National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myelodysplastic Syndromes

Version 3.2024 — July 25, 2024

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

***Peter L. Greenberg, MD/Chair ‡ Þ**
Stanford Cancer Institute

Richard M. Stone, MD/Vice Chair ‡ †
Dana-Farber/Brigham and Women's Cancer Center

Yasmin Abaza, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Aref Al-Kali, MD ‡
Mayo Clinic Comprehensive Cancer Center

Sarah Anand, MD ‡ † ξ
University of Michigan Rogel Cancer Center

John M. Bennett, MD Þ † ≠
University of Rochester

Uma Borate, MD, MSc ‡
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Andrew M. Brunner, MD † ‡
Massachusetts General Hospital Cancer Center

Wanxing Chai-Ho, MD ‡
UCLA Jonsson Comprehensive Cancer Center

Peter Curtin, MD ‡ † ξ
City of Hope National Medical Center

Carlos M. de Castro, MD † ‡
Duke Cancer Institute

H. Joachim Deeg, MD † ‡ ξ
Fred Hutchinson Cancer Center

Amy E. DeZern, MD, MHS † ‡
Johns Hopkins Kimmel Cancer Center

Shira Dinner, MD † ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Karin Gaensler, MD ‡
UCSF Helen Diller Family Comprehensive Cancer Center

Zhubin Gahvari, MD, MS † ‡ ξ
University of Wisconsin Carbone Cancer Center

Guillermo Garcia-Manero, MD ‡ †
The University of Texas MD Anderson Cancer Center

Aaron Goldberg, MD, PhD Þ ‡
Memorial Sloan Kettering Cancer Center

Elizabeth A. Griffiths, MD Þ † ‡
Roswell Park Comprehensive Cancer Center

Tamanna Haque, MD ‡
Memorial Sloan Kettering Cancer Center

Meagan Jacoby, MD, PhD † ‡ ξ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Brian A. Jonas, MD, PhD † ‡
UC Davis Comprehensive Cancer Center

Sioban Keel, MD ‡
Fred Hutchinson Cancer Center

Rashmi Khanal, MD † ‡
Fox Chase Cancer Center

Ashwin Kishtagari, MD ‡
Vanderbilt-Ingram Cancer Center

Yazan Madanat, MD ‡ Þ
UT Southwestern Simmons Comprehensive Cancer Center

Lori J. Maness, MD ‡
Fred & Pamela Buffett Cancer Center

Shannon R. McCurdy, MD †
Abramson Cancer Center at the University of Pennsylvania

Christine McMahon, MD ‡
University of Colorado Cancer Center

Olatoyosi Odenike, MD ‡ †
The UChicago Medicine Comprehensive Cancer Center

Afaf Osman, MD ‡
Huntsman Cancer Institute at the University of Utah

Vishnu V. Reddy, MD ≠ †
O'Neal Comprehensive Cancer Center at UAB

David A. Sallman, MD ‡ †
Moffitt Cancer Center

Hamid Sayar, MD, MSc ‡
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Rory Shallis, MD ‡
Yale Cancer Center/Smilow Cancer Hospital

Abhay Singh, MD, MPH ‡
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Tiffany Tanaka, MD ‡ † ξ
UC San Diego Moores Cancer Center

Swapna Thota, MD ‡
St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

NCCN
Carly Cassara, MSc
Mary Dwyer, MS
Cindy Hochstetler, PhD
Emily Kovach

‡ Hematology
Þ Internal medicine
† Medical oncology
≠ Pathology
ξ Transplantation
* Discussion section writing committee

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Myelodysplastic Syndromes Panel Members

Summary of the Guidelines Updates

- Initial Evaluation (MDS-1)
- Spectrum of Indolent Myeloid Hematopoietic Disorders (MDS-2)
- Additional Testing and Classification (MDS-3)
- Management of Lower-Risk Disease (IPSS-R Very-Low-, Low-, Intermediate-Risk Disease (MDS-4)
- Management of Higher-Risk Disease (IPSS-R Intermediate-, High-, Very-High-Risk Disease (MDS-7)
- Supportive Care (MDS-8)

