National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes

Version 2.2020 — February 28, 2020

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2020 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 1.2020 include:

MDS-4

- Added: ***Symptomatic anemia with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation) or Ring sideroblasts <15% (or ring sideroblasts <5% without an SF3B1 mutation), See MDS-5.***

MDS-5

- Luspatercept-aamt has been added as an option for treatment of symptomatic anemia in patients with ring-sideroblastic (ring sideroblasts ≥15% or ≥5% with an *SF3B1* mutation) low-/intermediate-risk MDS.
- In pathway for ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an *SF3B1* mutation), serum EPO ≤500 mU/mL, if no response after ESA and G-CSF, removed ~~add lenalidomide~~.

MDS-5A

- Footnote z: Encouraging data are emerging demonstrating effectiveness of luspatercept for treating the anemia of ring sideroblastic lower-risk MDS patients. Fenaux P, Platzbecker U, Mufti GJ, et al. Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept in Transfusion-Dependent Patients with Lower- Risk Myelodysplastic Syndromes with Ring Sideroblasts. New Eng J Medicine 382:140-151, 2020.

Discussion (MS-1)

- The Discussion was updated to reflect the changes in the algorithm.

Updates in Version 1.2020 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 2.2019 include:

MDS-1

- Added *Consider testing bone marrow sample for fibrosis* to the 4th bullet under initial evaluation.

MDS-1A

- Modified footnote a: MDS is also suspected in the presence of peripheral blood dysplasia, blasts, or MDS-associated cytogenetic abnormalities. Cytopenias are defined as values lower than standard lab hematologic levels, being cognizant of age, sex, ethnic, and altitude norms. Greenberg PL, Tuechler H, Schanz J, et al. Blood 2016;128(16):2096-2097. For diagnostic features of primary and therapy-related MDS that require cytopenia(s) and hematopoietic cell dysplasia, see MDS-A (1 of 4).Modified footnote b: If standard cytogenetics (with ≥20 metaphases) cannot be obtained, *chromosome microarray [(CMA), also known as chromosome genomic array testing (CGAT)]* or MDS-related fluorescence in situ hybridization (FISH) *panel should be performed. If karyotype is normal, then consider CMA. Note that CMA will detect not only somatic but also constitutional (germline) changes.*
- Modified footnote d: Bone marrow or peripheral blood cells should be assayed for MDS-associated gene mutations using gene panels that include genes listed on MDS-C. These gene mutations can establish the presence of clonal hematopoiesis, which can help exclude benign causes of cytopenias in cases with non-diagnostic morphology, but do not establish a diagnosis of MDS in the absence of clinical diagnostic criteria. (See Genes Frequently Somatically Mutated in MDS [MDS-C] and Discussion). *As clonal hematopoiesis is a frequent consequence of aging, the finding of mutations in MDS-associated genes should be interpreted with caution and does not in isolation establish a diagnosis of MDS. The majority of patients with WHO-defined MDS have a somatic mutation detected in one of the commonly mutated MDS-associated genes*
- Modified footnote e: *An inherited hematologic malignancy predisposition syndrome may account for cytopenias with or without MDS in some patients, whether presenting to pediatric or adult care centers (eg, GATA2 deficiency syndrome, Shwachman-Diamond syndrome, telomere biology disorders, and others). Functional laboratory studies and constitutional (germline) genetic testing can assist in the diagnosis of these syndromes (see Hereditary Myeloid Malignancy Predisposition Syndromes [MDS-C, pages 3–7 of 7]).* ~~Constitutional mutations predisposing to hematologic malignancy are found in some patients with cytopenias with or without MDS (eg, GATA2 deficiency syndrome, Shwachman-Diamond syndrome, telomere biology disorder, and others). Patients harboring these constitutional (ie, germline) mutations can present to both pediatric and adult care centers. Fanconi anemia is evaluated by chromosome breakage analysis. Serum pancreatic isoamylase (pediatric and adult patients) and serum trypsinogen (pediatric patients) are often low in Shwachman-Diamond syndrome. Telomere biology disorders, such as dyskeratosis congenita, demonstrate shortened telomere lengths, which can be measured by FISH assays using leukocyte samples. Erythrocyte adenosine deaminase is often elevated in Diamond- Blackfan anemia. (See~~

Continued UPDATES

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Updates in Version 2.2020 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 2.2019 include:

~~**Hereditary myeloid malignancy syndromes: See Gene Mutations Associated with Hereditary Myeloid Malignancies [MDS-C, page 5 of 7].)**~~

- **Removed a footnote: Germline mutations of RUNX1 or GATA2 are found in some families with inherited thrombocytopenia and MDS. Fanconi anemia is evaluated by chromosome breakage analysis. Inherited disorders of telomerase complex genes, such as dyskeratosis congenita, demonstrate shortened telomere length, which can be measured by FISH assays using leukocyte samples (See Gene Mutations Associated with Hereditary Myeloid Malignancies [MDS-C, page 5 of 7] and Discussion).**

MDS-2

- **Additional testing, modified the 3rd bullet: *Consider* evaluating patients with chronic myelomonocytic leukemia (CMML) for *PDGFRβ* gene rearrangements at *5q32* ~~5q31-33 translocations~~.**
- **Removed: HLA typing if platelet support is indicated.**
- **Modified footnote m: CMML patients with this abnormality may respond well to tyrosine kinase inhibitors (TKIs) such as imatinib mesylate. Some patients may have *somatic copy-neutral loss of heterozygosity (cnLOH)*, *especially those encompassing JAK2* mutations.**

MDS-4

- **Removed footnote aa because it is included at the end of footnote u: Equine ATG ± cyclosporin A has been used in patients with MDS.**
- **New footnote z: Encouraging data are emerging demonstrating effectiveness of luspatercept for ring sideroblastic lower-risk MDS patients (Fenaux P, Platzbecker U, Mufti G, et al. The MEDALIST Trial: Luspatercept to Treat Anemia in Patients with Lower risk MDS with Ring Sideroblasts. Proc Am Soc Hematology, San Diego, Dec 2018, #1)**
- **New footnote aa: Emerging data are demonstrating effectiveness of ivosidenib and enasidenib for MDS patients with IDH1/2 mutations (Medeiros BC, Fathi AT, DiNardo CD, et al. Isocitrate dehydrogenase mutations in myeloid malignancies. Leukemia 2017;31:272-281.)**

MDS-5

- **Serum EPO ≤500 mU/mL, ring sideroblasts ≥15%: added lenalidomide for consistency with MDS-4.**

MDS-6

- **Modified footnote jj by adding: *Pre-transplant therapy with azacitidine, decitabine, or other modalities for 2–4 cycles is generally recommended in patients with ≥5% marrow blasts attempting to reduce post-transplant relapse by decreasing marrow blasts to <5% as a bridge transplant. This is particularly relevant in patients not receiving high-intensity conditioning. However, these agents should not be used in lieu of early transplantation or to delay transplantation until loss of response or disease progression. (Festuccia M, Deeg HJ, Gooley TA, et al. Minimal identifiable disease and the role of conditioning intensity in hematopoietic cell transplantation for MDS and AML evolving from MDS. Biol Blood Marrow Transplant 2016;22:1227-1233.***
- **Removed footnote kk: ~~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.~~**

MDS-7

- **Modified footnote qq by adding: *Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1* results of a single-blind, randomised, controlled, phase 2 superiority trial. *Lancet Haematol 2017;4(3):e127-e136.***

MDS-A (1 of 4)

- **Footnote b is new: The WHO classification notes that a subgroup of patients have therapy-related MDS, which may include any of the subtypes listed here. These patients tend to have poor-risk cytogenetics and many cases have demonstrated germline mutations in cancer susceptibility genes. See MDS-A (3 of 4).**
- **Footnote d is new: Per the WHO classification for MDS, the threshold for cell line dysplasia is ≥10% for myeloid and erythroid lineages; but for megakaryocytes a threshold of approximately 30% to 40% may provide improved specificity.**

MDS-A (2 of 4)

- **This page is new to the guidelines: Clinical Principles of MDS/MPN Overlap Neoplasms.**

MDS-A (3 of 4)

- **Updated page title.**
- **Added "Treatment" column to the table.**

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Updates in Version 2.2020 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 2.2019 include:

- Removed "Chronic neutrophilic leukemia (CNL) (BCR-ABL negative)" row from the table.
- Added 4 new footnotes:
  - Footnote e: Patients with a t(5;12) translocation associated with the ETV6-PDGFRβ fusion gene may respond to imatinib mesylate.
  - Footnote f: Patients with CMML may have associated systemic mastocytosis (SM-AHN) and *KIT*816V mutation responsive to midostaurin.
  - Footnote g: cnLOH is prevalent in MDS/MPN and BCR-ABL1–negative MPN with a reported frequency between 6% and 41%. CGAT/CMA is currently the only feasible technique available for the identification of cnLOH.
  - Footnote h: The rare aCML patients with CSF3R or JAK2 mutations may respond to ruxolitinib therapy due to their JAK-STAT pathway activation.

MDS-A (4 of 4)
- Updated reference list.

MDS-C (1 of 10)
- Modified introductory paragraph.
- Footnote e is new: There are microdeletions that would be missed by typical genetic sequencing or karyotype that affects some of the same genes that may be indicative of clonal hematopoiesis.

MDS-C (3 of 10)
- Reference 28 is new to this section.

MDS-C (4 of 10) and (5 of 10)
- Changed the title from "Gene Mutations Associated With Hereditary Myeloid Malignancies" to "Hereditary Myeloid Malignancy Predisposition Syndromes."
- These pages have been extensively revised.

MDS-C (7 of 10)
- Footnote b is new: Additional laboratory testing: RUNX1 mutant platelets may show platelet ultrastructure changes such as abnormal alpha granules and a deficiency of delta granules. Platelet aggregometry and platelet function analyzer testing may show platelet aggregation and secretion defects, such as decreased aggregation to epinephrine and collagen (so called aspirin-like defect).

MDS-C (8 of 10)
- Added 4 new footnotes:
  - Footnote c: Additional laboratory testing: Erythrocyte adenosine deaminase is often elevated.
  - Footnote e: Additional laboratory testing: Increased chromosomal breakage following exposure to a DNA cross-linking agent such as mitomycin C (MMC) or diepoxybutane (DEB). Testing is typically performed on peripheral blood lymphocytes. A subset of patients may undergo genetic somatic reversion to wild-type in peripheral blood lymphocytes. This reversion confers a growth advantage over the non-reverted Fanconi anemia lymphocytes. In such cases, testing may appear normal, or reveal only a small subpopulation of cells with increased chromosomal breakage. If there is a strong clinical suspicion for Fanconi anemia despite a negative blood test, chromosomal breakage may be tested on fibroblasts obtained from a skin biopsy.
  - Footnote f: Additional laboratory testing: Serum pancreatic isoamylase (pediatric and adult patients) and serum trypsinogen (pediatric patients) are often low.
  - Footnote g: Additional laboratory testing: Shortened telomere lengths measured by FISH assays on peripheral blood leukocyte subsets.

MDS-C (9 of 10)
- Added the following to Hematologic Findings/Myeloid Malignancy for Other rare DNA repair syndromes: MB*D4: early-onset AML with a high somatic mutation burden characterized by CG>TG changes including biallelic CG>TG mutations in DNMT3A.*

MDS-C (10 of 10)
- Reference 24 is new to this section.

INITIAL EVALUATION

Cytopenia(s), suspect myelodysplasia[a]

- H&P
- Complete blood count (CBC), platelets, differential, reticulocyte count
- Examination of peripheral smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping.[b] Consider testing bone marrow sample for fibrosis.
- Serum erythropoietin (prior to red blood cell [RBC] transfusion)
- RBC folate, serum B12[c]
- Serum ferritin, iron, total iron-binding capacity (TIBC)
- Documentation of transfusion history
- Thyroid-stimulating hormone (TSH)
- Lactate dehydrogenase (LDH)
- Consider genetic testing for somatic mutations (ie, acquired mutations) in genes associated with MDS[d]
- Consider additional molecular and genetic testing for hereditary hematologic malignancy predisposition in a subset of patients, particularly in younger patients[e]
- HIV testing if clinically indicated
- Consider evaluation of copper deficiency in patients with GI malabsorption, severe malnutrition, gastric bypass surgery, or patients on zinc supplementation
- Consider distinction from congenital sideroblastic anemia (CSA)[f]

Diagnosis of MDS established based on morphologic, cytogenetic, and clinical criteria[g,h] → See Additional Testing and Classification (MDS-2)

Diagnostic criteria for MDS not met but cytopenias present → See Spectrum of Indolent Myeloid Hematopoietic Disorders (MDS-D)

See footnotes on MDS-1A

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

FOOTNOTES FOR INITIAL EVALUATION OF MDS

[a] MDS is also suspected in the presence of peripheral blood dysplasia, blasts, or MDS-associated cytogenetic abnormalities. Cytopenias are defined as values lower than standard lab hematologic levels, being cognizant of age, sex, ethnic, and altitude norms. Greenberg PL, Tuechler H, Schanz J, et al. Blood 2016;128(16):2096-2097. For diagnostic features of primary and therapy-related MDS that require cytopenia(s) and hematopoietic cell dysplasia, see MDS-A (1 of 4).

[b] If standard cytogenetics (with ≥20 metaphases) cannot be obtained, chromosome microarray [(CMA), also known as chromosome genomic array testing (CGAT)] or MDS-related fluorescence in situ hybridization (FISH) panel should be performed. If karyotype is normal, then consider CMA. Note that CMA will detect not only somatic but also constitutional (germline) changes.

[c] RBC folate is a more representative measure of folate stores and is the preferred test to serum folate. Serum methylmalonic acid testing is an accurate way to assess B12 status.

[d] Bone marrow or peripheral blood cells should be assayed for MDS-associated gene mutations using gene panels that include genes listed on MDS-C. These gene mutations can establish the presence of clonal hematopoiesis, which can help exclude benign causes of cytopenias in cases with non-diagnostic morphology, but do not establish a diagnosis of MDS in the absence of clinical diagnostic criteria (See Genes Frequently Somatically Mutated in MDS [MDS-C] and Discussion). As clonal hematopoiesis is a frequent consequence of aging, the finding of mutations in MDS-associated genes should be interpreted with caution and does not in isolation establish a diagnosis of MDS. The majority of patients with WHO-defined MDS have a somatic mutation detected in one of the commonly mutated MDS-associated genes.

[e] An inherited hematologic malignancy predisposition syndrome may account for cytopenias with or without MDS in some patients, whether presenting to pediatric or adult care centers (eg, GATA2 deficiency syndrome, Shwachman-Diamond syndrome, telomere biology disorders, and others). Functional laboratory studies and constitutional (germline) genetic testing can assist in the diagnosis of these syndromes (See Hereditary Myeloid Malignancy Predisposition Syndromes [MDS-C, pages 3–7 of 7]).

[f] In younger patients, CSA is due to disordered mitochondrial heme synthesis, often with distinctive mutational and clinical features. Some of these patients will respond to pyridoxine or thiamine. CSA is not MDS (Fleming MD, ASH Education Book vol. 2011(1),525-531). CSA may appear late due to lyonization in X-linked sideroblastic anemia (not limited to younger patients).

[g] Confirm diagnosis of MDS according to WHO/NCCN criteria for classification (See MDS-A) with application of IPSS or IPSS-R (See MDS-D). The percentage of marrow myeloblasts based on morphologic assessment (aspirate smears preferred) should be reported. Flow cytometric estimation of blast percentage should not be used as a substitute for morphology in this context. In expert hands, expanded flow cytometry may be a useful adjunct for diagnosis in difficult cases (See Initial Evaluation in the Discussion).

[h] Patients with karyotypes t(8;21), t(15;17), or inv(16) are considered to have AML even if the marrow blast count is less than 20% (See NCCN Guidelines for Acute Myeloid Leukemia).

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ADDITIONAL TESTING

- **Consider flow cytometry (FCM) for MDS as a diagnostic aid[i] and consider FCM to evaluate for large granular lymphocyte (LGL)[j] and paroxysmal nocturnal hemoglobinuria (PNH) clone[k]**
- **Perform human leukocyte antigen (HLA) typing if hematopoietic stem cell transplant (HCT) candidate[l]**
- **Consider evaluating patients with chronic myelomonocytic leukemia (CMML) for *PDGFRβ* gene rearrangements at 5q32[m]**
- **Cytomegalovirus (CMV)-safe (CMV-negative or leukopheresed) blood products are recommended whenever possible for CMV-negative transplant candidates**

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

CLASSIFICATION

MDS
See Classification Systems (MDS-A [1 of 4]) and (MDS-B)

MDS/MPN overlap syndromes
See Principles, Classification System and Management (MDS-A [2 of 4])

Acute myeloid leukemia (AML)
(See NCCN Guidelines for Acute Myeloid Leukemia)

If negative for MDS/AML
See MDS-D[n]

[i] See Recommendations for Flow Cytometry (MDS-E) and Discussion.

[j] Marrow or peripheral blood cell FCM may be assayed, and T-cell gene rearrangement studies may be conducted if LGLs are detected in the peripheral blood. *STAT3* mutations are commonly found in T-LGL disease. Morgan E, Lee M, DeAngelo D, et al. Systematic *STAT3* mutation testing identifies patients with unsuspected T-cell large granular lymphocytic leukemia. ASH Annual Meeting Abstracts 2016; Session 624. Chan WC, Foucar K, Morice WG, Catovsky D. T-cell large granular lymphocytic leukemia. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC 2008:272-273.

[k] FCM analysis of granulocytes and monocytes from blood with FLAER (fluorescent aerolysin) and at least one GPI-anchored protein to assess the presence of a PNH clone. Dezern AE and Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom 2018 Jan; 94(1):16-22.

[l] Donors should be evaluated by high-resolution allele level typing for HLA-A, -B, -C, -DR, and -DQ. All full siblings should be evaluated for HLA match prior to unrelated donor match.

[m] CMML patients with this abnormality may respond well to tyrosine kinase inhibitors (TKIs) such as imatinib mesylate. Some patients may have somatic copy-neutral loss of heterozygosity (cnLOH), especially those encompassing *JAK2* mutations.

[n] Mutation panel may be useful in this context to validate indolent myeloid hematopoietic disorders.

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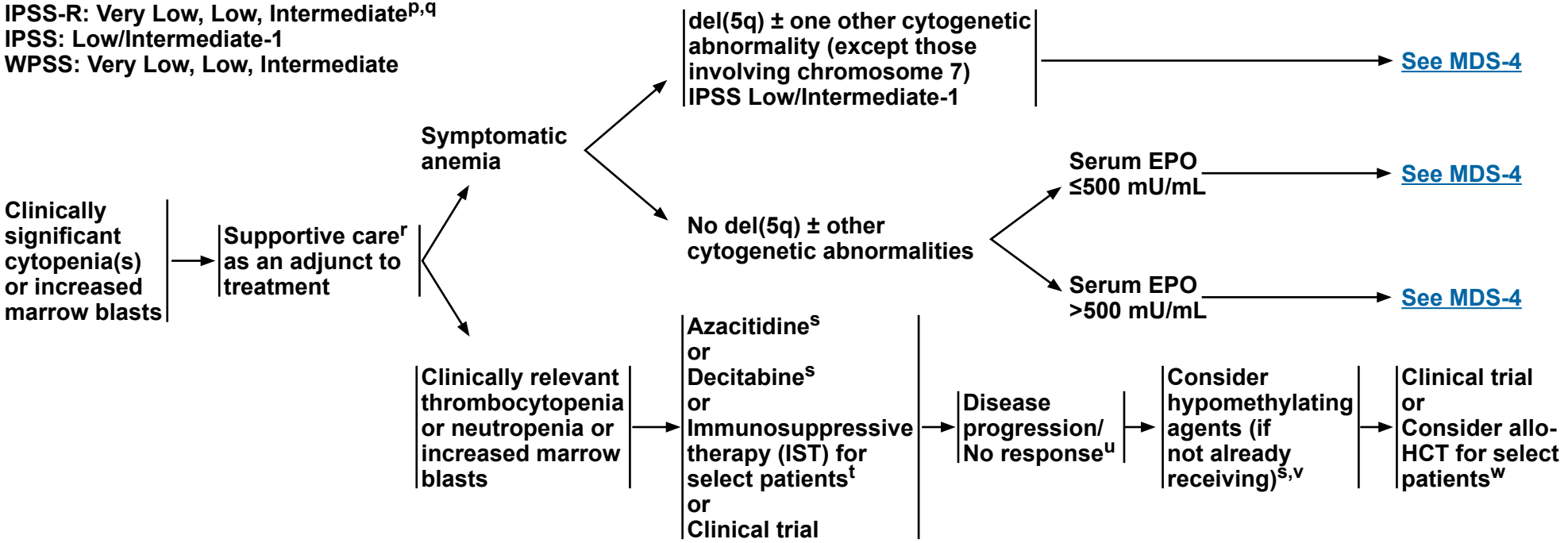
PROGNOSTIC CATEGORY[o]

IPSS-R: Very Low, Low, Intermediate[p,q]
IPSS: Low/Intermediate-1
WPSS: Very Low, Low, Intermediate

TREATMENT



[o] Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).

