NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes

Version 2.2014

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Summary of Guidelines Updates

Initial Evaluation (MDS-1)

Additional Testing and Classification (MDS-2)

2008 World Health Organization (WHO) Classification of MDS (MDS-3)

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

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

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

Prognostic Category Low, Intermediate-1 Treatment (MDS-7)

Prognostic Category Intermediate-2, High Treatment (MDS-9)

Evaluation of Related Anemia/Treatment of Symptomatic Anemia (MDS-10)

Recommendations for Flow Cytometry (MDS-A)

Supportive Care (MDS-B)

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2014 of the NCCN Guidelines from Version 1.2014 include:

**DISCUSSION**
- The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2014 of the NCCN Guidelines from Version 2.2013 include:

**MDS-1**
- Modified footnote “b”: Confirm diagnosis of MDS according to FAB or WHO criteria for classification with application of IPSS. See Classification Systems (MDS-3 and MDS-5). The percentage of marrow myeloblasts based on morphologic assessment (aspirate smears preferred) should be reported. Flow cytometric estimation of blast percentage should not be used as a substitute for morphology in this context. In expert hands, expanded flow cytometry may be a useful adjunct for diagnosis in difficult cases (See Discussion section, MS-5-6).

**MDS-3**
- Removed French-American-British (FAB) Classification of MDS tables.
- Added “Refractory anemia with excess blasts in transformation (RAEB-T) to the table with footnote “I”.

**MDS-4**
- Modified footnote “p”: “Examples include thrombocytosis, leukocytosis, and splenomegaly. In addition, RARS-T has been suggested as a provisional MDS/MPN entity for individuals with RARS and platelet counts $\geq 450,000 \times 10^3/\text{L}.$” [Chapter 4, in Swerdlow S, Campo E, Harris NL, et al (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 85-86.]

**MDS-5**
- Included Revised International Prognostic Scoring System (IPSS-R)
- Added the following footnotes:
  - Footnote “y”: 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), complex: 3 abnormalities; Very poor = Complex: >3 abnormalities.
  - Included the following websites for accessing the IPSS-R calculator tool: [http://www.ipss-r.com](http://www.ipss-r.com) or [http://mdsfoundation.org/calculator/index.php](http://mdsfoundation.org/calculator/index.php). A mobile App for the calculator tool is also available for smartphones at MDS IPSS-R.

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Updates in Version 1.2014 of the NCCN Guidelines from Version 2.2013 include:

**MDS-7**
- Added “IPSS-R: Very Low, Low, Intermediate” to the heading.
- Following “Clinically significant cytopenia(s)” added “or increased marrow blasts.”
- Following “Clinically relevant thrombocytopenia or neutropenia” added “or increased marrow blasts.”
- Changed “No response” to “Disease progression/no response.”
- Added footnote “bb”: “IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels. If patients initially are managed as lower risk but fail to respond, move to higher risk management strategies.”
- Moved “Immunosuppressive therapy (IST)” earlier under Azacytidine/decitabine under treatment. The section now reads: Azacytidine/decitabine or IST®® or Clinical trial.
- Footnote “ee” has been modified: “Patients generally ≤ 60 y, and ≤ 5% marrow blasts or those with hypocellular marrows, HLA-DR15 positivity, or PNH clone positivity.”

**MDS-8**
- Added “IPSS-R: Very Low, Low, Intermediate” to the heading.
- Under treatment, changed “No response” to “No response or intolerance.”
- Modified footnote “gg”: Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days monthly for 2-4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤ 500 mU/mL.

**MDS-9**
- Added “IPSS-R: Intermediate, High, Very High” to the heading.
- Modified footnote ll: “Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy should be used to decrease marrow blasts to an acceptable level prior to transplant.”

**MDS-10**
- Added footnote “gg” to lenalidomide. Footnote gg states: “Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days monthly for 2-4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤ 500 mU/mL.”

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INITIAL EVALUATION

Required:
- H&P
- CBC, platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping
- Serum erythropoietin (prior to RBC transfusion)
- RBC folate, serum B<sub>12</sub>
- 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<sup>b,c</sup>

See Additional Testing: Helpful in Some Clinical Situations (MDS-2)

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

Confirm diagnosis of MDS according to FAB or WHO criteria for classification with application of IPSS. See Classification Systems (MDS-3 and MDS-5). The percentage of marrow myeloblasts based on morphologic assessment (aspirate smears preferred) should be reported. Flow cytometric estimation of blast percentage should not be used as a substitute for morphology in this context. In expert hands, expanded flow cytometry may be a useful adjunct for diagnosis in difficult cases (See Discussion section, MS-6-7).

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

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

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# Classification Systems for De Novo MDS  (page 1 of 4)

## 2008 WHO Classification of MDS\(^k, l\)

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

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


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

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

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelomonocytic leukemia-1 (CMML-1)</td>
<td>&gt; 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</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 ('Overlap syndrome')</td>
<td>Dysplasia + myeloproliferative features&lt;sup&gt;g&lt;/sup&gt;, No prior MDS or MPN</td>
<td>Dysplasia + myeloproliferative features</td>
</tr>
</tbody>
</table>

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

<sup>p</sup>Examples include thrombocytosis, leukocytosis, and splenomegaly. In addition, RARS-T has been suggested as a provisional MDS/MPN entity for individuals with RARS and platelet counts ≥ 450,000 x10⁹/L [Chapter 4, in Swerdlow S, Campo E, Harris NL, et al (Eds.). World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. IARC Press, 2008, pp 85-86.]

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


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**Continued on next page**
### International Prognostic Scoring System (IPSS)\(^s,t\)

<table>
<thead>
<tr>
<th>Survival and AML evolution</th>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic variable</td>
<td>0</td>
</tr>
<tr>
<td>Marrow blasts (%)(^u)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype(^v)</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias(^w)</td>
<td>0/1</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Revised 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><strong>VERY LOW</strong> (19)</td>
<td>(\geq 1.5)</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td><strong>LOW</strong> (38)</td>
<td>(&gt;1.5-3)</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>INT</strong> (20)</td>
<td>(&gt;3.4-5)</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>HIGH</strong> (13)</td>
<td>(&gt;4.5-6)</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>VERY HIGH</strong> (10)</td>
<td>(&gt;6)</td>
<td>0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\(^s\)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.


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

\(^v\)Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (\(\geq 3\) 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.]

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


\(^t\)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.
### WHO-based Prognostic Scoring System (WPSS)\(^Z\)

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

#### WPSS risk

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

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


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**NCCN Guidelines Version 2.2014**

**Myelodysplastic Syndromes**

### PROGNOSTIC CATEGORY

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

#### Traitement

- **Symptomatic anemia**
  - Clinically significant cytopenia(s) or increased marrow blasts
    - Supportive care as an adjunct to treatment
  - No del(5q) ± other cytogenetic abnormalities
    - Serum EPO ≤ 500 mU/mL
      - See (MDS-8)
    - Serum EPO > 500 mU/mL
      - See (MDS-8)
  - Azacitidine/decitabine or Immunosuppressive therapy (IST)
    - Disease progression/No response
      - Clinical trial or Consider allo-HSCT for selected IPSS intermediate-1 patients

#### DISCUSSION

- Presence of comorbidities should also be considered for evaluation of prognosis (See references 128-133 in the Discussion section).
- IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels. If patients initially are managed as lower risk but fail to respond, move to higher risk management strategies.
- **See Supportive Care (MDS-B).**
- Patients generally ≤ 60 y, and ≤ 5% marrow blasts or those with hypocellular marrows, HLA-DR15 positivity, or PNH clone positivity.
- IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT (hematopoietic stem cell transplant): Allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).

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**PROGNOSTIC CATEGORY**

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

<table>
<thead>
<tr>
<th>del(5q) ± other cytogenetic abnormalities (for symptomatic anemia only)</th>
<th>Lenalidomide&lt;sup&gt;gg&lt;/sup&gt;</th>
<th>No response&lt;sup&gt;dd&lt;/sup&gt; or intolerance</th>
<th>Follow pathway below</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum EPO ≤ 500 mU/mL</td>
<td>Epoetin alfa (rHu EPO) ± G-CSF&lt;sup&gt;hh&lt;/sup&gt; or Darbepoetin alfa ± G-CSF&lt;sup&gt;hh&lt;/sup&gt;</td>
<td>No response&lt;sup&gt;dd&lt;/sup&gt;</td>
<td>Good probability to respond to IST&lt;sup&gt;ee&lt;/sup&gt;</td>
</tr>
<tr>
<td>Symptomatic anemia with no del(5q)</td>
<td>No response &lt;sup&gt;dd&lt;/sup&gt;</td>
<td>Good probability to respond to IST&lt;sup&gt;ee&lt;/sup&gt;</td>
<td>Follow appropriate pathway below</td>
</tr>
<tr>
<td>Serum EPO &gt; 500 mU/mL</td>
<td>Poor probability to respond to IST&lt;sup&gt;ff&lt;/sup&gt;</td>
<td>No response &lt;sup&gt;dd&lt;/sup&gt; or intolerance</td>
<td>No response &lt;sup&gt;dd&lt;/sup&gt; or intolerance</td>
</tr>
<tr>
<td></td>
<td>Antithymocyte globulin (ATG), cyclosporin A</td>
<td>No response &lt;sup&gt;dd&lt;/sup&gt; or intolerance</td>
<td>Follow clinical trial or Consider allo-HSCT for selected Intermediate-1 patients&lt;sup&gt;ff&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>aa</sup>Presence of comorbidities should also be considered for evaluation of prognosis (See references 128-133 in the Discussion section).

