

## NCCN

# Myelodysplastic Syndromes, Version 2.2017

## Clinical Practice Guidelines in Oncology

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### Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with a relatively heterogeneous spectrum of presentation. Major clinical problems associated with these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In the general population, the incidence rate of MDS is approximately 4.9 per 100,000 people per year.<sup>1</sup> MDS is rare among children/adolescents and young adults, with an incidence rate of 0.1 per 100,000 people per year in those aged

### Abstract

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of myeloid disorders with a highly variable disease course. Diagnostic criteria to better stratify patients with MDS continue to evolve, based on morphology, cytogenetics, and the presence of cytopenias. More accurate classification of patients will allow for better treatment guidance. Treatment encompasses supportive care, treatment of anemia, low-intensity therapy, and high-intensity therapy. This portion of the guidelines focuses on diagnostic classification, molecular abnormalities, therapeutic options, and recommended treatment approaches.

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### 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.**

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

### Please Note

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### Disclosures for the NCCN Myelodysplastic Syndromes Panel

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

Individual disclosures for the NCCN Myelodysplastic Syndromes Panel members can be found on page 87. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at [NCCN.org](http://NCCN.org).)

**These guidelines are also available on the Internet. For the latest update, visit [NCCN.org](http://NCCN.org).**

<40 years. However, among individuals between the ages of 70 and 79 years, the incidence rate increases to 30.2 per 100,000 people, and to 59.8 per 100,000 people among those aged  $\geq 80$  years.<sup>1</sup> The management of MDS is complicated by the generally advanced patient age (median age at diagnosis, 70–75 years),<sup>2</sup> attendant nonhematologic comorbidities, and relative inability of older patients to tolerate certain intensive forms of therapy. In addition, when MDS progresses into AML, these patients experience lower response rates to standard therapy than patients with de novo AML.<sup>3</sup>

## Diagnostic Classification Myelodysplastic Syndromes

Initial evaluation of patients with suspected MDS requires careful assessment of the peripheral blood

smear and blood counts, marrow morphology, cytogenetics, duration of abnormal blood counts, other potential causes of cytopenias, and concomitant illnesses. To establish the diagnosis of MDS, careful morphologic review and correlation with the patient's clinical features are important, because a number of medications and viral infections (including HIV infection) can cause morphologic changes in marrow cells similar to MDS.<sup>3,4</sup> The NCCN Guidelines for MDS include the WHO 2016 classification system for diagnostic evaluations.

To assist in providing consistency in the diagnostic guidelines for MDS, an International Working Group (IWG) recommended that minimal diagnostic criteria for this disease include 2 prerequisites: (1) stable cytopenia (for  $\geq 6$  months unless accom-

Text cont. on page 68.

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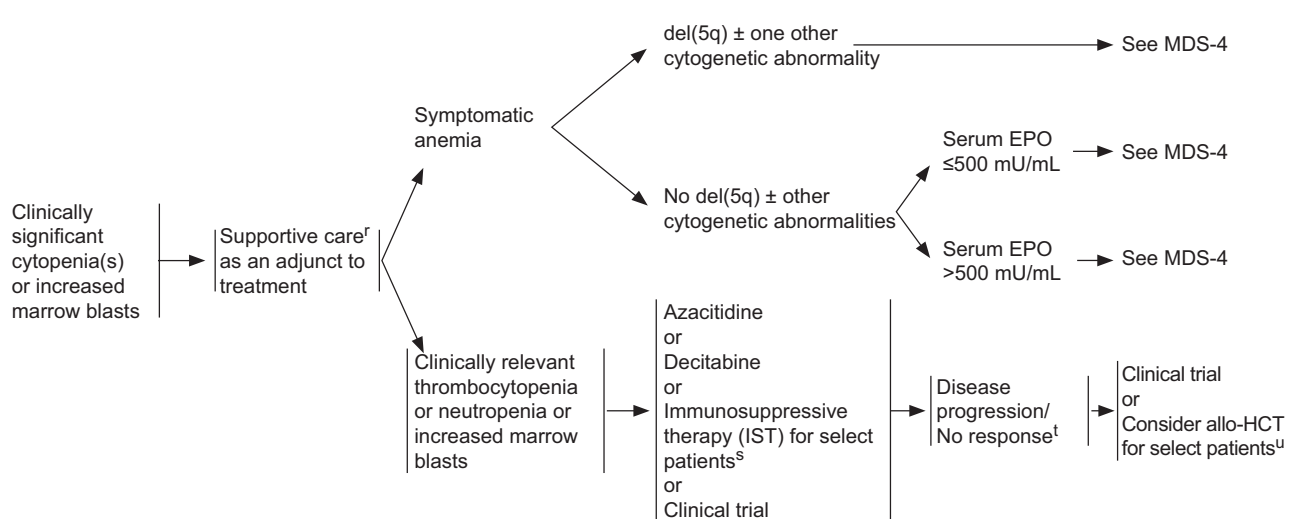
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PROGNOSTIC CATEGORY<sup>o</sup>  
IPSS: Low/Intermediate-1  
IPSS-R: Very Low, Low, Intermediate<sup>p,q</sup>  
WPSS: Very Low, Low, Intermediate

## TREATMENT



<sup>o</sup>Presence of comorbidities should also be considered for evaluation of prognosis. (See Comorbidity Indices in the Discussion.)

<sup>p</sup>Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending on additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels.

<sup>q</sup>If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.

<sup>r</sup>See Supportive Care (MDS-7).

<sup>s</sup>Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, HLA-DR15 positivity, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG ± cyclosporin A.

<sup>t</sup>Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006;108:419-425.

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

MDS-3

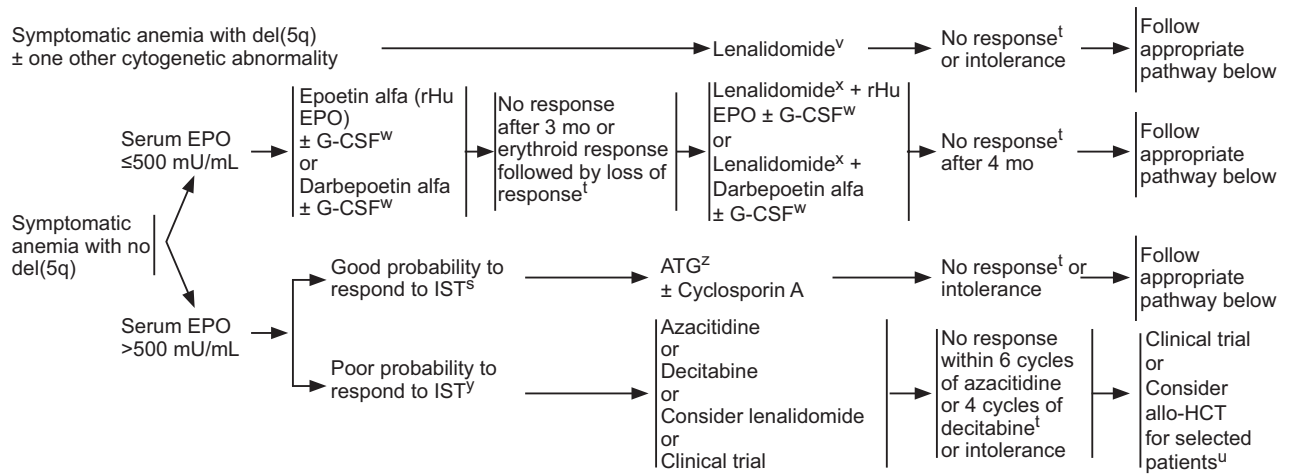
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**PROGNOSTIC CATEGORY<sup>o</sup>**

IPSS: Low/Intermediate-1  
 IPSS-R: Very Low, Low, Intermediate<sup>p,q</sup>  
 WPSS: Very Low, Low, Intermediate

**TREATMENT**



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<sup>u</sup>IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. Both

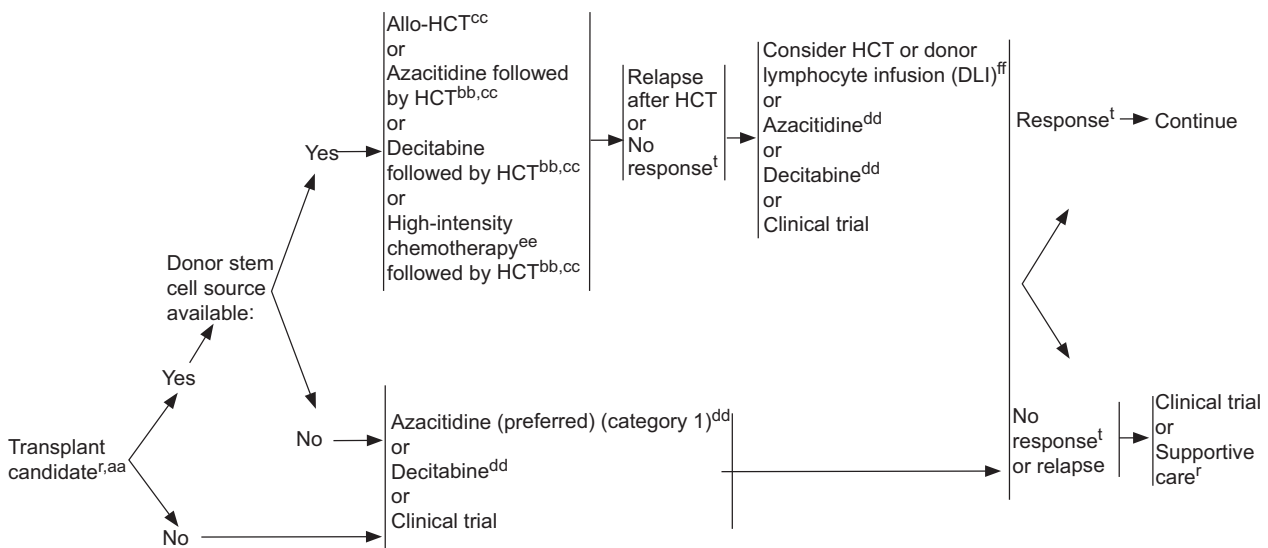
allogeneic-matched sibling and matched unrelated donor (MUD) transplants, including standard and reduced-intensity preparative approaches, may be considered.  
<sup>v</sup>Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days or 28 days monthly for 2 to 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. Patients with monosomy 7 are an exception and should be treated in the intermediate-2, high prognostic category (see MDS-5).  
<sup>w</sup>See dosing of hematopoietic cytokines (MDS-6).  
<sup>x</sup>Lenalidomide 10 mg daily if ANC > 0.5, platelets > 50,000; Toma A, Kosmider O, Chevret S, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. Leukemia. 2016;30(4):897-905.  
<sup>y</sup>Patients lack features listed in footnote s.  
<sup>z</sup>Equine ATG ± cyclosporin A has been used in patients with MDS (See Discussion).