[p] 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 lower risk if their score is ≤3.5 vs. higher risk if score is >3.5. Pfeilstöcker M, Tuechler H, Sanz G, et al. Blood 2016;128(7):902-910.

[q] If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.

[r] See Supportive Care (MDS-7).

[s] Some studies have demonstrated clinical benefit with low doses of azacitidine or decitabine for lower-risk MDS. Jabbour E, Short NJ, Montalban-Bravo G, et al. Blood 2017;130(13):1514-1522.

[t] Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG ± cyclosporin A.

[u] Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.

[v] For patients with severe or refractory thrombocytopenia, eltrombopag or romiplostim can be considered. Oliva EN, Alati C, Santini V, et al. Lancet Hematol 2017;4(3):e127-e136. Fenaux P, Muus P, Kantarjian H, et al. Br J Haematol 2017;178(6):906-913. See Discussion.

[w] IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. (Matched sibling, unrelated donor, or alternative [haploidentical or cord blood when appropriate] donor, including standard and reduced-intensity preparative approaches, may be considered).

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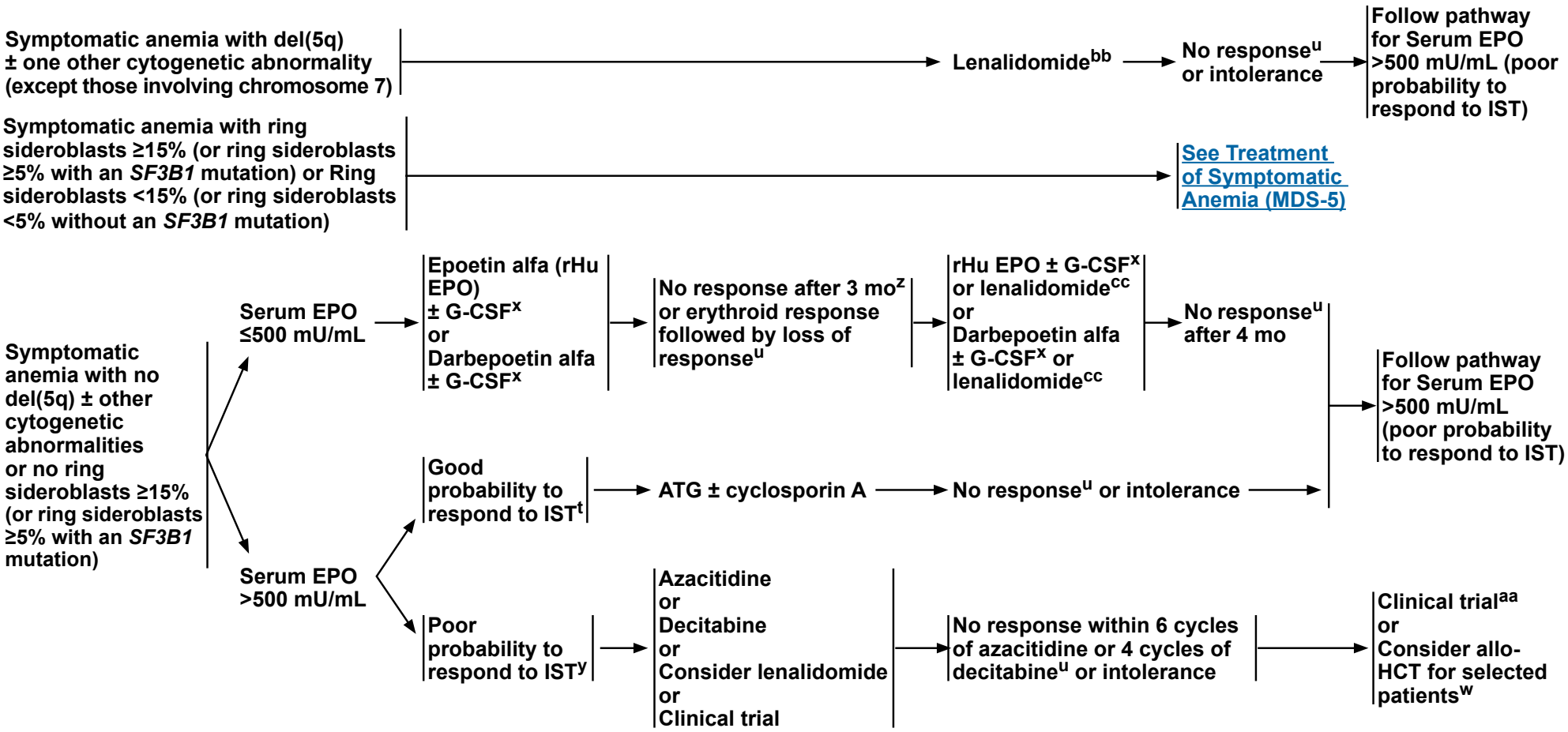
PROGNOSTIC CATEGORY[o]
IPSS-R: Very Low, Low, Intermediate[p,q]
IPSS: Low/Intermediate-1
WPSS: Very Low, Low, Intermediate

TREATMENT



See footnotes on page MDS-5A.

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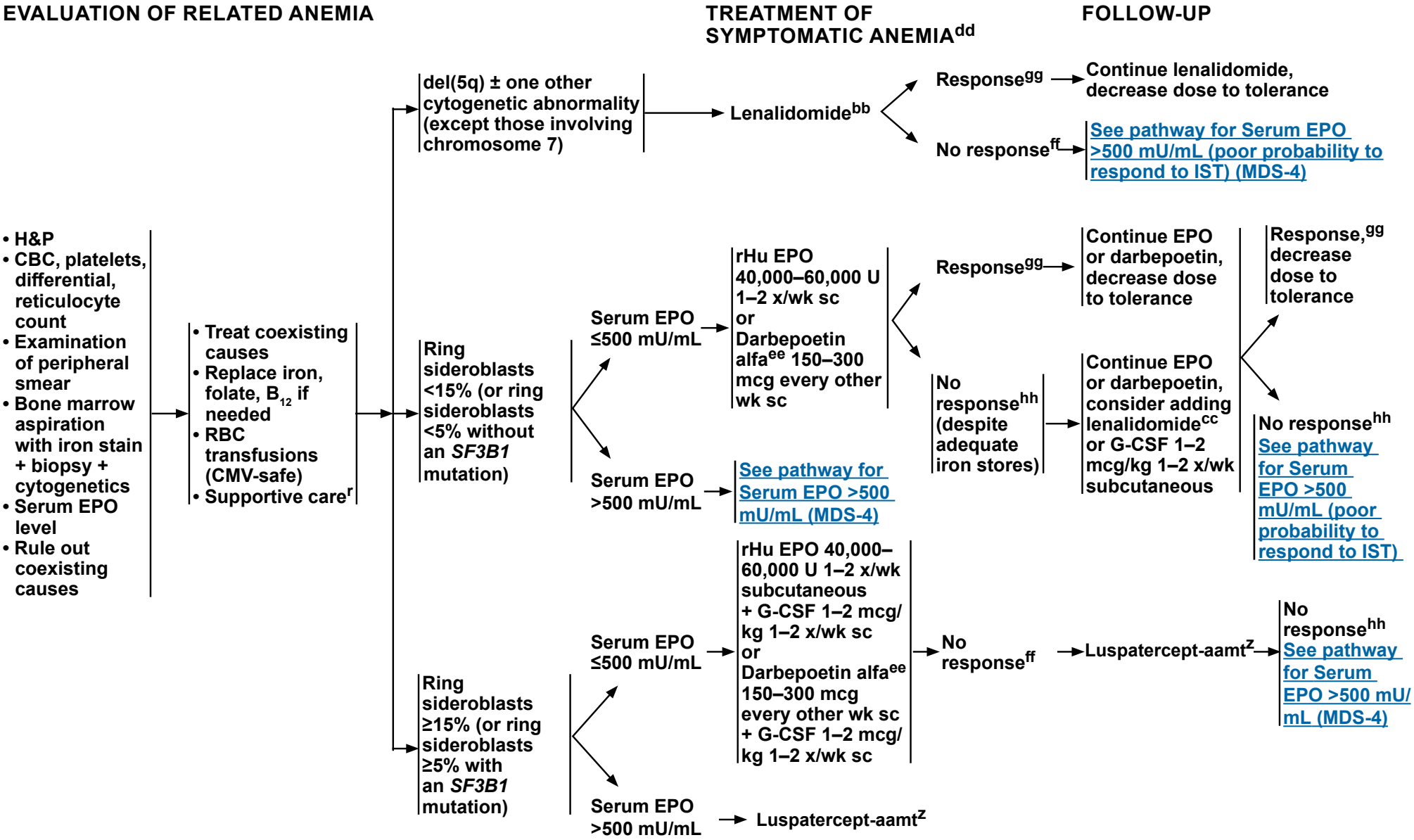

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FOOTNOTES

[o] Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).

[p] 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 lower risk if their score is ≤3.5 vs. higher risk if score is >3.5. Pfeilstöcker M, Tuechler H, Sanz G, et al. Blood 2016;128(7):902-910.

[q] If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.

[r] See Supportive Care (MDS-7).

[t] Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG ± cyclosporin A.

[u] Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.

[w] IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. (Matched sibling, unrelated donor, or alternative [haploidentical or cord blood when appropriate] donor, including standard and reduced-intensity preparative approaches, may be considered).

[x] See dosing of hematopoietic cytokines (MDS-5).

[y] Patients lack features listed in footnote t.

[z] Encouraging data are emerging demonstrating effectiveness of luspatercept for treating the anemia of ring sideroblastic lower-risk MDS patients. Fenaux P, Platzbecker U, Mufti GJ, et al. Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept in Transfusion-Dependent Patients with Lower- Risk Myelodysplastic Syndromes with Ring Sideroblasts. New Eng J Medicine 382:140-151, 2020.

[aa] Emerging data are demonstrating effectiveness of ivosidenib and enasidenib for MDS patients with IDH1/2 mutations (Medeiros BC, Fathi AT, DiNardo CD, et al. Isocitrate dehydrogenase mutations in myeloid malignancies. Leukemia 2017;31:272-281).

[bb] 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 2–4 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. Use caution for patients with low platelet count; consider modifying lenalidomide dose. Sekeres MA, Maciejewski JP, Giagounidis AAN, et al. J Clin Oncol 2008;26(36):5943-5949. Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category (see MDS-6).

[cc] Lenalidomide 10 mg daily if ANC >0.5, platelets >50,000; Toma A, Kosmider O, Chevret S, et al. Leukemia 2016;30(4):897-905.

[dd] Refers predominantly to lower-risk IPSS-R and IPSS patients.

[ee] At some institutions, darbepoetin alfa has been administered using doses up to 500 mcg every other week.

[ff] Lack of 1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 3 to 4 months of treatment.

[gg] Target hemoglobin range 10 to 12 g/dL; not to exceed 12 g/dL.

[hh] Lack of 1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 6 to 8 weeks of treatment.

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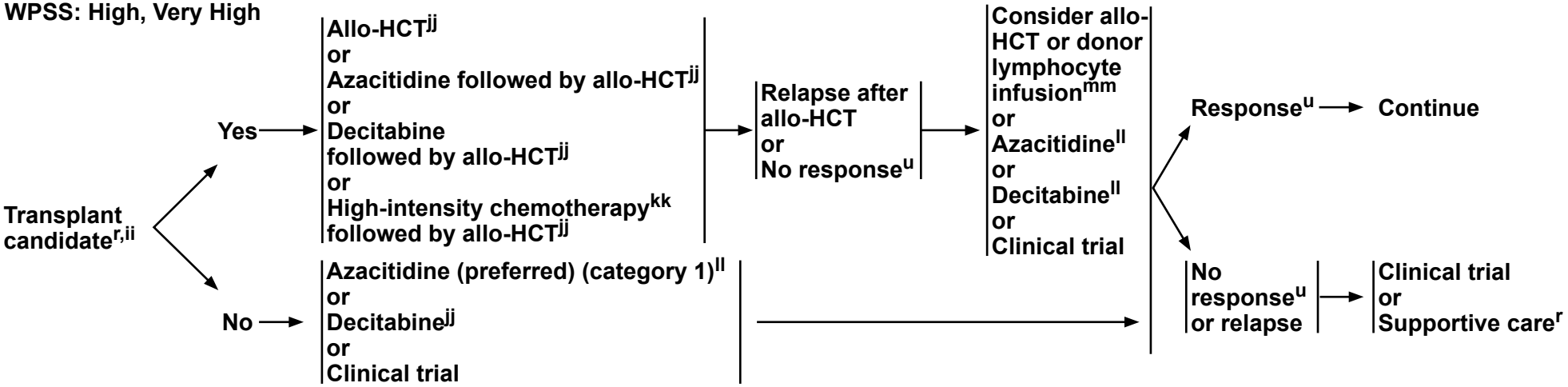
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PROGNOSTIC CATEGORY[o]

IPSS-R: Intermediate,[p] High, Very High
IPSS: Intermediate-2, High
WPSS: High, Very High

TREATMENT



[o] Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).

[p] 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 lower risk if their score is ≤3.5 vs. higher risk if score is >3.5. Pfeilstöcker M, Tuechler H, Sanz G, et al. Blood 2016;128(7):902-910.

[r] See Supportive Care (MDS-7).

[u] Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.

[ii] 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.

[jj] Allogeneic hematopoietic stem cell transplant from most suitable donor (matched sibling, unrelated, or alternative [haploidentical or cord blood] donor). Pre-transplant therapy with azacitidine, decitabine, or other modalities for 2–4 cycles is generally recommended in patients with ≥5% marrow blasts attempting to reduce post-transplant relapse by decreasing marrow blasts to <5% as a bridge transplant. This is particularly relevant in patients not receiving high-intensity conditioning. However, these agents should not be used in lieu of early transplantation or to delay transplantation until loss of response or disease progression (Festuccia M, Deeg HJ, Gooley TA, et al. Minimal identifiable disease and the role of conditioning intensity in hematopoietic cell transplantation for MDS and AML evolving from MDS. Biol Blood Marrow Transplant 2016;22:1227-1233).

[kk] 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.

[ll] 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 4–6 cycles to assess response to these agents. In patients who have clinical benefit, continue treatment with the hypomethylating agent as maintenance therapy.

[mm] Consider second transplant or donor lymphocyte infusion immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.

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SUPPORTIVE CARE[nn]

- Clinical monitoring
- Psychosocial support (See NCCN Guidelines for Survivorship)
- Quality-of-life assessment
- Transfusions[oo]:
  - RBC transfusions (CMV-safe) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mcL. Irradiated products are suggested for transplant candidates.
- Antibiotics are recommended for bacterial infections, but no routine prophylaxis is recommended except in patients with recurrent infections.
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.
- Iron chelation:
  - If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for patients who have lower-risk MDS or who are potential transplant candidates (LOW/INT-1). For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL[pp] (See Discussion). Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox or deferoxamine.
- Cytokines:
  - EPO: See Anemia Pathway (MDS-5)
    - ◊ EPO refers to the following agents: epoetin alfa and epoetin alfa-epbx.
  - G-CSF:
    - ◊ G-CSF refers to the following agents: filgrastim, filgrastim-sndz, and tbo-filgrastim. Not recommended for routine infection prophylaxis.
    - ◊ Consider use in neutropenic patients with recurrent or resistant infections.
    - ◊ Combine with EPO for anemia when indicated. See Anemia Pathway (MDS-5).
    - ◊ Platelet count should be monitored.
- Clinically significant thrombocytopenia
  - In patients with lower-risk MDS who have severe or life-threatening thrombocytopenia, consider treatment with a thrombopoietin-receptor agonist.[qq]

[nn] See NCCN Guidelines for Supportive Care.

[oo] Avoid transfusions for arbitrary hemoglobin thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke. In situations where transfusions are necessary, transfuse the minimum units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin level. Hicks L, Bering H, Carson K, et al. The ASH Choosing Wisely campaign: five hematologic tests and treatments to question. Blood 2013;122:3879-3883.

[pp] Clinical trials in MDS are currently ongoing with oral chelating agents.

[qq] Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. Cancer 2014;120:1838-1846. Platzbecker U, Wong RS, Verma A, et al. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: a multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. Lancet Haematol 2015;2:e417-e426. Oliva EN, Alati C, Santini V, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. Lancet Haematol 2017;4(3):e127-e136.

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2016 WHO CLASSIFICATION OF MDS[a,b,1]

Subtype	Blood	Bone Marrow
MDS with single lineage dysplasia (MDS-SLD)[c]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts[d,2]
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if *SF3B1* mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, <15% ring sideroblasts (or <5% ring sideroblasts if *SF3B1* mutation present), <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occasions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts ± one other abnormality except -7/del(7q)
Refractory cytopenia of childhood (Provisional WHO category)	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts

[a] The 2016 WHO classification for AML includes entity "AML with myelodysplasia-related changes" that encompasses patients who were previously categorized in the FAB classification of MDS as RAEB-T. AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML that arises without antecedent hematologic disorder and may have a more indolent course. Some clinical trials designed for high-grade MDS may allow enrollment of patients with AML-MDS. Patients with 20% to 29% marrow blasts AND a stable clinical course for at least 2 months may be considered as either MDS or AML and may be more akin to MDS (prior FAB RAEB-T) than to AML. Such patients may be considered for treatment as either MDS or AML. Individuals with *FLT3* and *NPM1* mutations are more likely to have AML than MDS. See Discussion.

[b] The WHO classification notes that a subgroup of patients have therapy-related MDS, which may include any of the subtypes listed here. These patients tend to have poor-risk cytogenetics and many cases have demonstrated germline mutations in cancer susceptibility genes. See MDS-A (3 of 4).

[c] This category encompasses refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS, unclassified.

[d] Per the WHO classification for MDS, the threshold for cell line dysplasia is ≥10% for myeloid and erythroid lineages; but for megakaryocytes a threshold of approximately 30% to 40% may provide improved specificity.