<sup>bb</sup>IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels. If patients initially are managed as lower risk but fail to respond, move to higher risk management strategies.


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

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

<sup>hh</sup>See dosing of hematopoietic cytokines (MDS-10).

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

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

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

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**NCCN Guidelines Version 2.2014**  
**Myelodysplastic Syndromes**

### Prognostic Category

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-intensity therapy candidate</strong></td>
<td>- Transplant candidate and Donor available</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Allo-HSCT</td>
<td>If relapse</td>
</tr>
<tr>
<td>No</td>
<td>Azacitidine (preferred) (category 1)/decitabine or High-intensity chemotherapy or Clinical trial</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>Continue</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not high-intensity therapy candidate</th>
<th>Azacitidine (preferred) (category 1)/decitabine or High-intensity chemotherapy or Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response</td>
<td>Clinical trial or Supportive care</td>
</tr>
</tbody>
</table>

---

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**Supportive Care (MDS-B):**


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

- IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon 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 should 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 HSCT.

- Hematopoietic stem cell transplant (HSCT): 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.

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

| Serum EPO ≤ 500 mU/mL | Response
|------------------------|----------|
| Del(5q) ± other cytogenetic abnormalities | Lenalidomide
| Ring sideroblasts < 15% | Continue EPO, decrease dose to tolerance

- **Serum EPO > 500 mU/mL**
  - **Response**
  - **No response**

**FOLLOW-UP**

- **Continue lenalidomide, decrease dose to tolerance**
- **See IPSS: Low/Intermediate-1**
- **WPSS: Very Low, Low, Intermediate (MDS-8)**

**SERUM EPO > 500 mU/mL**

- **Response**
- **No response**

**Lenalidomide**

- **No response**
- **Continue**
- **Decrease dose to tolerance**

**Serum EPO 500 mU/mL**

- **Response**
- **No response**

**Serum EPO > 500 mU/mL**

- **Response**
- **Decrease dose to tolerance**

**See IPSS: Low/Intermediate-1**

- **WPSS: Very Low, Low, Intermediate (MDS-8)**

**cc** See Supportive Care (MDS-8).

**99** Except for patients with low neutrophil counts or low platelet counts.

**R** Recommended initial dose is: 10 mg/d for 21 out of 28 days monthly for 2-4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤ 500 mU/mL.

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

- **tt** Lack of 1.5 gm/dL rise in Hb or decreased RBC transfusion requirement by 3-4 months of treatment.
- **ss** Lack of 1.5 gm/dL rise in Hb or decreased RBC transfusion requirement by 6-8 weeks of treatment.
- **tt** Target hemoglobin range 10-12 g/dL; not to exceed 12 g/dL.
Initial Evaluation (from MDS-1)

- Flow cytometry:
  - 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 (i.e., 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 Discussion section, MS-6-7).

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.
SUPPORTIVE CARE

- Clinical monitoring
- Psychosocial support
- 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/mm³. Irradiated products are suggested for transplant candidates.
  - Cytomegalovirus (CMV)-negative 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 > 20-30 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.
  - Patients with low creatinine clearance (< 40 mL/min) should not be treated with deferasirox.
- Cytokines:
  - EPO: See Anemia Pathway (MDS-9)
  - G-CSF or GM-CSF:
    - Not recommended for routine infection prophylaxis
    - Consider use if recurrent or resistant infections in neutropenic patient
    - Combine with EPO for anemia when indicated (See Anemia Pathway [MDS-9])
    - Platelet count should be monitored

1 See NCCN Guidelines for Supportive Care.
2 Clinical trials in MDS are currently ongoing with oral chelating agents.

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.
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.

Table of Contents

Overview.................................................................MS-2
Diagnostic Classification ........................................MS-2
Initial Evaluation .........................................................MS-5
Pediatric MDS...........................................................MS-8
Prognostic Stratification .............................................MS-9
  Prognostic Scoring Systems....................................MS-9
  Molecular Abnormalities in MDS..........................MS-13
  Comorbidity Indices..............................................MS-14

Therapeutic Options................................................MS-14
  Supportive Care ..................................................MS-15
  Low-Intensity Therapy ........................................MS-19
  High-Intensity Therapy ..........................................MS-24

Recommended Treatment Approaches.........................MS-24
  Therapy for Lower Risk Patients (IPSS Low, Intermediate-1, IPSS-R Very Low, Low and Intermediate, or WPSS Very Low, Low, and Intermediate) ..........................................................MS-24
  Therapy for Higher Risk Patients (IPSS Intermediate-2, High, IPSS-R Intermediate, High, Very High, or WPSS High, Very High) ...MS-25

Evaluation and Treatment of Related Anemia .................MS-27

Summary .................................................................MS-29

References ....................................................................MS-30
Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with relatively heterogeneous spectrums of presentation. The major clinical problems in these disorders are morbidities caused by patients’ cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In the general population, the incidence rate of MDS is approximately 5 per 100,000 people per year. MDS is rare among children/adolescents and young adults, with an incidence rate of 0.2 per 100,000 people per year in those under 40 years of age; however, among individuals older than age 70, the incidence rate increases to approximately 26 per 100,000 people, and the rate increases further to 48 per 100,000 people among those 80 years and older.

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

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 have led to important advances in treatment or have yielded new information on biological factors that may have prognostic significance in MDS.

Diagnostic Classification

Initial evaluation of patients with suspected MDS requires careful assessment of their peripheral blood smear and blood counts, marrow morphology, duration of their abnormal blood counts, other potential causes for their cytopenias and concomitant illnesses. The NCCN Guidelines for MDS includes the World Health Organization (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 lines have been used by most histopathologists to diagnose MDS. These changes include megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in the early myeloid and erythroid precursors, and dysmorphic megakaryocytes. Patients with MDS are classified as having one of five subtypes of disease: refractory anemia (RA); RA with ringed sideroblasts (RARS); RA with excess of blasts (RAEB); RAEB in transformation (RAEB-t); and chronic myelomonocytic leukemia (CMML). MDS are generally indolent, with patients’ blood counts remaining relatively stable over at least several months.

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

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

In 2001, the World Health Organization (WHO) proposed a classification for MDS. The report suggested modifying the FAB definitions of MDS. Although most prior data require dysplasia in at least two lineages for the diagnosis of MDS, the WHO guidelines accept unilineage dysplasia for the diagnosis of RA and RARS provided that other causes of the dysplasia are absent and the dysplasia persists for at least 6 months. To establish the diagnosis of MDS, careful morphologic review and correlation with the patient’s clinical features are important, because a number of medications and viral infections (including HIV infection) may cause morphologic changes in marrow cells similar to MDS.

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 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, and the MDS/MPN unclassifiable group. The distinction between CMML-1 and CMML-2 is based on the percentage of blasts plus monocytes in peripheral blood and bone marrow. CMML had been categorized by FAB as MDS; by the International MDS Risk Analysis Workshop (IMRAW) as proliferative type (WBC ≥ 12,000/mm³) (a myeloproliferative disorder (MPD) or non-proliferative type (dysplastic MDS)). The MDS/MPN unclassifiable group includes the provisional entity, RARS associated with marked thrombocytosis (RARS-T), which includes cases that present with clinical and morphological features consistent with MDS, and thrombocytosis (platelet counts ≥ 450 × 10⁹/L). The morphology of RARS-T is characterized by RARS features (no blasts in peripheral blood, dysplastic erythroid proliferation, ring sideroblasts ≥15% of erythroid precursors, and <5% blasts in marrow) with
proliferation of large atypical megakaryocytes similar to those seen in essential thrombocythemia or primary myelofibrosis; up to 60% of RARS-T cases have the JAK2 V617F mutation or MPL W515K/L mutation.\textsuperscript{16}

The WHO classification excludes RAEB-t patients from MDS (proposing that AML should now include patients with 20% or more marrow blasts, rather than the previously used cut-off of 30% or more). However, MDS are not only related to blast quantitation, but also possess a differing pace of disease related to distinctive biologic features that differ from \textit{de novo} AML.\textsuperscript{17,18} In addition, therapeutic responses generally differ between these two patient groups.

The 2008 WHO classifications have helped clarify the clinical differences between the FAB RAEB-t patients and AML.\textsuperscript{19} The current WHO classification lists the entity ‘AML with myelodysplasia-related changes’, which encompasses patients with AML post-MDS, AML with multilineage dysplasia and AML with MDS-associated cytogenetic abnormalities.\textsuperscript{19} According to the 2008 WHO classification, some patients with AML with myelodysplasia-related changes having 20% to 29% marrow blasts, especially those arising from MDS (considered RAEB-t by the FAB classification) may behave in a manner more similar to MDS than to AML.

The decision to treat patients having marrow blasts in the range of 20% to 30% with intensive AML therapy is thus complex and should be individualized. The clinician should consider such factors as age, antecedent factors, cytogenetics, comorbidities, pace of disease, performance status and patient’s goal for treatment. The NCCN MDS panel currently endorses reporting and using the WHO classification system. However, as indicated on MDS-3, RAEB-t patients (with 20–30% blasts AND a stable clinical course for at least 2 months) should be considered as either MDS or AML. Such patients have previously been included in and benefited from many therapeutic trials for MDS should continue to be eligible for MDS-type therapy. Thus, the MDS Panel recommends using the WHO classification but having the RAEB-t patient subgroup considered as either MDS or AML. Studies have provided evidence supportive of the use of the WHO proposals.\textsuperscript{20–24}

AML evolving from MDS (AML-MDS) is often more resistant to standard cytotoxic chemotherapy than \textit{de novo} AML, which arises without antecedent hematologic disorder. High-risk MDS, AML-MDS, and some elderly patients with AML may have a more indolent course in terms of short-term progression compared with patients with standard presentations of \textit{de novo} AML. Separate protocols for treating patients with standard presentation of \textit{de novo} AML and for these other patient groups (such as MDS-AML, elderly AML, and high-risk MDS groups) seem appropriate (see NCCN Guidelines for Acute Myeloid Leukemia).