MDS-4

PROGNOSTIC CATEGORY<sup>o</sup>

IPSS: Intermediate-2, High  
IPSS-R: Intermediate,<sup>p</sup> High, Very High  
WPSS: High, Very High

## TREATMENT



<sup>o</sup>Presence of comorbidities should also be considered for evaluation of prognosis. See Comorbidity Indices in the Discussion.

<sup>p</sup>Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending on additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels.

<sup>r</sup>See Supportive Care (MDS-7).

<sup>t</sup>Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006;108:419-425.

<sup>aa</sup>Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

<sup>bb</sup>Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability. However, these agents should not be used to delay available HCT.

<sup>cc</sup>HCT: Allogeneic-matched sibling including standard and reduced-intensity preparative approaches or MUD.

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

<sup>ee</sup>High-intensity chemotherapy:

- clinical trials with investigational therapy (preferred), or
- standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HCT.

<sup>ff</sup>Consider second transplant or DLI immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.

MDS-5

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## Myelodysplastic Syndromes Version 2:2017

FREQUENT MUTATIONS IN MDS-ASSOCIATED GENES LIKELY TO INDICATE CLONAL HEMATOPOIESIS<sup>§</sup>

| Mutated Gene <sup>†</sup> | Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes <sup>†</sup>                    | Overall Incidence | Clinical Significance   |
|---------------------------|--|-------------------|---|
| <i>TET2</i>               | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u><br><u>Missense</u> : any in codons 1134–1444 or 1842–1921 | 20%–25%           | Associated with normal karyotypes. More frequent in CMML (40%–60%).   |
| <i>DNMT3A</i>             | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u><br><u>Missense</u> in codon R882                          | 12%–18%           | Associated with a poor prognosis in patients without SF3B1 mutations.   |
| <i>ASXL1</i>              | <u>Nonsense</u> or <u>Frameshift</u>   | 15%–25%           | Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (40%–50%).  |
| <i>EZH2</i>               | <u>Nonsense</u> or <u>Frameshift</u>   | 5%–10%            | Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).   |
| <i>SF3B1</i>              | <u>Missense</u> : E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, D781                            | 20%–30%           | Strongly associated with ring sideroblasts and more frequent in MDS-RS (80%). Independently associated with a more favorable prognosis.                               |
| <i>SRSF2</i>              | <u>Missense</u> : P95  | 10%–15%           | More frequent in CMML (40%) and associated with a poor prognosis.   |
| <i>U2AF1</i>              | <u>Missense</u> : S34, Q157  | 8%–12%            | Associated with a poor prognosis.   |
| <i>ZRSR2</i>              | <u>Nonsense</u> or <u>Frameshift</u>   | 5%–10%            | Associated with a poor prognosis.   |
| <i>TP53</i>               | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u><br><u>Missense</u> : any in codons except P47S and P72R   | 8%–12%            | Independently associated with a poor prognosis. More frequent with complex karyotypes (50%) and del(5q) (15%–20%). May predict resistance or relapse to lenalidomide. |
| <i>STAG2</i>              | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u>   | 5%–10%            | Associated with a poor prognosis.   |
| <i>NRAS</i>               | <u>Missense</u> : G12, G13, Q61  | 5%–10%            | Associated with a poor prognosis, particularly in patients predicted to have lower-risk MDS. More frequent in CMML and JMML (~15%).                                   |
| <i>CBL</i>                | <u>Missense</u> : any in codons 366–420  | <5%               | More frequent in CMML (10%–20%) and JMML (15%).   |
| <i>JAK2</i>               | <u>Missense</u> : V617F  | <5%               | More frequent in MDS/MPN-RS-T (50%).  |
| <i>NF1</i>                | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u>   | <5%               | More frequent in CMML (5%–10%) and in JMML (30%) where it is often germline.  |
| <i>RUNX1</i>              | <u>Nonsense</u> or <u>Frameshift</u>   | 10%–15%           | Independently associated with a poor prognosis in MDS. May be familial in very rare cases.  |
| <i>ETV6</i>               | <u>Nonsense</u> or <u>Frameshift</u>   | <5%               | Independently associated with a poor prognosis. May be familial in very rare cases.   |
| <i>IDH1</i>               | <u>Missense</u> : R132   | <5%               | More frequent in AML.   |
| <i>IDH2</i>               | <u>Missense</u> : R140Q, R172  | <5%               | More frequent in AML. Associated with a poor prognosis.   |
| <i>SETBP1</i>             | <u>Missense</u> : E858, T864, I865, D868, S869, G870   | <5%               | Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).  |
| <i>PHF6</i>               | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u>   | <5%               | More frequent in cases with excess blasts, but no association with survival.  |
| <i>BCOR</i>               | <u>Nonsense</u> or <u>Frameshift</u> or <u>Splice Site</u><br><u>Missense</u> : in codon N1425                       | <5%               | Associated with a poor prognosis. More frequent in CMML (5%–10%).   |

**Table:** This table lists gene mutations likely to be somatic (acquired, not congenital) and disease related and therefore presumptive evidence of MDS. Other mutations in these genes can occur in MDS, as can mutations in other frequently mutated genes like *TET2* and *DNMT3A*, but these may have less certain significance (ie, possible germline variants or less specific for MDS). All mutated genes are not unique to MDS and must be interpreted in the appropriate clinical context (eg, cytopenias, <20% bone marrow blasts, no other AML defining criteria). Not all MDS patients will have a mutation in one of these genes.

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

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

<sup>‡</sup>Mutation type definitions: **Nonsense** – a mutation that changes an amino acid codon into a premature stop codon. **Frameshift** – the insertion or deletion of DNA base pairs that changes the amino acid reading frame. **Missense** – a mutation that changes one amino acid codon into another (eg, K700E indicates that the lysine [K] at codon 700 was mutated to a glutamic acid [E]). If no new amino acid is specified for a codon in the table, then it may be mutated into one of several possible amino acids (eg, R882 indicates that the arginine [R] at position 882 can be mutated in more than one way). **Splice Site** – a mutation that alters the first or second bases immediately before or after an exon.

References for this table are available in these guidelines at NCCN.org (see MDS-C, 2 of 4)

MDS-C  
1 of 4



## GERMLINE MUTATIONS WITH PREDISPOSITION FOR MDS/AML/MPN: ESTABLISHED &amp; EMERGING FAMILIAL SYNDROMES

| Affected Gene   | Typical Age at Transformation    | Potentially Associated Diseases or Syndromes   | Clinical Phenotypes  |
|---|----------------------------------|--|--|
| <b>Familial MDS/AML</b>   |                                  |  |  |
| <i>RUNX1</i>  | Early to mid adulthood           | Familial platelet disorder with predisposition to AML  | Mild to moderate thrombocytopenia and/or platelet dysfunction prior to development of MDS/AML.   |
| <i>GATA2</i>  | Childhood to young adulthood     | MonoMAC syndrome, Emberger syndrome, pulmonary alveolar proteinosis, hereditary lymphedema, congenital deafness, cutaneous warts   | Immunodeficiency with marked susceptibility to EBV, HPV, and other viruses, atypical mycobacteria, and fungal infections. Transformation to MDS/AML is usually preceded by a period of bone marrow failure. Monosomy 7 and/or somatic ASXL1 mutations are often present at transformation. |
| <i>ETV6</i>   | Childhood to young adulthood     | Dysmorphic facial features and developmental delay. Increased risk for colon and skin cancers, myopathy, and autoimmune disorders.   | Chronic thrombocytopenia typically precedes transformation. May transform to myeloid malignancy or acute lymphoblastic leukemia.   |
| <i>CEBPA</i>  | Early to mid adulthood           | None described   | Typically no chronic prodrome. Most often transforms to AML, typically acquiring a second <i>CEBPA</i> mutation. High penetrance. Relapses may represent second primary transformation events.   |
| <i>DDX41</i>  | Mid to late adulthood            | Autoimmune disorders   | Typically no chronic prodrome. May present as MDS or AML and may acquire second <i>DDX41</i> mutation.   |
| <i>ANKRD26</i>  | Childhood to mid adulthood       | Thrombocytopenia, leukocytosis   | Moderate thrombocytopenia and/or platelet dysfunction. Dysmegakaryopoiesis is striking, and caution should be exercised before using this as the sole criteria for defining MDS in these patients.   |
| <i>SRP72</i>  | Unknown                          | Congenital sensorineural hearing loss  | Bone marrow failure or aplasia may precede transformation.   |
| <b>Classical Inherited Bone Marrow Failure Syndromes</b>  |                                  |  |  |
| <i>TERT/TERC</i>  | Early to mid adulthood           | Nail and skin changes, sensorineural deafness, cirrhosis, hereditary pulmonary fibrosis, emphysema, and signs of early aging (premature graying of hair). Increased risk for head and neck cancers, anogenital cancers, and skin cancer. | Transformation to MDS/AML is usually preceded by a period of bone marrow failure. Adult patients may not have any associated physical findings.  |
| <i>FANCD1, FRAXA, FANCB, FANCD3, FANCD4, FANCD5, FANCD6, FANCD7, FANCD8, FANCD9, FANCD10, FANCD11, FANCD12, FANCD13, FANCD14, FANCD15, FANCD16, FANCD17, FANCD18, FANCD19, FANCD20, FANCD21, FANCD22, FANCD23, FANCD24, FANCD25, FANCD26, FANCD27, FANCD28, FANCD29, FANCD30, FANCD31, FANCD32, FANCD33, FANCD34, FANCD35, FANCD36, FANCD37, FANCD38, FANCD39, FANCD40, FANCD41, FANCD42, FANCD43, FANCD44, FANCD45, FANCD46, FANCD47, FANCD48, FANCD49, FANCD50, FANCD51, FANCD52, FANCD53, FANCD54, FANCD55, FANCD56, FANCD57, FANCD58, FANCD59, FANCD60, FANCD61, FANCD62, FANCD63, FANCD64, FANCD65, FANCD66, FANCD67, FANCD68, FANCD69, FANCD70, FANCD71, FANCD72, FANCD73, FANCD74, FANCD75, FANCD76, FANCD77, FANCD78, FANCD79, FANCD80, FANCD81, FANCD82, FANCD83, FANCD84, FANCD85, FANCD86, FANCD87, FANCD88, FANCD89, FANCD90, FANCD91, FANCD92, FANCD93, FANCD94, FANCD95, FANCD96, FANCD97, FANCD98, FANCD99, FANCD100</i> | Childhood to mid adulthood       | Fanconi anemia or dyskeratosis congenita. Dysmorphic features, short stature, nail and skin changes, thumb hypoplasia, dysmorphic facial features, pulmonary fibrosis.   | Chronic bone marrow failure and aplastic anemia typically precede transformation to clonal neoplasms. Adult patients may not have any associated physical findings.  |
| <i>ELA2, HAX1, GFI1</i>   | Childhood to early adulthood     | Severe congenital neutropenia  | Variable rates of transformation, often after prolonged G-CSF therapy for neutropenia.   |
| <b>Other Inherited Syndromes Associated with MDS/AML/MPN</b>  |                                  |  |  |
| <i>TP53</i>   | Late childhood through adulthood | Li-Fraumeni syndrome. Increased risk of brain tumors, sarcomas, colon, and breast cancers among others.  | Therapy-related neoplasms may emerge after treatment for solid tumors. Complex karyotypes are common as with somatic <i>TP53</i> mutations.  |
| <i>PTPN11, CBL, KRAS, NF1</i>   | Infancy to early childhood       | Noonan syndrome, neurofibromatosis   | Typically presents as JMML.  |
| <i>BLM</i>  | Infancy to early childhood       | Bloom syndrome   | Short stature, immunodeficiency, microcephaly, high-pitched voice, hypogonadism  |
| <i>ATG2B/GSKIP</i>  | Unknown                          | Myeloproliferative neoplasms   | Typically no chronic prodrome. Can present with myeloproliferative/myelodysplastic overlap features or AML.  |
| <i>BRCA1/BRCA2</i>  | Adulthood                        | Increased risk for breast cancer, male breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer among others.   | Therapy-related neoplasms may emerge after treatment for solid tumors.   |