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References on page MDS-A (4 of 4)

CLINICAL PRINCIPLES OF MDS/MPN OVERLAP NEOPLASMS

- **Clinical, morphologic and mutational diagnostic features and treatment approaches for the various nosologic MDS/MPN subtypes are shown in the Table on MDS-A (3 of 4).**
- **Prognostic classification systems have been developed for CMML patients with features similar to those for MDS. Proliferative CMML (WBC >12,000/mm3) has a worse prognosis than the differentiative form.**
- **Mutational findings are listed in the Table on MDS-A (3 of 4) with a major consistency in CMML, indicating *ASXL1* as being an adverse prognostic feature.**
- **Therapeutic approaches in CMML have generally been the model for treating the other MDS/MPN, with hypomethylating agent treatment for intermediate- and higher-risk patients, and using these agents as a bridge to allogeneic HCT for those patients deemed to be transplant-eligible.**
- **The trajectory of disease progression may differ in the disparate clinical entities based on their underlying molecular features. Thus, expectant clinical monitoring is needed to assess potential change in patient's clinical status, needing altered management of the disorder.**
- **Transplant eligibility principles include patients having fit performance status, their age, and having a donor.**
- **Treatment response criteria for CMML have been developed by an international consortium of investigators.**
- **Patients with CMML may have systemic mastocytosis with associated hematologic neoplasm (SM-AHN) with a *KIT*816V mutation in the neoplastic monocytes and mast cells. These patients may have marked hepatosplenomegaly, mast cell activation symptoms, or cutaneous lesions with elevated serum tryptase levels. The mastocytosis may be responsive to midostaurin treatment. Each disease should be treated independently depending on its severity, being aware of drug-drug interactions.**

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References on page MDS-A (4 of 4)

MYELODYSPLASTIC/MYELOPROLIFERATIVE OVERLAP NEOPLASMS (MDS/MPN), 2017 WHO CLASSIFICATION AND MANAGEMENT[1,2]

Subtype	Blood	Bone Marrow	Frequent Mutations	Treatment
Chronic myelomonocytic leukemia (CMML)-0	>1x10^9/L monocytes, <2% blasts ≥10% monocytes	Dysplasia in ≥1 hematopoietic line, <5% blasts	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[3,4]	Observation[e,f,11-21]
CMML-1	>1x10^9/L monocytes, 2%–4% blasts ≥10% monocytes	Dysplasia in ≥1 hematopoietic line, 5%–9% blasts	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[3,4]	Consider HMA[e,f,11-21]
CMML-2	>1x10^9/L monocytes, 5%–19% blasts or Auer rods ≥10% monocytes	Dysplasia in ≥1 hematopoietic line, 10%–19% blasts or Auer rods	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[3,4]	HMA ± ruxolitinib and/or allogeneic HSCT[e,f,11-24]
Atypical chronic myeloid leukemia (aCML), *BCR-ABL* negative[g]	WBC >13x10^9/L, neutrophil precursors ≥10%, <20% blasts, dysgranulopoiesis	Hypercellular, <20% blasts	*SETBP1, ETNK1*[5]	Consider HMA and/or ruxolitinib and/or allogeneic HSCT[h,25,26]
Juvenile myelomonocytic leukemia (JMML)	>1x10^9/L monocytes, <20% blasts ≥10% monocytes, increased HbF	>1x10^9/L monocytes <20% blasts Ph negative GM-CSF hypersensitive	*PTPN11, NF1, N/KRAS, CBL, SETBP1, JAK3*[6,7]	Allogeneic HSCT
MDS/MPN, unclassifiable ("Overlap syndrome")	Dysplasia + myeloproliferative features, No prior MDS or MPN	Dysplasia + myeloproliferative features	*TET2, NRAS, RUNX1, CBL, SETBP1, ASXL1*[8]	Consider HMA and/or allogeneic HSCT
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)	Dysplasia + myeloproliferative features, platelets ≥450 x10^9/L, ≥15% ring sideroblasts	Dysplasia + myeloproliferative features	*SF3B1, JAK2*[9,10] *MPL, CALR*	Consider HMA and/or lenalidomide[27]

[e] Patients with a t(5;12) translocation associated with the *ETV6-PDGFRβ* fusion gene may respond to imatinib mesylate.
[f] Patients with CMML may have associated systemic mastocytosis (SM-AHN) and *KIT*816V mutation responsive to midostaurin.
[g] cnLOH is prevalent in MDS/MPN and *BCR-ABL1*–negative MPN with a reported frequency between 6% and 41%. CGAT/CMA is currently the only feasible technique available for the identification of cnLOH.
[h] The rare aCML patients with *CSF3R* or *JAK2* mutations may respond to ruxolitinib therapy due to their JAK-STAT pathway activation.

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References on page MDS-A (4 of 4)

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INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)[a,1]

Survival and AML Evolution					
	Score Value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)[b]	<5	5-10	—	11-20	21-30
Karyotype[c]	Good	Intermediate	Poor	—	—
Cytopenia[d]	0/1	2/3	—	—	—

IPSS Risk Category (% IPSS pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥2.5	0.4	0.2

For IPSS: Low/Intermediate-1, see MDS-3 and MDS-4
For IPSS: Intermediate-2/High, see MDS-6

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R[2])

	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic[e]	Very good	—	Good	—		Poor	Very
Marrow blasts (%)	≤2	—	>2-<5	—	5-10	>10	—
Hemoglobin	≥10	—	8-<10	<8	—	—	—
Platelets	≥100	50-<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

IPSS-R Risk Category (% IPSS-R pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT[3] (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7

For IPSS-R: Very Low/Low/Intermediate, see MDS-3 and MDS-4
For IPSS-R: Intermediate/High/Very High, see MDS-6

[a]IPSS should be used for initial prognostic and planning purposes. WPSS permits dynamic estimation of prognosis at multiple time points during the course of MDS.
[b]Patients with 20%–29% blasts may be considered to have MDS (FAB) or AML (WHO).
[c]Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. [This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML and not MDS.]
[d]Cytopenias: neutrophil count <1,800/mcL, platelets <100,000/mcL, Hb <10 g/dL.
[e]Cytogenetic risks: Very good = -Y, del(11q); Good = normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor = complex: >3 abnormalities.

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Continued

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WHO-BASED PROGNOSTIC SCORING SYSTEM (WPSS)[3,4]

Variable	Variable Scores			
	0	1	2	3
WHO category	RCUD, RARS, MDS with isolated del(5q)	RCMD	RAEB-1	RAEB-2
Karyotype[f]	Good	Intermediate	Poor	—
Severe anemia (hemoglobin <9 g/dL in males or <8 g/dL in females)	Absent	Present	—	—

WPSS Risk	Sum of Individual Variable Scores	Median Survival (y) from Diagnosis	Median Time (y) to AML Progression from Diagnosis
Very Low	0	11.6	NR
Low	1	9.3	14.7
Intermediate	2	5.7	7.8
High	3–4	1.8	1.8
Very High	5–6	1.1	1.0

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

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GENES FREQUENTLY SOMATICALLY MUTATED IN MDS[a,e]

This table lists gene mutations likely to be somatic (acquired, not congenital) and disease-related and therefore presumptive evidence of MDS. Other mutations (not listed in the table below) in these genes can occur in MDS. Additionally, some of these mutations can occur in the context of aging and do not in isolation establish a diagnosis of MDS, nor does the absence of mutations in these genes exclude a diagnosis of MDS in the correct clinical context.

Mutated Gene[b]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[c]	Overall Incidence	Clinical Significance
TET2	Nonsense or Frameshift or Splice Site Missense: any in codons 1134–1444 or 1842–1921	20%–25%	Associated with normal karyotypes. More frequent in CMML (40%–60%). Common in clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS).
DNMT3A	Nonsense or Frameshift or Splice Site Missense in codons G543, R635, S741, R736, R739, S770, M880, R882, W893, P904, A910	12%–18%	More frequent occurrence in AML, particularly R882 mutations. Common in CHIP and CCUS.
ASXL1	Nonsense or Frameshift	15%–25%	Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (40%–50%). Common in CHIP and CCUS.
EZH2	Nonsense or Frameshift	5%–10%	Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).
SF3B1	Missense: 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.
SRSF2	Missense or In-Frame Deletion: involving codon P95	10%–15%	More frequent in CMML (40%) and associated with a poor prognosis.
U2AF1	Missense: S34, Q157	8%–12%	Associated with a poor prognosis.
ZRSR2	Nonsense or Frameshift	5%–10%	Associated with a poor prognosis.
RUNX1[d]	Nonsense or Frameshift	10%–15%	Independently associated with a poor prognosis in MDS.
TP53[d]	Nonsense or Frameshift or Splice Site Missense: 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.
STAG2	Nonsense or Frameshift or Splice Site	5%–10%	Associated with a poor prognosis.
NRAS[d]	Missense: 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%).
CBL[d]	Missense: any in codons 366–420	<5%	More frequent in CMML (10%–20%) and JMML (15%).
NF1[d]	Nonsense or Frameshift or Splice Site	<5%	More frequent in CMML (5%–10%) and in JMML (30%) where it is often germline.

[a] 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. 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.

[b] 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.

[c] 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.

[d] Constitutional (germline) mutations in these genes can occur and cause a hematopoietic phenotype. Mutations identified in testing blood or marrow for somatic mutations associated with MDS can identify constitutional (germline) mutations. Distinguishing constitutional from somatic mutations often requires sequencing DNA from a non-hematopoietic tissue in MDS.

[e] There are microdeletions that would be missed by typical genetic sequencing or karyotype that affects some of the same genes that may be indicative of clonal hematopoiesis.

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References on MDS-C (3 of 10)

GENES FREQUENTLY SOMATICALLY MUTATED IN MDS[a]

This table lists gene mutations likely to be somatic (acquired, not congenital) and disease-related and therefore presumptive evidence of MDS. Other mutations (not listed in the table below) in these genes can occur in MDS. Additionally, some of these mutations can occur in the context of aging and do not in isolation establish a diagnosis of MDS, nor does the absence of mutations in these genes exclude a diagnosis of MDS in the correct clinical context.

Mutated Gene[b]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[c]	Overall Incidence	Clinical Significance
JAK2	Missense: V617F	<5%	More frequent in MDS/MPN-RS-T (50%); can occur in conjunction with *SF3B1*.
CALR	Frameshift: after codon 352	<5%	Observed in MDS/MPN-RS&T where it can occur in conjunction with *SF3B1* mutations.
MPL	Missense: W515L/K	<5%	Observed in MDS/MPN-RS&T where it can occur in conjunction with *SF3B1* mutations.
ETV6[d]	Nonsense or Frameshift	<5%	Independently associated with a poor prognosis.
GATA2[d]	Nonsense or Frameshift or Splice Site Missense: in codons 349–398		Associated with a poor prognosis.
DDX41[d]	Nonsense or Frameshift or Splice Site Missense: in codon R525H		Constitutional (germline) mutations in this gene can occur.
IDH1	Missense: R132	<5%	More frequent in AML.
IDH2	Missense: R140Q, R172	<5%	More frequent in AML. Associated with a poor prognosis.
SETBP1	Missense: E858, T864, I865, D868, S869, G870	<5%	Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).
PHF6	Nonsense or Frameshift or Splice Site	<5%	More frequent in cases with excess blasts, but no association with survival.
BCOR	Nonsense or Frameshift or Splice Site	<5%	Associated with a poor prognosis. More frequent in CMML (5%–10%).
FLT3	Internal Tandem Duplication or Missense: in codon D835		Associated with a poor prognosis.
WT1	Nonsense or Frameshift or Splice Site		Associated with a poor prognosis.
NPM1	Frameshift: W288fs*12		Associated with a poor prognosis.
STAT3	Missense: any codons 584–674	<5%	Occurs in large granular lymphocyte leukemia (LGL) associated with MDS; associated with immune bone marrow failure.
PPM1D	Nonsense or Frameshift	~5%	Associated with therapy-related MDS, but not associated with adverse prognosis independent of *TP53*. Common in CHIP and CCUS.

[a] 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. 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.

[b] 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.

[c] 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.

[d] Constitutional (germline) mutations in these genes can occur and cause a hematopoietic phenotype. Mutations identified in testing blood or marrow for somatic mutations associated with MDS can identify constitutional (germline) mutations. Distinguishing constitutional from somatic mutations often requires sequencing DNA from a non-hematopoietic tissue in MDS.

[e] There are microdeletions that would be missed by typical genetic sequencing or karyotype that affects some of the same genes that may be indicative of clonal hematopoiesis.

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References on MDS-C (3 of 10)

GENES FREQUENTLY SOMATICALLY MUTATED IN MDS

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HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

- Recognition of these predisposition syndromes is clinically relevant.
  - Patients may require surveillance for disease-specific serious extra-hematopoietic complications and malignant clonal hematopoiesis, often respond poorly to immunosuppressive therapies, and should hematopoietic stem cell transplantation (HSCT) be considered, require specialized consideration of a familial donor and potentially a reduced-intensity conditioning regimen. The recognition of a familial genetic disorder also allows for appropriate genetic counseling and follow-up of affected family members.
- Constitutional mutations predisposing to myeloid malignancy can occur without clinical stigmata of an inherited disorder or family history due to phenotypic heterogeneity, which reflects overlapping features between inherited syndromes and also variable expressivity within a syndrome. Also, a concerning family history of an inherited disorder is not expected in patients in whom the disease-causing mutation occurred de novo.
  - Given these complexities, single-gene testing for diagnosis may lack adequate sensitivity in the initial evaluation of a patient (but can be used for mutation-directed testing in a patient with a known familial mutation). Panel-based genetic testing should be considered.
- Accurate interpretation of germline (or somatic) mutations is essential for effective medical care.
  - The interpretation of genetic testing remains subjective and complex. Interpretations can differ based on interlaboratory classification rules, access to unique case-level data, and other evidence. Additionally, mutations initially deemed to be nonpathogenic may need to be reconsidered and reclassified as pathogenic as additional data emerge in the field or vice versa (ie, mutations initially deemed to be pathogenic may need to be reconsidered and reclassified as nonpathogenic).
- Mutations identified in testing blood or marrow for somatic mutations associated with MDS can identify constitutional (germline) mutations.
  - Distinguishing constitutional vs. somatic mutations often requires sequencing DNA from a non-hematopoietic tissue in MDS.
- Genetic testing performed to identify somatic mutations arising in malignant cells is often not designed to detect germline (that is, inherited) mutations and may thus be inadequate for evaluation of an underlying inherited hematologic malignancy predisposition syndrome. Specifically, these somatic mutation panels may not target the relevant genomic locus and/or detect relevant copy number aberrations implicated in inherited disorders.
- Next-generation sequencing and chromosome genomic array testing are complementary in detecting both mutations and copy number aberrations and copy neutral loss of heterozygosity in the genes associated with these disorders.

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HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

- When clinically possible, cultured skin fibroblasts are the recommended DNA source for germline testing in order to exclude somatic mutations and to avoid false negatives due to peripheral blood/marrow somatic mosaicism.
  - Testing utilizing this DNA source upfront (as opposed to initial testing of DNA from blood or marrow) may avoid unnecessary treatment delay, effort, cost, and anxiety surrounding counseling patients regarding possible inherited variants detected on tumor-only testing that subsequently proves to be acquired.
- Patients harboring these constitutional mutations can present to both pediatric and adult care centers.
  - For example, older patients who harbor germline predisposition mutations may demonstrate longer latency for disease development, as seen with germline *DDX41* mutations. Younger patients with MDS and those with therapy-related myeloid malignancies may be more likely to harbor germline variants in these predisposition genes.
- Careful pre- and post-test genetic counseling are recommended when pursuing germline genetic testing. This should include discussion of the risks, benefits, and limitations of testing and the implications of test results for family members.
- Additional laboratory testing (apart from genetic testing) can assist in diagnosing these disorders.
  - Fanconi anemia is evaluated by chromosome breakage analysis. Serum pancreatic isoamylase (pediatric and adult patients) and serum trypsinogen (pediatric patients) are often low in Shwachman-Diamond syndrome. Telomere biology disorders, such as dyskeratosis congenita, demonstrate shortened telomere lengths, which can be measured by FISH assays using leukocyte subsets. Erythrocyte adenosine deaminase is often elevated in Diamond-Blackfan anemia.

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References on MDS-C (10 of 10)

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Germline predisposition for myeloid neoplasms ***without*** cytopenia(s), dysplasia, or other organ dysfunction prior to myeloid malignancy presentation			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
CEBPA[1]	*CEBPA*	AML	AML is often favorable risk, somatic *CEBPA* mutations are a frequent second event (with different somatic mutations occurring with AML recurrence[2]), ~ 5%–10% of *CEBPA* double-mutant AML cases harbor germline mutations.[3]
DDX41[4]	*DDX41*	AML, MDS, CML	Late age of onset of hematologic malignancies; NHL, Hodgkin lymphoma.[5]
14q32.2 genomic duplication[6]	Includes *ATG2B* and *GSKIP*	AML, MPN, CMML (highly penetrant)	Familial MPN. Earlier age of onset compared to sporadic MPN.

[a] The list of genes associated with inherited myeloid malignancy predisposition is continually evolving.

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Continued
References on MDS-C (10 of 10)

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Germline predisposition for myeloid neoplasms ***with*** pre-existing cytopenia(s) and/or other organ dysfunction prior to myeloid malignancy presentation			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
ANKRD26[7]	*ANKRD26*	Moderate thrombocytopenia with mild bleeding manifestations; platelet size is usually not enlarged; dysmegakaryopoiesis[8]/AML, MDS	
ETV6[9,10]	*ETV6*	Thrombocytopenia and mild bleeding manifestations; platelet size is usually not enlarged[11]/AML, MDS	ALL (typically precursor B-cell ALL)[9,11]
GATA2 deficiency syndrome[12,13]	*GATA2*	Bone marrow failure; B-/NK-/CD4-cell lymphocytopenia, monocytopenia[14]/AML/ MDS (highly penetrant)	Immune deficiency (viral infections, warts, disseminated nontuberculous mycobacterial infections), wide range of extra-hematopoietic manifestations (eg, lymphedema, sensorineural hearing loss, pulmonary alveolar proteinosis[15]).
Familial platelet disorder with associated myeloid malignancy[b,16,17]	*RUNX1*	Thrombocytopenia and abnormal platelet function/AML/MDS (highly penetrant)	Typical age of onset of AML/MDS is 20–40 y. Anticipation may lead to occurrence in younger individuals in subsequent generations; eczema; ALL.
MIRAGE syndrome[18]	*SAMD9*	Transient or permanent cytopenias and marrow failure/AML, MDS	Typically presents in infancy; phenotype associated with inherited mutations as opposed to de novo mutations may be less severe[19]; myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MDS with monosomy 7/-7q, somatic genetic aberrations in hematopoietic cells often occur that result in loss of the mutant *SAMD9* allele.[18]
Ataxia-pancytopenia syndrome[20,21]	*SAMD9L*	Transient or permanent cytopenias and marrow failure/AML, MDS	Variable neurologic findings (eg, gait disturbance, nystagmus, cerebellar atrophy and white matter hyperintensities[22]); immune deficiency; MDS with monosomy 7/-7q, somatic genetic aberrations in hematopoietic cells often occur that result in loss of the mutant *SAMD9* allele.[20]
SRP72[23]	*SRP72*	Marrow failure/MDS	Congenital sensorineural deafness.

[a] The list of genes associated with inherited myeloid malignancy predisposition is continually evolving.
[b] Additional laboratory testing: *RUNX1* mutant platelets may show platelet ultrastructure changes such as abnormal alpha granules and a deficiency of delta granules. Platelet aggregometry and platelet function analyzer testing may show platelet aggregation and secretion defects, such as decreased aggregation to epinephrine and collagen (so called aspirin-like defect).

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References on MDS-C (10 of 10)

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Classical inherited bone marrow failure syndromes			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
Diamond-Blackfan anemia[c]	*RPL5, RPL11, RPL15, RPL23, RPL26, RPL27, RPL31, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, TSR2, GATA1*	Anemia and marrow erythroid hypoplasia/ AML, MDS	Cardiac anomalies, Cathie facies, genitourinary anomalies, cleft lip/palate, short stature; sarcomas; elevated erythrocyte adenosine deaminase.
Fanconi anemia[d,e]	*FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCDE, FANCF, FANCG, FANCI, FANCJ/BRIP1/BACH1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANQ/ERCC4, FANCR/ RAD51, FANCS/BRCA1, FANCT/UNE2T, FANCU/XRCC2, FANCV/REV7*	Bone marrow failure/AML, MDS	Short stature, skin pigmentation (café-au-lait or hypopigmented spots), skeletal anomalies (thumbs, arms), multiple other congenital anomalies; squamous cell carcinomas of head/neck/vulva/vagina, liver tumors, additional solid tumors associated with *FANCD1* include brain and Wilms tumors; therapy-related neoplasms may emerge after treatment for solid tumors; increased chromosome fragility.
Shwachman-Diamond syndrome[f]	*SBDS, EFL1, DNAJC21*	Bone marrow failure/AML, MDS	Pancreatic insufficiency, skeletal abnormalities; low serum trypsinogen or pancreatic isoamylase.
Telomere biology disorders[g]	*ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RTEL1, TERC, TERT, TINF2, USB1, WRAP53*	Bone marrow failure/AML, MDS	Idiopathic pulmonary fibrosis, emphysema, early hair graying, osteoporosis, pulmonary arteriovenous malformations and hepatopulmonary syndrome, liver fibrosis-cirrhosis, esophageal stricture, enterocolitis, immune deficiency; rare cases manifest as dyskeratosis congenita with nail dystrophy, rash, oral leukoplakia; squamous cell carcinomas of head/neck/GI tract; shortened telomere lengths.
Congenital neutropenia	*ELANE, G6PC3, GFI1, HAX1*	Neutropenia/AML, MDS	
Myeloid neoplasms associated with Down syndrome	*Trisomy 21, GATA1*	Transient abnormal myelopoiesis/AML, MDS	Down syndrome; acute megakaryoblastic leukemia.

