase II clinical trials in patients with TD-MDS.\(^{214-216}\) A large, multicenter, phase III, randomized controlled trial is currently underway to evaluate outcomes of deferasirox compared with placebo in patients with MDS; the primary endpoint of this ongoing study is event-free survival (registered at clinicaltrials.gov; NCT00940602). The prescribing information for deferasirox contains a black-box warning pertaining to the increased risks for renal or hepatic impairment/failure and GI bleeding in certain patient populations, including patients with high-risk MDS. Deferasirox is contraindicated in patients with high-risk MDS. A third oral chelating agent, deferiprone, was approved (October 2011) in the United States for the treatment of patients with transfusional iron overload due to thalassemia when current chelation therapy is inadequate.\(^{217}\) FDA approval was based on results from a retrospective analysis of data pooled from previous safety and efficacy studies of deferiprone in patients with transfusion-related iron overload refractory to existing chelation therapy. The prescribing information for deferiprone contains a black-box warning pertaining to risks for agranulocytosis, which can lead to serious infections and death.\(^{217}\) Controversy remains regarding the use of this agent.

There are ongoing clinical trials in patients with MDS receiving oral iron-chelating agents to address whether iron chelation alters the natural
history of patients who are TD. The NCCN Task Force report, titled *Transfusion and Iron Overload in Patients with Myelodysplastic Syndromes*, provides detailed evidence regarding iron chelation in patients with MDS.\(^{218}\)

The NCCN Guidelines Panel recommends consideration of once-daily deferoxamine SC or deferasirox/ICL670 orally to decrease iron overload (aiming for a target ferritin level less than 1000 ng/mL) in the following IPSS Low- or Intermediate-1-risk patients: 1) patients who have received or are anticipated to receive greater than 20 RBC transfusions; 2) patients for whom ongoing RBC transfusions are anticipated; and 3) patients with serum ferritin levels greater than 2500 ng/mL.

As mentioned above, a black-box warning by the FDA and Novartis was added to the prescribing information for deferasirox.\(^{211}\) Following post-marketing use of deferasirox, there were case reports of acute renal failure, or hepatic failure, some of which were fatal. Most of the fatalities reported were in patients with multiple comorbidities and in advanced stages of their hematologic disorders. Additionally, there were post-marketing reports of cytopenias, including agranulocytosis, neutropenia, and thrombocytopenia and GI bleeding in patients treated with deferasirox; some cases resulted in death. The relationship of these episodes to treatment with deferasirox has not yet been established. However, it is recommended that patients on deferasirox therapy be closely monitored. Monitoring should include measurement of serum creatinine and/or creatinine clearance and liver function tests prior to initiation of therapy and regularly thereafter. Deferasirox should be avoided in patients with creatinine clearance less than 40 mL/min.\(^ {211}\)

**Low-Intensity Therapy**

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

**Hypomethylating Agents**

As a form of relatively low-intensity chemotherapy, the DNA methyl transferase inhibitor (DMTI) hypomethylating agents AzaC and decitabine (5-aza-2'-deoxycytidine) have been shown in randomized phase III trials to decrease the risk of leukemic transformation and, in a portion of patients, to improve survival.\(^ {219-222}\) In a phase III trial that compared AzaC with supportive care in patients from all IPSS risk groups (N = 191; previously untreated in 83%), hematologic responses occurred in 60% of patients in the AzaC arm (7% CR, 16% partial response [PR], and 37% hematologic improvement) compared with a 5% hematologic improvement (and no responses) in patients receiving supportive care.\(^ {222}\) The median time to AML progression or death was significantly prolonged in the AzaC arm compared with patients receiving supportive care (21 vs. 13 months; \(P = .007\)). Further improvement was seen in patients who received AzaC earlier in the course of disease, suggesting that the drug prolonged the duration of stable disease. Subsequently, Silverman and colleagues\(^ {223}\) provided a summary of three AzaC studies in a total of 306 patients with high-risk MDS.\(^ {223}\) In this analysis, which included patients receiving either SC or intravenous (IV) delivery of the drug (75 mg/m²/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of AzaC-treated patients and partial remissions were rare; hematologic improvement was seen in 23% to 36% of these patients. Ninety percent of the responses occurred prior to cycle 6 with a median number of cycles to first response of 3.\(^ {223}\) 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%) demonstrated that AzaC
was superior to conventional care (ie, standard chemotherapy or supportive care) regarding OS. AzaC was associated with a significantly longer median survival compared with conventional care (24.5 vs. 15 months; HR, 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 MDS patients with progressing or relatively high-risk disease. This drug has been approved by the FDA for the treatment of patients with MDS. The drug is generally administered at a dose of 75 mg/m²/day SC 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, patients whose marrow blast counts require lowering prior to HCT). 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 showed that among patients with disease responding to AzaC, response quality was improved in 48% with continued therapy. Although most patients with responding disease achieved a first response by 6 cycles of therapy, up to 12 cycles were required for the majority of responders to attain a best response. In this study, the median number of cycles from first response to best response was 3 to 3.5 cycles, and patients with responding disease received a median of 8 additional cycles (range, 0–27 cycles) beyond first response.