To assist in providing consistency in diagnostic guidelines of MDS, an International Consensus Working Group recommended that minimal diagnostic criteria for this disease include required diagnostic prerequisites: stable cytopenia (for at least 6 months unless accompanied by a specific karyotype or bilineage dysplasia, in which case only 2 months of stable cytopenias are needed) and the exclusion of other potential disorders as a primary reason for dysplasia or/and cytopenia. In addition to these two diagnostic prerequisites, the diagnosis of MDS requires at least one of three MDS-related (decisive) criteria: i) dysplasia (≥10% in one or more of the three major bone marrow lineages), ii) a blast cell count of 5% to19%, and iii) a specific MDS-associated karyotype, e.g. del(5q), del(20q), +8, or -7/del(7q). Further, several co-criteria help confirm the diagnosis of MDS. These co-criteria include studies with flow cytometry, bone marrow histology...
and immunohistochemistry, or molecular markers (to detect or exclude abnormal CD34 antigenic expression, fibrosis, dysplastic megakaryocytes, atypical localization of immature progenitors [ALIP], myeloid clonality).  

**Initial Evaluation**

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

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

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

If patients require platelet transfusions for severe thrombocytopenia, human leukocyte antigen (HLA) typing (A, B) may be helpful. For hematopoietic stem cell transplant (HSCT) candidates, the patient's CMV status and full HLA typing (A, B, C, DR, and DQ) of the patient and potential donors are needed. Bone marrow flow cytometry for assessing the % of CD34+ cells (blast cells are usually CD34+), and HIV screening, if clinically indicated, may also be valuable in some clinical situations. It should be emphasized, however, that estimates of blast percentage by flow cytometry do not provide the same prognostic information as the blast percentage derived from morphologic evaluation. Accordingly, data from flow cytometry should not be used in lieu of the determination of morphologic blast percentage by an experienced hematopathologist. The screening for paroxysmal nocturnal hemoglobinuria (PNH) and HLA-DR15 is potentially useful for determining which patients may be more responsive to immunosuppressive therapy, particularly in young patients with normal cytogenetics and hypoplastic MDS (see Prognostic Stratification below). 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, which in turn leads to deficiency of proteins that are normally linked to the cell membrane of blood cells via a GPI anchor. Deficiency in GPI-anchored proteins such as those involved in complement inhibition (e.g., CD55, CD59) leads to complement sensitivity of red blood cells and subsequent hemolysis. Flow cytometry is the established method for detecting GPI-anchor-deficient cells for the
diagnosis of PNH. Recent data showed that fluorescent aerolysin (FLAER), a protein that specifically binds to GPI anchors, was a reliable marker for detecting GPI-anchor-deficient clones among granulocytes or monocytes, with high sensitivity. For evaluation of PNH clone, it is recommended that multiparameter flow cytometry analysis of granulocytes and monocytes using FLAER, and at least one GPI-anchored protein, be conducted. 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.

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

Discrete from basic flow cytometric evaluation at presentation for 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 diagnosis of MDS, exclude differential diagnostic possibilities, and in some patients, provide prognostic information. To achieve these purposes, the flow analysis should use appropriate antibody combinations with four fluorescence channel instrumentation. Multiple aberrancies should be present for diagnosis of MDS, as single aberrancies are not infrequent in normal populations. For followup studies, antibody combinations may be tailored to detect specific abnormalities found in the initial evaluation. While aberrancies have also been described in erythroid cells, erythroid analysis is not provided by most flow cytometry laboratories. The European LeukemiaNET recently developed a flow cytometric score based on reproducible parameters using CD34 and CD45 as 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 those with non-clonal cytopenias as controls (n=380). This population of patients was chosen for the study because low-grade MDS often lack specific diagnostic markers (e.g., ring sideroblasts, clonal cytogenetic abnormalities) and, therefore, may be difficult to diagnose based on morphology alone. Bone marrow samples from patients with MDS showed different flow cytometric patterns compared with samples from patients with non-clonal cytopenias with regards to the following: increased CD34+ myeloblast-related cluster size (defined by wider distribution of CD45 expression and greater side scatter characteristics [SSC]), decreased CD34+ B-progenitor cluster size (defined by relatively low CD45 expression and low SSC), aberrant myeloblast CD45 expression (based on lymphocyte to myeloblast CD45 ratio) and decreased granulocyte SSC value (based on 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 value and negative predictive value was 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 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, requirements for both technical and interpretational expertise, and need for greater consensus on specific antibody combinations and procedures that are most informative and cost effective, flow cytometric assays should be performed by experienced laboratories, and used in general practice only when diagnosis is uncertain with traditional approaches (e.g., blood counts, morphology, cytogenetics, increased blasts). Flow cytometry studies may also be used to assess the possibility of large granular lymphocytic (LGL) disease, if relevant as indicated by LGLs being present in the peripheral blood. Additional genetic screening should be considered for patients with familial cytopenias, which will help evaluate for Fanconi’s anemia or dyskeratosis congenita (DC). Shortened telomere length has been associated with diseases of bone marrow failure, including inherited disorders such as DC, particularly in the presence of mutations in the DKC1, TERT or TERC genes that encode for components of the telomere complex. Telomere length can be measured by 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 a cause of a relatively rare autosomal dominant familial platelet disorder that predisposes to myeloid malignancies. In affected families with the RUNX1 lesions, the incidence of MDS/AML is high, ranging from 20-60%; 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 present 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’s anemia and MDS/AML. 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. Recently, heritable mutations in GATA2 were identified in families with highly penetrant early-onset MDS and/or AML. The mutations showed an autosomal dominant pattern of inheritance, and affected individuals with this familial form of MDS/AML had poor outcomes in the absence of allogeneic stem cell transplant. Identification of familial MDS is of clinical importance because it is associated with chromosomal fragility and such patients may therefore respond differently to hypomethylating agents; more importantly, family members may not be eligible as donors for allogeneic hematopoietic stem cell transplant.

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

The frequency of activating mutations of the tyrosine kinase known as Janus Kinase 2 (JAK2) in MDS and de novo AML is lower compared to that in myeloproliferative disorders. If one encounters thrombocytosis in patients with MDS, screening for JAK2 mutations may be helpful. A positive test for JAK2 mutation is consistent with presence of a myeloproliferative component of their disorder.
Recent flow cytometric studies suggest the potential utility of this methodology for characterizing MDS marrow blast cells and as an aid for assessing prognosis of these patients.\textsuperscript{56,57} However, due to the non-standardized nature of these analyses, further investigations are warranted prior to suggesting their routine use.

There have been reports that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.\textsuperscript{58-60} Thus, assessment of copper and ceruloplasmin levels may be indicated as part of the initial diagnostic workup of suspected MDS in certain instances. Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,\textsuperscript{58-60} prior gastrointestinal surgery,\textsuperscript{58,59} and a history of vitamin B12 deficiency.\textsuperscript{59,61}

**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{62-64} MDS in children is strongly associated with congenital disorders.\textsuperscript{65} Genetic syndromes are evident in 50% of cases, including Down syndrome,\textsuperscript{56-68} trisomy 8 syndrome,\textsuperscript{69} Fanconi anemia,\textsuperscript{70,71} congenital neutropenia (Kostmann syndrome),\textsuperscript{72,73} Diamond-Blackfan anemia,\textsuperscript{74} Shwachman-Diamond syndrome,\textsuperscript{75} dyskeratosis congenita, neurofibromatosis type 1, Bloom syndrome, Noonan syndrome,\textsuperscript{76} and Dubowitz syndrome. Prior exposure to cytotoxic therapy, such as alkylating agents, epipodophyllotoxins, and topoisomerase II inhibitors,\textsuperscript{77-80} and radiation\textsuperscript{81,82} increases the risk for MDS.

The revised WHO classification (2008) separates myeloproliferative disorders into three groups: MDS (refractory cytopenia of childhood [RCC], RAEB, RAEB-t or AML with MDS-related changes); myelodysplastic/myeloproliferative disease (juvenile myelomonocytic leukemia [JMML]); and Down syndrome disease (transient abnormal myelopoiesis and myeloid leukemia of Down syndrome).\textsuperscript{10} RCC is the most common subtype of MDS found in children, accounting for approximately 50% of cases.\textsuperscript{64} Abnormal karyotypes are found in 30% to 50% of children with MDS,\textsuperscript{83} more commonly numerical anomalies; fewer than 10% show structural abnormalities. Monosomy 7 is the most common cytogenetic abnormality, occurring in 30% of cases,\textsuperscript{84,85} followed by trisomy 8 and 21. The del(5q) abnormality is rarely seen in children.\textsuperscript{86} Clinically, isolated refractory anemias are uncommon in children. Thrombocytopenia and/or neutropenia, often accompanied by hypocellular marrow, is a common presentation. Fetal hemoglobin levels are often elevated.