[a] The list of genes associated with inherited myeloid malignancy predisposition is continually evolving.
[c] Additional laboratory testing: Erythrocyte adenosine deaminase is often elevated.
[d] Some Fanconi anemia genes overlap with inherited breast and ovarian cancer genes.
[e] Additional laboratory testing: Increased chromosomal breakage following exposure to a DNA cross-linking agent such as mitomycin C (MMC) or diepoxybutane (DEB). Testing is typically performed on peripheral blood lymphocytes. A subset of patients may undergo genetic somatic reversion to wild-type in peripheral blood lymphocytes. This reversion confers a growth advantage over the non-reverted Fanconi anemia lymphocytes. In such cases, testing may appear normal, or reveal only a small subpopulation of cells with increased chromosomal breakage. If there is a strong clinical suspicion for Fanconi anemia despite a negative blood test, chromosomal breakage may be tested on fibroblasts obtained from a skin biopsy.
[f] Additional laboratory testing: Serum pancreatic isoamylase (pediatric and adult patients) and serum trypsinogen (pediatric patients) are often low.
[g] Additional laboratory testing: Shortened telomere lengths measured by FISH assays on peripheral blood leukocyte subsets.

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References on MDS-C (10 of 10)

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Germline predispositions for myeloid neoplasms and solid tumor cancers			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
Constitutional mismatch repair deficiency	*EPCAM, MLH1, MSH2, MSH6, PMS2*	AML, MDS	Café-au-lait spots; ALL, lymphomas, central nervous system, GI, and other tumors; microsatellite instability of tumor cells.
Hereditary breast and ovarian cancer[d]	*BRCA1, BRCA2*	AML, MDS	Breast and ovarian cancers, other tumors. Therapy-related neoplasms may emerge after treatment for solid tumors.
Li-Fraumeni syndrome	*TP53*	AML, MDS	AML and MDS are associated with complex karyotypes as seen with somatic *TP53* mutations; ALL, adrenocortical carcinoma, brain cancer, breast cancer, choroid plexus carcinoma, colon cancer, lung carcinoma, sarcoma, other tumors; therapy-related neoplasms may emerge after treatment for solid tumors.
RASopathies	*CBL, KRAS, NF1, PTPN11*	AML, MDS	Mutations induce constitutive activation of RAS/MAPK pathways and cause many syndromic findings and hematologic and solid tumor cancer risk (neuro-cardio-fascio cutaneous syndrome), eg, neurofibromatosis type 1 and Noonan syndrome, which predispose to development of JMML or an MPN.
Other rare DNA repair syndromes	*BLM, MBD4*	AML, *MBD4:* early-onset AML with a high somatic mutation burden characterized by CG>TG changes including biallelic CG>TG mutations in DNMT3A[24]	Bloom syndrome: pre- and postnatal growth retardation, photosensitive skin changes, immunodeficiency, insulin resistance, microcephaly, high-pitched voice, hypogonadism, and increased risk of early onset of multiple cancers.

[a] Not all of the listed individual genes under the Gene column have been reported in myeloid malignancies.
[d] Some Fanconi anemia genes overlap with inherited breast and ovarian cancer genes.

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

Continued
References on MDS-C (10 of 10)

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

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SPECTRUM OF INDOLENT MYELOID HEMATOPOIETIC DISORDERS[a,b,c,d,e]

Feature	ICUS	IDUS	CHIP	CCUS	MDS
Somatic mutation	–	–	+/–[c]	+/–[c]	+/–
Clonal karyotypic abnomality	–	–	+/–[c]	+/–[c]	+/–
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

[a]Regular monitoring of blood counts in these patients should be instituted after evaluation as in MDS-1 (generally at least every 3–6 months).
[b]For patients with MDS, see MDS-3, MDS-4, MDS-C, and MDS-D.
[c]Has one or more of these (+) features: either has a clonal karyotypic abnormality (present in ≥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.
[d]Patients with pathogenic mutations with >10% variant allele frequency AND ≥2 somatic mutations, spliceosome gene mutations, or mutations of *RUNX1* or *JAK2* have positive predictive values for myeloid neoplasms (MDS, MPN, or AML). Isolated mutations of *DNMT3A, TET2*, and *ASXL1* have less predictive value.
[e]*DNMT3A, TET2, ASXL1, RUNX1, JAK2, PPM1D, TP53,* and splicing factor genes are the most frequently mutated genes associated with CHIP.

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RECOMMENDATIONS FOR FLOW CYTOMETRY

Initial Evaluation (See MDS-1)

- **FCM:**
  - **Consideration should be given to obtain FCM testing at initial evaluation of MDS to include antibody combinations to characterize blasts and to identify abnormal lymphoid populations (such as increased hematogones, which may mimic blasts, leading to erroneous myeloblast quantitation). For example, a combination using anti-CD45, -CD34, -CD33, and -CD19 (with forward scatter and side scatter) could be useful.**
  - **It is understood that the blast percent for both diagnosis and risk stratification should be determined by morphologic assessment, not solely by FCM. If blasts are increased and morphologic questions arise regarding their subtype (ie, myeloid or lymphoid), they should be characterized with a more elaborate panel of antibodies.**
  - **In diagnostically difficult cases, in expert hands, an expanded panel of antibodies to demonstrate abnormal differentiation patterns or aberrant antigen expression may help confirm diagnosis of MDS (See Initial Evaluation in the Discussion).**
  - **Flow cytometric abnormalities are often seen in MDS, and in some cases may correlate with observed morphologic abnormalities. They may also help diagnostically in patients with clinical suspicion of MDS who have no significant morphologic dysplasia and whose chromosome/FISH studies are either negative or normal.**
  - **FCM is most useful in detecting aberrant immature myeloid lineages often observed in myelodysplastic syndromes.[1-6] Flow analysis will detect aberrant expression of B- or T-cell antigens on myeloid precursors, and selective loss or gain of additional markers (eg, loss or dim expression of CD33, CD34, CD56, CD38, or CD117) on myeloid precursors. Flow will help in cytopenia associated with LGL expansion by detecting increase of CD56/CD57+ cells. CMML-associated monocytic aberrancies can be easily detected by combination of CD64/CD14, and CD16 loss or dim[6] expression. In addition, qualitative abnormalities in mature myeloid lineages, eg, hypogranular late myelocytes, bands/Pelger-Huet cells, and neutrophils will have abnormal flow patterns (low or negative for CD16 or CD10). However, the erythroid lineage dysplasia (dyserythropoiesis) detection by FCM is limited[4,7] due to variable RBC lysing methods used in preparing flow mononuclear cell suspension. Megakaryocytic dysplasia cannot be assessed in FCM.**

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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 indicated.

NCCN Guidelines Version 2.2020
Myelodysplastic Syndromes

Discussion

This discussion corresponds to the NCCN Guidelines for Myelodysplastic Syndromes. Last updated on 02/28/2020.

Table of Contents

Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with a relatively heterogeneous spectrum of presentation. The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In the general population, the incidence rate of MDS is approximately 4.5 per 100,000 people per year.[1] MDS is rare among children/adolescents and young adults, with an incidence rate of 0.1 per 100,000 people per year in those younger than 40 years of age. However, among individuals between the ages of 70 and 79 years, the incidence rate increases to 26.9 per 100,000 people, and further to 55.4 per 100,000 people among those 80 years of age and older.[1]

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

The multidisciplinary panel of MDS experts for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) meets annually to update recommendations on standard approaches to the diagnosis and treatment of MDS in adults. These recommendations are based on a review of recent clinical evidence that has led to important advances in treatment or has yielded new information on biological factors that may have prognostic significance in MDS.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Myelodysplastic Syndromes, an electronic search of the PubMed database was performed to obtain key literature using the following search term: myelodysplastic syndromes. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[4]

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

The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnostic Classification

Myelodysplastic Syndromes

The 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 that are similar to MDS.[3,5] The NCCN Guidelines for Myelodysplastic Syndromes include the WHO 2016 classification system for diagnostic evaluations.

To assist in providing consistency in the diagnostic guidelines for MDS, an International Consensus Working Group recommended that minimal diagnostic criteria for this disease include two prerequisites: stable cytopenia (for at least 6 months unless accompanied by a specific karyotype or bilineage dysplasia, in which case only 2 months of stable cytopenias are needed), and the exclusion of other potential disorders as a primary reason for dysplasia or cytopenia or both. In addition, the diagnosis of MDS requires at least one of three MDS-related (decisive) criteria: 1) dysplasia (≥10% in one or more of the three major bone marrow lineages); 2) a blast cell count of 5%–19%; and 3) a specific MDS-associated karyotype [eg, del(5q), del(20q), +8, or -7/del(7q)]. Furthermore, several co-criteria may help confirm the diagnosis of MDS. These co-criteria include 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).[6]

Consistent with these recommendations, as stated by WHO, the features that are central for the diagnosis of MDS entail well-defined dysplasia in one or more 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.[7] 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.[8]

In 2001, WHO proposed an alternative classification for MDS that was modified from the original French-American-British (FAB) definitions.[9-11] Since then, the WHO classification has been updated twice, once in 2008 and again in 2016. The current WHO guidelines identify six entities of MDS: MDS with single lineage dysplasia (MDS-SLD); MDS with ring sideroblasts (MDS-RS); MDS with multilineage dysplasia (MDS-MLD); MDS with excess blasts (MDS-EB); MDS with isolated del(5q) ± one other abnormality except -7/del(7q); and MDS unclassifiable (MDS-U) (see *2016 WHO Classification of MDS* in the algorithm). There is an additional provisional entity termed "refractory cytopenia of childhood" (RCC). MDS-SLD includes refractory anemia (RA; unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), and refractory thrombocytopenia (unilineage dysmegakaryocytopoiesis). The latter two were previously classified as MDS-U in 2001 but were reclassified in the 2008 update.[12] In the context of MDS-SLD, the threshold for cell line dysplasia is ≥10% for myeloid and erythroid lineages; but for megakaryocytes, a threshold of approximately 30% to 40% may provide improved specificity in distinguishing normal from dysplastic bone marrow.[13]

A review article discusses the major changes and the rationale behind the revisions in the 2016 WHO classification of MDS and AML evolving from MDS.[14] The 2016 WHO classification stratifies MDS-RS based on single lineage dysplasia (MDS-RS-SLD) and multilineage dysplasia (MDS-RS-MLD). The presence of the *SF3B1* mutation is associated with the presence of ring sideroblasts.[15] 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. MDS-EB cases are separated into those with less than 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 who were 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), which is associated with poor outcomes.[16] 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 to the single mutation del(5q).[17-19] Due to low reproducibility, another change in the 2016 update includes the requirement for 1% blasts in the peripheral blood on two 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 up to 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."[20] It was noted in the 2008 WHO classification that some patients with AML with myelodysplasia-related changes who have 20% to 29% marrow blasts may behave in a manner more similar to MDS than to AML. Data suggest that these patients have less aggressive disease and improved outcomes and therapeutic responses compared to patients with greater than 30% blasts and should be considered a favorable group of AML.[21] The NCCN 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 when compared with de novo AML.[22,23] 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 originally 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 (see *2016 WHO Classification of MDS*), the NCCN Guidelines allow for patients with 20% to 29% blasts AND a stable clinical course for at least 2 months to be considered as having either MDS or AML. Individuals with *FLT3* and *NPM1* mutations are more likely to have AML than MDS.[24] 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. The clinician should consider such factors as age, antecedent factors, cytogenetics, comorbidities, pace of disease, performance status, and the patient's goal of treatment. This recommendation is further supported by the results from several validation studies and analyses.[25-29]

The WHO classifications are revised to improve both the diagnostic and prognostic capabilities of these entities. MDS with del(5q) generally has a relatively good prognosis[16] and is highly responsive to lenalidomide therapy.[30] With a moderate degree of variability, MDS-EB and MDS-EB-T patients generally have a relatively poor prognosis, with a median survival

ranging from 5 to 12 months. In contrast, MDS-RS-SLD (RA) or MDS-RS patients 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% of MDS-EB cases and 65% of MDS-EB-T cases within 2 years.[3] In contrast, the incidence of transformation for RA was 5% in the first year and 10% within 2 years. None of the MDS-RS patients developed leukemia within 2 years.

Biologic evidence indicates that similar clinical phenotypes, including lower blast counts, older age, lower white blood cell (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-non-mutated cases. This suggests that SF-mutated cases comprised a distinct entity among MDS/AML[31,32] 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 is de novo AML, especially those AML cases that do not have *TP53* mutations nor those typical of secondary MDS,[32] which arises without *a known* antecedent hematologic disorder. High-risk MDS, AML-MDS, and some elderly patients with AML may have a more indolent clinical course in terms of short-term progression compared with patients who have standard presentations of de novo AML. This emphasizes the need to treat at least some patients with a standard presentation of de novo AML[32] differently than patients with indolent MDS (see NCCN Guidelines for Acute Myeloid Leukemia).

Myelodysplastic/Myeloproliferative Neoplasms

The category of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) was added to the 2008 update of the WHO classification of myeloid neoplasms. This category 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 ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) and the MDS/MPN, unclassifiable (MDS/MPN-U) groups are also included in this category.[33,34] (See *Myelodysplastic/Myeloproliferative Overlap Neoplasms (MDS/MPN), 2017 WHO Classification and Management* in the algorithm).

CMML has been subdivided into two groups based on molecular and clinical differences: proliferative-type CMML (WBC count ≥13 x 10^9/L) and dysplastic type CMML (WBC < 13 x 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 have been created in the 2016 classification (previously only two groups were identified) and are defined as follows: CMML-0, for patients with less than 2% peripheral blood blasts and less than 5% bone marrow blasts; CMML-1 for patients with 2% to 4% peripheral blood blasts and/or 5% to 9% bone marrow blasts; and CMML-2 for patients with 5% to 19% peripheral blood blasts, 10% to 19% bone marrow blasts, and/or the presence of Auer rods (see *Myelodysplastic/Myeloproliferative Overlap Neoplasms (MDS/MPN), 2017 WHO Classification and Management* in the algorithm). Mutations in the following genes are frequently associated with CMML: *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *NRAS*, and *CBL*.[35,36] The management of CMML depends on the characteristics of the patient's disease and is typically focused on supportive care and cytoreductive therapy.[37] Asymptomatic, low-risk patients may be observed until disease progression.[37-39] In patients with CMML-1 and CMML-2, hypomethylating agents, decitabine and azacitidine (AzaC) have demonstrated efficacy,[37-41]

and emerging data suggest utility of ruxolitinib in this context.[42] Patients with higher-risk IPSS-R and those with lower-risk IPSS-R with poor-risk genetic features, profound cytopenias, and high transfusion burden are candidates for hematopoietic stem cell transplantation (HSCT).[37,38,43,44] Patients with a t(5;12) translocation associated with the *ETV6-PDGFRβ* fusion gene may respond to imatinib mesylate.[37,45,46] Patients with CMML may also have systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and *KIT*816V mutation responsive to midostaurin.[47,48]

The second subtype, aCML, is rare and has similar neutrophilia as the chronic neutrophilic leukemia (CNL) subtype of MPN. However, molecular characterization may distinguish the two entities. Copy-neutral loss of heterozygosity (cnLOH) is commonly observed in MDS/MPN and *BCR-ABL1*–negative MPN with a reported frequency between 6% and 41%.[49] Currently, chromosomal microarray [(CMA), also known as chromosome genomic array testing (CGAT)] is the only feasible technique available to identify cnLOH.[49] The presence of *CSF3R* mutations is strongly associated with CNL but is present in less than 10% of aCML cases.[50,51] 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 a third of aCML patients.[52-55] The use of hypomethylating agents in aCML is a rational application of their established activity in MDS and CMML.[56-58] Emerging data suggest that rare aCML patients with *CSF3R* or *JAK2* mutations may respond to ruxolitinib therapy in combination with hypomethylating agents due to their JAK-STAT pathway activation.[49,57,59] Although the data on HSCT procedures are limited, allogeneic HSCT is the only treatment modality that can induce long-term remissions in aCML.[54,56,57,60]

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 equal to or greater than 1 x 10^9/L; blast percentage in the peripheral blood and bone marrow less than 20%; splenomegaly; and the absence of *BCR/ABL1* rearrangement. Although there are no mutations that are exclusive to this disease subtype, the most frequently mutated genes in JMML are *PTPN11* (40%–50%), *NRAS* (15%–20%), *KRAS* (10%–15%), *CBL* (15%–18%), and *NF1* (10%–15%).[61,62] In some patients, these mutations may be present as germline variants where they are frequently associated with Noonan syndrome or other congenital syndromes (see *Genes Frequently Somatically Mutated in MDS* in the algorithm).[62] In patients who do not have genetic features of JMML, monosomy 7 or any other chromosomal abnormality must be present with at least two 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*. Allogeneic HSCT is the main treatment option for JMML.[54,63]

MDS/MPN-U is a rare diagnosis, making up less than 5% of all myeloid disorders.[64] This disorder is a myeloid neoplasm with mixed MDS/MPN features at onset, but does not meet the WHO criteria for any other MDS/MPN, MDS or MPN.[13] The diagnostic criteria include: clinical and morphologic features consistent with MDS and thrombocytosis (platelet counts ≥450 × 10^9/L), and WBC count ≥13 x 10^9/L.[13] The most frequently mutated genes associated with MDS/MPN-U include *TET2*, *NRAS*, *RUNX1*, *CBL*, *SETBP1*, and *ASXL1*.[13,51,53,65] There is no optimal treatment consensus for MDS/MPN-U patients who are not eligible for allogeneic HSCT.[54] In a series of 85 patients with WHO-defined MDS/MPN-U, most of the patients received hypomethylating agents, which was associated with improved overall survival (OS) compared to other treatment approaches (16.4 months vs. 11.5 months).[54,64] These alternate non-transplant approaches included interferon alpha, thalidomide, and lenalidomide.[64]

MDS-RS-T includes cases that present with clinical and morphologic features consistent with MDS and thrombocytosis (platelet counts ≥450 × 10^9/L).[66] The morphology of MDS-RS-T is characterized by MDS-RS features (no blasts in the peripheral blood, dysplastic erythroid proliferation, ring sideroblasts ≥15% of erythroid precursors, and <5% blasts in marrow) with proliferation of large atypical megakaryocytes similar to those seen in essential thrombocythemia or primary myelofibrosis. 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-T as a full entity.[67-70] *SF3B1* mutations are associated with the presence of ring sideroblasts and frequently have the *JAK2* V617F mutation or *MPL* W515K/L mutation.[66] In contrast to MDS-RS, *SF3B1* mutations do not change the required percentage of ring sideroblasts for diagnostic classification. *MPL* and *CALR* mutations occur in MDS/MPN-RS-T but are infrequent.[71] Case reports suggest efficacy of lenalidomide at alleviating the need for red blood cell (RBC) transfusions in patients with MDS/MPN-RS-T.[71-73] If cytopenias predominate, hypomethylating agents may also be considered as a treatment strategy.[74]

Indolent Myeloid Hematopoietic Disorders

The spectrum of indolent myeloid hematopoietic disorders encompasses four groups: idiopathic cytopenia of undetermined significance (ICUS); idiopathic dysplasia of unknown significance (IDUS); clonal hematopoiesis of indeterminate potential (CHIP); and clonal cytopenia of undetermined significance (CCUS). Based on somatic mutation, clonal karyotypic abnormality, marrow dysplasia, and cytopenia features, patients can be classified within the spectrum (see *Spectrum of Indolent Myeloid Hematopoietic Disorders* in the algorithm). These disorders can evolve into MDS or AML, though the frequency of progression may differ among the four groups.

CHIP and CCUS are defined by the presence of a clonal karyotypic abnormality (present in ≥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 to other pre-malignant conditions, there is a higher risk of subsequent hematologic disease compared to patients who do not have somatic mutations.[75,76] Additionally, shorter survival in these patients compared with aged-matched controls has been demonstrated and may be attributed to non-hematologic causes.[76] The most frequently mutated genes associated with CHIP include *DNMT3A*, *TET2*, *ASXL1*, *RUNX1*, *JAK2*, *PPM1D*, *TP53*, and SF genes.[76-78] Patients with pathogenic mutations with >10% variant allelic frequency and ≥2 somatic mutations, spliceosome gene mutations, or mutations of *RUNX1* or *JAK2* have positive predictive values for myeloid neoplasms (ie, MDS, MPN, AML).[79] Isolated mutations of *DNMT3A*, *TET2*, and *ASXL1* have less predictive value.[79] 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.[80] Data are limited regarding natural history and disease progression for these two disorders.