An alternative 5-day schedule of AzaC has been evaluated, both as an SC regimen (including both the 5-2-2 schedule: 75 mg/m²/d SC for 5 days followed by 2 days of no treatment, then 75 mg/m²/d for 2 days, every 28 days; and the 5-day schedule: 75 mg/m²/d SC for 5 days every 28 days) and as an IV regimen (75 mg/m²/d IV for 5 days every 28 days). Although response rates with the 5-day regimens appeared similar to the approved 7-day dosing schedule, survival benefit with AzaC has only been demonstrated using the 7-day schedule.

Similarly, the other DMTI hypomethylating agent, decitabine, given IV and administered with a regimen that required hospitalization of patients, has shown encouraging results for the therapy of patients with higher-risk MDS. As the treatment regimen was generally associated with low-intensity–type toxicities, it is also considered to be a “low-intensity therapy.” In earlier phase II studies, approximately 30% of patients experienced cytogenetic conversion, with an overall response rate of 49%, and a 64% response rate in patients with a high-risk IPSS score; results were similar to those seen in AzaC studies.

A phase III randomized trial of decitabine (15 mg/m² IV infusion over 3 hours every 8 hours [ie, 45 mg/m²/d] on 3 consecutive days every 6 weeks for up to 10 cycles) compared with supportive care in adult patients (N = 170) with primary and secondary MDS (IPSS INT-1, 31%; INT-2, 44%; High risk, 26%) indicated higher response rates, remission durations, times to AML progression, and survival benefits in the INT-2 and High-risk groups. Overall response rate (CR + PR) with decitabine was 17% (median duration, 10 months), with an additional 13% of patients showing hematologic improvement. The probability of progression to AML or death was 1.68-fold greater for supportive care patients than for patients receiving decitabine. Based on this study and three supportive phase II trials, the drug has also been approved by the FDA for treating MDS patients.

In a recent phase III randomized trial, decitabine was compared with best supportive care in patients age 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{221} Median progression-free survival was significantly improved in patients receiving decitabine compared with supportive care (6.6 vs. 3 months; HR, 0.68; 95% CI, 0.52–0.88; \(P = .004\)), and the risk of AML progression at 1 year was significantly reduced with decitabine (22\% vs. 33\%; \(P = .036\)). However, no significant differences were observed between decitabine and supportive care for the primary endpoint of OS (10 vs. 8.5 months, respectively) or for median AML-free survival (8.8 vs. 6.1 months, respectively).\textsuperscript{221} In the decitabine arm, a CR and PR was 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). 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{221}

Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated. In 2007, Kantarjian and colleagues\textsuperscript{232} provided an update to their study of 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens.\textsuperscript{232} Patients received 1 of 3 different schedules of decitabine, including both SC and IV administration with a mean of 7 courses of therapy. Responses were improved with the longer duration of therapy. Overall, 80 patients (70\%) responded with 40 patients (35\%) achieving a CR and 40 (35\%) achieving a PR. The median remission duration was 20 months with a median survival time of 22 months. The three different schedules of decitabine were compared in another randomized study of 95 patients with MDS or CMML, receiving 20 mg/m\textsuperscript{2} IV daily for 5 days; 20 mg/m\textsuperscript{2} SC daily for 5 days; or 10 mg/m\textsuperscript{2} IV daily for 10 days.\textsuperscript{233} The 5-day IV schedule was considered the optimal schedule. The CR rate in this arm was 39\%, compared with 21\% in the 5-day SC arm and 24\% in the 10-day IV arm (\(P < .05\)).