## Myelodysplastic Syndromes Version 2:2017

| Spectrum of Indolent Myeloid Hematopoietic Disorders <sup>1,2</sup> |      |      |                  |                  |     |
|---|------|------|------------------|------------------|-----|
| Feature   | ICUS | IDUS | CHIP             | CCUS             | MDS |
| Somatic mutation  | -    | -    | +/- <sup>3</sup> | +/- <sup>3</sup> | +/- |
| Clonal karyotypic abnormality                                       | -    | -    | +/- <sup>3</sup> | +/- <sup>3</sup> | +/- |
| Marrow dysplasia  | -    | +    | -                | -                | +   |
| Cytopenia   | +    | -    | -                | +                | +   |

ICUS, idiopathic cytopenia of unknown significance;  
 IDUS, idiopathic dysplasia of unknown significance;  
 CHIP, clonal hematopoiesis of indeterminate potential;  
 CCUS, clonal cytopenia of unknown significance;  
 MDS, myelodysplastic syndromes

<sup>1</sup>Regular monitoring of blood counts in these patients should be instituted after evaluation as in MDS-1 (generally at least every 6 months).

<sup>2</sup>For patients with MDS, see MDS-3, MDS-4, and MDS-C .

<sup>3</sup>Has one or more of these (+) features: either has a clonal karyotypic abnormality (present in  $\geq 2$  metaphases) and/or a somatic mutation (present at  $>2\%$  variant allele frequency). Evaluation of mutations should include sequencing or panels incorporating at least the 21 most frequently mutated MDS-related genes as noted on MDS-C. Somatic mutations in more rarely mutated genes can also provide evidence for CHIP or CCUS.

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MDS-D



Text cont. from page 61.

panied by a specific karyotype or bilineage dysplasia, in which case only 2 months of stable cytopenias are needed), and (2) the exclusion of other potential disorders as a primary reason for dysplasia or cytopenia or both. In addition, the diagnosis of MDS requires  $\geq 1$  of 3 MDS-related (decisive) criteria: (1) dysplasia ( $\geq 10\%$  in  $\geq 1$  of the 3 major bone marrow lineages); (2) a blast cell count of 5% to 19%; and (3) a specific MDS-associated karyotype [eg, del(5q), del(20q), +8, or -7/del(7q)]. Furthermore, several co-criteria may help confirm a diagnosis of MDS and include aberrant immunophenotype by flow cytometry, abnormal bone marrow histology and immunohistochemistry, or the presence of molecular markers (ie, abnormal CD34 antigen expression, fibrosis, dysplastic megakaryocytes, atypical localization of immature progenitors, myeloid clonality).<sup>5</sup>

Consistent with these recommendations, as stated by WHO, features that are central for a diagnosis of MDS entail well-defined dysplasia in  $\geq 1$  hematopoietic cell lines in addition to cytopenias. Cytopenias need to be persistent (for at least 4–6 months) and lack other underlying conditions serving as a primary cause of the cytopenia.<sup>6</sup> Further, analyses of studies, including the MDS databases, which generated the International Prognostic Scoring System (IPSS) and Revised IPSS (IPSS-R), have shown that the use of standard hematologic values to define cytopenic cut points for MDS diagnosis are more appropriate than the WHO-recommended prognostic cytopenia cut points.<sup>7</sup>

In 2001, the WHO proposed an alternative classification for MDS that was modified from the original French-American-British (FAB) definitions.<sup>8–10</sup> Since then, the WHO classification has been updated twice (2008 and 2016). The current WHO guidelines identify 6 entities of MDS: MDS with single lineage dysplasia (MDS-SLD); MDS with ring sideroblasts (MDS-RS); MDS with multilineage dysplasia; MDS with excess blasts (MDS-EB); MDS with isolated del(5q); and MDS unclassifiable (MDS-U). There is an additional provisional entity termed “refractory cytopenia of childhood.” MDS-SLD includes refractory anemia (unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), and refractory thrombocytopenia (unilineage dysmegakaryocytopoiesis). The latter 2 were previously classified as MDS-U in 2001 but were reclassified in the 2008 update.<sup>11</sup>

An article by Vardiman et al<sup>12</sup> discusses the major changes and rationale behind the revisions in the 2016 WHO classification of MDS and AML evolving from MDS. The 2016 WHO classification stratifies MDS-RS based on SLD (MDS-RS-SLD) and multilineage dysplasia. The presence of the *SF3B1* mutation is associated with the presence of RS. The updated WHO classification expanded the definition of MDS-RS to include patients who have the *SF3B1* mutation but lack excess blasts or an isolated del(5q) abnormality. Further, MDS-EB cases are separated into patients with  $< 10\%$  marrow blasts (MDS-EB-1) and those with 10% to 19% marrow blasts (MDS-EB-2). It should also be noted that the denominator used for determining blast percentage in all myeloid neoplasms was redefined to include all nucleated bone marrow cells as opposed to only nonerythroid cells. This modification will shift a select group of patients previously categorized as AML, not otherwise specified (the specific subentity was M6 AML [erythroleukemia]) to MDS-EB.

The del(5q) entity is defined by the presence of this deletion and can include one additional cytogenetic abnormality, with the exception of monosomy 7 or del(7q). The modification of this definition stemmed from data that showed a prognostic stratification among patients with del(5q) based on the number of additional cytogenetic abnormalities compared with the single mutation del(5q).<sup>13–15</sup> Due to low reproducibility, another change in the 2016 update includes the requirement for 1% blasts in the peripheral blood on 2 separate occasions prior to diagnosing MDS-U.

The division between MDS and AML is a continued area of debate. The original FAB definition of MDS included patients with  $\leq 30\%$  blasts. The 2001 WHO classification reduced the upper limit for blast percentage for MDS to 19%, rather than the previous cutoff of 29%, thereby reclassifying these patients as AML with myelodysplasia-related changes.<sup>16</sup> It was noted in the 2008 WHO classification that AML in some patients with myelodysplasia-related changes who have 20% to 29% marrow blasts may behave in a manner more similar to MDS than AML. Data suggest that these patients have less aggressive disease and improved outcomes and therapeutic responses compared with patients with  $> 30\%$  blasts, and this should be considered favorable.<sup>17</sup> The NCCN Guidelines Panel recognizes that MDS are not only related

to blast quantitation, but they also possess a differing pace of disease related to distinctive biologic features compared with de novo AML.<sup>18,19</sup> Therefore, the NCCN panel classifies patients who have 20% to 29% marrow blasts as “MDS-EB in transformation (MDS-EB-T),” a term carried over from the original FAB classification. The MDS panel recommends using the WHO classification with the qualifier that the MDS-EB-T patient subgroup be considered as either MDS or AML. As indicated in the algorithm, the NCCN Guidelines allow for patients with 20% to 29% blasts and a stable clinical course for  $\geq 2$  months to be considered as either MDS or AML. The decision to treat these patients with intensive AML therapy is complex and should be individualized. Patients who have previously been included in and benefitted from therapeutic trials for MDS should continue to be eligible for MDS-type therapy. Clinicians should consider factors such as age, antecedent factors, cytogenetics, comorbidities, pace of disease, performance status (PS), and the patient’s goal of treatment. This recommendation is further supported by the results from several validation studies and analyses.<sup>20–24</sup>

The WHO classifications were revised to improve both the diagnostic and prognostic capabilities of these entities. MDS with del(5q) generally has a relatively good prognosis<sup>25</sup> and is highly responsive to lenalidomide therapy.<sup>26</sup> With a moderate degree of variability, patients with MDS-EB or MDS-EB-T generally have a relatively poor prognosis, with a median survival ranging from 5 to 12 months. In contrast, patients with MDS-RS-SLD (refractory anemia) or MDS-RS have a median survival of approximately 3 to 6 years. The proportion of these individuals with disease that transforms to AML ranges from 5% to 15% in the low-risk MDS-RS-SLD/MDS-RS group, to 40% to 50% in the relatively high-risk MDS-EB/MDS-EB-T group. In a study evaluating time to disease evolution, 25% of MDS-EB cases and 55% of MDS-EB-T cases underwent transformation to AML in the first year, increasing to 35% and 65%, respectively, within 2 years.<sup>3</sup> In contrast, the incidence of transformation for RA was 5% in the first year and 10% within 2 years. None of the patients with MDS-RS developed leukemia within 2 years.

Biologic evidence indicates that similar clinical phenotypes, including lower blast counts, older age, lower WBC counts, and higher erythroblast counts in

bone marrow, are seen in patients with splicing factor (SF) mutations among the MDS-EB, MDS-EB-T, and some AML categories compared with SF-nonmutated cases. This suggests that SF-mutated cases comprised a distinct entity among MDS/AML<sup>27,28</sup> and that SF-mutant MDS-EB/MDS-EB-T constitutes a related disorder overriding the artificial separation between AML and MDS. AML evolving from MDS (AML-MDS) is often more resistant to standard cytotoxic chemotherapy than de novo AML, especially those AML cases that do not have TP53 mutations nor those typical of secondary MDS,<sup>28</sup> which arises without a known antecedent hematologic disorder. Patients with high-risk MDS, AML-MDS, and some elderly patients with AML may have a more indolent clinical course in terms of short-term progression compared with patients who have standard presentations of de novo AML. This emphasizes the need to treat at least some patients with a standard presentation of de novo AML<sup>28</sup> differently than those with indolent MDS (see NCCN Guidelines for AML; available online at NCCN.org).