Two recent studies have focused on the role of mutational analysis in indolent malignant disease. In a prospective analysis of 144 patients, Kwok and colleagues[81] 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 ICUS patients had a somatic mutation or chromosomal abnormality similar to MDS; these

patients were characterized as CCUS. The similar mutational features may have a role in the diagnostic value of these disorders.[81]

Cargo et al[80] evaluated mutational features associated with ICUS in patients with disease that developed into progressive dysplasia or AML.[80] Although this study was not designed to evaluate the diagnostic role of mutations, detection of mutational features predicted progression to high-risk disease and OS. The study proposes that patients who are defined as poor-risk may benefit from early intervention.

NCCN recommends that following 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.

Pediatric MDS

Several differences exist between adult and childhood myelodysplasia. MDS and myelodysplasia are quite rare in children, occurring in 1 to 4 cases per million per year with a median age of 6.8 years.[82-84] MDS in children is strongly associated with congenital disorders.[85] Genetic syndromes are evident in 50% of cases, including Down syndrome,[86-88] trisomy 8 syndrome,[89] Fanconi anemia,[90,91] congenital neutropenia (Kostmann syndrome),[92,93] Diamond-Blackfan anemia,[94] Shwachman-Diamond syndrome,[95] dyskeratosis congenita (DC),[96] neurofibromatosis type 1,[97] Bloom syndrome,[98,99] Noonan syndrome,[100] and Dubowitz syndrome.[101] Prior exposure to cytotoxic therapy (eg, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors)[102-105] or radiation[106,107] increases the risk for MDS.

The 2008 WHO classification separates pediatric myeloproliferative diseases (MPDs) into three groups: MDS (RCC, MDS-EB, MDS-EB-T, or AML with MDS-related changes); myelodysplastic disease/MPD (JMML); and Down syndrome disease (transient abnormal myelopoiesis and myeloid leukemia of Down syndrome).[34] RCC is the most common subtype of MDS found in children, accounting for approximately 50% of cases.[84] Abnormal karyotypes are found in 30% to 50% of children with MDS;[108] most common are numerical anomalies with less than 10% showing structural abnormalities. Monosomy 7 is the most common cytogenetic abnormality, occurring in 30% of cases,[109,110] followed by trisomy 8[111,112] and trisomy 21.[113] The del(5q) abnormality is rarely seen in children.[114] Clinically, isolated RAs are uncommon in children. Thrombocytopenia and/or neutropenia, often accompanied by hypocellular marrow, is a common presentation. Fetal hemoglobin levels are frequently elevated.

Differential diagnoses include aplastic anemia (AA) and AML. Compared to AA, children with MDS have a significantly elevated mean corpuscular volume; clonal hematopoiesis is confirmatory. Higher expression of *p53*, lower expression of survivin, or the presence MDS-related cytogenetic abnormalities can also help differentiate MDS from AA.[115] Compared with AML, low WBC count, multi-lineage dysplasia, and clonal hematopoiesis with numerical, rather than structural, cytogenetic abnormalities suggest MDS. A bone marrow blast count of less than 20% also suggests MDS, but biological features are more important than a strict blast cutoff value. Monosomy 7 strongly suggests MDS. When patients present with AML, the marrow frequently shows dysplastic features, but this does not necessarily indicate that the AML arose after MDS. Indeed, criteria for the diagnosis of MDS in a patient who presents with AML are stringent.[116] Dysplasia in bone marrow cells may also be due to other etiologies including infection (eg, Parvo virus,[117,118] herpes viruses,[119] HIV), deficiencies of B_{12} and copper,[120] drug therapy, and chronic disease.[121] Congenital dyserythropoietic anemia, congenital sideroblastic anemia, and Pearson syndrome should also be excluded.

Children with Down syndrome have an increased risk of developing leukemia (50-fold greater risk if younger than 5 years of age), and are usually categorized as having acute megakaryoblastic leukemia (AMKL, M7).[86,88,122,123] This commonly has a prodromal phase of cytopenia(s) similar to MDS and may be considered a spectrum of the same disease. Prognosis of patients with Down syndrome and AMKL is quite good with an 80% cure rate when treated with intensive chemotherapy. Hematopoietic cell transplantation (HCT) is not indicated in first complete remission for these children. Newborns with Down syndrome can develop abnormal myelopoiesis with leukocytosis, circulating blasts, anemia, and thrombocytopenia, but this resolves spontaneously within weeks to months. Approximately 20% of children with Down syndrome, who have transient abnormal myelopoiesis, will subsequently develop AMKL.[87]

There is a paucity of clinical trials due to the rarity and heterogeneity of MDS in children. The primary goal of treatment is generally a cure rather than palliation. HCT is the only curative option in childhood MDS with 3-year disease-free survival rates of approximately 50%.[124-126] Myeloablative therapy with busulfan, cyclophosphamide, and melphalan, followed by either matched family or matched unrelated donor allogeneic HCT is the treatment of choice for children with MDS. Other treatments such as chemotherapy, growth factors, and immunosuppressive therapy (IST) have a limited role. Prognosis for untreated MDS depends on the rate of progression to AML. The stage of the disease at the time of HCT strongly predicts outcome.[110]

Patients with RCC have a median time to progression to advanced MDS of 1.7 years,[110] but the time to progression is highly variable, depending on the underlying cause of MDS and standard prognostic factors.[127] Patients with JMML have a variable prognosis; some younger patients with favorable genetics and clinical features have resolution of JMML without treatment, while others progress rapidly despite allogeneic HCT.[128]

Children diagnosed before the age of 2 years have the best prognosis. Poor prognostic features include high hemoglobin F, older age, and thrombocytopenia.

Pediatric AML or MDS with monosomy 7 has a poor prognosis with conventional therapies. A recent review of 16 patients with AML and MDS with monosomy 7 treated by two transplant programs from 1992 to 2003 (MDS, n = 5; therapy-related MDS [t-MDS], n = 3; AML, n = 5; therapy-related AML [t-AML], n = 3) reported a 2-year event-free survival of 69%.[129] Four of the 5 deaths occurred in patients transplanted with active leukemia. Seven of 8 MDS patients were alive without evidence of disease (6 in first complete remission, 1 in second complete remission, and 1 death due to complications).[129]

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

Evaluation

Several types of evaluations are needed to determine the clinical status of patients with MDS. Understanding clinical status is necessary for diagnostic and prognostic categorization and to determine treatment options.

Initial Evaluation

Clinical history should include the timing, severity, and tempo of abnormal cytopenias; prior infections or bleeding episodes; and number of transfusions. Cytopenias are defined as values lower than standard laboratory hematologic levels, being aware of age, sex, ethnic, and

altitude norms.[8] Concomitant medications and comorbid conditions require careful assessment. Because MDS are relatively indolent disorders, blood count stability is used to distinguish MDS from evolving AML. Other possible causes of cytopenias require careful evaluation.

In addition to establishing current blood and reticulocyte counts, clinicians need a peripheral blood smear evaluation to determine the degree of dysplasia and, thus, potentially dysfunctional cells. Bone marrow aspiration with Prussian blue stain for iron and a biopsy are needed to evaluate the degree and relative proportions of hematopoietic cell maturation abnormalities, percentage of marrow blasts, marrow cellularity, presence or absence of ring sideroblasts (and presence of iron per se), and fibrosis. Cytogenetics for bone marrow samples (by standard karyotyping methods) should be obtained, because they are of major prognostic importance. If standard cytogenetics with 20 or more metaphases cannot be obtained, CMA/CGAT[49] or MDS-related fluorescence in situ hybridization (FISH) panel should be performed. If karyotype is normal, the CMA should be considered. However, CMAs detect both somatic and germline or constitutional changes.

Other useful laboratory screening tests include serum erythropoietin (sEpo), vitamin B_{12}, RBC folate levels, serum ferritin, iron, and total iron-binding capacity (TIBC). RBC folate and serum folate levels should not be considered equivalent, and RBC folate is preferred. RBC folate levels are more indicative of folate stores, whereas serum folate levels are reflective of recent nutrition. However, if RBC folate cannot be evaluated, serum folate should be considered as an alternative, though clinicians should be advised of the limitations. Serum ferritin levels may be nonspecific, particularly in the face of inflammatory conditions such as rheumatoid arthritis. In such cases, obtaining the serum iron levels and TIBC along with serum ferritin may be helpful. As hypothyroidism and other thyroid disorders can lead to anemia, patients should also be evaluated for levels of thyroid-stimulating hormone.[130] HIV testing should also be performed, if clinically indicated.

Elevated levels of lactate dehydrogenase (LDH) are predictive of a decreased survival. LDH is a measure of the systemic inflammation that occurs as a result of tissue turnover or hemolysis. The IPSS and IPSS-R identified LDH as a prognostic feature and other studies have supported the association. In a retrospective study, LDH levels taken at diagnosis were stratified in patients categorized as IPSS-R intermediate. Patients with LDH levels equal to or higher than 320 U/L (n = 8) had a significantly shorter overall OS than patients with levels below 320 U/L (n = 28; 347 days vs. 1339 days, respectively; $P = .03$).[131]

There have been reports that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.[132-134] Copper deficiency is an etiology of anemia, neutropenia, and bone marrow dysplasia that may be under-recognized. There are rare patients with clinical presentation consistent with MDS that may be deficient in copper and for whom copper supplementation may resolve hematologic abnormalities. Copper and ceruloplasmin level assessments should be considered as part of the initial diagnostic workup in patients suspected of having low-risk MDS, especially those with gastrointestinal (GI) disorders and neuropathy.[135] Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,[132-134] prior GI surgery,[132,133] a history of vitamin B_{12} deficiency,[133,136] severe malnutrition, and a history of zinc supplementation.

Bone marrow or peripheral blood cells should be assayed for somatic mutations in genes associated with MDS (see *Genes Frequently Somatically Mutated in MDS* in the algorithm) as these gene mutations may be clinically useful in specific contexts. For example, mutations in splice factor genes are much more common in patients with MDS, MDS-RS, and CMML compared to other myeloid neoplasms. Approximately

40% of MDS patients will carry a mutation in one of the three most frequently mutated splice factors: *SF3B1*, *SRSF2*, and *U2AF1*.[137] A typical mutation in one of these genes indicates the presence of clonally derived hematopoiesis and may help determine diagnosis in the appropriate clinical context.

Mutations of *SF3B1* are associated with the presence of ring sideroblasts and are highly prevalent in patients with MDS-RS or MDS-RS-T (>80%).[68] Mutations of *JAK2* are found in 50% of MDS-RS-T, though it is much rarer in other subtypes. Mutations of *SRSF2* are enriched in patients with CMML, although it is not unique to this subtype. Patients with JMML will often have mutations in one of the tyrosine kinase signaling genes such as *PTPN11*, *NF1*, *NRAS*, *KRAS*, or *CBL*.[62] In many cases, these mutations are congenital and part of a larger syndrome.

Typical mutations in other genes (see *Genes Frequently Somatically Mutated in MDS* in the algorithm) can also establish the presence of clonal hematopoiesis, but they are less specific for disease subtype. Of note, several mutated genes associated with MDS (eg, *TET2*, *DNMT3A*, *SF3B1*, *EZH2*, *NRAS*, *BRAF*, *TP53*) can be mutated in other neoplasms, including lymphoid malignancies. Rare patients can have dual diagnoses (eg, MDS and chronic lymphocytic leukemia), which can confound the interpretation of sequencing results. Therefore, the presence of mutations must be interpreted in an appropriate clinical context consistent with MDS. Acquired mutations of *TET2* and *DNMT3A* are frequent in MDS but have also been identified in older persons with clonal hematopoiesis and normal blood counts. Whether mutations of these or other genes are predictive of MDS in patients with cytopenias who do not meet morphologic diagnostic criteria for MDS is not known. Therefore, somatic mutations should not be used as presumptive evidence of MDS in the absence of other diagnostic features. Patients with cytopenias who lack bone marrow findings diagnostic of MDS can have somatic mutations indicative of clonal hematopoiesis, and as indicated above, those with pathogenic mutations with >10% variant allelic frequency and ≥2 somatic mutations, spliceosome gene mutations, or mutations of *RUNX1* or *JAK2* have positive predictive values for myeloid neoplasms (ie, MDS, MPN, AML).[79] The mere presence of a mutation is not a substitute for the pathologic diagnosis of MDS (ie, requiring dysplasia) and should not be used as the sole indication for treatment. Mutations in some non-MDS genes may indicate the presence of neoplasms that can mimic MDS. These include *CALR* mutations associated with primary myelofibrosis, *CSF3R* mutations associated with aCML and CNL, and *STAT3* mutations associated with large granular lymphocyte (LGL) leukemia.

For discussion regarding the prognostic value of molecular abnormalities, see *Molecular Abnormalities in MDS.*

Additional molecular and genetic screening should be considered for patients with a predisposition for hereditary hematologic malignancies. Potentially associated diseases or syndromes may include GATA2 deficiency syndrome, Shwachman-Diamond syndrome, telomere biology disorder, and others (see *Hereditary Myeloid Malignancy Predisposition Syndromes* in the algorithm). Shortened telomere length has been associated with diseases of bone marrow failure, including inherited disorders such as DC, particularly in the presence of mutations in the *DKC1*, *TERT,* or *TERC* genes that encode for components of the telomere complex.[138,139] Telomere length can be measured by FISH assays using leukocyte (or leukocyte subset) samples.[138,140] Other genetic lesions, such as those occurring in the *RUNX1* or *GATA2* gene, have been implicated in familial cases of MDS and other myeloid malignancies.

Lesions within the *RUNX1* gene (mutations, deletions, or translocations) have been identified as one cause of a relatively rare autosomal-dominant familial platelet disorder that predisposes these patients to myeloid malignancies.[141,142] In affected families with the *RUNX1* lesions, the

incidence of MDS/AML is high, ranging from 20% to 60% in which the median age of onset is 33 years.[143] This familial platelet disorder is characterized by the presence of thrombocytopenia, and a tendency for mild-to-moderate bleeding generally presents from childhood; however, some affected individuals may not display these clinical characteristics.[143] Different types of genetic lesions in *RUNX1* account for the variable phenotypes associated with familial platelet disorder between different families. Cryptic genetic lesions in *RUNX1* have been reported in some patients with Fanconi anemia and MDS/AML.[144] Identification of Fanconi anemia is clinically important, because it is associated with chromosomal fragility that results in variability of disease response to hypomethylating agents.

The *GATA2* gene codes for a transcription factor involved in gene regulation during the development and differentiation of hematopoietic cells, and its expression were shown to correlate with severe dysplasia in patients with primary MDS.[145] Heritable mutations in *GATA2* were identified in families with highly penetrant, early-onset MDS and/or AML.[146] The mutations showed an autosomal-dominant pattern of inheritance, and affected individuals with this familial form of MDS/AML had poor outcomes in the absence of allogeneic HCT.[146] More importantly, family members may not be eligible as donors for allogeneic HCT.

Additional Testing

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

The screening for paroxysmal nocturnal hemoglobinuria (PNH) or STAT3-mutant cytotoxic T-cell clones is potentially useful for determining which patients may be more responsive to IST, particularly young patients with normal cytogenetics and hypoplastic MDS[147-149] (see *Prognostic Stratification*). PNH is a rare acquired disorder of the blood arising from mutations in the *PIGA* gene resulting in defective synthesis of the glycophosphatidylinositol (GPI) anchor. This, in turn, leads to a deficiency of proteins that are normally linked to the cell membrane of blood cells via a GPI anchor.[150-153] Deficiency in GPI-anchored proteins such as those involved in complement inhibition (eg, CD55, CD59) leads to complement sensitivity of RBCs and subsequent hemolysis.[150,151] Flow cytometry is the established method for detecting GPI-anchor–deficient cells for the diagnosis of PNH. Fluorescent aerolysin (FLAER), a protein that specifically binds to GPI anchors, has been shown to be a highly specific and reliable marker for detecting GPI-anchor–deficient clones among granulocytes or monocytes.[154] For evaluation of PNH clonogenicity, it is recommended that multiparameter flow cytometry analysis of granulocytes and monocytes using FLAER, and at least one GPI-anchored protein, be conducted.[150,151,154] It should be emphasized that although evidence of a minor PNH clone may be present in about 20% of patients with MDS, there is usually no evidence of PNH-related hemolysis in these patients.

Cases of patients with myelodysplastic features and clonal expansion of LGLs have been reported.[155-158] In one of these studies, 3 out of 9 patients responded to IST as indicated by improved blood counts.[155] Although patients with both MDS and LGL did not respond as well as LGL patients (33% vs. 66%; $P = .01$), the presence of the T-cell clone

may reflect a target for IST. A second study reported improved outcomes in 61 MDS patients with LGL clonogenicity receiving anti-thymocyte globulin (ATG).[156] Moreover, the MDS-SLD RA subtype was determined as a favorable predictor of response compared to non-MDS-SLD RA patients (odds ratio [OR], 0.15; 95% CI, 0.04–0.59; *P* = .005).[156]

Bone marrow biopsy staining for reticulin is helpful for evaluating the presence and degree of bone marrow fibrosis.[159] Increased reticulin fibers in the marrow at diagnosis are seen in approximately 5% to 10% of MDS cases.[160-163] MDS with fibrosis is not considered a distinct subtype of MDS but rather is relegated to the unclassifiable category in the most recent WHO classification.[14] These patients frequently present with severe pancytopenia; decreased survival in these patients has been reported.[160,161]

In addition to basic flow cytometric evaluation at presentation for characterization of blasts and evaluation of lymphoid populations, expanded flow cytometry may be a useful adjunct for diagnosis of MDS in difficult cases. In expert hands (both in terms of technical sophistication and interpretation), flow cytometry may demonstrate abnormal differentiation patterns or aberrant antigen expression in myeloid or progenitor cells, which may help confirm a diagnosis of MDS, exclude differential diagnostic possibilities, and, in some patients, provide prognostic information.[164-168] Flow analysis should use appropriate antibody combinations with four fluorescence channel instrumentation.[164-168] Multiple aberrancies should be present for the diagnosis of MDS, as single aberrancies are not infrequent in normal populations. For follow-up studies, antibody combinations may be tailored to detect specific abnormalities implicated in the initial evaluation. While aberrancies have also been described in erythroid cells, most flow cytometry laboratories do not provide erythroid analysis.

The European LeukemiaNET developed a flow cytometric score based on the reproducible parameters of CD34 and CD45 markers to aid in the diagnosis of MDS.[169] The scoring system was developed using multicenter retrospective data from patients with low-grade MDS (defined as <5% marrow blasts; n = 417) and patients with non-clonal cytopenias as controls (n = 380). This patient population was selected because low-grade MDS often lack specific diagnostic markers (eg, ring sideroblasts, clonal cytogenetic abnormalities), which makes it difficult to diagnose based on morphology alone. Bone marrow samples from patients with MDS compared with samples from patients with non-clonal cytopenias showed different flow cytometric patterns, including: 1) increased CD34+ myeloblast-related cluster size (defined by a wider distribution of CD45 expression and greater side scatter [SSC] characteristics); 2) decreased CD34+ B-progenitor cluster size (defined by a relatively low CD45 expression and low SSC); 3) aberrant myeloblast CD45 expression (based on the lymphocyte to myeloblast CD45 ratio); and 4) a decreased granulocyte SSC value (based on the granulocyte to lymphocyte SSC ratio).[169] These four parameters were included in a logistic regression model, and a weighted score (derived from regression coefficients) was assigned to each parameter. The sum of the scores provided the overall flow cytometric score for each sample, with a score of 2 or higher defined as the threshold for MDS diagnosis.[169] Using this flow cytometric score in the learning cohort, a correct diagnosis of MDS was made with 70% sensitivity and 93% specificity. Among MDS patients without specific markers of dysplasia, 65% were correctly identified. The positive predictive and negative predictive values were 92% and 74%, respectively. These outcomes were confirmed in the validation cohort, which showed 69% sensitivity and 92% specificity.[169] This flow cytometric scoring system demonstrated a high diagnostic power in differentiating low-grade MDS from non-clonal cytopenias, and may be particularly useful in establishing a diagnosis in situations where traditional diagnostic methods are

indeterminate. Further independent validation studies are warranted to determine the utility of this method.