Several retrospective studies have evaluated the role of cytoreductive therapy with hypomethylating agents prior to allogeneic HCT (with both myeloablative and reduced-intensity conditioning [RIC] regimens).\textsuperscript{234-237} These studies suggest that hypomethylating agents may provide a feasible alternative to induction chemotherapy regimens prior to transplant, and may serve as a bridge to allogeneic HCT.

Currently, AzaC and decitabine are considered to be therapeutically similar, although the improved survival of higher-risk patients treated with AzaC compared to control patients in a phase III trial, as indicated above, supports the preferred use of AzaC in this setting. A lack of CR, PR or hematologic improvement, or frank progression to AML (in particular with loss of control [proliferation] of peripheral counts or excess toxicity that precludes continuation of therapy) may be indicative of disease that fails to respond to hypomethylating agents. The minimum number of courses prior to considering the treatment 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 Guidelines Panel generally feels that treatment should be continued if there is ongoing response and if there are no toxicities. Modifications should be made to the dosing frequency for individual patients in the event of toxicity.

As data have predominantly indicated altered natural history and decreased evolution to AML in patients who respond to DMTI hypomethylating agents, the major candidates for these drugs are
patients with IPSS INT-2- or High-risk disease or IPSS-R Intermediate-, High-, or Very-High-risk disease with any of the following criteria:

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

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 sEpo levels who are not expected to respond to (or who relapsed after) IST.

**Biologic Response Modifiers and Immunosuppressive Therapy**

The currently available non-chemotherapy, low-intensity agents (biologic response modifiers) include: 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 phase II trials.3,238-243

Use of anti-immune type therapy with ATG, with or without cyclosporine,240,243 has been shown in several studies to be most efficacious in MDS patients with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a PNH clone.28,29 Researchers from the NIH have updated their analysis of 129 patients treated with IST. The patients were treated with equine ATG alone, cyclosporine alone, or in combination.30 This study demonstrated markedly improved response rates in the subgroup of patients 60 years of age or younger with IPSS INT-1 risk or patients with high response probability characteristics as indicated by their prior criteria (i.e., HLA-DR15+, age, number of transfusions).30

Both equine and rabbit ATG are available in the United States for IST. A randomized study from the NIH compared the activity of equine versus rabbit ATG, combined with cyclosporine, in previously untreated patients with severe AA (N = 120) who were not eligible for transplant.244,245 Rabbit ATG was inferior to equine ATG as shown by the lower 6-month hematologic response rate (primary endpoint, 37% vs. 68%; P < .001) and higher number of deaths (14 vs. 4 patients); the 3-year survival rate was significantly inferior with rabbit ATG compared with equine ATG (76% vs. 96%; P = .04).245 The 3-year cumulative incidence of relapse was not significantly different between treatment groups (11% vs. 28%, respectively).244 Within the setting of MDS, however, only limited data are available regarding the comparative effectiveness of the two ATG formulations. In a relatively small phase II study in patients with MDS (N = 35; primarily RA subtype), both equine and rabbit ATG were shown to be feasible and active.246 Some institutions have used tacrolimus in place of cyclosporine A based on the limited data that showed similar efficacy with lower incidence of adverse events in children with aplastic anemia.247,248

A recent study showed that STAT3 mutant cytotoxic T lymphocyte clones were found in a small proportion (5%) of MDS patients (including those lacking LGLs), which associated with HLA-DR15 positivity, marrow hypocellularity, and neutropenia.31 Despite lack of a survival difference in the STAT3-mutated versus non-mutated MDS patients treated with IST in this small cohort, these findings suggest that STAT3-mutant CTL clones may facilitate persistently dysregulated autoimmune activation akin to that present in other MDS patients responsive to IST.31
Lenalidomide (a thalidomide analog) is an immunomodulating agent with activity in patients with lower-risk MDS. Beneficial results have been particularly evident for patients with the del(5q) chromosomal abnormality. A multicenter phase II trial of lenalidomide (10 mg/d for 21 days every 4 weeks or 10 mg daily) in anemic RBC TD-MDS patients with del(5q), with or without additional cytogenetic abnormalities (N = 148), demonstrated that the hematologic response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained. RBC-TI (assessed at 24 weeks) occurred in 67% of patients; among patients with IPSS Low/INT-1 risk (n=120), 69% achieved TI. 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, 55%; thrombocytopenia, 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 (due to the drug’s renal route of excretion). Lenalidomide has been approved by the FDA for the treatment of TD anemia in IPSS Low/INT-1–risk MDS patients with del(5q) with or without additional cytogenetic abnormalities.