- Pathologic-Morphologic Classifications of Myelodysplastic Neoplasms 2023 (MDS-A)
- Clinical Principles of Myelodysplastic/Myeloproliferative Neoplasm (MDS/MPN) Overlap Neoplasms (MDS-A)
- MDS/MPN Classification (MDS-A)
- AML-Defining Genetic Abnormalities: WHO 2022 and ICC (MDS-A)
- Prognostic Scoring Systems (MDS-B)
- Genes Frequently Somatically Mutated in MDS (MDS-C)
- Genetic Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes (MDS-D)
- Gene Mutations Associated with Hereditary Myeloid Malignancy Predisposition Syndromes (MDS-E)
- Recommendations for Flow Cytometry (MDS-F)

Abbreviations (ABBR-1)

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 2.2024 include:

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

MDS-5
- MDS-SF3B1 (low blasts) algorithm updated:
  - New pathway added: Imetelstat (if serum EPO >500 mU/mL [ineligible for ESAs])
  - No response after luspatercept-aamt, algorithm updated:
    - ◊ Serum EPO ≤500 mU/mL:
      - *Imetelstat (category 1) or....*
      - No response to *imetelstat or ESAs ± G-CSF.*
    - ◊ Serum EPO >500 mU/mL: Imetelstat added

MDS-6
- Serum EPO ≤500 mU/mL, no response to ESAs (despite adequate iron stores) or luspatercept-aamt, algorithm updated:
  - Imetelstat (category 1) added as a therapy option.
  - No response to *imetelstat or*...
  - Imetelstat (if not previously used)(category 1) added.
- Serum EPO >500 mU/mL, poor probability to resond to IST, algorithm updated:
  - Other recommended regimens: *...or Imetelstat (if not prevoiusly used).*
  - No response...*or imetelstat*...

MDS-6A
- Footnote ll added: Initial dosing is 7.1 mg/kg IV monthly with potential dose decrements since frequent transient thrombocytopenia and neutropenia may occur. Starting platelet and neutrophil levels should be ≥75,000 and ≥1,500, respectively (Platzbecker U, et al. Lancet 2024;403:249).
- Footnote uu added: This does not apply to patients with MDS-5q, since this patient population was not studied.

Updates in Version 2.2024 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 1.2024 include:

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2024 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 3.2023 include:

Global changes
- References were updated and added as appropriate throughout the Guidelines.
- "rHu EPO" changed to "epoetin alfa" throughout the Guidelines.

MDS-1
- Initial Evaluation
  - 4th bullet revised: ...~~Consider~~ *Recommend* testing bone marrow sample *with reticulin stain* for fibrosis.
  - 6th bullet revised: RBC folate, ~~serum B12~~ *and vitamin B12 evaluation*
  - 11th bullet revised: Genetic testing for somatic mutations (ie, acquired mutations) in genes associated with myelodysplastic syndromes (MDS) ~~is highly recommended~~.

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 3.2023 include:

MDS-1A
- Footnotes for Initial Evaluation of MDS
  - Footnote c, 2nd sentence revised: ...Serum methylmalonic acid testing is an accurate way to assess B12 status *and is mandatory to the vitamin B12 evaluation, particularly for patients with possible pernicious anemia*.
  - Footnote f, 4th sentence revised: CSA may appear late due to lyonization in X-linked sideroblastic anemia ~~(not limited to younger patients and patients >60 years of age at risk for germline DDX41 and short telomere syndromes)~~.
  - Footnote g, 1st sentence revised: Confirm diagnosis of MDS according to WHO/~~NCCN~~ *International Consensus Classification (ICC)* criteria for classification...
  - Footnote h revised by adding: "See AML-Defining Genetic Abnormalities: WHO 2022 and ICC (MDS-A 4 of 5)."

MDS-2
- Spectrum of Indolent Myeloid Hematopoietic Disorders
  - ◊ Page extensively updated.

MDS-3
- Footnote t revised: Patients with CMML with ~~this abnormality~~ *PDGFRB rearrangement* may respond well to tyrosine kinase inhibitors such as imatinib mesylate...