Because of the associated expense, the requirement for both technical and interpretational expertise, and the need for greater consensus on specific antibody combinations and procedures that are most informative and cost-effective, flow cytometric assays should be performed by experienced laboratories and used in general practice only when diagnosis is uncertain with traditional approaches (eg, blood counts, morphology, cytogenetics, increased blasts). Flow cytometry studies may also be used to assess the possibility of LGL disease, as indicated by LGLs present in the peripheral blood.[170] In addition, *STAT3* mutations are commonly found in T-LGL disease.[171]

Determination of platelet-derived growth factor receptor beta (*PDGFRβ*) gene rearrangements at 5q32 may be helpful to evaluate in CMML patients.[172] The activation of this gene encoding a receptor tyrosine kinase for *PDGFRβ* has been identified in some of these patients.[173,174] Data have shown that CMML/MPD patients with *PDGFRβ* fusion genes may respond well to treatment with the tyrosine kinase inhibitor imatinib mesylate.[45,175,176]

Evaluation of Related Anemia

Major morbidities of MDS include symptomatic anemia and associated fatigue. Progress has been made in the management of MDS-related anemia; however, the health care provider must also identify and treat any coexisting causes of anemia. Standard assessments should be performed to look for other causes of anemia, such as GI bleeding, hemolysis, renal disease, and nutritional deficiency. If needed, iron, folate, or vitamin B_{12} studies should be obtained and the cause of depletion corrected, if possible. After excluding or providing proper treatment for these causes of anemia, further consideration for treating MDS-related anemia should be undertaken. Anemia related to MDS commonly presents as a hypoproductive macrocytic anemia, often associated with suboptimal elevation of sEpo levels.[3,177] Bone marrow aspiration with iron stain, biopsy, and cytogenetics should be used to determine WHO subtype, iron status, and the level of ring sideroblasts.

Prognostic Stratification

Although the diagnostic criteria allow for categorization of patients with MDS, the highly variable clinical outcomes within these subgroups indicate prognostic limitations. The morphologic features contributing to this variability include the wide range of marrow blast percentages for patients with MDS-EB (5%–19%) and CMML (1%–19%); marrow cytogenetics; and the degree and number of morbidity-associated cytopenias. These well-perceived problems for categorizing patients with MDS have led to the development of additional risk-based stratification systems.[178,179]

Prognostic Scoring Systems

IPSS

The IPSS for primary MDS emerged from deliberations of the International MDS Risk Analysis Workshop (IMRAW).[16] Compared with previous classification systems, the risk-based IPSS markedly improved prognostic stratification of MDS cases. The IPSS was developed based on the combined cytogenetic, morphologic, and clinical data from a relatively large group of MDS cases included in previously reported prognostic studies.[16,178] FAB morphologic criteria were used to establish the diagnosis of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible etiologies for the cytopenias, such as drugs, other diseases, or incipient evolution to AML. CMML was subdivided into proliferative and non-proliferative subtypes. Patients with proliferative-type CMML (those with WBC counts >12,000/mcL) were excluded from this analysis.[16] Patients with non-proliferative CMML (with WBC counts of ≤12,000/mcL plus other features of MDS) were included.[180]

Significant independent variables for determining survival and AML evolution outcomes were marrow blast percentage, number of cytopenias, and cytogenetic subgroup (good, intermediate, and poor). Patients with the chromosome anomalies t(8;21) or inv(16) were considered to have AML and not MDS, regardless of the blast count. Age was also a critical variable for survival, although not for AML evolution. The percentage of marrow blasts was divisible into four categories: 1) less than 5%; 2) 5% to 10%; 3) 11% to 20%; and 4) 21% to 30%.

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

To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroup, and number of cytopenias) were generated.[16] By combining the risk scores for the three major variables, patients were stratified into four distinctive risk groups in terms of both survival and AML evolution: low, intermediate (int)-1, int-2, and high. When either cytopenias or cytogenetic subtypes were omitted from the classification, discrimination among the four subgroups was much less precise. Both for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods.[16]

WPSS

Data have indicated a benefit to the addition of other clinical variables to the IPSS to improve the accuracy of prognosis. The WHO classification-based prognostic scoring system (WPSS) incorporates the WHO morphologic categories, the IPSS cytogenetic categories, and the degree of RBC transfusion dependence.[181] This system demonstrated that the requirement for RBC transfusions is a negative prognostic factor for patients in the lower-risk MDS categories. In addition, depth of anemia *per se* has additive and negative prognostic importance for the intermediate IPSS categories.[182] As compared with the four groups defined by the IPSS, the WPSS classifies patients into five risk groups differing in both survival and risk of AML. The five risk groups are: very low, low, intermediate, high, and very high. Following the initial report by Malcovati et al,[181] there have been confirmatory studies demonstrating the usefulness of the WPSS.[183-185] The initial WPSS has been refined to address the notion that the requirement for RBC transfusion may be somewhat subjective. In the refined WPSS, the measure of the degree of anemia by transfusion dependency is replaced by the presence (or absence) of severe anemia, defined as hemoglobin levels less than 9 g/dL for males and less than 8 g/dL for females.[186] This approach allows for an objective assessment of anemia, while maintaining the prognostic implications of the five risk categories defined in the original WPSS (as mentioned above).[186]

IPSS-R

The IPSS-R defines five risk groups (very low, low, intermediate, high, and very high) versus the four groups in the initial IPSS.[187] The IPSS-R, which was derived from an analysis of a large dataset from multiple international institutions, refined the original IPSS by incorporating the following into the prognostic model: more detailed cytogenetic subgroups, separate subgroups within the “marrow blasts <5%” group, and a depth of cytopenias measurement defined with cutoffs for hemoglobin levels,

platelet counts, and neutrophil counts. In the IPSS-R, the cytogenetic subgroups comprise five risk groups (vs. three in the original IPSS) based on a cytogenetic scoring system for MDS published in 2012.[17] Other parameters including age, performance status, serum ferritin, LDH, and beta-2 microglobulin provided additional prognostic information for survival outcomes, but not for AML evolution; age was more prognostic among lower-risk groups compared with the higher-risk groups.[187] The predictive value of the IPSS-R was validated in a number of independent studies based on registry data, including studies that evaluated outcomes for patients treated with hypomethylating agents.[188-193]

In a multiregional study of MDS patient registry data from Italy (N = 646), significant differences in outcomes among the IPSS-R risk categories were found for OS, AML evolution, and progression-free survival (PFS) (later defined as leukemic evolution or death from any cause).[194] Notably, the predictive power (based on Harrell's C statistics) of the IPSS-R was found to be greater than the IPSS, WPSS, and refined WPSS for the three outcome measures mentioned above. The investigators acknowledged the limitation of a short follow-up (median, 17 months) in the study cohort.[194]

In a retrospective analysis of data from lower-risk MDS (IPSS low or int-1) patients in a large multicenter registry (N = 2410) in Spain, the IPSS-R could identify 3 risk categories (very low, low, intermediate) within the IPSS low-risk group with none of the patients categorized as IPSS-R high or very high.[195] Within the IPSS int-1–risk group, the IPSS-R further stratified patients into four risk categories (very low, low, intermediate, high) with only 1 patient categorized as very high risk. The IPSS-R was significantly predictive of survival outcomes in both the subgroups of IPSS low and int-1 patients. Within the IPSS low-risk group, median survival based on the IPSS-R risk categories was 118.8 months for very low, 65.9 months for low, and 58.9 months for intermediate ($P < .001$). Within the IPSS int-1 risk group, median survival based on the IPSS-R risk categories was 113.7 months for very low, 60.3 months for low, 30.5 months for intermediate, and 21.2 months for high risk ($P < .001$).[195] In addition, within the IPSS int-1 risk group (but not for the IPSS low-risk group), IPSS-R was significantly predictive of the 3-year rate of AML evolution.[195] Thus, in this analysis, the IPSS-R appeared to provide prognostic refinement within the IPSS int-1 group, with a large proportion of patients (511 of 1096 IPSS int-1 patients) identified as having poorer prognosis (median survival, 21–30 months). This study also applied the refined WPSS to further stratify the IPSS low and int-1 risk groups, and was able to identify a group of patients (refined WPSS high-risk group) within the IPSS int-1 group who had poorer prognosis (185 of 1096 IPSS int-1 patients; median survival, 24.1 months). However, the IPSS-R identified a larger proportion of poor-risk IPSS int-1 patients than the refined WPSS (47% vs. 17%).[195]

In a retrospective database analysis of MDS patients from a single institution (N = 1088), median OS according to IPSS-R risk categories was 90 months for very-low-, 54 months for low-, 34 months for intermediate-, 21 months for high-, and 13 months for very-high-risk groups ($P < .005$).[191] The median follow-up in this study was 70 months. IPSS-R was also predictive of survival outcomes among the patients who received therapy with hypomethylating agents (n = 618). Compared to patients not receiving AzaC, a significant survival benefit with AzaC was shown only for the groups of patients with very-high-risk (median survival, 18 vs. 25 months, respectively; $P < .028$) and high-risk IPSS-R (median survival, 15 vs. 9 months, respectively; $P = .005$). In addition, significantly longer OS with allogeneic HCT was only observed for patients at high (median survival, 40 vs. 19 months without HCT; $P < .005$) and very high (median survival, 31 vs. 12 months without HCT; $P < .005$) risk.[191] The IPSS-R may therefore provide a tool for therapeutic decision-making.

A recent study applied the IPSS-R to a series of t-MDS and oligoblastic t-AML (ot-AML) patients.[196] Although some IPSS-R cutpoints were suboptimal for t-MDS/ot-AML patients, the overall IPSS-R scores separated t-MDS/ot-AML patients into five risk groups, with each category showing statistical differences in OS as well as AML progression probability in t-MDS. These findings indicated that the major IPSS-R variables (bone marrow blast count, cytopenias, and cytogenetic data) remained powerful predictors in the therapy-related setting. However, compared to *de novo* MDS/oligoblastic AML, the median OS for each IPSS-R risk group of patients was shorter in t-MDS/ot-AML, particularly in the very-low- and low-risk groups. These differences likely reflect a number of factors, including different biology and clinical approaches (eg, treatment, primary disease, and its therapies) between t-MDS/ot-AML and *de novo* disease. Data from the MDS Clinical Research Consortium similarly demonstrated the improved prognostic value of the IPSS-R in 370 t-MDS patients compared to the IPSS, the global MD Anderson risk model, or the t-MDS MD Anderson model.[197] Further studies are warranted to better evaluate the impact of specific therapies and more refined variables and their cutpoints for analysis of this heterogeneous group of patients.

Other recent studies have confirmed the value of the IPSS-R in treated as well as untreated patients.[193,198-200] Since more accurate risk stratification by the IPSS-R compared to the IPSS and WPSS has been demonstrated,[198] the IPSS-R categorization is preferred, although other systems have good value. It is understood that some ongoing studies are using the IPSS or WPSS. Thus, a transition period is expected before more uniform prognostic risk stratification is accepted by the field. Recent analysis of patients in the International Working Group (IWG) for the Prognosis of MDS database, which generated the IPSS-R, indicated that optimal prognostic separation of lower versus higher-risk patients was obtained by a dichotomization based on 3.5 scoring points of the IPSS-R raw score (ie, ≤3.5 vs. >3.5).[201]

LR-PSS

The Lower-Risk Prognostic Scoring System (LR-PSS), developed by investigators at the MD Anderson Cancer Center, is a prognostic model used in the evaluation of MDS, and was designed to help identify patients with lower-risk disease (IPSS low or int-1) who may have a poor prognosis.[202] The prognostic model was developed using clinical and laboratory data from patients with IPSS low- (n = 250) and int-1– (n = 606) risk MDS. Factors associated with decreased survival were identified and a prognostic model was constructed based on the results of multivariate Cox regression analysis. The final model included the following factors that were independent predictors for survival outcomes: unfavorable cytogenetics, older age (≥60 years), decreased hemoglobin (<10 g/dL), decreased platelet count (<200 × 10^9/L), and higher percentage of bone marrow blasts (≥4%).[202] Importantly, the cytogenetic categories in this system were derived from the previously defined IPSS categories rather than from the more refined IPSS-R. Each of these factors was given a weighted score, and the sum of the scores (range, 0–7 points) was used to generate 3 risk categories: a score of 0 to 2 points was assigned to category 1, a score of 3 or 4 was assigned to category 2, and a score of 5 to 7 was assigned to category 3. Using this scoring system, median survival was 80.3 months for category 1, 26.6 months for category 2, and 14.2 months for category 3; the 4-year survival rates were 65%, 33%, and 7%, respectively. The scoring system allowed for further stratification into these 3 risk categories for both the IPSS low-risk and IPSS int-1–risk subgroups.[202] The LR-PSS may be useful in identifying patients with lower-risk disease who have poorer prognosis and require earlier treatment.

The prognostic value of the LR-PSS has been validated in several independent studies.[69,195,203-205] In a retrospective analysis of data from

lower-risk MDS (IPSS low or int-1) patients in the multicenter Spanish registry (N = 2410), the LR-PSS was able to further stratify these lower-risk patients into 3 risk categories.[195] The LR-PSS was significantly predictive of survival outcomes in both the subgroups of IPSS low and int-1 patients. Within the IPSS low-risk group, median survival was 130.3 months for category 1 (low risk), 69.7 months for category 2 (intermediate risk), and 58.4 months for category 3 (high risk) using the LR-PSS–risk categories ($P < .001$); the corresponding median survival values within the IPSS int-1–risk group using the LR-PSS–risk categories were 115.2 months, 51.3 months, and 24.1 months, respectively ($P < .001$). An important proportion of patients (334 of 1096 patients; 30.5%) within the IPSS int-1–risk group were identified as having a poorer prognosis as indicated by their inclusion in the high-risk group (24.1 months). Within the IPSS int-1–risk group (but not for IPSS low risk), the LR-PSS was significantly predictive of the rate of AML evolution at 3 years.[195]

Data from a cohort of lower-risk MDS patients from two centers (N = 664) demonstrated a median survival according to the LR-PSS risk categories of 91.4 months for category 1, 35.6 months for category 2, and 22 months for category 3.[205] Using data from the same cohort of patients, median survival according to the IPSS-R–risk groups was 91.4 months for IPSS-R very good, 35.9 months for good, and 27.8 months for the combined intermediate-, high-, and very-high-risk groups. Both of these prognostic scoring systems were significantly predictive of survival outcomes. The predictive powers (based on Harrell's C statistics) of the LR-PSS and IPSS-R were 0.64 and 0.63, respectively.[205]

Molecular Abnormalities in MDS

In recent years, several gene mutations have been identified among patients with MDS that may, in part, contribute to the clinical heterogeneity of the disease course, and thereby influence the prognosis of patients. Such gene mutations will be present in the majority of newly diagnosed patients, including most patients with normal cytogenetics. Several studies examining large numbers of MDS tumor samples have identified more than 40 recurrently mutated genes with greater than 80% of patients harboring at least one mutation.[69,206-208] 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 a third of patients. Several of these gene mutations are associated with adverse clinical features such as complex karyotypes (*TP53*), excess bone marrow blast proportion (*RUNX1*, *NRAS*, and *TP53*), and severe thrombocytopenia (*RUNX1*, *NRAS*, and *TP53*).

Despite associations with clinical features considered by prognostic scoring systems, mutations in several genes hold independent prognostic value. Mutations of *TP53*, *EZH2*, *ETV6*, *RUNX1*, and *ASXL1* have been shown to predict decreased OS in multivariable models adjusted for IPSS or IPSS-R risk groups in several studies of distinct cohorts.[206,208] Within IPSS risk groups, a mutation in one or more of these genes identifies patients whose survival risk resembles that of patients in the next highest IPSS risk group (eg, the survival curve for int-1–risk patients with an adverse gene mutation was similar to that of patients assigned to the int-2–risk group by the IPSS).[206] When applied to patients stratified by the IPSS-R, the presence of a mutation in one or more of these five genes was associated with shorter OS for patients in the low- and intermediate-risk groups.[208] Thus, the combined analysis of these gene mutations and the IPSS or IPSS-R may improve upon the risk stratification provided by these prognostic models alone. Mutations of *ASXL1* have also been shown to carry independent adverse prognostic significance in CMML.[209,210] Other mutated genes have been associated with decreased OS, including *DNMT3A*, *U2AF1*, *SRSF2*, *CBL*, *PRPF8*, *SETBP1*, and *KRAS*.[206,208,211-214] 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.[15,208,215]

TET2 mutations have been shown to impact the response to hypomethylating agents.[216,217] Patients with mutated *TET2* had an 82% response rate to AzaC compared to 45% of patients with wild-type *TET2* (*P* = .007). Response duration and OS were not statistically different.[216] Another study identified 39 genes that were mutated in 213 patients with MDS treated with AzaC or decitabine.[217] A higher response to hypomethylating agents in patients with the *TET2* mutation, albeit to a lesser degree, was seen (response rate, 55% vs. 44%; *P* = .14). This improved response was more pronounced when patients with *ASXL1* mutations and those with only low abundance *TET2* mutations were excluded (OR, 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.

Mutations of *TP53* are strongly associated with complex and monosomal karyotypes. However, approximately 50% of patients with a complex karyotype have no detectable *TP53* abnormality and have an OS that is comparable to that of patients with non-complex karyotypes. Therefore, *TP53* mutation status may be useful for refining the prognosis of these patients typically considered to have higher-risk disease.[206] 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.[218,219] These mutations are associated with diminished response or relapse after treatment with lenalidomide.[220,221] In these cases, *TP53* mutations may be secondary events and are often present in small subclones that can expand during treatment. More sensitive techniques may be required to identify the presence of subclonal, low-abundance *TP53* mutations prior to treatment.

Mutations identified in peripheral blood samples can accurately reflect mutations detected in the bone marrow of patients with MDS when more sensitive sequencing techniques are used to detect them.[222]

Comorbidity Indices

Patients with MDS predominantly comprise an elderly adult population, posing potential challenges in terms of treatment tolerability and outcomes due to the presence of comorbid conditions. About 50% of patients with newly diagnosed MDS present with one or more comorbidities, with cardiac disease and diabetes among the most frequently observed conditions.[223-227] Assessment of the presence and degree of comorbidities using tools such as the Charlson Comorbidity Index (CCI) or the Hematopoietic Stem Cell Transplantation-Specific Comorbidity Index (HCT-CI) has demonstrated the significant prognostic influence of comorbidities on the survival outcome of patients with MDS.[223,225-227] Recent studies have shown that comorbidity (as measured by HCT-CI or Adult Comorbidity Evaluation-27) was a significant prognostic factor for survival, independent of IPSS.[224,227] In these studies, comorbidity indices provided additional prognostic information for survival outcomes in patients categorized as IPSS intermediate or high risk, but not for patients considered to have low-risk disease.

Conversely, in another study, comorbidity (as measured by HCT-CI or CCI) was a significant predictor of OS and event-free survival in patients within the low-risk or int-1–risk groups, but not in the int-2–risk or high-risk groups.[225] Comorbidity has also been shown to provide additional risk stratification among WPSS risk categories (for very low-, low-, and intermediate-risk groups but not for high- or very-high-risk groups), prompting the development of a new MDS-specific comorbidities index

that can be used in conjunction with WPSS for the assessment of prognosis.[228] Improved risk stratification has also been demonstrated with the incorporation of the Myelodysplastic Syndromes Comorbidity Index with the IPSS-R.[200] At this time, the NCCN MDS Panel makes no specific recommendations with regard to the optimal comorbidity index to be used for patients with MDS. However, a thorough evaluation of the presence and extent of comorbid conditions remains an important aspect of treatment decision-making and management of patients with MDS.