A phase III randomized controlled trial compared the activity of lenalidomide (5 mg daily for 28 days or 10 mg daily for 21 days of a 28-day cycle) versus placebo in RBC-TD patients (N = 205) with lower-risk MDS (IPSS Low- and INT-1 risks) and del(5q). The primary endpoint of RBC-TI greater than or equal to 26 weeks, was achieved in a significantly greater proportion of patients treated with lenalidomide 5 mg or 10 mg versus placebo (37% vs. 57% vs. 2%, respectively; \( P \leq .0001 \) for both lenalidomide groups vs. placebo). Among patients achieving RBC-TI with lenalidomide, onset of erythroid response was rapid, with a median time of 4.2 weeks and 4.3 weeks in the 5-mg and 10-mg lenalidomide groups, respectively. Cytogenetic response rates were significantly higher for the lenalidomide 5 mg (23%; \( P = .0299 \)) and 10 mg (57%; \( P < .0001 \)) groups compared with placebo (0%); CR rates were observed in 12% and 35% of patients in the lenalidomide 5-mg and 10-mg groups, respectively. The estimated 2-year cumulative risk to AML progression was 17% (95% CI, 8.7–33.3), 12.6% (95% CI, 5.4–27.7), and 16.7% (95% CI, 8.3–32.0) in the lenalidomide 5-mg, 10-mg, and placebo groups, respectively. This increased to 35% (95% CI, 21.4–54.6), 31% (95% CI, 18.1–48.8), and 43.3% (95% CI, 27.6–63.1), respectively, at the estimated 4-year mark. The median OS between the lenalidomide 5-mg, 10-mg, and placebo groups (3.5 vs. 4.0 vs. 2.9 years, respectively) was not statistically significant; however, median survival was significantly longer in patients who achieved RBC-TI (5.7 years; 95% CI, 3.2–no response) compared to nonresponders (2.7 years; 95% CI, 2.0–4.7). The most common grade 3 or 4 adverse events were myelosuppression and deep vein thrombosis (DVT). Grade 3 or 4 neutropenia was reported in 77%, 75%, and 16% of patients in the lenalidomide 5-mg, 10-mg, and placebo arms, respectively; thrombocytopenia occurred in 37%, 38%, and 2% of patients, respectively. Grade 3 or 4 DVT occurred in 3 patients in the lenalidomide 10-mg arm and in one patient in the placebo arm.

A recent comparative analysis evaluated outcomes of patients with RBC-TD IPSS Low/INT-1–risk MDS with del(5q) receiving lenalidomide (based on data from the two aforementioned trials [n = 295]) compared with no treatment (based on data from untreated patients in a multicenter registry [n = 125]). 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 rates were 23% and 20%, respectively; 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 OS probabilities were 90% with lenalidomide and 74% in the untreated cohort; the corresponding 5-year probability was 54% and 40.5%, respectively, with a median OS of 5.2 years and 3.8 years ($P = .755$; Kaplan-Meier plot with left truncation to adjust for differences in timing of study entry between cohorts). Based on multivariate analysis using Cox proportional hazard models (also with left truncation), lenalidomide was associated with a significantly decreased risk of death compared with no treatment (HR, 0.597; 95% CI, 0.399–0.894; $P = .012$). Other independent factors associated with a 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.