Differential diagnoses include aplastic anemia (AA) and AML. Compared to AA, children with MDS have significantly elevated mean corpuscular volume (MCV); clonal hematopoiesis is confirmatory. Higher expression of p53 and low survivin and MDS-related cytogenetic abnormalities can also help differentiate MDS from AA.\textsuperscript{87} Compared with AML, low WBC, multi-lineage dysplasia, and clonal hematopoiesis with numerical, rather than structural, cytogenetic abnormalities suggest MDS. 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 diagnosis of MDS in a patient who presents with AML are stringent.\textsuperscript{88} Dysplasia in bone marrow cells may also be due to other etiologies including infection (e.g., Parvo virus,\textsuperscript{89,90} herpes viruses,\textsuperscript{91} HIV), deficiencies of B12 and copper,\textsuperscript{92} drug therapy, and chronic disease. 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 less than 5 years old), usually acute megakaryoblastic leukemia (AMKL, M7). 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 80% cure rate with intensive chemotherapy. HSCT 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 later develop AMKL.

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. HSCT is the only curative option in childhood MDS with 3-year disease-free survival rates of approximately 50%. Myeloablative therapy with busulfan, cyclophosphamide, melphalan, followed by either matched family or matched unrelated donor allogeneic HSCT is the treatment of choice for children with MDS. Other treatments such as chemotherapy, growth factors, and immunosuppressive therapy have a limited role. Prognosis for untreated MDS depends upon the rate of progression to AML. The stage of the disease at the time of HSCT strongly predicts outcome.

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 upon the underlying cause of MDS and standard prognostic factors. Patients with JMML have a variable prognosis, with some younger patients with favorable genetics and clinical features having resolution of JMML without treatment, and others progressing rapidly despite allogeneic HSCT. Children diagnosed before age 2 years have the best prognosis. Poor prognostic features include high hemoglobin F, older age, and thrombocytopenia.

Pediatric AML or MDS with monosomy 7 is associated with 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, n=3; AML, n=5; and therapy-related AML, n=3) reported a 2-year event-free survival of 69%. 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).

As the NCCN Guidelines for MDS focus on recommendations for the diagnosis, evaluation and treatment of adult patients with MDS, the discussions that follow pertain to adults.

**Prognostic Stratification**

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

**Prognostic Scoring Systems**

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW.
used systems, the risk-based IPSS has markedly improved prognostic stratification of MDS cases. In this analysis, cytogenetic, morphologic, and clinical data were combined and collated from a relatively large group of MDS cases that had been included in previously reported prognostic studies.\textsuperscript{13,101} FAB morphologic criteria were used to establish the diagnoses of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible etiologies for the cytopenias, such as drugs, other diseases, or incipient evolution to AML. CMML was subdivided into proliferative and non-proliferative subtypes. Patients with proliferative type CMML (those with white blood cell counts greater than 12,000/mcL) were excluded from this analysis.\textsuperscript{13} Patients with non-proliferative CMML (with white blood cell counts of 12,000/mcL or less as well as other features of MDS) were included in the analysis.\textsuperscript{102}

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

Cytopenias were defined for the IPSS as having hemoglobin level less than 10 g/dL, an absolute neutrophil count (ANC) below 1,800/mcL, and platelet count below 100,000/mcL. Patients with normal marrow karyotypes, del(5q) alone, del(20q) alone, and -Y alone had relatively good prognoses (70%), whereas patients with complex abnormalities (three or more chromosome anomalies) or chromosome 7 anomalies had relatively poor prognoses (16%). The remaining patients were intermediate in outcome (14%). Of the patients in the “complex” category, the vast majority had chromosome 5 or 7 abnormalities in addition to other anomalies.

To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroup, and number of cytopenias) were generated.\textsuperscript{13} 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.\textsuperscript{13}

Recent data have indicated that additional clinical variables are additive to the IPSS regarding prognosis for MDS patients. The WHO-classification based prognostic scoring system (WPSS) incorporates the WHO morphologic categories, the IPSS cytogenetic categories and the patients’ need or lack of RBC transfusion dependence.\textsuperscript{103} 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 \textit{per se} has additive and negative prognostic import for the intermediate IPSS categories.\textsuperscript{104} As compared with the four groups defined by the IPSS, the WPSS classifies patients into five risk groups differing in both survival and risk of AML. The five risk groups are: Very low, Low, Intermediate, High, and Very high. Following initial report of the usefulness of WPSS by Malcovati et al.,\textsuperscript{103} there have been confirmatory studies.\textsuperscript{105-107} The initial WPSS has recently been refined to address the notion that the requirement for RBC transfusion may be somewhat subjective. In the refined WPSS, the measure of the
degree of anemia by transfusion dependency is replaced by the presence (or absence) of severe anemia, defined as hemoglobin levels <9 g/dL for males and <8 g/dL for females. 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). At this time, there is still an ongoing debate whether the WPSS offers an improvement over the IPSS. Based on the current available data, the NCCN MDS Panel has included the WPSS in the current version of the treatment algorithm with a category 2B designation.

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 defined 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 depth of cytopenias defined with cut-offs for hemoglobin, platelet, and neutrophil counts. In the IPSS-R, the cytogenetic subgroups comprise five risk groups (versus 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 recently validated in a number of independent studies based on registry data, including in 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, AML evolution, and progression-free survival (latter defined as leukemic evolution or death from any cause). Notably, in this cohort, the predictive power (based on Harrell’s C statistics) of IPSS-R was found to be greater than IPSS, WPSS and refined WPSS for the three outcome measures mentioned above. The investigators acknowledged the short follow up (median 17 months) of 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) from Spain, the IPSS-R could identify 3 risk categories (Very Low, Low, Intermediate) within the IPSS Low-risk group with none of the patients categorized as IPSS-R High or Very High. Within the IPSS INT-1-risk group, the IPSS-R further stratified patients into 4 risk categories (Very Low, Low, Intermediate, High) but with only 1 patient categorized as Very High risk. The IPSS-R was significantly predictive of survival outcomes in both the subgroups of IPSS Low and INT-1 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<0.001). 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<0.001). 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) being identified as having poorer prognosis (median survival 21–30 months). This study also applied the refined WPSS to further stratify the IPSS Low and INT-1 risk groups, and was able to identify a group of patients (refined WPSS High risk group) within the IPSS INT-1 group who had poorer prognosis (185 of 1096...
IPSS INT-1 patients; median survival 24.1 months). However, the IPSS-R identified a larger proportion of poor-risk IPSS INT-1 patients than the refined WPSS (47% vs. 17%). Outcomes of risk stratification using the MD Anderson Lower-Risk Prognostic Scoring System are discussed in the section below. In a retrospective database analysis of MDS patients from a single institution (N=1029), median overall survival according to IPSS-R risk categories was 82 months for Very Low, 57 months for Low, 41 months for Intermediate, 24 months for High and 14 months for Very High risk groups ($P<0.005$). The median follow up in this study was 68 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 hypomethylating agents was shown only for the group of patients with Very High risk IPSS-R (median 16 vs. 7 months with no hypomethylating therapy; $P<0.005$). In addition, significantly longer overall survival with allogeneic HSCT was only observed for patients with High (median 42 vs. 21 months without HSCT; $P=0.004$) and Very High (median 31 vs. 12 months without HSCT; $P<0.005$) risks. The IPSS-R may therefore provide a tool for therapeutic decision-making, although prospective studies are needed to confirm these findings. Further evaluation is warranted and ongoing regarding the utility of the IPSS-R in both the settings of clinical trials and routine clinical practice.

The Lower-Risk Prognostic Scoring System (LR-PSS) developed by investigators at 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 results of multivariate Cox regression analysis. The final model included the following factors that were independent predictors for survival outcomes: unfavorable cytogenetics, older age ($\geq$ 60 years), decreased hemoglobin (<10 g/dL), decreased platelet counts (<50 $\times$ 10$^9$/L or 50–200 $\times$ 10$^9$/L), and higher percentage of bone marrow blasts ($\geq$ 4%). Important to note, however, is that the cytogenetic categories in this system were derived from the previously defined IPSS categories rather than from the more refined IPSS-R. Each of these factors were given a weighted score, and the sum of the scores (ranging from a total of 0 to 7 points) were used to generate 3 risk categories; a score of 0 to 2 points was assigned to category 1, score of 3 or 4 was category 2 and a score of 5 to 7 was category 3. Using this scoring system, median survival was 80.3 months for category 1, 16.6 months for category 2, and 14.2 months for category 3; the 4-year survival rates were 65%, 33%, and 7%, respectively. The scoring system allowed for further stratification into these 3 risk categories for both the subgroup of patients with IPSS Low-risk and IPSS INT-1-risk disease. The LR-PSS could therefore be a useful tool to identify patients with lower risk disease who may have poorer prognosis and may require earlier treatment. The prognostic value of the LR-PSS has been validated in several independent studies.

In a retrospective analysis of data from lower risk MDS (IPSS Low or INT-1) patients in the multicenter Spanish registry (N=2410), the LR-PSS was able to further stratify these lower risk patients into 3 risk categories. The LR-PSS was significantly predictive of survival outcomes in both the subgroups of IPSS Low and INT-1 patients. Within the IPSS Low risk group, median survival using the LR-PSS risk categories was 130.3 months for category 1 (low risk), 69.7 months for category 2 (intermediate risk), and 58.4 months for category 3 (high risk) ($P<0.001$); the corresponding median survival values within the IPSS INT-1 risk patients were 115.2 months, 51.3
months, and 24.1 months, respectively ($P<0.001$). The LR-PSS identified an important proportion of patients (334 of 1096 patients; 30.5%) within the IPSS INT-1 risk group who had poorer prognosis (median survival 24 months, as above). In addition, within the IPSS INT-1 risk group (but not for IPSS Low risk), LR-PSS was significantly predictive of the rate of AML evolution at 3 years. In another analysis using data from a cohort of lower risk MDS patients from two centers (N=664), median survival according to the LR-PSS risk categories was 91.4 months for category 1, 35.6 months for category 2, and 22 months for category 3. Using data from the same cohort of patients, median survival according to the IPSS-R risk groups was 91.4 months for IPSS-R Very Good, 35.9 months for Good, and 27.8 months for the combined Intermediate/High/Very High risk groups. Both of these prognostic scoring systems were significantly predictive of survival outcomes. The predictive power (based on Harrell’s C statistics) of LR-PSS and IPSS-R was 0.64 and 0.63, respectively.