Therapeutic Options

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

If the patient was only recently evaluated, determining the relative stability of the patient's blood counts over several months is important to assess whether the disease progresses, including incipient transformation to AML. In addition, this assessment permits determination of other possible etiologies for cytopenias. The patient's preference for a specific approach is also important in deciding treatment options. The therapeutic options for MDS include supportive care, low-intensity therapy, high-intensity therapy including allogeneic 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.[229-231]

For the MDS therapeutic algorithm, all patients should receive relevant supportive care. Following that, the MDS Panel has proposed initially stratifying patients with clinically significant cytopenia(s) into two major risk groups: 1) 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 two risk groups depending on evaluation of additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels.[187] In addition, intermediate-risk patients with disease that 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 natural history of disease 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 t-MDS have poorer prognoses than those with primary MDS, including a substantial proportion with poor-risk cytogenetics. These patients are generally managed as having higher-risk disease.

Supportive Care

Currently, the standard of care for MDS management includes supportive care measures (see *Supportive Care* in the algorithm and the NCCN Guidelines for Supportive Care). This entails observation, clinical monitoring, psychosocial support, and QOL assessment. Major efforts should be directed toward addressing the relevant QOL domains (eg, physical, functional, emotional, spiritual, social), which adversely affect the patient. Supportive care should include RBC transfusions for symptomatic anemia as needed (CMV-safe) or platelet transfusions for bleeding events; however, platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding. Both the number of transfusions as well as the number of packed RBCs per transfusion should

be kept to a minimum in non-cardiac patients and in patients anticipated to be heavily transfused. The NCCN Guidelines Panel is in agreement with the 2013 American Society of Hematology (ASH) Choosing Wisely® initiative addressing hematologic tests and treatments.[232] There was non-uniform consensus among the panel members based on differing institutional policies regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agreed that all directed-donor products and transfused products for potential HCT patients should be irradiated. Additionally, CMV-safe (CMV-negative or leukopheresed) blood products are recommended whenever possible for CMV-negative recipients. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding episodes refractory to platelet transfusions or for profound thrombocytopenia. Hematopoietic cytokine support should be considered for refractory symptomatic cytopenias.[233] For example, recombinant human granulocyte colony-stimulating factor (G-CSF) or GM-CSF treatment could be considered for neutropenic MDS patients with recurrent or resistant bacterial infections.

Management of Thrombocytopenia

Severe thrombocytopenia is associated with an increased risk for bleeding events, and is currently managed with platelet transfusions. The mechanism of thrombocytopenia in patients with MDS may be attributed to decreased platelet production (possibly related to regulatory pathways involving the production and/or metabolism of endogenous thrombopoietin [TPO]) as well as increased destruction of bone marrow megakaryocytes or circulating platelets.[234,235] Increased endogenous TPO levels have been reported among patients with MDS compared with healthy individuals.[235] At the same time, TPO receptor sites per platelet were decreased among patients with MDS compared with healthy subjects. The RA subgroup (as defined by Bennett et al[236]) appeared to have the highest TPO levels compared with MDS-EB or MDS-EB-T patients, while the number of TPO receptor sites remained similar across subtypes.[235] Studies have reported that high endogenous TPO levels correlated with decreased platelet counts in RA patients, but not in MDS-EB or MDS-EB-T patients.[235,237] This observation suggests that the regulatory pathway for endogenous TPO may be further disrupted in the latter group, potentially due to overexpression of TPO receptors in blasts that could lead to an inadequate TPO response.[235,237]

Several studies are investigating the role of the TPO receptor agonist romiplostim in the treatment of thrombocytopenia in patients with lower-risk MDS.[238-243] Phase I/II studies with romiplostim showed promising rates of platelet response (46%–65%) in patients with lower-risk MDS.[239,241] Randomized placebo-controlled studies in patients treated for lower-risk MDS have reported beneficial effects of romiplostim in terms of decreased bleeding events, reduced need for platelet transfusions in patients receiving hypomethylating agents,[238,240] and decreased frequency of dose reductions or delays in patients receiving lenalidomide therapy.[242] In a randomized study including patients with low- or int-1–risk MDS (n = 250), romiplostim was associated with increased platelet counts and decreased overall bleeding events (P = .026 after 58 weeks of treatment compared to the placebo group).[244] However, due to the early drug discontinuation, interpretation of these data is limited. Following up on previous studies,[239,244] an open-label extension study evaluated the long-term safety and efficacy of romiplostim in 60 patients with lower-risk MDS and found that most patients achieved durable responses.[245] A model to predict response to romiplostim indicated that lower-risk MDS, lower baseline TPO levels (<500 pg/mL), and limited platelet transfusion history had the greatest effect on subsequent platelet response to romiplostim.[243]

Eltrombopag is another TPO receptor agonist that has been shown to increase normal megakaryopoiesis in vitro in bone marrow cells isolated from patients with MDS.[246,247] Ongoing phase I and II clinical trials are investigating the activity and safety of this agent for the treatment of

thrombocytopenia in patients with lower-risk MDS. Early data from a phase II, multicenter, prospective, placebo-controlled study indicate that eltrombopag may significantly improve platelet counts and fatigue.[248] This study enrolled 70 patients with low-risk or IPSS intermediate-1 risk MDS and severe thrombocytopenia who were randomized 2:1 to receive eltrombopag or placebo. At the time of interim analysis, 23 patients (50%) receiving eltrombopag had an improvement in platelet counts compared with 2 patients (8%) in the placebo control group (P = .016), while there were no significant changes in the placebo group.[248] A recent follow-up report with additional patients (n = 90) demonstrated improved platelet responses in patients in the eltrombopag group when compared to the placebo group (47% vs. 3%, respectively; P = .0017).[249]

A phase II trial is evaluating eltrombopag in combination with hypomethylating agents in adults who have had greater than 4 cycles of hypomethylating agents but who have disease that fails to respond to treatment or disease that continues to have ongoing cytopenias.[250] Out of 23 patients enrolled in the study, 16 had an evaluable response. Although platelet improvement was seen in 3 patients and 8 patients remain on study with stable disease, these results are very preliminary and a larger prospective trial is needed.[250] Another phase II trial is evaluating eltrombopag for thrombocytopenia in adult patients with intermediate-2 or high-risk MDS and AML.[251]

Concerns for potential proliferation of leukemic blasts in response to exogenous TPO have been raised in earlier in vitro studies, particularly for high-risk MDS cases.[252,253] Results from ongoing clinical trials with TPO mimetics will help to elucidate the risks for leukemic transformations in patients with MDS. It should be noted that neither romiplostim nor eltrombopag are currently approved for use in patients with MDS.

Management of Iron Overload

RBC transfusions are a key component in the supportive care of MDS patients. Although the specific therapies patients receive may alleviate RBC transfusion need, a substantial proportion of MDS patients may not respond to these treatments and may develop iron overload and its consequences.[254] Thus, effective treatment of transfusional siderosis in MDS patients may be necessary.

Studies in patients requiring relatively large numbers of RBC transfusions (eg, thalassemia, MDS) have demonstrated the pathophysiology and adverse effects of chronic iron overload on hepatic, cardiac, and endocrine function. Increased non-transferrin–bound iron, generated when plasma iron exceeds transferrin-binding capacity, combines with oxygen to form hydroxyl and oxygen radicals. These toxic elements cause lipid peroxidation and cell membrane, protein, DNA, and organ damage.[255,256]

Although limited, there is evidence suggesting that organ dysfunction can result from iron overload in patients with MDS.[257-259] Retrospective data indicate that transfusional iron overload might be a contributor of increased mortality and morbidity in early-stage MDS.[260] The WPSS has shown that the requirement for RBC transfusion is a negative prognostic factor for patients with MDS.[181] In a meta-analysis including 8 observational studies, patients receiving iron chelation therapy had a longer median survival time compared to patients who did not receive therapy. The mean difference in median OS was 61.2 months, further supporting the need to control transfusional iron overload.[261] However, prospective studies are required to substantiate the value of iron chelation in these patients.

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The NCCN Panel Members recommend monitoring serum ferritin levels and number of RBC transfusions received as a practical

means to determine iron stores and assess iron overload. Monitoring serum ferritin may be useful, aiming to decrease ferritin levels to less than 1000 mcg/L. It is recognized that such measurements, though useful, are less precise than SQUID (Superconducting Quantum Interference Device), or more recently T2* MRI, to provide a specific measurement of hepatic iron content.[262,263]

Reversal of some of the consequences of iron overload in MDS and other iron overload states by iron chelation therapy has been shown in patients in whom the most effective chelation occurred.[231,256] This included transfusion independence (TI) in a subset of the small group of MDS patients who had undergone effective deferoxamine chelation for 1 to 4 years.[264] In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.[265] Such findings have major implications for altering the morbidity of MDS patients, particularly those with pre-existing cardiac or hepatic dysfunction.

The availability of iron chelators, such as deferoxamine[266] and deferasirox,[267-269] provide potentially useful drugs to more readily treat iron overload. Deferoxamine (given as intramuscular or subcutaneous [SC] injections) is indicated for the treatment of chronic iron overload due to transfusion-dependent (TD) anemias.[266] Deferasirox (given orally) is indicated for the treatment of chronic iron overload due to blood transfusions.[267] Deferasirox has been evaluated in multiple phase II clinical trials in patients with TD-MDS.[270-272] A large, multicenter, phase III, randomized controlled trial is currently underway to evaluate outcomes of deferasirox compared with placebo in patients with MDS; the primary endpoint of this ongoing study is event-free survival (registered at clinicaltrials.gov; NCT00940602). The prescribing information for deferasirox contains a black-box warning pertaining to the increased risks for renal or hepatic impairment/failure and GI bleeding in certain patient populations, including patients with high-risk MDS. Deferasirox is contraindicated in patients with high-risk MDS.

A third oral chelating agent, deferiprone, was approved (October 2011) in the United States for the treatment of patients with transfusional iron overload due to thalassemia when current chelation therapy is inadequate.[273] FDA approval was based on results from a retrospective analysis of data pooled from previous safety and efficacy studies of deferiprone in patients with transfusion-related iron overload refractory to existing chelation therapy. The prescribing information for deferiprone contains a black-box warning pertaining to risks for agranulocytosis, which can lead to serious infections and death.[273] Controversy remains regarding the use of this agent.

There are ongoing clinical trials in patients with MDS receiving oral iron-chelating agents to address whether iron chelation alters the natural history of patients who are TD. The NCCN Task Force report, titled *Transfusion and Iron Overload in Patients with Myelodysplastic Syndromes*, provides detailed evidence regarding iron chelation in patients with MDS.[274]

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

As mentioned above, a black-box warning was added to the prescribing information for deferasirox.[267] Following post-marketing use of deferasirox, there were case reports of acute renal failure, or hepatic failure, some of which were fatal. Most of the fatalities reported were in patients with

multiple comorbidities and in advanced stages of their hematologic disorders. Additionally, there were post-marketing reports of cytopenias, including agranulocytosis, neutropenia, and thrombocytopenia, and GI bleeding in patients treated with deferasirox; some cases resulted in death. The relationship of these episodes to treatment with deferasirox has not yet been established. However, it is recommended that patients on deferasirox therapy be closely monitored. Monitoring should include measurement of serum creatinine and/or creatinine clearance and liver function tests prior to initiation of therapy and regularly thereafter. Deferasirox and deferoxamine should be avoided in patients with creatinine clearance less than 40 mL/min.[267]

Treatment of Related Anemia

Erythropoiesis-stimulating agents (ESAs) such as recombinant human Epo (rHu Epo) or the longer-acting darbepoetin, with or without G-CSF, have been evaluated in the treatment of symptomatic anemia in patients with MDS. Studies predominantly in lower-risk MDS patients have demonstrated erythroid response rates of 40% and 60% (combined major and minor responses using IWG response criteria) in the initial trials.[275,276] Clinical trial results in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than epoetin.[275-278] The improved response rates may in part be due to the dosage used (150–300 mcg SC per week) or to the fact that better-risk patients were enrolled in studies of darbepoetin compared to epoetin. Features predictive of response have included relatively low basal sEpo levels, low percentage of marrow blasts, and few prior RBC transfusions.

In a phase II study of patients with MDS (RA, MDS-RS, and MDS-EB; N = 50), Epo combined with G-CSF (n = 47 evaluable) resulted in hematologic responses in 38% of patients (complete response [CR], 21%).[279] 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.[279] Median survival, including in patients from a prior study, was 26 months (N = 71). Among patients with low-risk IPSS, median survival had not been reached at 5 years; the 5-year survival rate was 68%. Median survival times among the int-1– and int-2–risk groups were 27 months and 14 months, respectively. AML progression occurred in 28% of patients overall during the observation period. The frequency of AML progression in the low-, int-1–, int-2–, and high-risk groups were 12%, 21%, 45%, and 100%, respectively. Among patients with responding disease who received maintenance treatment with Epo and G-CSF, the median duration of response was 24 months.[279]

A subsequent analysis of combined data from three phase II Nordic trials (n = 121) on the long-term outcomes with Epo plus G-CSF (given for 12–18 weeks and followed by maintenance in responders) in patients with MDS reported a hematologic response rate of 39% with a median duration of response of 23 months.[280] 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 fewer than 2 units of RBC transfusions per month. No significant association was found between the treatment and frequency of AML progression.[280]

Similar findings were reported in a study from the French myelodysplasia group, which analyzed outcomes with ESAs (epoetin or darbepoetin), with or without G-CSF, in MDS patients with anemia (N = 403).[281] Based on the IWG 2000 criteria, the hematologic response rate was 62% with a median

duration of 20 months; the corresponding results from the IWG 2006 criteria were 50% and 24 months, respectively. IPSS low- 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. The frequency of AML progression was similar between the cohorts.[281] In a phase II study that evaluated darbepoetin (given every 2 weeks for 12 weeks), with or without G-CSF (added at 12 weeks in non-responders), 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.[282] 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.[282]

Collectively, these studies suggest that ESAs may provide clinical benefit to patients in the lower-risk group with symptomatic anemia. Limited data are available on the effectiveness of ESAs in the treatment of anemia in lower-risk patients with del(5q). Epo has been shown to promote the growth of cytogenetically normal cells isolated from patients with del(5q), while having minimal proliferative effects on MDS progenitor cells from these patients in vitro.[283] 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.[281,284] Duration of response in these patients was significantly decreased compared with patients without del(5q) (mean duration, 25–27 months).[284] Based on multivariate analysis, del(5q) was a significant predictor of a shorter response duration with treatment (see *Prognostic Category Low, Intermediate-1 Treatment* in the algorithm).[281]

In March 2007 and 2008, the FDA announced alerts and strengthened safety warnings for the use of ESAs based on observed increased mortality and possible tumor promotion and thromboembolic events *in non-MDS patients* receiving ESAs when dosing to achieve a targeted hemoglobin level greater than 12 g/dL. Specifically, the study patients had chronic kidney failure; were receiving radiation therapy for various malignancies, including head and neck cancer, advanced breast cancer, lymphoid cancer, or non-small cell lung cancer; were patients with cancer not receiving chemotherapy; or were orthopedic surgery patients. However, ESAs have been used safely in large numbers of adult MDS patients and have become important for symptomatic improvement of anemia caused by this disease, often with a decrease in RBC transfusion requirements. Studies assessing the long-term use of Epo with or without G-CSF in MDS patients have shown no negative impact of such treatment on survival or AML evolution when compared to either randomized controls[285] or historical controls.[280,281]

Jadersten et al[280] reported improved survival in low-risk MDS patients with low transfusion need following treatment with these agents.[280] In another study, improved survival and decreased AML progression of IPSS low or int-1 patients following Epo treatment, with or without G-CSF, compared to the historical control IMRAW database patients were reported.[281] Thus, these data do not indicate a negative impact of these drugs in the treatment of MDS. Given these data, the NCCN Panel recommends the use of ESAs in the management of symptomatic anemia in MDS patients, with a target hemoglobin range of 10 to 12 g/dL but not exceeding 12 g/dL. Clinical trials with other experimental agents that are reportedly capable of increasing hemoglobin levels should be explored in patients with disease that 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 in non-renal disease applications. Following a public comment period, it was determined that the scope of the NCD should be revised to include cancer and related neoplastic conditions. The narrowed scope of the NCD excludes MDS as it is defined in the report as a premalignant condition and not an oncologic disease.[286] Thus, local Medicare contractors may continue to make reasonable and necessary determinations on the use of ESAs that are not determined by the NCD.

Treatment of MDS-Related ESA-Refractory Anemia

Anemia associated with lower-risk MDS generally becomes resistant to available treatment, leading to a dependence on RBC transfusions, iron overload, and decreased quality of life and survival.[187,287-289] In November 2019, the FDA approved the use of luspatercept for the treatment of anemia in adult patients with beta thalassemia who require regular RBC transfusions. Luspatercept is a recombinant fusion protein made up of a modified extracellular domain of the human activin receptor type IIB linked to the human IgG1 Fc domain that binds transforming growth factor beta (TGFβ) ligands to reduce SMAD2 and SMAD3 signaling, which enables erythroid maturation.[290] Encouraging data are emerging demonstrating the effectiveness of luspatercept for treating anemia of ring sideroblastic lower-risk MDS in patients who are refractory to ESAs.[289,291] In a phase III trial (MEDALIST), patients with very-low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts who had been receiving regular RBC transfusions were either treated with luspatercept (n = 153) or given placebo (n = 76).[289] In this trial, eligible patients were ≥18 years of age; had MDS with ring sideroblasts according to the WHO criteria (ie, either ≥15% ring sideroblasts or ≥5% ring sideroblasts if an *SF3B1* mutation was present, and with <5% bone marrow blasts); and had disease that was refractory to or was unlikely to respond to ESAs.[289] During weeks 1 through 24 of treatment, 38% of patients in the luspatercept group, compared to 13% of those in the placebo group, met the study primary end point of transfusion independence for 8 weeks or longer ($P < .001$).[289] The median duration of the longest single continuous period of response to luspatercept was 30.6 weeks.[289] The most common adverse events associated with luspatercept included fatigue, diarrhea, asthenia, nausea, and dizziness, which decreased over time.[289]

In a phase II multicenter, open-label, dose-finding study (PACE-MDS), adult patients (≥18 years of age) with low- or intermediate-1 risk MDS or non-proliferative CMML who had anemia with or without RBC transfusion support were treated with luspatercept (n = 58).[291] Of importance, 78% of the treated patients had ≥15% ring sideroblasts, which was a positive predictor of response. Some patients were enrolled in a dose-escalation cohort (n = 27) receiving luspatercept once every 21 days at doses ranging from 0.125–1.75 mg/kg over a maximum of 12 weeks. Other patients enrolled in the dose-expansion cohort (n = 31) received luspatercept doses ranging from 1.0–1.75 mg/kg, and patients could be treated for up to 5 years.[291] Thirty-two of 51 patients (63%) who received higher doses of luspatercept (0.75–1.75 mg/kg) achieved hematologic improvement-erythroid, defined as: hemoglobin concentration increase of ≥1.5 g/dL from baseline for at least 14 days in low transfusion burden patients, and a reduction in RBC transfusion of ≥4 RBC units or ≥50% reduction in RBC units over 8 weeks versus pre-treatment transfusion burden in high transfusion burden patients.[291]

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.[292-295] In a phase III trial that compared AzaC with supportive care in patients from all IPSS risk groups (N = 191; previously untreated in 83%), hematologic responses occurred in 60% of patients in the AzaC arm (7% CR, 16% partial response [PR], and 37% hematologic improvement) compared with a 5% hematologic improvement (and no responses) in patients receiving supportive care.[295] The median time to AML progression or death was significantly prolonged in the AzaC arm compared with patients receiving supportive care (21 vs. 13 months; *P* = .007). Further improvement was seen in patients who received AzaC earlier in the course of disease, suggesting that the drug prolonged the duration of stable disease. Subsequently, Silverman and colleagues[296] provided a summary of three AzaC studies in a total of 306 patients with high-risk MDS.[296] In this analysis, which included patients receiving either SC or intravenous (IV) delivery of the drug, complete remissions were seen in 10% to 17% of AzaC-treated patients and partial remissions were rare; hematologic improvement was seen in 23% to 36% of these patients. Ninety percent of the responses occurred prior to cycle 6 with a median number of cycles to first response of 3.[296] 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.[292] AzaC was associated with a significantly longer median survival compared with conventional care (24.5 vs. 15 months; HR, 0.58; 95% CI, 0.43–0.77; *P* = .0001), thus providing support for the use of this agent in patients with higher-risk disease.