### MDS/Myeloproliferative Neoplasms

The category of MDS/myeloproliferative neoplasms (MDS/MPN) was added to the 2008 update of the WHO classification for myeloid neoplasms, and includes chronic myelomonocytic leukemia (CMML); atypical chronic myeloid leukemia (aCML), BCR-ABL1 negative; and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features. The MDS/MPN with RS (MDS/MPN-RS) and thrombocytosis group and MDS/MPN-U group are also included in this category.<sup>29</sup>

CMML has been subdivided into 2 groups based on molecular and clinical differences: proliferative-type CMML (WBC count,  $\geq 13 \times 10^9/L$ ) and dysplastic-type CMML (WBC count,  $< 13 \times 10^9/L$ ). In addition to the WBC count, the percentage of blasts plus monocytes in the peripheral blood and bone marrow has demonstrated prognostic significance. Three blast-based groups were created in the 2016 classification (previously only 2 groups were identified) and are defined (1) CMML-0, for patients with  $< 2\%$  peripheral blood blasts and  $< 5\%$  bone marrow blasts; (2) CMML-1 for those with 2% to 4% peripheral blood blasts and/or 5% to 9% bone marrow blasts; and (3) CMML-2 for those with 5% to

19% peripheral blood blasts, 10% to 19% bone marrow blasts, and/or the presence of Auer rods.

The second subtype, aCML, is rare and has similar neutrophilia as the chronic neutrophilic leukemia subtype of MPN. However, molecular characterization may distinguish the 2 entities. The presence of *CSF3R* mutations are strongly associated with chronic neutrophilic leukemia but is present in <10% of aCML cases.<sup>30</sup> Other MPN-associated driver mutations (ie, *JAK2*, *CALR*, *MPL*) are uncommon in aCML. The presence of *SETBP1* or *ETNK1* mutations (or both) is reported in up to one-third of patients with aCML.<sup>31–33</sup>

JMML is a rare childhood cancer that presents in infants and young children. Clinical and hematologic criteria for the diagnosis of JMML include peripheral blood monocyte count  $\geq 1 \times 10^9/L$ , blast percentage in the peripheral blood and bone marrow <20%, splenomegaly, and the absence of *BCR/ABL1* rearrangement. Although there are no mutations exclusive to JMML, the most frequently mutated genes are *PTPN11* (40%–50%), *NRAS* (15%–20%), *KRAS* (10%–15%), *CBL* (15%–18%), and *NF1* (10%–15%). In some patients, these mutations may be present as germline variants, wherein they are frequently associated with Noonan syndrome or other congenital syndromes.<sup>34</sup> In patients without genetic features of JMML, monosomy 7 or any other chromosomal abnormality must be present with at least 2 of the following: hemoglobin F increased for age, myeloid or erythroid precursors on peripheral blood smear, granulocyte-macrophage colony-stimulating factor (GM-CSF) hypersensitivity in colony assay, and hyperphosphorylation of *STAT5*.

MDS-RS-T includes cases that present with clinical and morphologic features consistent with MDS and thrombocytosis (platelet counts  $\geq 450 \times 10^9/L$ ).<sup>35</sup> The morphology of MDS-RS-T is characterized by MDS-RS features (no blasts in the peripheral blood, dysplastic erythroid proliferation, RS  $\geq 15\%$  of erythroid precursors, and <5% blasts in marrow) with proliferation of large atypical megakaryocytes similar to those in essential thrombocythemia or primary myelofibrosis. The frequency of spliceosome gene *SF3B1* mutations in up to 60% of MDS-RS-T cases has resulted in the inclusion of MDS/MPN-RS with thrombocytosis as a full entity.<sup>36–39</sup> *SF3B1* mutations are associated with the presence of RS and frequently have the *JAK2* V617F or *MPL* W515K/L muta-

tions.<sup>35</sup> In contrast to MDS-RS, *SF3B1* mutations do not change the required percentage of RS for diagnostic classification.

### Indolent Myeloid Hematopoietic Disorders

The spectrum of indolent myeloid hematopoietic disorders encompasses 4 groups: idiopathic cytopenia of unknown significance (ICUS), idiopathic dysplasia of unknown significance (IDUS), clonal hematopoiesis of indeterminate potential (CHIP), and clonal cytopenia of unknown significance (CCUS). Based on somatic mutation, clonal karyotypic abnormality, marrow dysplasia, and cytopenia features, patients can be classified within the spectrum (see MDS-D, page 67). These disorders can evolve into MDS or AML, though the frequency of progression may differ among the 4 groups.

CHIP and CCUS are defined by the presence of a clonal karyotypic abnormality (present in  $\geq 2$  metaphases) and/or a somatic mutation in a gene involved in hematopoiesis (present at >2% variant allele frequency); there is an absence of marrow dysplasia in these patients. CCUS differs from CHIP by having the presence of cytopenia. Although CHIP is generally benign and has a low likelihood of progression compared with other premalignant conditions, there is a higher risk of subsequent hematologic disease compared with patients without somatic mutations.<sup>40,41</sup> Additionally, shorter survival in these patients compared with aged-matched controls has been demonstrated and may be attributed to nonhematologic causes.<sup>41</sup> ICUS and IDUS have no known cause, lack somatic mutations or clonal karyotypic abnormalities, and differ from each other only by the presence of cytopenia or marrow dysplasia, respectively. There is significant heterogeneity within ICUS, with some patients experiencing spontaneous resolution of disease and others developing a myeloid neoplasm.<sup>42</sup> Data are limited regarding natural history and disease progression for these 2 disorders.

Two recent studies have focused on the role of mutational analysis in indolent malignant disease. In a prospective analysis of 144 patients, Kwok et al<sup>43</sup> utilized a 22-gene panel to determine the frequency of MDS-associated mutations. Among these patients, 17% were categorized as MDS, 15% as ICUS with mild dysplasia, and 69% as ICUS without dysplasia. Further analysis showed that 35% of patients with ICUS had a somatic mutation or chromosomal

abnormality similar to MDS, and were characterized as CCUS. Similar mutational features may have a role in the diagnostic value of these disorders.<sup>43</sup> Cargo et al<sup>42</sup> evaluated mutational features associated with ICUS in patients with disease that developed into progressive dysplasia or AML. Although this study was not designed to evaluate the diagnostic role of mutations, detection of mutational features predicted progression to high-risk disease and overall survival (OS). It does, however, propose that patients who are defined as poor-risk may benefit from early intervention.

NCCN recommends that after the initial evaluation, regular monitoring of blood counts in patients with these indolent myeloid hematopoietic disorders occur at least every 6 months. More frequent monitoring may be recommended based on clinical expertise.

### Molecular Abnormalities in MDS

In recent years, several gene mutations have been identified among patients with MDS that may, in part, contribute to the clinical heterogeneity of the disease course, and thereby influence the prognosis of patients (see MDS-C, page 65). Such gene mutations are present in the majority of newly diagnosed patients, including those with normal cytogenetics. Several studies examining large numbers of MDS tumor samples have identified >40 recurrently mutated genes with >80% of patients harboring at least one mutation.<sup>38,44-46</sup> The most frequently mutated genes were *TET2*, *SF3B1*, *ASXL1*, *DNMT3A*, *SRSF2*, *RUNX1*, *TP53*, *U2AF1*, *EZH2*, *ZRSR2*, *STAG2*, *CBL*, *NRAS*, *JAK2*, *SETBP1*, *IDH1*, *IDH2*, and *ETV6*, although no single mutated gene was found in more than one-third of patients. Several of these gene mutations are associated with adverse clinical features such as complex karyotypes (*TP53*), excess bone marrow blast proportion (*RUNX1*, *NRAS*, and *TP53*), and severe thrombocytopenia (*RUNX1*, *NRAS*, and *TP53*).

Despite associations with clinical features considered by prognostic scoring systems, mutations in several genes hold independent prognostic value. Mutations of *TP53*, *EZH2*, *ETV6*, *RUNX1*, and *ASXL1* have been shown to predict decreased OS in multivariable models adjusted for IPSS or IPSS-R risk groups in several studies of distinct cohorts.<sup>44,46</sup>

Within IPSS risk groups, a mutation in  $\geq 1$  of these genes identifies patients whose survival risk resembles that of patients in the next highest IPSS risk group (eg, the survival curve for intermediate [int]-1-risk patients with an adverse gene mutation was similar to that of patients assigned to the int-2-risk group by the IPSS).<sup>44</sup> When applied to patients stratified by the IPSS-R, the presence of a mutation in  $\geq 1$  of these genes was associated with shorter OS for patients in the low- and intermediate-risk groups.<sup>46</sup> Thus, the combined analysis of these gene mutations and the IPSS or IPSS-R may improve the risk stratification provided by these prognostic models alone. Mutations of *ASXL1* have also been shown to carry independent adverse prognostic significance in CMML.<sup>47,48</sup> Other mutated genes have been associated with decreased OS, including *DNMT3A*, *U2AF1*, *SRSF2*, *CBL*, *PRPF8*, *SETBP1*, and *KRAS*.<sup>44,46,49-52</sup> Only mutations of *SF3B1* have been associated with a more favorable prognosis even after adjustment for the IPSS-R in several, but not all, studies.<sup>46,53</sup>

*TET2* mutations have been shown to impact response to hypomethylating agents.<sup>54,55</sup> Patients with mutated *TET2* had an 82% response rate to azacitidine (AzaC) compared with 45% of patients with wild-type *TET2* ( $P=.007$ ); response duration and OS were not statistically different.<sup>54</sup> Another study identified 39 genes that were mutated in 213 patients with MDS treated with AzaC or decitabine.<sup>55</sup> A higher response to hypomethylating agents in those with the *TET2* mutation, albeit to a lesser degree, was seen (response rate, 55% vs 44%;  $P=.14$ ). This improved response was more pronounced when patients with *ASXL1* mutations and those with a low abundance *TET2* mutations were excluded (odds ratio, 3.65;  $P=.009$ ). Mutations in *TP53* and *PTPN11* correlated with shorter OS but did not affect drug response. However, the predictive capabilities of these mutations are modest. The status of these molecular markers in patients should not preclude the use of hypomethylating agents nor be used to influence the selection of hypomethylating agents.

*TP53* mutations are strongly associated with complex and monosomal karyotypes. However, approximately 50% of patients with a complex karyotype have no detectable *TP53* abnormality and have an OS comparable to that of patients with noncomplex karyotypes. Therefore, *TP53* muta-



tion status may be useful for refining the prognosis of these patients typically considered to have higher-risk disease.<sup>44</sup> Patients with del(5q), either as an isolated abnormality or often as part of a complex karyotype, have a higher rate of concomitant *TP53* mutations.<sup>56,57</sup> These mutations are associated with diminished response or relapse after treatment with lenalidomide.<sup>58,59</sup> In these cases, *TP53* mutations may be secondary events and are often present in small subclones that can expand during treatment. More sensitive techniques may be required to identify the presence of subclonal low-abundance *TP53* mutations before treatment.