MDS-4
- Management of Lower-Risk Disease
  - For clinically relevant thrombocytopenia or neutropenia, preferred and other recommended stratification was removed.
  - Footnotes
    - ◊ Footnote cc revised: *Treatment* failure would be considered if no response within 3–6 mo. Response should be evaluated based on International Working Group (IWG) criteria: Cheson BD, et al. Blood 2006;108:419-425; *Platzbecker U, et al. Blood 2019;133:1020-1030*. (Also for MDS-6A)
    - ◊ Footnote ee, 2nd sentence revised: Matched sibling, unrelated donor, ~~or alternative (~~haploidentical *donor*, or cord blood ~~when appropriate)~~ donor, including standard and reduced-intensity preparative approaches, may be considered. (Also for MDS-6A)

MDS-5
- Management of Lower-Risk Disease - Treatment of Symptomatic Anemia
  - Algorithm pathway "MDS-5q (low blasts) del(5q) ± one other cytogenetic abnormality (except those involving chromosome 7) IPSS Low/Intermediate-1" separated by "Serum EPO >500 mU/mL" and " Serum EPO ≤500 mU/mL" and revised as follows:
    - ◊ For serum EPO >500 mU/mL, lenalidomide is a category 1, preferred recommendation.
    - ◊ For serum EPO ≤500 mU/mL, lenalidomide is a preferred recommendation and ESAs are other recommended options.

MDS-6
- Management of Lower-Risk Disease - Treatment of Symptomatic Anemia
  - Algorithm pathway symptomatic anemia with no del(5q) ± other cytogenetic abnormalities with RS <15% (or RS <5% with an SF3B1 mutation) updated as follows:
    - ◊ For Serum EPO >500 mU/mL, "Good probability to respond to IST" was updated as follows:
      - – Preference stratification was removed.
      - – "ATG + cyclosporin A + eltrombopag" and "ATG + cyclosporin A" were changed to "ATG + cyclosporin A ± eltrombopag."
      - – ATG + eltrombopag removed as an option.
      - – ATG (category 3) removed as an option.

MDS-6A
- Footnote hh revised by adding: Lenalidomide exposure has been associated with a selective advantage and the expansion of TP53-mutated clones (Sperling AS, et al. Blood 2022;140:1753-1763). Additional consideration for and/or closer monitoring of particular patients may be warranted.

Continued
UPDATES

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 3.2023 include:

- Footnote ii revised by adding: For lack of response, escalate the dose.
- Footnote jj added: An FDA-approved biosimilar is an appropriate substitute for epoetin alfa. (Also for MDS-8)
- Footnote kk, 2nd sentence revised: Data have emerged *for patients with non-sideroblastic lower-risk MDS with anemia* indicating similar but more prolonged responses *with luspatercept* compared to ESAs, ~~although more treatment-related adverse events were noted in the luspatercept arm of the trial (Garcia-Manero G, et al. J Clin Oncol 2023; 16:Abstract 7003~~ *Platzbecker U, et al. Lancet 2023;402:373-385*).
- Footnote mm and footnote nn revised from "Lack of 1.5 gm/dL rise..." to "Lack of ≥1.5 gm/dL rise..."
- Footnote pp removed: IST includes equine ATG ± cyclosporin A ± eltrombopag.
- Footnote ss added: ATG may be omitted when clinically indicated.

MDS-7A

- Footnote yy revised: ...(Garcia JS, et al. ~~ASH Annual Meeting 2020:Abstract 656~~ *Blood 2023;142:Abstract 319). Emerging data have also shown utility of olutasidenib for treating patients with IDH1 mutations (Cortes J, et al. Blood 2023;142:Abstract 1872)...*
- Footnote aaa revised: *Treatment* failure would be considered if no response within 3–6 mo. Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425. *Zeidan AM, et al. Blood 2023;141:2047-2061.*

MDS-8

- Supportive Care
  - Bullets related to pre-transplant removed:
    - ◊ Transplant and non-transplant patients should receive support.
    - ◊ Transfusion products should be irradiated with 25 Gy or per institution standard.
    - ◊ Patients with ≥5% marrow blasts who are candidates for reduced-intensity conditioning are encouraged to receive "debulking" therapy with HMA or induction chemotherapy. Transplantation should be carried out as long as patients are responding; it should not be delayed until the response is lost.
  - Cytokines:
    - ◊ EPO was replaced with ESAs.
    - ◊ 2nd sub-bullet revised by removing epoetin alfa-epbx and adding darbepoetin alfa.
  - Footnote eee revised from "Clinical trials in MDS are currently ongoing with oral chelating agents" to "Hoeks M, et al. Haematologica 2020;105:640-651; Yang S, et al. Br J Haematol 2022;197:e9-e11; Angelucci E, et al. Ann Intern Med 2020;172:513-522."