AzaC therapy should be considered for treating MDS patients with progressing or relatively high-risk disease. This drug has been approved by the FDA for the treatment of patients with MDS and is generally administered at a dose of 75 mg/m^2/day SC 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 prior to HCT). Although the optimal duration of therapy with AzaC has not been defined, some data suggest that continuation of AzaC beyond first response may improve remission quality. 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.[297] 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.[297] In this study, the median number of cycles from first response to best response was 3 to 3.5 cycles, and patients with responding disease received a median of 8 additional cycles (range, 0–27 cycles) beyond first response.[297]

An alternative 5-day schedule of AzaC has been evaluated, both as an SC regimen (including the 5-2-2 schedule: 75 mg/m^2/day SC for 5 days followed by 2 days of no treatment, then 75 mg/m^2/day for 2 days, every 28 days; and the 5-day schedule: 75 mg/m^2/day SC for 5 days every 28 days)[298] and as an IV regimen (75 mg/m^2/day IV for 5 days every 28 days).[299] Although response rates with the 5-day regimens appeared similar to the approved 7-day dosing schedule,[298,299] survival benefit with AzaC has only been demonstrated using the 7-day schedule.

Decitabine, given IV and administered with a regimen that required hospitalization of patients, has also shown encouraging results for the

therapy of patients with higher-risk MDS. As the treatment regimen was generally associated with low-intensity–type toxicities, it is also considered to be a "low-intensity therapy." In earlier phase II studies, approximately 30% of patients experienced cytogenetic conversion,[300] with an overall response rate of 49%, and a 64% response rate was seen in patients with a high-risk IPSS score[301]; results were similar to those seen in AzaC studies.[293,302]

A phase III randomized trial of decitabine (15 mg/m^2 IV infusion over 3 hours every 8 hours [ie, 45 mg/m^2/day] on 3 consecutive days every 6 weeks for up to 10 cycles) compared with supportive care in adult patients (N = 170) with primary and secondary MDS (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.[293] Overall response rate (CR + PR) with decitabine was 17% (median duration, 10 months), with an additional 13% of patients showing hematologic improvement. The probability of progression to AML or death was 1.68-fold greater for supportive care patients than for patients receiving decitabine. Based on this study and three supportive phase II trials,[303] the drug has also been approved by the FDA for treating MDS patients.

In another phase III randomized trial with this regimen, decitabine was compared with best supportive care (BSC) in patients aged 60 years or older (N = 233; median age, 70 years; range, 60–90 years) with higher-risk MDS (IPSS int-1, 7%; int-2, 55%; high risk, 38%) not eligible for intensive therapy.[294] Median PFS was significantly improved in patients receiving decitabine compared with supportive care (6.6 vs. 3 months; HR, 0.68; 95% CI, 0.52–0.88; *P* = .004), and the risk of AML progression at 1 year was reduced with decitabine (22% vs. 33%; *P* = .036). However, no significant differences were observed between decitabine and supportive care for the primary endpoint of OS (10 vs. 8.5 months, respectively) or for median AML-free survival (8.8 vs. 6.1 months, respectively).[294] In the decitabine arm, a CR and PR were observed in 13% and 6% of patients, respectively, with hematologic improvement in an additional 15%; in the supportive care arm, hematologic improvement was seen in 2% of patients (with no hematologic responses). 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.[294]

In 2007, Kantarjian and colleagues[304] provided an update to their study of 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens.[304] Patients received 1 of 3 different schedules of decitabine, including both SC and IV administration with a mean of 7 courses of therapy. Responses were improved with the longer duration of therapy. Overall, 80 patients (70%) responded with 40 patients achieving a CR and 40 achieving a PR. The median remission duration was 20 months with a median survival time of 22 months. The three different schedules of decitabine were compared in another randomized study of 95 patients with MDS or CMML, receiving 20 mg/m^2/day IV for 5 days; 20 mg/m^2/day SC for 5 days; or 10 mg/m^2/day IV for 10 days.[305] The 5-day IV schedule was considered the optimal schedule. The CR rate in this arm was 39%, compared with 21% in the 5-day SC arm and 24% in the 10-day IV arm ($P < .05$). 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 prior to allogeneic HCT (with both myeloablative and reduced-intensity conditioning [RIC] regimens).[306-309] These studies suggest that hypomethylating agents may provide a feasible alternative to induction chemotherapy regimens prior to transplant, and may serve as a bridge to allogeneic HCT. A randomized

trial comparing the two strategies is currently ongoing (clinicaltrials.gov NCT01812252). However, these agents should not be used in lieu of early transplantation or to delay transplantation until loss of response or disease progression.[310]

AzaC and decitabine are considered to be therapeutically similar, although the improved survival of higher-risk patients treated with AzaC compared to control patients in a phase III trial, as indicated above, supports the preferred use of AzaC in this setting 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 prior to 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 who respond to DMTI hypomethylating agents, the 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 delay in receipt of that procedure is anticipated (eg, due to need to further reduce the blast count, improve patient performance status, or identify a donor). In these circumstances, the drugs may be used as a bridging therapy for that procedure; or
- Patients who are not expected to respond to (or who relapsed after) ESAs or IST.

Biologic Response Modifiers and Immunosuppressive Therapy

The currently available non-chemotherapy, low-intensity agents (biologic response modifiers) include: ATG, cyclosporine, and lenalidomide, all of which have shown some efficacy in phase II and phase III trials.[3,311-316]

Use of IST with ATG, with or without cyclosporine,[314,316] has been shown in several studies to be most efficacious in MDS patients with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a PNH clone.[147,317] Researchers from the NIH have updated their analysis of 129 patients treated with IST with equine ATG alone, cyclosporine alone, or in combination.[149] This study demonstrated markedly improved response rates in the subgroup of patients 60 years of age or younger with IPSS int-1 risk or patients with high response probability characteristics as indicated by their prior criteria (ie, age, number of transfusions, possibly HLA-DR15 status).[149]

Although equine ATG has been found to be more effective than rabbit ATG for treating AA,[318] only limited data within the setting of MDS are available regarding the comparative effectiveness of the two ATG formulations. In a relatively small phase II study in patients with MDS (N = 35; primarily RA subtype), both equine and rabbit ATG were shown to be feasible and active.[319] Some institutions have used tacrolimus in place of cyclosporine A based on the limited data that showed similar efficacy with lower incidence of adverse events in children with AA.[320,321]

A recent study showed that STAT3-mutant cytotoxic T-lymphocyte clones are present in a small proportion (5%) of MDS patients (including those lacking LGLs), which is associated with HLA-DR15 positivity, marrow hypocellularity, and neutropenia.[148] Despite lack of a survival difference in the STAT3-mutated versus non-mutated MDS patients treated with IST in

this small cohort, these findings suggest that STAT3-mutant cytotoxic T-lymphocyte clones may facilitate persistently dysregulated autoimmune activation akin to that present in other MDS patients responsive to IST.[148]

Lenalidomide (a thalidomide analog) is an immunomodulating agent with activity in patients with lower-risk MDS.[30,322] Beneficial results have been particularly evident for patients with the del(5q) chromosomal abnormality.[30,322,323] A multicenter phase II trial of lenalidomide (10 mg/day for 21 days every 4 weeks or 10 mg daily) in anemic RBC-TD MDS patients with del(5q), with or without additional cytogenetic abnormalities (N = 148), demonstrated that the hematologic response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained.[30] RBC-TI (assessed at 24 weeks) occurred in 67% of patients; among patients with IPSS low/int-1 risk (n = 120), 69% achieved TI.[30] Cytogenetic responses were achieved in 62 of 85 evaluable patients (73%); 45% had a complete cytogenetic response. The most common grade 3 or 4 adverse events included myelosuppression (neutropenia, 55%; thrombocytopenia, 44%), which often required treatment interruption or dose reduction. Thus, careful monitoring of blood counts during the treatment period is mandatory when using this agent, particularly in patients with renal dysfunction (due to the drug's renal route of excretion). Lenalidomide has been approved by the FDA for the treatment of TD anemia in IPSS low/int-1–risk MDS patients with del(5q) with or without additional cytogenetic abnormalities.

A phase III randomized controlled trial compared the activity of lenalidomide (5 mg/day for 28 days or 10 mg/day for 21 days every 28 days) versus placebo in RBC-TD patients (N = 205) with lower-risk MDS (IPSS low- and int-1 risks) and del(5q).[324] The primary endpoint of RBC-TI greater than or equal to 26 weeks was achieved in a significantly greater proportion of patients treated with lenalidomide (5 mg or 10 mg) versus placebo (37% vs. 57% vs. 2%, respectively; $P \leq .0001$ for both lenalidomide groups vs. placebo). Among patients achieving RBC-TI with lenalidomide, onset of erythroid response was rapid, with a median time of 4.2 weeks and 4.3 weeks in the 5-mg and 10-mg lenalidomide groups, respectively.[324] 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. The estimated 2-year cumulative risk to AML progression was 17% (95% CI, 8.7–33.3), 12.6% (95% CI, 5.4–27.7), and 16.7% (95% CI, 8.3–32.0) in the lenalidomide 5-mg, 10-mg, and placebo groups, respectively. This increased to 35% (95% CI, 21.4–54.6), 31% (95% CI, 18.1–48.8), and 43.3% (95% CI, 27.6–63.1), respectively, at the estimated 4-year mark. The median OS 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 to nonresponders (2.7 years; 95% CI, 2.0–4.7). The most common grade 3 or 4 adverse events were myelosuppression and deep vein thrombosis (DVT). Grade 3 or 4 neutropenia was reported in 77%, 75%, and 16% of patients 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 DVT occurred in 3 patients in the lenalidomide 10-mg arm and in one patient in the placebo arm.[324]

A recent comparative analysis evaluated outcomes of patients with RBC-TD IPSS low/int-1–risk MDS with del(5q) receiving lenalidomide (based on data from the two aforementioned trials [n = 295]) compared with no treatment (based on data from untreated patients in a multicenter registry [n = 125]).[325] 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; the corresponding 5-year rates were 23% and 20%, respectively; the median time to AML progression had not been reached in either cohort at the 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; the corresponding 5-year OS probabilities were 54% and 40.5%, respectively, with a median OS of 5.2 years and 3.8 years (P = .755).[325] 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.[325]

A phase II study evaluated lenalidomide treatment in RBC-TD patients (N = 214) with low- or int-1–risk MDS without del(5q).[326] Results showed that 26% of the non-del(5q) patients (56 of 214) achieved TI after a median of 4.8 weeks of treatment. TI continued for a median duration of 41 weeks. The median rise in hemoglobin was 3.2 g/dL (range, 1.0–9.8 g/dL) for those achieving TI. A 50% or greater reduction in transfusion requirement was noted in an additional 37 patients (17%), yielding an overall rate of hematologic improvement of 43%. The most common grade 3 or 4 adverse events were neutropenia (30%) and thrombocytopenia (25%).

An international phase III study of 239 patients with IPSS low- or int-1–risk MDS and RBC-TD and lacking the del(5q) abnormality evaluated the role of lenalidomide treatment.[311] Patients receiving lenalidomide (n = 160) compared to 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 greater than 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 4 or more 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 the patients 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.[311] Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents for non-del(5q) MDS patients, particularly addressing the characterization of the subgroup of patients with MDS who responded to lenalidomide. The NCCN Guidelines Panel recommends lenalidomide be considered for patients with symptomatically anemic non-del(5q) MDS with anemia that 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/day for 21 days every 28 days) with patients receiving lenalidomide in conjunction with rHu Epo (60,000 U/wk).[327] 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 groups (13.8% vs. 24.2%; P = .13). However, in a subgroup analysis that excluded heavily RBC-TD patients (defined as receiving greater than 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.[327]

High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy or HCT.[3,328] 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.[329]

A high degree of multi-drug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS[330] 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 multi-drug resistance modulators are important, as both positive[331,332] and negative[333] studies have been published.

Allogeneic HCT from an HLA-matched sibling, matched unrelated, or alternative (including haploidentical or cord blood when appropriate) donor is a preferred approach for treating select patients with MDS, particularly those with high-risk disease.[334-344] 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 who relapse 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 lower-risk MDS patients (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.[345] Comparative clinical trials are needed to address these issues.

Recommended Treatment Approaches

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

Regarding the therapeutic options for lower-risk patients with clinically significant cytopenias or increased bone marrow blasts, the NCCN Guidelines Panel recommends stratifying these patients into several groups. Patients with del(5q) chromosomal abnormalities alone or with one other cytogenetic abnormality, except those involving chromosome 7, 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.[346,347] The recommended dose of lenalidomide in this setting is 10 mg/day for 21 days, every 28 days, or 28 days monthly; response should be assessed 2 to 4 months after initiation of treatment. In patients with a clinically significant decrease in neutrophil or platelet counts, caution is required and may warrant either use of a modified dose of lenalidomide or withdrawing lenalidomide as an option. In the previously discussed phase III trial with lenalidomide in patients with del(5q), patients with low neutrophil counts (<500 cells/mcL) or platelet counts (<25,000 cells/mcL) were excluded from the study.[324] An alternative option to lenalidomide in patients with del(5q) and symptomatic anemia may include an initial trial of ESAs in cases where sEpo levels are 500 mU/mL or less. 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, alone or with one other cytogenetic abnormality and with symptomatic anemia, are categorized on

the basis of sEpo levels. Levels of less than or equal to 500 mU/mL should be treated with ESAs (rHu Epo or darbepoetin) with or without G-CSF (see *Evaluation of Related Anemia/Treatment of Symptomatic Anemia* in the algorithm). Patients with normal cytogenetics, less than 15% ring sideroblasts, and sEpo levels of 500 mU/mL or less may respond to Epo if relatively high doses are administered.[233,348,349] The Epo dose required is 40,000 to 60,000 SC units 1 to 2 times per 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 of treatment.[279,350-352] 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 needs to be verified before instituting Epo or darbepoetin therapy. If no response occurs with these agents alone, the addition of G-CSF should be considered. Evidence suggests that G-CSF (and, to a lesser extent, GM-CSF) has synergistic erythropoietic activity when used in combination and markedly enhances the erythroid response rates due to enhanced survival of red cell precursors.[279,349-351] This is particularly evident for patients with greater than or equal to 15% ring sideroblasts in the marrow (and sEpo level ≤500 mU/mL), as the very low response rates to Epo or darbepoetin alone in this subgroup are markedly enhanced when combined with G-CSF.[279,351]

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in initially neutropenic patients or to double the neutrophil count in patients who are initially non-neutropenic. For this purpose, an average of 1 to 2 mcg/kg SC G-CSF is administered either daily or 1 to 2 times per week.[279,349-351] Detection of erythroid responses generally occurs within 6 to 8 weeks of treatment. If no response occurs within this timeframe, 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.[351,353] This cytokine treatment is not suggested for patients with endogenous sEpo levels greater than 500 mU/mL due to the very low erythroid response rate to these drugs in this patient population. In patients who do not respond 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.

In patients with sEpo levels ≤500 mU/mL and ≥15% ring sideroblasts, or ≥5% ring sideroblasts with an *SF3B1* mutation, if no response is observed after 2 months of ESA treatment with or without G-CSF, treatment with luspatercept is recommended.[289] In addition, in patients with sEpo levels >500 mU/mL and ring sideroblasts, treatment with luspatercept is recommended.

After treatment with either ESA with or without G-CSF and/or lenalidomide, and luspatercept as described, if no response is seen after 4 to 6 months, non-responders should be considered for IST (ATG, with or without 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 who are aged 60 years or younger with less than or equal to 5% marrow blasts; 2) patients who have hypocellular marrows; 3) patients with PNH clone positivity; or 4) patients with STAT3-mutant cytotoxic T-cell clones.

Alternatively, treatment with AzaC, decitabine, or lenalidomide should be considered for patients predicted to have a poor probability of responding or who have not responded to IST. A phase II prospective study of MDS patients, who were IPSS low or int-1 with symptomatic anemia with disease that was not expected to respond or that failed to respond to Epo, showed that AzaC was well-tolerated.[354] Although neutropenia and thrombocytopenia were adverse events (47% and 19% of patients, respectively), these toxicities were transient. Other non-hematologic toxicities were mild. AzaC treatment was effective in 60% of patients in the study. Patients with no response to hypomethylating agents or lenalidomide in this setting should be considered for participation in a clinical trial with other relevant agents, or for allogeneic HCT (see *Therapy for Higher-Risk Patients*). Emerging data are demonstrating effectiveness of ivosidenib and enasidenib for MDS patients with *IDH1* or *IDH2* mutations.[355]

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

Patients without symptomatic anemia, who have other clinically relevant cytopenias (particularly clinically severe thrombocytopenia) or increased bone marrow blasts, should be considered for treatment with AzaC, decitabine, IST (if there is a good probability of responding to these agents), or a clinical trial. Some studies have shown clinical benefit with low doses of AzaC or decitabine.[356] If there is disease progression or no response, allogeneic HCT can be considered in select lower-risk MDS patients (IPSS int-1, IPSS-R, and WPSS intermediate patients) with severe cytopenias. TPO agonists may also be considered in these patients.[244,249,357]

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

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

Treatment for higher-risk patients is dependent on whether they are possible candidates for intensive therapy (eg, allogeneic HCT, intensive chemotherapy). Clinical features relevant for this determination include patient age, performance status, 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 needs particular consideration. Regardless, supportive care should be provided for all patients.

Intensive Therapy

Allogeneic Hematopoietic Cell Transplantation

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.[358]

To aid therapeutic decision-making regarding the timing and selection of MDS patients for HCT, a study compared outcomes with HLA-matched sibling HCT in MDS patients 60 years of age or younger to data in non-treated MDS patients from the IMRAW/IPSS database.[359] Using a Markov decision analysis, this investigation indicated that IPSS int-2 and high-risk patients 60 years of age or younger 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).[359] A retrospective study evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HCT.[183] 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).[183]

Based on data regarding RIC for transplantation from two studies[360,361] and two comprehensive reviews of the field,[362,363] patient age and disease status generally dictated the type of conditioning. Patients older than 55 or 65 years, particularly if they had less than 10% marrow myeloblasts, generally received RIC; if the blast count was high, pre-HCT debulking therapy was often given. Younger patients, regardless of marrow blast burden, most frequently received high-dose conditioning. Variations on these approaches would be considered by the individual transplant physician based on patient features and the specific regimen utilized at that center. Some general recommendations have been presented in a review article.[364]

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 non-relapse mortality, OS, and PFS.[365] 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.[366,367] 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 IPSS MDS compared to other non-transplant therapies. However, a potential improvement in life expectancy was seen in patients with int–2– or high-risk IPSS MDS.[368] It is recognized that there are even fewer data available in regard to patients who are 75 years of age or older.

Intensive Chemotherapy

For patients eligible for intensive therapy but lacking 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.[369] 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.

Non-Intensive 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, 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 AzaC and the control arm (19% vs. 18%).[292] 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 who show clinical benefit, treatment with hypomethylating agents should be continued as maintenance therapy. Results from a phase III trial comparing decitabine to BSC in higher-risk patients who were 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.[294]

Two reports from the phase III, international, multicenter, randomized AZA-001 trial have evaluated AzaC compared to conventional care regimens (CCR) in patients with higher-risk MDS. Patients randomized to the CCR group received the most appropriate of the three protocol-specified CCR options, including AzaC, intensive chemotherapy, or BSC.[370,371] The OS was increased with AzaC treatment compared to CCR (HR, 0.58; 95% CI, 0.43–0.77; *P* < .001), and a greater number of patients achieved hematologic improvement (49% vs. 29%; *P* < .0001).[370] The earlier report from the same trial showed improved OS and tolerability in elderly patients (defined as ≥75 years of age) with good performance status.[371] 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 data from the phase III trial that showed superior median survival with AzaC compared to BSC.

Supportive Care Only

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

Summary

The NCCN Guidelines are based on extensive evaluation of the reviewed risk-based data and indicate current approaches for managing patients with MDS. Five drugs approved by the FDA for treating specific subtypes of MDS include lenalidomide for patients with del(5q) cytogenetic abnormalities; AzaC and decitabine for treating higher-risk or non-responsive patients; and deferasirox and deferoxamine for iron chelation in the treatment of iron overload. However, as a substantial proportion of MDS patient subsets lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents, along with supportive care, remain the hallmark of disease management. 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 needing investigation.[350,352,353,372,373] 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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