**Molecular Abnormalities in MDS**

In recent years, various gene mutations have been identified among patients with MDS, which may in part contribute to the clinical heterogeneity of the disease course, and thereby influence the prognosis of patients. Such gene mutations may be present in a substantial proportion of newly diagnosed patients, including in patients with normal cytogenetics. In a recent genetic study in samples from patients with MDS (N=439), at least one gene mutation was identified in 52% of samples and multiple gene mutations were found in 18% of samples. The most frequently occurring genetic lesions were mutations in the TET2, ASXL1, RUNX1, TP53, EZH2, NRAS, JAK2, ETV6, CBL, and IDH2 genes. Mutations in TET2 are among the most common genetic lesions reported in patients with MDS (about 20% of cases), and appears to confer a more favorable prognosis compared to cases without TET2 mutations. In the present analysis, the presence of TET2 mutations was found to be associated with normal karyotype and a median survival similar to that of the overall patient cohort. Mutations in ASXL1 is another relatively common lesion in patients with MDS (about 15% of cases) and as also reported in another recent study, is associated with significantly shorter overall survival. Mutations in TP53 were associated with complex karyotype and chromosome 17 abnormalities. Importantly, TP53 mutations were associated with the worse prognosis with respect to survival outcomes, which confirms earlier reports of the significant negative prognostic impact of TP53 mutations in MDS.

Among the frequently occurring genetic lesions mentioned above, mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 were found to be significant independent predictors of decreased overall survival in a multivariable regression model that also included age and IPSS risk groups as variables. When these five poor-risk gene mutations were integrated into the survival analysis by IPSS categories, the presence of a mutation was shown to shift the survival curve of the IPSS risk category to resemble that of the next highest IPSS risk level (e.g., survival plot for low-risk IPSS group with a gene mutation was similar to that for INT-1 risk). Thus, the combined analysis of the gene mutational status and IPSS may improve upon the risk stratification provided by assessment of IPSS alone. Common molecular abnormalities involving the RNA splicing machinery have also been reported in patients with MDS, including gene mutations in SRSF2 (11–12%), U2AF1/U2AF35 (5–7%), ZRSR2 (3–11%), and SF3B1 (14.5–16%). Mutations in SRSF2 and ZRSR2 have been associated with...
poorer survival outcomes and increased risks for leukemic transformation. Further evaluations are warranted to establish the role of these different genetic lesions on risk stratification systems in MDS. Nevertheless, it is becoming clear that evaluation of genetic and molecular abnormalities play an increasingly important role in determining the overall prognosis of patients with MDS.

Comorbidity Indices

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

Therapeutic Options

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

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

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 that fall under the IPSS-R Intermediate category may be managed as Very Low/Low risk or High/Very High risk depending upon evaluation of additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels. In addition, those 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 upon IWG response criteria, the major therapeutic aim for patients in the lower risk group would be hematologic improvement, whereas for those in the higher risk group, alteration of the disease natural history is viewed as paramount. Cytogenetic response and quality of life parameters are also important outcomes to assess. The algorithms outline management of primary MDS only. Most patients with therapy-related MDS have poorer prognoses than those with primary MDS, including a substantial proportion with poor risk cytogenetics. These patients are generally managed as having higher risk disease.

Supportive Care

Currently, the standard of care in the community for MDS management includes supportive care (see Supportive Care section in the Guidelines and NCCN Supportive Care Guidelines). This entails observation, clinical monitoring, psychosocial support, and quality-of-life (QOL) assessment. Major efforts should be directed toward addressing the relevant QOL domains (e.g., physical, functional, emotional, spiritual, social), which adversely affect the patient. Supportive care should include red blood cell transfusions for symptomatic anemia as needed (generally leukocyte-reduced) or platelet transfusions for bleeding events; however, platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding. There was non-uniform consensus among the panel members based on differing institutional policies regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agreed that all directed-donor products and transfused products for potential stem cell transplant patients should be irradiated. Additionally, CMV negative blood products are recommended whenever possible for CMV negative recipients. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding episodes refractory to platelet transfusions or for profound thrombocytopenia.

**Hematopoietic Cytokines**

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

Erythropoiesis-stimulating agents (ESAs) such as recombinant human erythropoietin (Epo) or darbepoetin, with or without G-CSF, has 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 hematologic response in 38% of patients (complete response [CR] in 21%). Epo and G-CSF appeared to have synergistic activity. Lower serum Epo levels (<500 mU/mL) and lower pretreatment RBC transfusion requirement (<2 units per month) were associated with higher response rate; response rates were not significantly different across IPSS risk groups. Median survival (N=71; including patients from a prior study) was 26 months. Among patients with low-risk IPSS,
median survival had not been reached at 5 years; the 5-year survival rate was 68%. Median survival among 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 responding patients who received maintenance treatment with Epo and G-CSF, the median duration of response was 24 months. A subsequent analysis on long-term outcomes with Epo combined with G-CSF (given 12–18 weeks, followed by maintenance in responders) in patients with MDS (n=121; patients from 3 phase II Nordic trials) reported a hematologic response rate of 39% with a median duration of response of 23 months. Long-term outcomes of these patients were compared with outcomes from untreated patients (n=237) as controls. Based on multivariate Cox regression analysis, treatment with Epo plus G-CSF was associated with significantly improved survival outcomes (hazard ratio=0.61, 95% CI 0.44–0.83; P=0.002). An exploratory analysis revealed that the association between treatment and survival was significant only for the IPSS low-risk group. In addition, the survival benefit with treatment was observed only in patients requiring fewer than 2 units of RBC transfusions per month. No significant association was found between treatment and frequency of AML progression. Similar findings were reported in a study from the French group, which analyzed outcomes with ESAs (epoetin or darbepoetin), with or without G-CSF, in MDS patients with anemia (N=403). Based on IWG 2000 criteria, hematologic response rate was 62% with a median duration of response of 20 months. Based on IWG 2006 criteria, the corresponding results were 50% and 24 months, respectively. IPSS low/INT-1-risk was associated with significantly higher response rates and longer response durations. In a comparison of outcomes (in the subset of low/INT-1-risk group with anemia) between treated patients (n=284) and a historical cohort of untreated patients (n=225), multivariate analysis showed a significant association between treatment with ESAs and survival outcomes. The frequency of AML progression was similar between the cohorts. In a phase II study that evaluated darbepoetin (given every 2 weeks for 12 weeks), with or without G-CSF (added at 12 weeks in non-responders), in MDS patients with lower-risk IPSS with anemia (and with serum Epo levels <500 mU/mL), hematologic response rate was 48% at 12 weeks and 56% at 24 weeks. Median duration of response was not reached with a median follow up of 52 months. The 3-year cumulative incidence of AML progression was 14.5% and the 3-year survival rate was 70%. This study also showed improvements in QOL parameters among responding patients. Collectively, these studies suggest that ESAs may provide clinical benefit in patients with lower risk MDS with symptomatic anemia. Limited data are available on the effectiveness of ESAs in the treatment of anemia in lower risk patients with del(5q). Epo has been shown to promote the growth of cytogenetically normal cells isolated from patients with del(5q), while having minimal proliferative effects on MDS progenitor cells from these patients in vitro. Retrospective studies from the French group reported hematologic response rates of 46% to 64%, with a median duration of response of 11 months (and mean duration of 13–14 months) among patients with del(5q) treated with ESAs, with or without G-CSF. Duration of response in these patients was significantly decreased compared with that in patients without del(5q) (mean duration 25–27 months). Based on multivariate analysis, del(5q) was a significant predictor of shorter response duration with treatment. The use of ESAs to treat symptomatic anemia is discussed further under the Guidelines recommendations for “Therapy for Lower Risk Patients” and under “Evaluation and Treatment of Related Anemia”.

Severe thrombocytopenia is associated with increased risks for bleeding events, and is currently managed with platelet transfusions. The mechanism of thrombocytopenia in patients with MDS may be attributed to decreased platelet production (possibly related to regulatory pathways involving the production and/or metabolism of endogenous thrombopoietin (TPO)) as well as increased destruction of bone marrow megakaryocytes or circulating platelets.\textsuperscript{144,145} Endogenous thrombopoietin (TPO) levels has been reported to be increased among patients with MDS compared with those of healthy individuals.\textsuperscript{145} At the same time, TPO receptor (c-mpl) sites per platelet appear to be decreased among patients with MDS compared with healthy subjects. Within patients with MDS, those with RA 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.\textsuperscript{145} In addition, studies have reported that high endogenous TPO levels correlated with decreased platelet counts in RA patients, but not in RAEB or RAEB-t patients.\textsuperscript{145,146} This observation suggest 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 inadequate TPO response.\textsuperscript{145,146} A number of studies are investigating the role of the thrombopoietin receptor agonist romiplostim in the treatment of thrombocytopenia in patients with lower risk MDS.\textsuperscript{147-151} Phase I/II studies with romiplostim showed promising rates of platelet response (46–65\%) in patients with lower risk MDS.\textsuperscript{148,150} Recent randomized placebo-controlled studies in patients treated for lower risk MDS have reported beneficial effects of romiplostim in terms of decreased bleeding events and reduced needs for platelet transfusions in patients receiving hypomethylating agents.\textsuperscript{147,149} and decreased frequency of dose reductions or delays in those receiving lenalidomide therapy.\textsuperscript{151} Eltrombopag is another thrombopoietin receptor agonist that has been shown to increase normal megakaryopoiesis \textit{in vitro} in bone marrow cells isolated from patients with MDS.\textsuperscript{152,153} Ongoing phase I and II clinical trials are investigating the activity and safety of this agent in the treatment of thrombocytopenia in patients with MDS. Concerns for potential proliferation of leukemic blasts in response to exogenous TPO have been raised in early \textit{in vitro} studies in the past, particularly for high-risk MDS cases.\textsuperscript{154,155} Results from ongoing clinical trials with the TPO mimetics mentioned above 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 of the supportive care for MDS patients. Although the specific therapies patients receive may alleviate RBC transfusion need, a substantial proportion of MDS patients may not respond to these treatments and may develop iron overload as well as its consequences.\textsuperscript{156} Thus, effective treatment of such transfusional siderosis in MDS patients is necessary.