A phase II study evaluated lenalidomide treatment in RBC-TD patients ($N = 214$) with Low- or INT-1–risk MDS without del(5q). Results showed that 26% of the non-del(5q) patients (56 of 214) achieved TI after a median of 4.8 weeks of treatment. TI continued for a median duration of 41 weeks. The median rise in hemoglobin was 3.2 g/dL (range, 1.0–9.8 g/dL) for those achieving TI. A 50% or greater reduction in transfusion requirement was noted in an additional 37 patients (17%), yielding an overall rate of hematologic improvement of 43%. The most common grade 3 or 4 adverse events were neutropenia (30%) and thrombocytopenia (25%). A recent abstract presented early data from an international phase III study of 239 patients with IPSS Low- or INT-1–risk MDS and RBC-transfusion dependency and lacking the del(5q) abnormality. Patients receiving lenalidomide ($n = 160$) compared to patients receiving placebo ($n = 79$) had a higher rate of RBC-TI (26.9% vs. 2.5%; $P < .001$) that lasted a median duration of 8.2 months (range, 5.2–17.8 months). TI persisting greater than 168 days was seen in 17.5% of patients receiving lenalidomide and 0% of patients in the placebo cohort. Incidence of treatment-related mortality was 2.5% in both groups. However, the incidence of myelosuppression was higher in the lenalidomide-treated group. Comparing the patients receiving lenalidomide versus placebo, the incidence of grade 3 or 4 neutropenia was 61.9% versus 11.4%, respectively, and the rate of thrombocytopenia was 35.6% versus 3.8%, respectively. Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents for non-del(5q) MDS patients, particularly addressing long-term outcomes. The NCCN Guidelines Panel recommends lenalidomide be considered for patients with symptomatically anemic non-del(5q) MDS whose anemia did not respond to initial therapy.

**High-Intensity Therapy**

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

A high degree of multi-drug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS and is associated with decreased responses and shorter response durations in patients treated with many of the standard chemotherapy induction regimens. Thus, chemotherapeutic agents used to treat “resistant-type” AML, and agents
that modulate this resistance, are now being evaluated for the treatment of patients with advanced MDS. Although several studies using multi-drug resistance modulators were positive in this setting, others were not. Ongoing clinical trials evaluating other multi-drug resistance modulators are important as both positive and negative studies have been published.

Allogeneic HCT 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. Matched non-myeloablative transplant regimens and matched unrelated donor HCTs are becoming options at some centers. In certain investigative settings, autologous bone marrow or peripheral blood stem cell transplantation is being considered. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been prospectively established. Comparative clinical trials are needed to address these issues.

Recommended Treatment Approaches

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

Regarding the therapeutic options for lower-risk patients with clinically significant cytopenias or increased bone marrow blasts, the NCCN Guidelines Panel recommends stratifying these patients into several groups. Patients with del(5q) chromosomal abnormalities and symptomatic anemia should receive lenalidomide. Studies have shown the relative safety of lenalidomide in these patients and improved QOL outcomes in randomized clinical trials. The recommended dose of lenalidomide in this setting is 10 mg once daily for 21 days, every 28 days or 28 days monthly; response should be assessed 2 to 4 months after initiation of treatment. However, lenalidomide should be avoided in patients with a clinically significant decrease in neutrophil or platelet counts; in the previously discussed phase III trial with lenalidomide in patients with del(5q), patients with low neutrophil counts (<500 cells/mcL) or platelet counts (<25,000 cells/mcL) were excluded from the study. An alternative option to lenalidomide in patients with del(5q) and symptomatic anemia may include an initial trial of ESAs in cases where sEpo levels are 500 mU/mL or less.

Patients without the del(5q) abnormality with symptomatic anemia are categorized on the basis of sEpo levels. Levels of less than or equal to 500 mU/mL should be treated with ESAs (rHu Epo or darbepoetin) with or without G-CSF (see Evaluation of Related Anemia/Treatment of Symptomatic Anemia on page MDS-12). Non-responders should be considered for IST (with ATG or cyclosporine) if there is a high likelihood of response to such therapy. In patients with lower-risk MDS, the most appropriate candidates for IST include patients who are age 60 years or younger; are HLA-DR15 positive; have a PNH-positive clone; or have less than or equal to 5% marrow blasts or hypocellular marrow. Alternatively, treatment with AzaC, decitabine, or lenalidomide should be considered, particularly in the case of non-response to IST. 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 HCT (see Therapy for Higher-Risk Patients in the Discussion).