Mutations identified in peripheral blood samples can accurately reflect mutations detected in the bone marrow of patients with MDS when more sensitive sequencing techniques are used to detect them.<sup>60</sup>

## Therapeutic Options

The IPSS or IPSS-R risk categories are used in the initial planning of therapeutic options because they provide a risk-based patient evaluation (category 2A recommendation). In addition, factors such as patient age, PS, and presence of comorbidities are critical determinants, because they have a major influence on the patient's ability to tolerate certain intensive treatments. The WHO-based Prognostic Scoring System (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 blood counts over several months is important to assess whether the disease progresses, including incipient transformation to AML. In addition, this assessment permits determination of other possible etiologies for cytopenias. Patient preference for a specific approach is also important in deciding treatment options. Therapeutic options for MDS include supportive care, low-intensity therapy, high-intensity therapy including allogeneic hematopoietic cell transplantation (HCT), and participation in a clinical trial. In evaluating results of therapeutic trials, the panel found it important for studies to use the standardized IWG response criteria.<sup>61-63</sup>

For the MDS therapeutic algorithm, all patients should receive relevant supportive care. Following that, the MDS Guidelines Panel proposed initially stratifying patients with clinically significant cytopenias into 2 major risk groups: (1) lower-risk patients

(ie, IPSS low, int-1; IPSS-R very low, low, intermediate; WPSS very low, low, intermediate); and (2) higher-risk patients (ie, IPSS int-2, high; IPSS-R intermediate, high, very high; WPSS high, very high). Patients who fall under the IPSS-R intermediate category may be managed as either of the risk groups depending on evaluation of additional prognostic factors such as age, PS, serum ferritin levels, and serum lactate dehydrogenase levels.<sup>64</sup> In addition, intermediate-risk patients whose disease does not respond to therapy for lower-risk disease would be eligible to receive therapy for higher-risk MDS.

Based on IWG response criteria, the major therapeutic aim for patients in the lower-risk group would be hematologic improvement, whereas for those in the higher-risk group, alteration of the disease natural history is viewed as paramount. Cytogenetic response and quality-of-life (QOL) parameters are also important outcomes to assess. The algorithm outlines 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.

## Treatment of Related Anemia

Erythropoiesis-stimulating agents (ESAs), such as recombinant human erythropoietin (rHu Epo) or the longer-acting darbepoetin, with or without granulocyte CSF (G-CSF), have been evaluated in the treatment of symptomatic anemia in patients with MDS. Studies predominantly in lower-risk patients with MDS have demonstrated erythroid response rates of 40% and 60% (combined major and minor responses using IWG response criteria) in the initial trials.<sup>65,66</sup> Clinical trial results in patients with MDS have suggested that overall response rates to darbepoetin are similar to or possibly higher than epoetin.<sup>65-68</sup> The improved response rates may, in part, be due to the dosage (150–300 mcg subcutaneously per week) or to the fact that better-risk patients were enrolled in studies of darbepoetin compared with epoetin. Features predictive of response have included relatively low basal serum Epo (sEpo) levels, low percentage of marrow blasts, and few prior red blood cell (RBC) transfusions.

In a phase II study of patients with MDS (refractory anemia, MDS-RS, and MDS-EB; N=50), Epo combined with G-CSF (n=47 evaluable) resulted in

hematologic responses in 38% (complete response [CR], 21%).<sup>69</sup> Epo and G-CSF appeared to have synergistic activity. Lower sEpo levels (<500 mU/mL) and a lower pretreatment RBC transfusion requirement (<2 units per month) were associated with a higher response rate; response rates were not significantly different across IPSS risk groups.<sup>69</sup> Median survival, including patients from a prior study, was 26 months (N=71). Among patients with low-risk IPSS, median survival was not reached at 5 years; the 5-year survival rate was 68%. Median survival times among the int-1- and int-2-risk groups were 27 and 14 months, respectively. AML progression occurred in 28% of patients overall during the observation period. The frequency of AML progression in the low-, int-1-, int-2-, and high-risk groups were 12%, 21%, 45%, and 100%, respectively. Among patients with responding disease who received maintenance treatment with Epo and G-CSF, median duration of response was 24 months.<sup>69</sup>

A subsequent analysis of combined data from 3 phase II Nordic trials (n=121) on long-term outcomes with Epo plus G-CSF (given for 12–18 weeks and followed by maintenance in responders) in patients with MDS reported a hematologic response rate of 39% with a median duration of response of 23 months.<sup>70</sup> Long-term outcomes were compared with outcomes from untreated patients (n=237) as controls. Based on multivariate Cox regression analysis, treatment with Epo plus G-CSF was associated with a significantly improved survival outcome (hazard ratio [HR], 0.61; 95% CI, 0.44–0.83; *P*=.002). An exploratory analysis revealed that the association between treatment and survival was significant only for the IPSS low-risk group and was further restricted to patients requiring <2 units of RBC transfusions per month. No significant association was found between treatment and frequency of AML progression.<sup>70</sup>

Similar findings were reported in a study from the French myelodysplasia group, which analyzed outcomes with ESAs (epoetin or darbepoetin), with or without G-CSF, in patients with MDS and anemia (N=403).<sup>71</sup> Based on the IWG 2000 criteria, the hematologic response rate was 62%, with a median duration of 20 months; corresponding results from the IWG 2006 criteria were 50% and 24 months, respectively. IPSS low- or int-1-risk was associated with significantly higher response rates and longer response durations. In a comparison of outcomes (in the low-

or int-1-risk subset with anemia) between treated patients (n=284) and a historical cohort of untreated patients (n=225), multivariate analysis showed a significant association between treatment with ESAs and survival outcomes; frequency of AML progression was similar between the cohorts.<sup>71</sup> In a phase II study that evaluated darbepoetin (every 2 weeks for 12 weeks) with or without G-CSF (added at 12 weeks in nonresponders), patients in the lower-risk IPSS group with anemia (and sEpo levels <500 mU/mL) had hematologic response rates of 48% at 12 weeks and 56% at 24 weeks.<sup>72</sup> Median duration of response was not reached at the median follow-up of 52 months. The 3-year cumulative incidence of AML progression was 14.5%, and the 3-year survival rate was 70%. This study also showed improvements in QOL parameters among patients with responding disease.<sup>72</sup>

Collectively, these studies suggest that ESAs may provide a clinical benefit to patients in the lower-risk group with symptomatic anemia. Limited data are available on the effectiveness of ESAs in the treatment of anemia in lower-risk patients with del(5q). Epo has been shown to promote the growth of cytogenetically normal cells isolated from patients with del(5q), while having minimal proliferative effects on MDS progenitor cells from these patients *in vitro*.<sup>73</sup> Retrospective studies from the French group reported hematologic response rates between 46% and 64%, with a median response duration of 11 months (mean duration, 13–14 months) among patients with del(5q) treated with ESAs with or without G-CSF.<sup>71,74</sup> Duration of response in these patients was significantly decreased compared with patients without del(5q) (mean duration, 25–27 months).<sup>74</sup> Based on multivariate analysis, del(5q) was a significant predictor of a shorter response duration with treatment (see MDS-4, page 63).<sup>71</sup>

In March 2007 and 2008, the FDA announced alerts and strengthened safety warnings for the use of ESAs based on observed increased mortality and possible tumor promotion and thromboembolic events in patients without MDS receiving ESAs when dosing to achieve a targeted hemoglobin level >12 g/dL. Specifically, the patients had chronic kidney failure; were receiving radiation therapy for various malignancies, including head and neck cancer, advanced breast cancer, lymphoid cancer, or non-small cell lung cancer; were patients with cancer not receiving chemotherapy; or were patients who had undergone



orthopedic surgery. However, ESAs have been used safely in large numbers of adult patients with MDS and have become important for symptomatic improvement of anemia caused by this disease, often with a decrease in RBC transfusion requirements. Studies assessing the long-term use of Epo with or without G-CSF in patients with MDS have shown no negative impact of such treatment on survival or AML evolution when compared with either randomized<sup>75</sup> or historical controls.<sup>70,71</sup>

Jadersten et al<sup>70</sup> reported improved survival in patients with low-risk MDS with low transfusion need after treatment with these agents. In another study, improved survival and decreased AML progression was reported in patients with IPSS low- or int-1-risk disease after Epo treatment, with or without G-CSF, compared with the historical control IMRAW database patients.<sup>71</sup> Thus, these data do not indicate a negative impact of these drugs in the treatment of MDS. Given these data, the NCCN Guidelines Panel recommends the use of ESAs in the management of symptomatic anemia in patients with MDS, with a target hemoglobin range of 10 to 12 g/dL but not to exceed 12 g/dL. Clinical trials with other experimental agents that are reportedly capable of increasing hemoglobin levels should be explored in patients whose disease is not responding to standard therapy. These drugs should be used in the context of therapeutic approaches for the underlying prognostic risk group.

In March 2007, the Centers for Medicare & Medicaid Services (CMS) generated a National Coverage Determination (NCD) on the use of ESAs for nonrenal disease applications. Following a public comment period, it was determined that the scope of the NCD should be revised to include cancer and related neoplastic conditions. The narrowed scope of the NCD excludes MDS because it is defined in the report as a premalignant condition and not an oncologic disease.<sup>76</sup> Thus, local Medicare contractors may continue to make reasonable and necessary determinations on the use of ESAs not determined by the NCD.

### Low-Intensity Therapy

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

**Hypomethylating Agents:** The DNA methyltransferase inhibitor (DMTI) hypomethylating agents AzaC and decitabine (5-aza-2'-deoxycytidine) have been shown in randomized phase III trials to decrease the risk of leukemic transformation and, in a portion of patients, to improve survival.<sup>77-80</sup> In a phase III trial that compared AzaC with supportive care in patients from all IPSS risk groups (N=191; 83% previously untreated), hematologic responses occurred in 60% of patients in the AzaC arm (7% CR, 16% partial response [PR], and 37% hematologic improvement) compared with a 5% hematologic improvement (and no responses) in patients receiving supportive care.<sup>80</sup> The median time to AML progression or death was significantly prolonged in the AzaC arm compared with patients receiving supportive care (21 vs 13 months;  $P=.007$ ). Further improvement was seen in patients who received AzaC earlier in the disease course, suggesting that AzaC prolonged the duration of stable disease. Subsequently, Silverman et al<sup>81</sup> provided a summary of 3 AzaC studies in a total of 306 patients with high-risk MDS.<sup>81</sup> In this analysis, which included patients receiving either subcutaneous or intravenous drug delivery, complete remissions were seen in 10% to 17% of AzaC-treated patients and partial remissions were rare; hematologic improvement was seen in 23% to 36%. Ninety percent of the responses occurred before cycle 6, with a median number of cycles to first response of 3.<sup>81</sup> The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. Results from a phase III randomized trial in patients (N=358) with higher-risk MDS (IPSS int-1, 5%; int-2, 41%; high risk, 47%) demonstrated that AzaC was superior to conventional care (ie, standard chemotherapy or supportive care) regarding OS.<sup>77</sup> AzaC was associated with a significantly longer median survival compared with conventional care (24.5 vs 15.0 months; HR, 0.58; 95% CI, 0.43-0.77;  $P=.0001$ ), thus providing support for the use of this agent in patients with higher-risk disease.