Studies in patients requiring relatively large numbers of RBC transfusions (e.g., thalassemia and MDS) have demonstrated the pathophysiology and adverse effects of chronic iron overload on hepatic, cardiac and endocrine function. Increased non-transferrin bound iron (NTBI) levels, generated when plasma iron exceeds transferrin 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.\textsuperscript{157,158} Although limited, there is evidence suggesting that organ dysfunction can result from iron overload in patients with MDS.\textsuperscript{159-161} Retrospective data suggest that transfusional iron overload might be a contributor of
increased mortality and morbidity in early stage MDS.\textsuperscript{162} The WPSS has shown that requirement for RBC transfusion is a negative prognostic factor for patients with MDS.\textsuperscript{103}

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The NCCN panel members recommend monitoring serum ferritin levels and number of RBC transfusions received to assess iron overload as practical means to determine iron stores. Monitoring serum ferritin may be useful, aiming to decrease ferritin levels to <1,000 mcg/L. It is recognized that such measurements, though useful, are less precise than SQUID (Superconducting Quantum Interference Device) or the more recent development of specific measurement of hepatic iron content using MRI.\textsuperscript{163,164}

Reversal of some of the consequences of iron overload in MDS and other iron overload states (e.g., thalassemia) by iron chelation therapy has been shown in patients in whom the most effective chelation occurred.\textsuperscript{136,158} This included transfusion independence in a portion of a small group of carefully studied MDS patients who had undergone effective deferoxamine chelation for 1 to 4 years.\textsuperscript{165} In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.\textsuperscript{166} 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\textsuperscript{167} and deferasirox\textsuperscript{168-170} provides potentially useful drugs to more readily treat this iron overload state. Deferoxamine (given as intramuscular or subcutaneous injections) is indicated for the treatment of chronic iron overload due to transfusion-dependent anemias.\textsuperscript{167} Deferasirox (given orally) is indicated for the treatment of chronic iron overload due to blood transfusions.\textsuperscript{168} This agent has been evaluated in multiple phase II clinical trials in patients with transfusion-dependent MDS.\textsuperscript{171-174} A large multicenter phase III randomized controlled trial is currently underway to evaluate outcomes with deferasirox compared with placebo in patients with MDS; the primary endpoint of this ongoing study is event-free survival (registered at clinicaltrials.gov; NCT00940602). The prescribing information for deferasirox contains a black-box warning pertaining to increased risks for renal or hepatic impairment/failure and gastrointestinal bleeding in certain patient populations, including in patients with high-risk MDS. Deferasirox is contraindicated in patients with high-risk MDS. A third oral chelating agent, deferiprone, was approved (October 2011) in the U.S. for the treatment of patients with transfusional iron overload due to thalassemia when current chelation therapy is inadequate.\textsuperscript{175} Controversy remains with regards to the use of this agent, however, as the FDA approval was based on results from a retrospective analysis of existing data pooled from previous safety and efficacy studies of deferiprone in patients with transfusion-related iron overload refractory to existing chelation therapy. The prescribing information for deferiprone contains a black-box warning pertaining to risks for agranulocytosis, which can lead to serious infections and death.\textsuperscript{175}

Clinical trials in MDS are ongoing with oral iron chelating agents to address the question whether iron chelation alters the natural history of patients with MDS who are transfusion dependent. A NCCN task force report titled “Transfusion and Iron Overload in Patients with MDS”, discusses in detail the available evidence regarding iron chelation in patients with MDS.\textsuperscript{176}

The NCCN Guidelines panel recommends considering chelation with deferoxamine SC or deferasirox/ICL670 orally once daily to decrease iron overload in IPSS low or intermediate-1 risk patients who have
received or are anticipated to receive greater than 20 RBC transfusions, for whom ongoing RBC transfusions are anticipated and for those with serum ferritin > 2500 ng/mL, aiming to decrease ferritin levels to <1000 ng/ml.

As mentioned above, a black-box warning by the FDA and Novartis was added to the prescribing information for deferasirox. Following post-marketing use of deferasirox, there were case reports of acute renal failure, or hepatic failure, some with a fatal outcome. Most of the fatalities reported were in patients with multiple co-morbidities and who were in advanced stages of their hematological disorders. Additionally, there were post-marketing reports of cytopenias, including agranulocytosis, neutropenia and thrombocytopenia and GI bleeding in patients treated with deferasirox where some of the patients died. The relationship of these episodes to treatment with deferasirox has not yet been established. However, it is recommended to closely monitor patients on deferasirox therapy including measurement of serum creatinine and/or creatinine clearance and liver function tests prior to initiation of therapy and regularly thereafter. Deferasirox should be avoided in patients with creatinine clearance <40 mL/min.

Low-Intensity Therapy

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

Hypomethylating Agents

As a form of relatively low-intensity chemotherapy, the DNA methyl transferase inhibitor (DMTI) hypomethylating agents 5-azacytidine (AzaC) and decitabine (5-aza-2′-deoxycytidine) have been shown in randomized phase III trials to decrease the risk of leukemic transformation, and, in a portion of the patients, to improve survival. In a phase III trial that compared AzaC with supportive care in patients with MDS (N=191; previously untreated in 83%; all IPSS risk groups), hematologic responses occurred in 60% of patients in the AzaC arm (7% complete response, 16% partial response, 37% hematologic improvement) compared with a 5% hematologic improvement (and no responses) in patients receiving supportive care. The median time to AML progression or death was significantly prolonged with AzaC compared with supportive care (21 vs. 13 months; P=0.007). Additionally, the time to progression to AML or death was improved in patients who received AzaC earlier in the course of disease, suggesting that the drug prolonged the duration of stable disease. Subsequently, Silverman and colleagues provided a summary of three studies of AzaC in a total of 306 patients with high-risk MDS. In this analysis, which included patients receiving either subcutaneous or intravenous delivery of the drug (75 mg/m²/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of AzaC-treated patients; partial remissions were rare; 23% to 36% of patients had hematologic improvement. Ninety percent of the responses were seen by cycle 6 and the median number of cycles to first response was three. The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. 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 (standard chemotherapy or supportive care) regarding overall survival. AzaC was associated with a significantly longer median survival compared with conventional care (24.5 vs. 15 months; hazard ratio=0.58, 95% CI 0.43–0.77; P=0.0001), thus providing support for the use of this agent in patients with higher risk disease.
AzaC therapy should be considered for treating MDS patients with progressing or relatively high-risk disease. This drug has been approved by the FDA for treatment of patients with MDS. The drug is generally administered at a dose of 75 mg/m$^2$/day subcutaneously for 7 days every 28 days for at least 4 to 6 courses. Treatment courses may need to be extended further or may be used as a bridging therapy to more definitive therapy (e.g., HSCT, for patients whose marrow blast counts require lowering prior to that procedure). Although the optimal duration of therapy with AzaC has not been defined, some data suggest that continuation of AzaC beyond first response may improve remission quality. Secondary analysis from the aforementioned phase III randomized trial of AzaC in patients with higher risk MDS showed that among patients responding to AzaC, response quality was improved in 48% with continued therapy; although most responding patients achieved a first response by 6 cycles of therapy, up to 12 cycles was required for the majority of responders to attain a best response. An alternative 5-day schedule of AzaC has been evaluated, both as a subcutaneous regimen (including the 5-2-2 schedule: 75 mg/m$^2$/day SC for 5 days followed by 2 days of no treatment, then 75 mg/m$^2$/day for 2 days, every 28 days; also, 5-day schedule: 75 mg/m$^2$/day SC for 5 days every 28 days) and as an intravenous regimen (75 mg/m$^2$/day 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 intravenously and administered with a regimen which required hospitalization of patients, has also shown encouraging results for the therapy of patients with higher risk MDS. As the treatment regimen was generally associated with low intensity-type toxicities, it is also considered to be ‘low-intensity therapy’. In earlier phase II studies, the drug resulted in cytogenetic conversion in approximately 30% of patients, with an overall response rate of 49%, and a 64% response rate in patients with a high-risk IPSS score. Comparison of results of these studies with those of AzaC showed similarity.