Anemic patients with sEpo level greater than 500 mU/mL should be evaluated to determine whether they have a good probability of responding to IST. Non-responders to IST would be considered for treatment with AzaC, decitabine, or a clinical trial. Patients with sEpo levels greater than 500 mU/mL who have a low probability of responding to IST should be considered for treatment with AzaC,
decitabine, or lenalidomide. Non-responders to these treatments could be considered for a clinical trial or for allogeneic HCT. 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, decitabine, ISTs (if there is a good probability of responding to these agents), or a clinical trial.

Data from a phase III randomized trial of AzaC showed significantly higher rates of major platelet improvement with AzaC compared with conventional care (33% vs. 14%; \( P = 0.0003 \)); however, the rates for major neutrophil improvements were similar between AzaC and the control arm (19% vs. 18%). Furthermore, the study was limited to the inclusion of patients with higher-risk MDS.\(^{219} \) Recently, a phase II prospective study of MDS patients who are IPSS Low or INT-1 with symptomatic anemia, and whose disease is not expected to respond or has failed to respond to EPO, has shown that AzaC is well-tolerated.\(^{282} \) Although neutropenia and thrombocytopenia were adverse events (47% and 19% of patients, respectively), these toxicities were transient. Other non-hematologic toxicities were mild. AzaC treatment was effective in 60% of patients in the study. Patients who do not respond to hypomethylating agents should be considered for treatment with IST, a clinical trial, or an allogeneic HCT.

While these guidelines provide a framework in which to treat MDS patients, careful monitoring for disease progression and consideration of the patient’s preferences remain major factors in the decision and timing of the treatment regimen initiated.
group, there was only a slight gain in life expectancy if HCT was delayed; therefore, decisions should probably be made on an individual basis (eg, dependent on platelet or neutrophil counts). A retrospective study evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HCT. The data suggest that lower-risk patients (based on WPSS risk score) do very well following allogeneic HCT, with a 5-year OS of 80%. With increasing WPSS scores, the probability of 5-year survival after HCT declined progressively to 65% (Intermediate risk), 40% (High risk), and 15% (Very High risk).

Based on data regarding RIC for transplantation from two reported series and two comprehensive reviews of the field, patient age and disease status generally dictated the type of conditioning to be utilized. Patients older than 55 or 60 years, particularly if they had less than 10% marrow myeloblasts, generally received RIC; if the blast count was high, pre-HCT debulking therapy was often given. Younger patients, regardless of marrow blast burden, most frequently received high-dose conditioning. Variations on these approaches would be considered by the individual transplant physician based on patient features and the specific regimen utilized at that center. Some general recommendations have been presented in a review article.

There are limited data regarding the use of allogeneic HCT in older adults with MDS; however, studies suggest that age alone should not be an exclusionary factor for eligibility. In a prospective allogeneic transplant trial using nonmyeloablative conditioning, 372 patients between the ages of 60 and 75 years with hematologic malignancies (AML, MDS, CLL, lymphoma, and multiple myeloma) were shown to have no association between age and non-relapse mortality, OS, and PFS. The study supports the use of comorbidities and disease status, rather than age alone, as criteria for determining the eligibility of patients for allogeneic HCT.

Other retrospective studies have also evaluated transplant-related mortality in older patients with MDS receiving RIC for allogeneic transplant. No increase in mortality was seen in either study. In a retrospective analysis of 514 patients with de novo MDS (ages 60–70 years), RIC allogeneic transplants were not associated with improved life expectancy for patients with low/INT-1 IPSS MDS compared to other non-transplant therapies. However, a potential improvement in life expectancy was seen in patients with INT-2/high risk IPSS MDS. It is recognized that there are even less data in patients who are 75 years of age or older.

**Intensive Chemotherapy**
For patients eligible for intensive therapy but lacking a donor stem cell source, or for patients in whom the marrow blast count requires reduction, consideration should be given to the use of intensive induction chemotherapy. Although the response rate and durability is lower than for standard AML, this treatment (particularly in clinical trials with novel agents) could be beneficial in some patients. For patients with a potential stem cell donor who require reduction of tumor burden (ie, to decrease the marrow blast count), achievement of even a partial remission may be sufficient to permit the HCT. For this purpose, AzaC, decitabine, or participation in clinical trials is also considered a valid treatment option.