AzaC therapy should be considered for treating patients progressing or relatively high-risk MDS. This drug has been FDA approved and is generally administered at a dose of 75 mg/m<sup>2</sup>/d subcutaneously for 7 days every 28 days for at least 6 courses. Treatment courses may need to be extended further or may be used as a bridging therapy to more definitive therapy (eg, patients whose marrow blast counts require lowering before HCT). Although the optimal

duration of therapy with AzaC has not been defined, some data suggest that continuation of AzaC beyond first response may improve remission quality. In a secondary analysis of the phase III randomized AZA-001 trial, continued AzaC therapy resulted in further improvement in response category in 48% of all responders.<sup>82</sup> Although most patients with responding disease achieved a first response by 6 cycles of therapy, up to 12 cycles were required for the majority of responders to attain a best response.<sup>82</sup> In this study, the median number of cycles from first response to best response was 3 to 3.5 cycles; patients with responding disease received a median of 8 additional cycles (range, 0–27 cycles) beyond first response.<sup>82</sup>

An alternative 5-day schedule of AzaC has been evaluated, both as a subcutaneous regimen (including the 5-2-2 schedule: 75 mg/m<sup>2</sup>/d subcutaneously for 5 days followed by 2 days of no treatment, then 75 mg/m<sup>2</sup>/d for 2 days, every 28 days; and the 5-day schedule: 75 mg/m<sup>2</sup>/d subcutaneously for 5 days every 28 days)<sup>83</sup> and as an intravenous regimen (75 mg/m<sup>2</sup>/d intravenously for 5 days every 28 days).<sup>84</sup> Although response rates with the 5-day regimen appeared similar to the approved 7-day dosing schedule,<sup>83,84</sup> survival benefit with AzaC has only been demonstrated using the 7-day schedule.

Decitabine, given intravenously and administered with a regimen that requires hospitalization, has also shown encouraging results for patients with higher-risk MDS. Because this treatment regimen was generally associated with low-intensity-type toxicities, it is also considered to be a “low-intensity therapy.” In earlier phase II studies, approximately 30% of patients experienced cytogenetic conversion,<sup>85</sup> with an overall response rate of 49%, and a 64% response rate in those with high-risk IPSS scores<sup>86</sup>; results were similar to those seen in AzaC studies.<sup>78,87</sup>

A phase III randomized trial of decitabine (15 mg/m<sup>2</sup> intravenous infusion over 3 hours every 8 hours [ie, 45 mg/m<sup>2</sup>/d] on 3 consecutive days every 6 weeks for up to 10 cycles) compared with supportive care in adult patients (N=170) with primary and secondary MDS (IPSS int-1, 30.5%; int-2, 43.5%; high risk, 26%) indicated higher response rates, remission durations, times to AML progression, and survival benefits in the int-2- and high-risk groups.<sup>78</sup> Overall response rate (CR + PR) with decitabine was 17% (median duration, 10 months), with an ad-

ditional 13% of patients showing hematologic improvement. The probability of progression to AML or death was 1.68-fold greater for patients receiving supportive care than for those receiving decitabine. Based on this study and 3 supportive phase II trials,<sup>88</sup> decitabine has also been FDA approved for patients with MDS.

In another phase III randomized trial with this regimen, decitabine was compared with best supportive care (BSC) in patients aged ≥60 years (N=233; median age, 70 years; range, 60–90 years) with higher-risk MDS (IPSS int-1, 7%; int-2, 55%; high risk, 38%) not eligible for intensive therapy.<sup>79</sup> Median progression-free survival (PFS) was significantly improved in patients receiving decitabine compared with BSC (6.6 vs 3.0 months; HR, 0.68; 95% CI, 0.52–0.88; *P*=.004), and the risk of AML progression at 1 year was reduced with decitabine (22% vs 33%; *P*=.036). However, no significant differences were observed between decitabine and BSC for the primary end point of OS (10.0 vs 8.5 months, respectively) or for median AML-free survival (8.8 vs 6.1 months, respectively).<sup>79</sup> In the decitabine arm, CR and PR were observed in 13% and 6% of patients, respectively, with hematologic improvement in an additional 15%; in the BSC arm, hematologic improvement was seen in 2% (with no hematologic responses). Decitabine was associated with significant improvements in patient-reported QOL measures (as assessed by the EORTC QOL Questionnaire C30) for the dimensions of fatigue and physical functioning.<sup>79</sup>

In 2007, Kantarjian et al<sup>89</sup> provided an update to their study of 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens. Patients received 1 of 3 different schedules of decitabine, including both subcutaneous and intravenous administration with a mean of 7 courses of therapy. Responses were improved with the longer duration of therapy. Overall, 80 patients (70%) experienced response, with 40 patients achieving CR and 40 achieving PR. Median remission duration was 20 months, with a median survival time of 22 months. The 3 different schedules of decitabine were compared in another randomized study of 95 patients with MDS or CMML receiving 20 mg/m<sup>2</sup>/d intravenously for 5 days; 20 mg/m<sup>2</sup>/d subcutaneously for 5 days; or 10 mg/m<sup>2</sup>/d intravenously for 10 days<sup>90</sup>; the 5-day intravenous schedule was considered the optimal schedule. The CR rate in the 5-day intrave-

nous was 39% compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day intravenous arm ( $P<.05$ ). Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated.

Several retrospective studies have evaluated the role of cytoreductive therapy with hypomethylating agents before allogeneic HCT (with both myeloablative and reduced-intensity conditioning [RIC] regimens).<sup>91–94</sup> These studies suggest that hypomethylating agents may provide a feasible alternative to induction chemotherapy regimens before transplant, and may serve as a bridge to allogeneic HCT. A randomized trial comparing the 2 strategies is currently ongoing (ClinicalTrials.gov identifier: NCT01812252).

AzaC and decitabine are considered to be therapeutically similar, although the improved survival of higher-risk patients treated with AzaC compared with control patients in a phase III trial, as indicated previously, supports the preferred use of AzaC in this setting until more trial data are available. A lack of CR, PR, or hematologic improvement or frank progression to AML (in particular with loss of control [proliferation] of peripheral counts or excess toxicity that precludes continuation of therapy) may be indicative of disease that fails to respond to hypomethylating agents. The minimum number of courses before considering the treatment a failure should be 4 courses for decitabine or 6 courses for AzaC. As discussed earlier, the optimal duration of therapy with hypomethylating agents has not been well-defined and no consensus exists. The NCCN Guidelines Panel generally feels that treatment should be continued if there is ongoing response and if there are no toxicities. Modifications should be made to the dosing frequency for individual patients in the event of toxicity.

As data have predominantly indicated altered natural history and decreased evolution to AML in patients whose disease responds to DMTI hypomethylating agents, major candidates for these drugs are (1) patients with IPSS int-2– or high-risk disease; or (2) IPSS-R intermediate-, high-, or very-high-risk disease with any of the following criteria:

- Patients who are not candidates for high-intensity therapy;
- Patients who are potential candidates for allogeneic HCT but for whom a delay in HCT is anticipated (eg, due to need to further reduce

the blast count, improve patient PS, identify a donor). In these circumstances, the drugs may be used as a bridging therapy for that procedure; or

- Patients whose disease is not expected to respond to (or who experienced relapsed after) ESA or immunosuppressive therapy (IST).

**Biologic Response Modifiers and IST:** Currently available nonchemotherapy, low-intensity agents (biologic response modifiers) include: antithymocyte globulin (ATG), cyclosporine, and lenalidomide, all of which have shown some efficacy in phase II and III trials.<sup>3,95–100</sup>

Use of IST with ATG, with or without cyclosporine,<sup>98,100</sup> has been shown in several studies to be most efficacious in patients with MDS with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a paroxysmal nocturnal hemoglobinuria (PNH) clone.<sup>101,102</sup> Researchers from the NIH have updated their analysis of 129 patients treated with IST with equine ATG alone, cyclosporine alone, or in combination.<sup>103</sup> This study demonstrated markedly improved response rates in the subgroup of patients aged  $\leq 60$  years with IPSS int-1–risk or patients with high response probability characteristics as indicated by their prior criteria (ie, age, number of transfusions, possibly HLA-DR15 status).<sup>103</sup>

Although equine ATG has been found to be more effective than rabbit ATG for treating aplastic anemia,<sup>104</sup> only limited data within the setting of MDS are available regarding the comparative effectiveness of the 2 ATG formulations. In a relatively small phase II study in patients with MDS ( $N=35$ ; primarily refractory anemia subtype), both equine and rabbit ATG were shown to be feasible and active.<sup>105</sup> Some institutions have used tacrolimus in place of cyclosporine A based on the limited data that showed similar efficacy with a lower incidence of adverse events in children with aplastic anemia.<sup>106,107</sup>

A recent study showed that STAT3-mutant cytotoxic T lymphocyte clones are present in a small proportion (5%) of patients with MDS (including those lacking large granular lymphocytes), which is associated with HLA-DR15 positivity, marrow hypocellularity, and neutropenia.<sup>108</sup> Despite lack of a survival difference in the STAT3-mutated versus nonmutated patients with MDS treated with IST in this small cohort, these findings suggest that STAT3-mutant cytotoxic T lymphocyte clones may facilitate

persistently dysregulated autoimmune activation, akin to that present in other patients with MDS responsive to IST.<sup>108</sup>

Lenalidomide (a thalidomide analog) is an immunomodulating agent with activity in patients with lower-risk MDS.<sup>26,109</sup> Beneficial results have been particularly evident for patients with the del(5q) chromosomal abnormality.<sup>26,109,110</sup> A multicenter phase II trial of lenalidomide (10 mg/d for 21 days every 4 weeks or 10 mg daily) in anemic RBC transfusion-dependent (TD) patients with MDS with del(5q), with or without additional cytogenetic abnormalities (N=148), demonstrated that the hematologic response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained.<sup>26</sup> RBC-transfusion independence (TI) (assessed at 24 weeks) occurred in 67% of patients; among patients with IPSS low-/int-1-risk (n=120), 69% achieved TI.<sup>26</sup> Cytogenetic responses were achieved in 62 of 85 evaluable patients (73%); 45% had a complete cytogenetic response. The most common grade 3 or 4 adverse events included myelosuppression (neutropenia, 55%; thrombocytopenia, 44%), which often required treatment interruption or dose reduction. Thus, careful monitoring of blood counts during the treatment period is mandatory when using lenalidomide, particularly in patients with renal dysfunction (due to the drug's renal route of excretion). Lenalidomide has been FDA approved for the treatment of TD anemia in IPSS low-/int-1-risk patients with MDS with del(5q) with or without additional cytogenetic abnormalities.