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

In a recent phase III randomized trial, decitabine was compared with best supportive care in older patients age ≥60 years (N=233; median age 70 years, range 60–90 years) with higher risk MDS (IPSS INT-1, 7%; INT-2, 55%; High-risk, 38%) not eligible for intensive therapy. Median progression-free survival (PFS) was significantly improved with decitabine compared with supportive care (6.6 vs.3 months; hazard ratio=0.68, 95% CI 0.52–0.88; P=0.004) and the risk of AML progression at 1 year was significantly reduced with decitabine (22% vs. 33%; P=0.036). However, no significant differences were observed.
between decitabine and supportive care for the primary endpoint of overall survival (10 vs. 8.5 months, respectively) or for median AML-free survival (8.8 vs. 6.1 months, respectively). In the decitabine arm, complete and partial responses were observed in 13% and 6% of patients, respectively, with hematologic improvement in an additional 15%; in the supportive care arm, hematologic improvement was seen in 2% of patients (with no hematologic responses). In addition, decitabine was associated with significant improvements in patient-reported QOL measures (as assessed by the EORTC QOL Questionnaire C30) for the dimensions of fatigue and physical functioning.

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

Several retrospective studies have evaluated the role of cytodestructive therapy with hypomethylating agents prior to allogeneic HSCT (with both myeloablative and reduced-intensity conditioning regimens). 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 HSCT.

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

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

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

- Patients who relapse after allogeneic HSCT.

In addition, hypomethylating agents are appropriate options for patients with IPSS Low or Intermediate-1-risk or IPSS-R Very Low or Low-risk disease without symptomatic anemia, or with symptomatic anemia and elevated serum Epo levels who are not expected to respond to (or who relapsed after) immunosuppressive therapy (IST).

**Biologic Response Modifiers and Immunosuppressive Therapy**

The non-chemotherapy, low-intensity agents (biologic response modifiers), currently available, include: anti-thymocyte globulin (ATG), cyclosporine, thalidomide, lenalidomide, anti-TNF receptor fusion protein, and vitamin D analogues, all of which have shown some efficacy in phase I and phase II trials.

Use of anti-immune type therapy with ATG with or without cyclosporine 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. Researchers from the NIH have updated their analysis of 129 patients treated with IST. The patients were treated with equine antithymocyte globulin (ATG) and cyclosporine alone or in combination. This study demonstrated markedly improved response rates in younger (≤60 years old) and IPSS INT-1 patients as well as in those with high response probability characteristics as indicated by their prior criteria (HLA-DR15+, age and number of transfusions). Both equine and rabbit ATG are available in the U.S. 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 aplastic anemia (N=120) who were not eligible for transplant. This study demonstrated that in this patient population, rabbit ATG was inferior to equine ATG as shown by the lower 6-month hematologic response rate (primary endpoint: 37% vs. 68%; P<0.001) and higher number of deaths (14 vs. 4 patients) resulting in decreased survival rates among patients treated with rabbit ATG. The 3-year survival rate was significantly inferior with rabbit ATG compared with equine ATG (76% vs. 96%; P=0.04). The 3-year cumulative incidence of relapse was not significantly different between treatment groups (11% vs. 28%, respectively). 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.

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

A recent 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 transfusion-dependent patients (N=205) with lower risk MDS (IPSS Low- and INT-1 risks) with del(5q).208 The primary endpoint was RBC-transfusion independence (TI) for ≥26 weeks, which was achieved in a significantly greater proportion of patients treated with lenalidomide 5 mg or 10 mg versus placebo (43% vs. 56% vs. 6%, respectively; *P*<0.001 for both lenalidomide groups vs. placebo). Among patients achieving RBC-TI with lenalidomide, onset of erythroid response was rapid, with 86% of patients experiencing response onset within the first two cycles (49% in Cycle 1).208 Among lenalidomide-treated patients with baseline sEpo levels >500 mU/mL, the 10 mg dose resulted in significantly higher rates of RBC-TI compared with the 5 mg dose (76% vs. 33%; *P*=0.004). Cytogenetic response rates were significantly higher for the lenalidomide 5 mg or 10 mg arms compared with placebo (25 vs. 50 vs. 0%, respectively; *P*<0.001 for both lenalidomide groups vs. placebo; *P*=NS between lenalidomide dose groups); complete response rates were observed in 16% and 29% of patients in the lenalidomide 5 mg and 10 mg arms, respectively. Median time to AML progression has not yet been reached in the lenalidomide treatment arms. No significant differences were observed in median overall survival between the lenalidomide 5 mg, 10 mg, and placebo groups (≥35.5 vs. 44.5 vs. 42 months, respectively). The most common grade 3 or 4 adverse events were myelosuppression and deep vein thrombosis (DVT). Grade 3 or 4 neutropenia was reported in 74%, 75%, and 15% of patients in the lenalidomide 5 mg, 10 mg, and placebo arms, respectively; thrombocytopenia occurred in 33%, 41%, and 1.5%, respectively. Grade 3 or 4 DVT occurred in 4 patients (6%) in the lenalidomide 10 mg arm, and one patient each in the lenalidomide 5 mg (1%) and placebo (1.5%) arms.208

A recent comparative analysis evaluated outcomes with 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) in patients with RBC transfusion-dependent IPSS Low/INT-1 risk MDS with del(5q).209 Untreated patients from the registry had received best supportive care, including RBC transfusion, iron chelation therapy and/or ESAs. The 2-year cumulative incidence of AML progression was 7% with lenalidomide and 12% in the untreated cohort; the corresponding 5-year rate was 23% and 20%, respectively. Thus, the median time to AML progression has not been reached in either cohort. Lenalidomide was not a significant factor for AML progression in either univariate or multivariate analyses. The 2-year overall survival probability was 90% with lenalidomide and 74% in the untreated cohort; the corresponding 5-year probability was 54% and 40.5%, respectively. The median overall survival was 5.2 years and 3.8 years, respectively (*P*=0.755; Kaplan-Meier plot with left truncation to adjust for differences in timing of study entry between cohorts).209 Based on multivariate analysis using Cox proportional hazard models (also with left truncation), lenalidomide was associated with significantly decreased risk of death compared with no treatment (HR=0.597, 95% CI 0.399–0.894; *P*=0.012). Other independent factors associated with
decreased risk of death were female sex, higher hemoglobin levels and higher platelet counts. Conversely, independent factors associated with increased risk of death included older age and greater RBC transfusion burden. 

A phase II study evaluated lenalidomide treatment in transfusion-dependent patients (N=214) with Low- or INT-1-risk MDS without the 5q deletion. Results showed 26% of the non-del(5q) patients (56 of 214) achieved TI after a median of 4.8 weeks of treatment. TI continued for a median duration of 41 weeks. The median rise in hemoglobin was 3.2 g/dL (range, 1.0–9.8 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%). Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents for non-del(5q) MDS patients. The NCCN Guidelines panel recommends considering lenalidomide for treatment of symptomatically anemic non-del(5q) patients whose anemia did not respond to initial therapy.

**High-Intensity Therapy**

High-intensity therapy includes intensive induction chemotherapy, or HSCT. 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, with associated decreased responses and shorter response durations with many standard treatment regimens used for induction chemotherapy. Thus, chemotherapeutic agents used to treat “resistant-type” AML, and agents that modulate this resistance, are now being evaluated for treating patients with advanced MDS. Although several studies using multi-drug resistance modulators were positive in this setting, others were not. Further clinical trials evaluating other multi-drug resistance modulators are ongoing.

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

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

Other patients with symptomatic anemia are categorized on the basis of their levels of sEpo. Those with levels ≤500 mU/mL should be treated with ESAs (recombinant human erythropoietin [rHu Epo] or darbepoetin) with or without granulocyte colony stimulating factor (G-CSF) (see section on Evaluation and Treatment of Related Anemia below). Non-responders should be considered for IST (with anti-thymoglobulin or cyclosporine) if there is a high likelihood of response to such therapy. In patients with lower risk MDS, the most appropriate candidates for IST include those who are age 60 years or younger, are HLA-DR15 positive, have a PNH positive clone, or have 5% or less marrow blasts or hypocellular marrow. Alternatively, or in the case of non-response to IST, treatment with AzaC or decitabine or lenalidomide should be considered. Patients with no response to hypomethylating agents or lenalidomide in this setting should be considered for participation in a clinical trial with other relevant agents, or for allogeneic HSCT (see section on Allogeneic Hematopoietic Stem Cell Transplantation [HSCT] below).

Anemic patients with sEpo level >500 mU/mL should be evaluated to determine whether they have a good probability of responding to IST. Non-responders to IST would be considered for treatment with AzaC, decitabine, or a clinical trial. Patients with sEpo levels >500 mU/mL who have a low probability of responding to IST should be considered for treatment with AzaC, decitabine, or lenalidomide. Others or non-responders to these treatments could be considered for a clinical trial or for allogeneic hematopoietic stem cell transplantation. Patients without symptomatic anemia who have other clinically relevant cytopenias (particularly clinically severe thrombocytopenia) or increased bone marrow blasts should be considered for treatment with AzaC or decitabine, ISTs (if there is a good probability of responding to these agents) or a clinical trial. Data from the phase III randomized trial of AzaC compared with conventional care showed significantly higher rates of major platelet improvement with AzaC compared with conventional care (33% vs.14%; \( P=0.0003 \)); it should be noted, however, that the rates for major neutrophil improvements were similar between AzaC and the control arm (19% vs.18%), and that the study was conducted in patients with higher risk MDS. Patients who do not respond to hypomethylating agents should be considered for treatment with IST, a clinical trial, or for allogeneic HSCT.

Careful monitoring for disease progression and consideration of the patient’s preferences play major roles in the timing and decision to embark on treatment for Lower or Higher Risk disease.