**Non-Intensive Therapy**
For higher-risk patients who are not candidates for intensive therapy, the use of AzaC, decitabine, or a relevant clinical trial should be considered. The NCCN Guidelines panel preferentially recommends AzaC (category 1) compared with decitabine based on data from a
phase III trial that showed superior median survival with AzaC compared to best supportive care. AzaC or decitabine should be continued for at least 4 to 6 cycles to assess response to these agents. For patients who show clinical benefit, treatment with hypomethylating agents should be continued as maintenance therapy. Results from a phase III trial comparing decitabine to supportive care in higher-risk patients whose treatment failed to demonstrate a survival advantage, although response rates were similar to those previously reported for AzaC. Two reports from the phase III, international, multicenter, randomized AZA-001 trial have evaluated AzaC compared to conventional care regimens (CCR) in patients with higher-risk MDS. Patients randomized to the CCR group received the most appropriate of the three protocol-specified CCR options, including AraC, intensive chemotherapy, or best supportive care. The OS was increased with AzaC treatment compared to CCR (HR, 0.58; 95% CI, 0.43–0.77; \( P < .001 \)) and a greater number of patients achieved hematologic improvement (49% vs. 29%; \( P < .0001 \)). The earlier report from the same trial showed improved OS and tolerability in elderly patients (defined as 75 years of age or older) with good performance status. It should be noted that to date, no head-to-head trials have compared AzaC with decitabine.

For some patients eligible for HCT therapy who require a reduction in tumor burden, the use of AzaC or decitabine may be a bridge to transplant by sufficiently decreasing the marrow blast count.

**Supportive Care Only**

For patients with adverse clinical features or disease progression despite therapy and the absence of reasonable specific anti-tumor therapy, adequate supportive care should be maintained.

**Evaluation and Treatment of Related Anemia**

Major morbidities of MDS include symptomatic anemia and associated fatigue. Progress has been made in the management of MDS-related anemia; however, the health care provider must also identify and treat any coexisting causes of anemia.

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

Anemia related to MDS commonly presents as a hypoproducive macrocytic anemia, often associated with suboptimal elevation of sEpo levels. Bone marrow aspiration with iron stain, biopsy, and cytogenetics should be used to determine WHO subtype, iron status, and the level of ring sideroblasts. Patients should also be considered for HLA-DR15 typing as indicated above.

Individuals having symptomatic anemia and del(5q), with or without other cytogenetic abnormalities, should receive a trial of lenalidomide. As previously discussed, an alternative option to lenalidomide may include an initial trial of ESAs in patients with sEpo levels of 500 mU/mL or less. Patients with normal cytogenetics, less than 15% ring sideroblasts, and sEpo levels of 500 mU/mL or less may respond to Epo if relatively high doses of rHu Epo are administered.
Epo dose required is 40,000 to 60,000 SC units 1 to 3 times a week. Erythroid responses generally occur within 6 to 8 weeks of treatment. A more prompt response may be obtained with a higher starting dose. This recommended Epo dose is much higher than the dose needed to treat renal causes of anemia wherein marrow responsiveness would be relatively normal. However, if a response occurs at the higher dose, the recommendation is to attempt a decrease to the lowest effective dose. The literature supports either daily dosing or dosing 2 to 3 times per week.

Iron repletion needs to be verified before instituting Epo or darbepoetin therapy. If no response occurs with these agents alone, the addition of G-CSF should be considered. Evidence suggests that G-CSF (and, to a lesser extent, GM-CSF) has synergistic erythropoietic activity when used in combination and markedly enhances the erythroid response rates. This is particularly evident for patients with greater than or equal to 15% ring sideroblasts in the marrow (and sEpo level ≤500 mU/mL) as the very low response rates to Epo or darbepoetin alone in this subgroup 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 initially neutropenic patients or to double the neutrophil count in patients who are initially non-neutropenic. For this purpose, an average of 1 to 2 mcg/kg SC G-CSF is administered either daily, or between 1 to 3 times per week. G-CSF is available in single-use vials or prefilled syringes containing 300 mcg or 480 mcg and requires refrigeration. Patients may be taught to self-administer the drug. Detection of erythroid responses generally occurs within 6 to 8 weeks of treatment. If no response occurs within this time frame, treatment should be considered a failure and discontinued. In the case of treatment failure, one should rule out and treat deficient iron stores. Clinical trials or supportive care are also treatment options for these patients. A validated decision model has been developed for predicting erythroid responses to Epo plus G-CSF based on the patient’s basal sEpo level and number of previous RBC transfusions. Improved QOL has been demonstrated in patients with responding disease. This cytokine treatment is not suggested for patients with endogenous sEpo levels greater than 500 mU/mL due to the very low erythroid response rate to these drugs in this patient population.