A phase III randomized controlled trial compared the activity of lenalidomide (5 mg/d for 28 days, or 10 mg/d for 21 days every 28 days) versus placebo in patients who were RBC-TD (N=205) with lower-risk MDS (IPSS low- and int-1-risks) and del(5q).<sup>111</sup> The primary end point of RBC-TI  $\geq 26$  weeks was achieved in a significantly greater proportion of patients treated with lenalidomide (5 mg or 10 mg) versus placebo (37% vs 57% vs 2%, respectively;  $P \leq .0001$  for both lenalidomide groups vs placebo). Among patients achieving RBC-TI with lenalidomide, onset of erythroid response was rapid, with a median time of 4.2 weeks and 4.3 weeks in the 5-mg and 10-mg lenalidomide groups, respectively.<sup>111</sup> Cytogenetic response rates were significantly higher for the lenalidomide 5-mg (23%;  $P = .0299$ ) and 10-mg (57%;  $P < .0001$ ) groups compared with

placebo (0%); CR rates were observed in 12% and 35% of patients in the lenalidomide 5-mg and 10-mg arms, respectively. Estimated 2-year cumulative risk to AML progression was 17% (95% CI, 8.7–33.3), 12.6% (95% CI, 5.4–27.7), and 16.7% (95% CI, 8.3–32.0) in the lenalidomide 5-mg, 10-mg, and placebo groups, respectively; this increased to 35% (95% CI, 21.4–54.6), 31% (95% CI, 18.1–48.8), and 43.3% (95% CI, 27.6–63.1), respectively, at the estimated 4-year mark. Median OS among the lenalidomide 5-mg, 10-mg, and placebo groups (3.5 vs 4.0 vs 2.9 years, respectively) was not statistically significantly different; however, median survival was significantly longer in patients who achieved RBC-TI (5.7 years; 95% CI, 3.2–no response) compared with nonresponders (2.7 years; 95% CI, 2.0–4.7). The most common grade 3 or 4 adverse events were myelosuppression and deep vein thrombosis. Grade 3 or 4 neutropenia was reported in 77%, 75%, and 16% of patients and thrombocytopenia occurred in 37%, 38%, and 2% of patients in the lenalidomide 5-mg, 10-mg, and placebo arms, respectively. Grade 3 or 4 deep vein thrombosis occurred in 3 patients in the lenalidomide 10-mg arm and 1 patient in the placebo arm.<sup>111</sup>

A recent comparative analysis evaluated outcomes of patients with RBC-TD IPSS low-/int-1-risk MDS with del(5q) receiving lenalidomide (based on data from the 2 aforementioned trials [n=295]) compared with no treatment (based on data from untreated patients in a multicenter registry [n=125]).<sup>112</sup> Untreated patients from the registry had received BSC, 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, and corresponding 5-year rates were 23% and 20%, respectively; median time to AML progression had not been reached in either cohort at time of publication. Lenalidomide was not a significant factor for AML progression in either univariate or multivariate analyses. The 2-year OS probabilities were 90% with lenalidomide and 74% in the untreated cohort; corresponding 5-year OS probabilities were 54% and 40.5%, respectively, with a median OS of 5.2 and 3.8 years ( $P = .755$ ).<sup>112</sup> Based on multivariate analysis using Cox proportional hazard models with left truncation, lenalidomide was associated with a significantly decreased risk of death compared with no treatment



(HR, 0.597; 95% CI, 0.399–0.894;  $P=.012$ ). Other independent factors associated with a decreased risk of death were female sex, higher hemoglobin levels, and higher platelet counts. Conversely, independent factors associated with increased risk of death included older age and greater RBC transfusion burden.<sup>112</sup>

A phase II study evaluated lenalidomide treatment in patients who were RBC-TD ( $N=214$ ) with low- or int-1–risk MDS without del(5q).<sup>113</sup> Results showed that 26% of the non-del(5q) patients (56 of 214) achieved TI after a median of 4.8 weeks; TI continued for a median duration of 41 weeks. Median increase in hemoglobin was 3.2 g/dL (range, 1.0–9.8 g/dL) for those achieving TI. A  $\geq 50\%$  reduction in transfusion requirement was noted in an additional 37 patients (17%), yielding an overall rate of hematologic improvement of 43%. The most common grade 3 or 4 adverse events were neutropenia (30%) and thrombocytopenia (25%).

An international phase III study of 239 patients with IPSS low- or int-1–risk MDS, RBC-TD, and lacking the del(5q) abnormality evaluated the role of lenalidomide treatment.<sup>95</sup> Patients receiving lenalidomide ( $n=160$ ) compared with placebo ( $n = 79$ ) had a higher rate of RBC-TI (26.9% vs 2.5%;  $P<.001$ ) that lasted a median duration of 31 weeks (95% CI, 20.7–59.1 weeks). TI persisting  $>8$  weeks was seen in 27% of patients receiving lenalidomide versus 2.5% of patients in the placebo cohort ( $P<.001$ ). Overall, 90% of patients had disease that responded to therapy within 16 weeks. Transfusion reduction of  $\geq 4$  units of packed RBCs was seen in 22% of lenalidomide-treated patients while no reduction was seen in the placebo group. Incidence of treatment-related mortality was 2.5% in both groups, however, the incidence of myelosuppression was higher in the lenalidomide-treated group. In comparing those receiving lenalidomide versus placebo, the incidence of grade 3 or 4 neutropenia was 61.9% versus 12.7%, respectively, and the rate of thrombocytopenia was 35.6% versus 3.8%, respectively.<sup>95</sup> Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents for patients with non-del(5q) MDS, particularly addressing the characterization of the subgroup who responded to lenalidomide. The NCCN Guidelines Panel recommends lenalidomide be considered for patients with symptomatically anemic non-del(5q) MDS with anemia whose disease did not respond to initial therapy.

A phase III randomized trial in lower-risk, ESA-refractory, non-del(5q) patients compared lenalidomide alone (10 mg/d for 21 days every 28 days) with patients receiving lenalidomide in conjunction with rHu Epo (60,000 U/wk).<sup>114</sup> Erythroid response after 4 treatment cycles was 23.1% (95% CI, 13.5–35.2) versus 39.4% (95% CI, 27.6–52.2;  $P=.044$ ), respectively. Overall, RBC-TI was not statistically different between the groups (13.8% vs 24.2%;  $P=.13$ ). However, in a subgroup analysis that excluded heavily RBC-TD patients (defined as receiving  $>4$  RBC units per 8 weeks) a statistically significant improvement was seen with the addition of rHu Epo (47% vs 16%;  $P=.04$ ), suggesting that lenalidomide may restore sensitivity of MDS erythroid precursors to Epo.<sup>114</sup>

### High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy or HCT.<sup>3,115</sup> Although these approaches have the potential to change the natural history of the disease, there is 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.<sup>116</sup>

A high degree of multidrug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS<sup>117</sup> and is associated with decreased responses and shorter response durations in patients treated with many of the standard chemotherapy induction regimens. Thus, chemotherapeutic agents used to treat “resistant-type” AML and agents that modulate this resistance are now being evaluated for the treatment of patients with advanced MDS. Ongoing clinical trials evaluating multidrug resistance modulators are important, because both positive<sup>118,119</sup> and negative<sup>120</sup> studies have been published.

Allogeneic HCT from an HLA-matched sibling or -matched unrelated donor is the preferred approach for treating select patients with MDS, particularly those with high-risk disease.<sup>121–128</sup> This includes both standard and RIC strategies. AzaC, decitabine, or other therapies may be used as a bridge to transplantation. These agents should not be used to delay HCT in patients who have available donors. In patients whose disease relapses after a prolonged remission following the first transplant, a second

transplant or donor lymphocyte infusion immune-based therapy may be considered. Allogeneic HCT may also be considered in select patients with lower-risk MDS (IPSS int-1, IPSS-R, and WPSS intermediate) with severe cytopenias. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been prospectively established.<sup>129</sup> Comparative clinical trials are needed to address these issues.

## Recommended Treatment Approaches

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

Regarding therapeutic options for lower-risk patients with clinically significant cytopenias or increased bone marrow blasts, the NCCN Guidelines Panel recommends stratifying these patients into several groups. Patients with del(5q) chromosomal abnormalities alone or with one other cytogenetic abnormality and symptomatic anemia should receive lenalidomide. Studies have shown the relative safety of lenalidomide in these patients and improved QOL outcomes in randomized clinical trials.<sup>130,131</sup> The recommended dose of lenalidomide in this setting is 10 mg/d for 21 days every 28 days, or 28 days monthly; response should be assessed 2 to 4 months after treatment initiation. However, lenalidomide should be avoided in those with a clinically significant decrease in neutrophil or platelet counts; in the previously discussed phase III trial with lenalidomide in patients with del(5q), those with low neutrophil counts (<500 cells/mL) or platelet counts (<25,000 cells/mL) were excluded.<sup>111</sup> An alternative option to lenalidomide in patients with del(5q) and symptomatic anemia may include an initial trial of ESAs in cases where sEpo levels are  $\leq 500$  mU/mL. If no response is seen to lenalidomide, these patients should follow treatment options for patients without the del(5q) abnormality.

Patients without the del(5q) abnormality with symptomatic anemia are categorized on the basis of sEpo levels. Levels of  $\leq 500$  mU/mL should be treated with ESAs (rHu Epo or darbepoetin) with or without G-CSF. Patients with normal cytogenetics, <15% RS, and sEpo levels  $\leq 500$  mU/mL may respond to Epo if relatively high doses are administered<sup>132–134</sup>; the Epo dose required is 40,000 to 60,000 subcutane-

ous units 1 to 2 times a week. Darbepoetin alfa should be given subcutaneously at a dose of 150 to 300 mcg every other week. Erythroid responses generally occur within 6 to 8 weeks.<sup>69,135–137</sup> A more prompt response may be obtained with a higher starting dose. The above recommended Epo dose is much higher than the dose needed to treat renal causes of anemia wherein marrow responsiveness would be relatively normal. However, if a response occurs at the higher dose, the recommendation is to attempt a decrease to the lowest effective dose. The literature supports either daily dosing or dosing 2 to 3 times per week.

Iron repletion should 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 due to enhanced survival of red cell precursors.<sup>69,133,135,136</sup> This is particularly evident for patients with  $\geq 15\%$  RS in the marrow (and sEpo level  $\leq 500$  mU/mL), because the very low response rates to Epo or darbepoetin alone in this subgroup are markedly enhanced when combined with G-CSF.<sup>69,136</sup>

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in initially neutropenic patients or to double the neutrophil count in those initially non-neutropenic. For this purpose, an average of 1 to 2 mcg/kg of subcutaneous G-CSF is administered either daily or 1 to 2 times per week<sup>69,133,135,136</sup>; detection of erythroid responses generally occurs within 6 to 8 weeks. If no response occurs within this time frame, treatment should be considered a failure and discontinued. In the case of treatment failure, one should rule out and treat deficient iron stores. Clinical trials or supportive care are also treatment options for these patients. A validated decision model has been developed for predicting erythroid responses to Epo plus G-CSF based on the patient's basal sEpo level and number of previous RBC transfusions.<sup>136,138</sup> This cytokine treatment is not suggested for patients with endogenous sEpo levels  $>500$  mU/mL due to the very low erythroid response rate to these drugs in this patient population.