**Therapy for Higher Risk Patients (IPSS Intermediate-2, High, IPSS-R Intermediate, High, Very High, or WPSS High, Very High)**

Treatment for higher risk patients is dependent on whether they are felt to be candidates for intensive therapy (e.g., allogeneic HSCT or intensive chemotherapy). Clinical features relevant for this determination include the patient’s age, performance status, absence of major comorbid conditions, psychosocial status, patient’s preference and availability of a suitable donor and caregiver. In addition, the
patient’s personal preference for type of therapy needs particular consideration. Supportive care should be provided for all patients.

**Intensive Therapy**

**Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

The potential for patients to undergo allogeneic HSCT is dependent upon several factors including the patient’s age, performance status, major comorbid conditions, psychosocial status, availability of a caregiver, IPSS or WPSS score and the availability of a suitable donor. For those patients who are transplant candidates, the first choice of a donor has remained an HLA-matched sibling, although results with HLA matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA haploidentical related donors, HSCT has become a viable option for many patients. High dose conditioning is typically used for younger patients, whereas the approach using reduced/low intensity conditioning (RIC) for HSCT is generally the strategy in older individuals.

To aid therapeutic decision-making regarding the timing and selection of MDS patients for HSCT, a study compared outcomes with HLA-matched sibling HSCT in MDS patients 60 years old or younger to the data in non-treated MDS patients from the IMRAW/IPSS database. Using a Markov decision analysis, this investigation indicated that IPSS INT-2 and High risk patients 60 years old or younger had the highest life expectancy if transplanted (from HLA identical siblings) soon after diagnosis, whereas patients with IPSS low risk had the best outlook if HSCT was delayed until MDS progressed; for patients in the INT-1 risk group there was only a slight gain in life expectancy if HSCT was delayed, and in this group, decisions should probably be made on an individual basis (e.g., dependent upon platelet or neutrophil counts).

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

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

**Intensive Chemotherapy**

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

**Non-Intensive Therapy**

For higher risk patients who are not candidates for intensive therapy, the use of AzaC, decitabine, or a relevant clinical trial should be considered. Based on the recently published results of the phase III trial showing superior median survival with AzaC compared to best supportive care, the NCCN Guidelines panel has made this a preferred category 1 recommendation compared with decitabine. Results from another recent phase III trial comparing decitabine to supportive care in higher risk patients failed to demonstrate a survival advantage although response rates are similar to those previously reported for AzaC.¹⁷⁹,²⁴⁴ However, it should be noted that no trials to date have compared AzaC head-to-head with decitabine.

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

**Supportive Care Only**

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

**Evaluation and Treatment of Related Anemia**

Major morbidities of MDS include symptomatic anemia and associated fatigue. Much progress has been made in improving the management of this anemia. However, along with giving specific treatment for anemia related to MDS, the health care provider must identify and treat any coexisting causes of anemia.

Standard assessments should be performed to look for other causes of anemia, such as gastrointestinal bleeding, hemolysis, renal disease, and nutritional deficiency. If needed, iron, folate, or vitamin B₁₂ studies should be obtained and the cause of depletion corrected, if possible. After excluding these causes of the anemia and providing proper treatment for them, further consideration for treating the anemia related to MDS should be undertaken. Currently, the standard of care for symptomatic anemic patients is red blood cell (RBC) transfusion support (using leuko-poor products). If the patient is a potential HSCT candidate, the panel recommends consideration of CMV negative (if the patient is CMV negative serologically) and irradiated transfused products.

Anemia related to MDS generally presents as a hypoproducive macrocytic anemia, often associated with suboptimal elevation of serum Epo levels.¹²⁴⁵ To determine WHO subtype, iron status, and the level of ring sideroblasts, bone marrow aspiration with iron stain, biopsy, and cytogenetics should be examined. Patients should also be considered for HLA-DR15 typing as indicated above.

Individuals having symptomatic anemia and del(5q) with or without other cytogenetic abnormalities should receive a trial of lenalidomide. As mentioned earlier, an alternative option to lenalidomide may include an initial trial of ESAs in patients with serum Epo levels 500 mU/mL or less. Those with normal cytogenetics and with <15% marrow ringed sideroblasts and serum Epo levels 500 mU/mL or less may respond to Epo if relatively high doses of recombinant human Epo are administered.¹³⁷,²₄⁶,²₄⁷ The Epo dose required is 40,000-60,000 units 1-3 times a week subcutaneously. Erythroid responses generally occur within 6 to 8 weeks of treatment.¹³⁸,²₄₈-²₅⁰ A more prompt response may be obtained by starting at the higher dose. This Epo dose is much higher than that needed to treat renal causes of anemia wherein
marrow responsiveness would be relatively normal. If a response occurs, the recommendation is to continue this dose but attempt to decrease it to tolerance. The literature supports daily or 2-3 times per week dosing.

Iron repletion needs to be verified before instituting Epo or darbepoetin therapy. If no response occurs with these agents alone, the addition of G-CSF should be considered. Evidence suggests that G-CSF (and, to a lesser extent, GM-CSF) has synergistic erythropoietic activity when used in combination and markedly enhances the erythroid response rates.138,247-249 This is particularly evident for patients with ≥15% ringed sideroblasts in the marrow (and serum Epo level ≤500 mU/mL) as the very low response rates in this subgroup to Epo or darbepoetin alone are markedly enhanced when combined with G-CSF.138,249

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in initially neutropenic patients or to double the neutrophil count in patients who are initially normal. For this purpose, an average of 1 to 2 mcg/kg subcutaneously is administered daily or 1 to 3 times per week.138,247-249 G-CSF is available in single use vials or prefilled syringes containing either 300 mcg or 480 mcg and requires refrigeration. Patients may be taught to self administer the drug. Again, detection of erythroid responses generally occurs within 6 to 8 weeks of treatment. If no response occurs in this time frame, treatment should be considered a failure and discontinued. In the case of treatment failure, one should rule out and treat deficient iron stores. Clinical trials or supportive care are also treatment options in this category of patients. A validated decision model has been developed for predicting erythroid responses to Epo plus G-CSF, based on the patient’s basal serum Epo level and number of previous RBC transfusions.249,251 Improved quality of life has been demonstrated in responding patients.251 This cytokine treatment is not suggested for patients with endogenous serum Epo levels >500 mU/mL due to the very low erythroid response rate to these drugs in this patient population.

Darbepoetin alfa is a longer-acting form of Epo. Studies predominantly with patients having lower risk MDS have demonstrated a substantial proportion of erythroid responses with the initial trials, showing response rates of 40% and 60% (combined major and minor responses using IWG response criteria).252,253 Results of clinical trials in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than to epoetin.252-255

These response rates may in part be due to the dosage used (150 to 300 mcg per week, subcutaneously) or to the fact that better risk patients were enrolled in studies of darbopoetin compared to epoetin. Features predictive of response have included relatively low basal serum Epo levels, low percentage of marrow blasts and relatively few prior RBC transfusions.

In March 2007 and 2008, the FDA announced alerts and strengthened safety warnings for the use of ESAs. They noted that increased mortality, possible tumor promotion and thromboembolic events were observed in non-MDS patients receiving ESAs when dosing has targeted hemoglobin levels >12 g/dL (study patients had chronic kidney failure; were receiving radiation therapy for various malignancies, or including head and neck, advanced breast cancer, lymphoid or non-small cell lung cancer; were cancer patients not receiving chemotherapy; or were orthopedic surgery patients). However, as indicated above, ESAs have been used safely in large numbers of adult MDS patients and have become important for symptomatic improvement of those affected by the anemia caused by
this disease, often with a decrease in RBC transfusion requirements. The NCCN Panel recommendations for use of ESAs in MDS have evolved from these and more recent data. In addition, studies assessing the long term use of Epo with or without G-CSF in MDS patients compared to either randomized controls or historical controls have shown no negative impact of such treatment on survival or AML evolution. In addition, results of the studies by Jadersten et al indicated improved survival in low-risk MDS patients with low transfusion need treated with these agents. The study by Park et al further indicated improved survival and decreased AML progression of IPSS Low/INT-1 patients treated with Epo/G-CSF compared to the historical control IMRAW database patients. Thus, these data do not indicate a negative impact of these drugs for treatment of MDS. Given these data, we endorse and reiterate our prior recommendations for ESA use in the management of symptomatic anemia in MDS, with a target hemoglobin range of 10 to 12 g/dL; the target should not exceed 12 g/dL.

In July 2007, the Centers for Medicare and Medicaid Services (CMS) modified the scope of their decision regarding use of ESAs in cancer and related neoplastic conditions to make no national coverage determination (NCD) on the use of ESAs in MDS (i.e., not restricting ESA use in MDS through the NCD). Thus, local Medicare contractors may continue to make reasonable and necessary determinations on uses of ESAs that are not determined by the NCD.

Clinical trials with other experimental agents which are reportedly capable of increasing hemoglobin levels should be explored in patients not responding to standard therapy. These drugs should be used in the context of therapeutic approaches for the patient’s underlying prognostic risk group.

Summary

These suggested practice guidelines are based on extensive evaluation of the reviewed risk-based data and indicate current approaches for managing patients with MDS. Four drugs have recently been approved by the FDA for treating specific subtypes of MDS: lenalidomide for MDS patients with del(5q) cytogenetic abnormalities, 5-azacytidine and decitabine for treating higher risk or non-responsive MDS patients, and deferasirox for iron chelation of iron overloaded MDS patients. However, as a substantial proportion of MDS patient subsets lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents along with supportive care remain the hallmark of management for this disease. The role of thrombopoietic cytokines for management of thrombocytopenia in MDS needs further evaluation. In addition, further determination of the effects of these therapeutic interventions on the patient’s quality of life is important. Progress toward improving management of MDS has occurred over the past few years and more such advances are anticipated using these guidelines as a framework for coordination of comparative clinical trials.
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