Darbepoetin alfa is a longer-acting form of Epo. Studies predominantly in lower-risk MDS patients have demonstrated a substantial proportion of erythroid response rates of 40% and 60% (combined major and minor responses using IWG response criteria) in the initial trials. Clinical trial results in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than epoetin. The improved response rates may in part be due to the dosage used (150–300 mcg SC per week) or to the fact that better-risk patients were enrolled in studies of darbepoetin compared to epoetin. Features predictive of response have included relatively low basal sEpo levels, low percentage of marrow blasts, and relatively few prior RBC transfusions.

In March 2007 and 2008, the FDA announced alerts and strengthened safety warnings for the use of ESAs based on observed increased mortality and possible tumor promotion and thromboembolic events in non-MDS patients receiving ESAs when dosing to achieve a targeted hemoglobin level greater than 12 g/dL. Specifically, the study patients had chronic kidney failure; were receiving radiation therapy for various malignancies, including head and neck cancer, advanced breast cancer, lymphoid cancer, or non-small cell lung cancer; were cancer patients not receiving chemotherapy; or were orthopedic surgery patients.
However, as indicated above, ESAs have been used safely in large numbers of adult MDS patients and have become important for symptomatic improvement of anemia caused by this disease, often with a decrease in RBC transfusion requirements. Studies assessing the long-term use of Epo with or without G-CSF in MDS patients have shown no negative impact of such treatment on survival or AML evolution when compared to either randomized controls\textsuperscript{180} or historical controls.\textsuperscript{180,183} Results from the studies by Jadersten et al\textsuperscript{180} indicated improved survival in low-risk MDS patients with low transfusion need following treatment with these agents.\textsuperscript{180} The study by Park et al\textsuperscript{183} further indicated improved survival and decreased AML progression of IPSS Low/INT-1 patients following Epo treatment, with or without G-CSF, compared to the historical control IMRAW database patients.\textsuperscript{183} Thus, these data do not indicate a negative impact of these drugs in the treatment of MDS. Given these data, the NCCN Panel recommends the use of ESAs in the management of symptomatic anemia in MDS patients, with a target hemoglobin range of 10 to 12 g/dL but not exceeding 12 g/dL.

In March 2007, the Centers for Medicare and Medicaid Services (CMS) generated a National Coverage Determination (NCD) on the use of ESAs in non-renal disease applications. Following a public comment period, it was determined that the scope of the NCD should be revised to include cancer and related neoplastic conditions. The narrowed scope of the NCD excludes MDS as it is defined in the report as a premalignant condition and not an oncologic disease.\textsuperscript{310} Thus, local Medicare contractors may continue to make reasonable and necessary determinations on the use 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 underlying prognostic risk group.

**Summary**

The NCCN Guidelines are based on extensive evaluation of the reviewed risk-based data and indicate current approaches for managing patients with MDS. Four drugs have been approved by the FDA for treating specific subtypes of MDS: lenalidomide for patients with del(5q) cytogenetic abnormalities; AzaC and decitabine for treating higher-risk or non-responsive patients; and deferasirox for iron chelation in the treatment of iron overload. However, as a substantial proportion of MDS patient subsets lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents, along with supportive care, remain the hallmark of disease management. The role of thrombopoietic cytokines for the management of thrombocytopenia in MDS needs further evaluation; determination of the effects of these therapeutic interventions on QOL is important.\textsuperscript{301,303,304,311,312} Progress toward improving the management of MDS has occurred over the past few years and more advances are anticipated with these guidelines providing a framework for coordination of comparative clinical trials.
Myelodysplastic Syndromes

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