In patients who do not experience response by 3 months or who have an erythroid response that is followed by a loss of response, lenalidomide may be combined with ESAs, with or without G-CSF. If



no response is seen after 4 months, nonresponders should be considered for IST (ATG ± 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: (1) patients aged ≤60 years with ≤5% marrow blasts; (2) patients who have hypocellular marrows; (3) patients with HLA-DR15 positivity; (4) patients with PNH clone positivity; or (5) patients with STAT3-mutant cytotoxic T-cell clones.

Alternatively, treatment with AzaC, decitabine, or lenalidomide should be considered for patients whose disease is predicted to have a poor probability of responding or whose disease has not responded to IST. A phase II prospective study of patients with MDS who were IPSS low- or int-1-risk with symptomatic anemia whose disease was not expected to respond or who failed to respond to Epo, showed that AzaC was well-tolerated.<sup>139</sup> Although neutropenia and thrombocytopenia were adverse events (47% and 19% of patients, respectively), these toxicities were transient. Other nonhematologic toxicities were mild. AzaC treatment was effective in 60% of patients. Patients with no response to hypomethylating agents or lenalidomide in this setting should be considered for participation in a clinical trial with other relevant agents or for allogeneic HCT (see MDS-5, see page 64).

Anemic patients with sEpo levels >500 mU/mL should be evaluated to determine whether they would be good candidates for IST. Nonresponders to IST would be considered for treatment with AzaC or decitabine, or enrolled on 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. Nonresponders to these treatments could be considered for a clinical trial or allogeneic HCT.

Patients without symptomatic anemia who have other clinically relevant cytopenias (particularly clinically severe thrombocytopenia) or increased bone marrow blasts should be considered for treatment with AzaC, decitabine, IST (if there is a good probability of responding to these agents), or a clinical trial (see MDS-3, page 62). If there is disease progression or no response, allogeneic HCT can be considered in select patients with lower-risk MDS (IPSS int-1, IPSS-R, and WPSS intermediate) with severe cytopenias. Thrombopoietin

(TPO) agonists may also be considered in these patients.<sup>140,141</sup>

Although these guidelines provide a framework in which to treat patients with MDS, careful monitoring for disease progression and consideration of the patient's preferences remain major factors in the decision and timing of the treatment regimen initiated.

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

Treatment for higher-risk patients is dependent on whether they are possible candidates for intensive therapy (eg, allogeneic HCT, intensive chemotherapy) (see MDS-5, page 64). Clinical features relevant for this determination include patient age, PS, absence of major comorbid conditions, psychosocial status, patient preference, and availability of a suitable donor and caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. The patient's personal preference for type of therapy should receive particular consideration. Regardless, supportive care should be provided for all patients.

**Intensive Therapy: Allogeneic HCT:** For patients who are transplant candidates, an HLA-matched sibling or HLA-matched unrelated donor can be considered. 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, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC for HCT is generally the strategy in older individuals.<sup>142</sup>

To aid therapeutic decision-making regarding the timing and selection of HCT for patients with MDS, a study compared outcomes with HLA-matched sibling HCT in patients with MDS aged ≤60 years to data in nontreated patients with MDS from the IMRAW/IPSS database.<sup>143</sup> Using a Markov decision analysis, this investigation indicated that IPSS int-2- and high-risk patients aged ≤60 years had the longest life expectancy if transplanted (from HLA-identical siblings) soon after diagnosis, whereas patients with IPSS low risk had the best outlook if HCT was delayed until MDS progressed. For patients in the int-1-risk group, there was only a slight

gain in life expectancy if HCT was delayed; therefore, decisions should be made on an individual basis (eg, dependent on platelet or neutrophil counts).<sup>143</sup> A retrospective study evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HCT.<sup>144</sup> The data suggest that lower-risk patients (based on WPSS risk score) do very well following allogeneic HCT, with a 5-year OS of 80%. With increasing WPSS scores, the probability of 5-year survival after HCT declined progressively to 65% (intermediate risk), 40% (high risk), and 15% (very high risk).<sup>144</sup>

Based on data regarding RIC for transplantation from 2 studies<sup>145,146</sup> and 2 comprehensive reviews of the field,<sup>147,148</sup> patient age and disease status generally dictated the type of conditioning. Patients >55 or 65 years, particularly if they had >10% marrow myeloblasts, generally received RIC; if the blast count was high, pre-HCT debulking therapy was often given. Younger patients, regardless of marrow blast burden, most frequently received high-dose conditioning. Variations on these approaches would be considered by the individual transplant physician based on patient features and the specific regimen utilized at that center. Some general recommendations have been presented in a review article.<sup>149</sup>

There are limited data regarding the use of allogeneic HCT in older adults with MDS; however, studies suggest that age alone should not be an exclusionary factor for eligibility. In a prospective allogeneic transplant trial using nonmyeloablative conditioning, 372 patients between the ages of 60 and 75 years with hematologic malignancies (AML, MDS, chronic lymphocytic leukemia, lymphoma, and multiple myeloma) were shown to have no association between age and nonrelapse mortality, OS, and PFS.<sup>150</sup> The study supports the use of comorbidities and disease status, rather than age alone, as criteria for determining the eligibility of patients for allogeneic HCT.

Other retrospective studies have also evaluated transplant-related mortality in older patients with MDS receiving RIC for allogeneic transplant<sup>151,152</sup>; no increase in mortality was seen in either study. In a retrospective analysis of 514 patients with de novo MDS (aged 60–70 years), RIC allogeneic transplants were not associated with improved life expectancy for patients with low- or int-1–risk IPSS MDS compared to other nontransplant therapies. However, a potential improvement in life expectancy was seen

in patients with int-2– or high-risk IPSS MDS.<sup>153</sup> It is recognized that there are even fewer data in patients aged  $\geq 75$  years.

**Intensive Chemotherapy:** For patients eligible for intensive therapy but who lack a donor hematopoietic cell source, or for patients in whom the marrow blast count requires reduction, consideration should be given to the use of intensive induction chemotherapy.<sup>154</sup> Although the response rate and durability are lower than for standard AML, this treatment (particularly in clinical trials with novel agents) could be beneficial in some patients. For patients with a potential hematopoietic cell donor who require reduction of tumor burden (ie, to decrease the marrow blast count), achievement of even a partial remission may be sufficient to permit the HCT.

**Nonintensive Therapy:** For higher-risk patients who do not have a suitable transplant donor and who are not candidates for intensive therapy, the use of AzaC or decitabine or a relevant clinical trial should be considered. Data from a phase III randomized trial of AzaC showed significantly higher rates of major platelet improvement with AzaC compared with conventional care (33% vs 14%;  $P=.0003$ ); however, the rates for major neutrophil improvements were similar between the AzaC and control arms (19% vs 18%).<sup>77</sup> AzaC or decitabine should be continued for a least 6 cycles of AzaC or 4 cycles of decitabine to assess response to these agents. For patients whose disease shows clinical benefit, treatment with hypomethylating agents should be continued as maintenance therapy. Results from a phase III trial comparing decitabine with BSC in higher-risk patients ineligible for intensive chemotherapy demonstrated a statistically significant improvement in PFS and reduced AML transformation; improvements in OS and AML-free survivals were also seen, though they did not reach statistical significance.<sup>79</sup>

Two reports from the phase III, international, multicenter, randomized AZA-001 trial have evaluated AzaC compared with conventional care regimens (CCR) in patients with higher-risk MDS. Patients randomized to the CCR group received the most appropriate of the 3 protocol-specified CCR options, including AraC, intensive chemotherapy, or BSC.<sup>155,156</sup> OS was increased with AzaC treatment compared with CCR (HR, 0.58; 95% CI, 0.43–0.77;  $P<.001$ ), and a greater number of patients achieved hematolog-

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ic improvement (49% vs 29%;  $P < .0001$ ).<sup>155</sup> The earlier report from the same trial showed improved OS and tolerability in elderly patients (aged  $\geq 75$  years) with good PS.<sup>156</sup> It should be noted that, to date, no head-to-head trials have compared AzaC with decitabine. Therefore, the panel preferentially recommends AzaC (category 1) versus decitabine based on the data from the phase III trial that showed superior median survival with AzaC compared with BSC.

**Supportive Care Only:** For patients with adverse clinical features or disease progression despite therapy and the absence of reasonable specific antitumor therapy, adequate supportive care should be maintained.

## Summary

These NCCN Guidelines are based on extensive evaluation of the reviewed risk-based data and indicate current approaches for managing patients

with MDS. Three drugs FDA approved for treating specific subtypes of MDS include lenalidomide for patients with del(5q) cytogenetic abnormalities, and AzaC and decitabine for treating higher-risk patients or those with nonresponsive disease. However, as a substantial proportion of subsets of patients with MDS lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents, along with supportive care, remain the hallmark of disease management. Evaluating the role of thrombopoietic cytokines for the management of thrombocytopenia in MDS and determining the effects of therapeutic interventions on QOL are important issues that need investigation.<sup>135,137,138,157,158</sup> Progress toward improving the management of MDS has occurred over the past few years, and more advances are anticipated with these guidelines providing a framework for coordination of comparative clinical trials.

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| Individuals Disclosures for the NCCN Smoking Cessation Panel |   |  |  |                |
|--|---|--|--|----------------|
| Panel Member   | Clinical Research Support/Data Safety Monitoring Board  | Scientific Advisory Boards, Consultant, or Expert Witness  | Promotional Advisory Boards, Consultant, or Speakers Bureau  | Date Completed |
| Aref Al-Kali, MD   | Ambit; ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Celgene Corporation; MedImmune Inc.; Novartis Pharmaceuticals Corporation; and Onconova | None   | None   | 1/29/16        |
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| John M. Bennett, MD*   | Celgene Corporation   | Amgen Inc.   | None   | 1/27/16        |
| Hetty Carraway, MD, MBA                                      | Celgene Corporation   | Amgen Inc.   | Celgene Corporation; and Sigma-Tau Pharmaceuticals, Inc.   | 6/14/16        |
| Carlos M. De Castro, MD                                      | None  | None   | None   | 4/4/16         |
| H. Joachim Deeg, MD  | None  | None   | None   | 7/5/16         |
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| Alison R. Walker, MD   | Gilead  | None   | None   | 12/6/16        |
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| Amer Zeidan, MBBS, MHS                                       | None  | ARIAD Pharmaceuticals, Inc.; and Incyte  | Celgene Corporation; and Pfizer Inc.   | 8/7/16         |

Courtney Smith, PhD, NCCN, as disclosed that she has Equity Interest/Stock Options in Johnson & Johnson, Opko Health Inc, ICON plc. The remaining NCCN Guidelines Staff have no conflicts to disclose.

\*The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict(s):

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