MDS-A 1 of 5

- Title changed from "Classification of Myelodysplastic Neoplasms (MDS)" to "Pathologic-Morphologic Classifications of Myelodysplastic Neoplasms 2023. Transition from Clinically-Based Classifications to New Systems Including Genomic Features in 2022."
- Page extensively revised.

MDS-A 2 of 5

- Clinical Principles of MDS/MPN Overlap Neoplasms
  - 4th bullet revised: Therapeutic approaches in CMML have generally been the model for treating the other MDS/MPN, with HMA ± *venetoclax* treatment for patients with intermediate- and higher-risk disease,...

MDS-A 3 of 5

- Table updated as follows:
  - Title changed from "MDS/MPN, 2022 WHO Classification" to "MDS/MPN Classification."
  - Added columns to include both WHO 2016 and ICC classifications; added features column; removed bone marrow column.

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

NCCN Guidelines Index
Table of Contents
Discussion

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2023 of the NCCN Guidelines for Myelodysplastic Syndromes from Version 3.2022 include:

- Added row for MDS/MPN with i(17q).
- Treatment column revised:
  - ◊ CMML-1: Consider HMA *or hydroxyurea*
  - ◊ CMML-2: HMA ± ~~ruxolitinib~~ *venetoclax...*
  - ◊ MDS/MPN with ring sideroblasts (RS) and thrombocytosis (T): luspatercept-aamt changed from a category 2B to a category 2A recommendation.

• Footnotes extensively revised.

MDS-A 4 of 5

• Table added: AML-Defining Genetic Abnormalities: WHO 2022 and ICC.

MDS-B 1 of 4

• Headers added to tables: Prognosis According to IPSS Risk Score and Prognosis According to IPSS-R Risk Score.

MDS-B 2 of 4

• Header added to table: Prognosis According to WPSS Risk Score.

MDS-B 3 of 4

• Footnote f added: The IPSS-M may have a role in clinical decision-making but requires confirmatory evidence to help assess its efficacy.

MDS-D 1 of 6

• "Heritable Hematologic Malignancy Predisposition Syndromes (HHMPS)" revised to "Hereditary Myeloid Malignancy Predisposition Syndromes (HMMPS)" throughout the page (Also for MDS-D [2 of 6] through MDS-D [5 of 6]).

• Whom to test, 2nd bullet revised from, "All patients with AML or MDS diagnosed at <50 years old" to "All patients with MDS and adults <50 y with AML."

MDS-D 2 of 6

• 3rd bullet, last sentence added: Additionally, as there can be genetic anticipation in the short telomere syndromes, a child may be clinically affected, and the genetically affected parent clinically unaffected or less severely affected.

MDS-D 5 of 6

• Limitations of the proposed approach, 2nd bullet added:
  - Initial testing: Telomere length measurement by flow-FISH to assess the risk of telomere-mediated disease in patients with hematologic malignancies where there are circulating malignant cells may be confounded or falsely shortened secondarily due to the malignancy itself. In such cases, germline genetic assessment should be performed in lieu of telomere length measurement and telomere length measurement should be assessed during remission where possible. In some cases of familial disease, assessment of telomere length in a relative with an identical variant in a telomere gene could also be used for interpreting the significance of the variant (optional). Additionally, if there are circulating malignant cells or the malignant cell composition in peripheral blood is unknown, the finding of abnormally short telomere length measurement alone should be interpreted with caution and additional evidence of a telomere-mediated process is needed including the presence of a germline variant of clinical features including a family history of pulmonary fibrosis.

MDS-E 1 of 6

• Heading modified: Gene Mutations Associated with ~~Heritable Hematologic~~ *Hereditary Myeloid* Malignancy Predisposition Syndromes. Also for MDS-E 2 of 6 through MDS-E 5 of 6.

MDS-E 3 of 6

• Row 5, Other phenotypes and clinical features updated by adding: G6PC3 mutations can be associated with congenital anomalies. HAX1 mutations can be associated with neurologic manifestations including seizures.

INITIAL EVALUATION

Cytopenia(s), suspect myelodysplasia[a]

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, reticulocyte count
- Examination of peripheral blood smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping.[b] Recommend testing bone marrow sample with reticulin stain for fibrosis
- Serum erythropoietin (EPO) (prior to red blood cell [RBC] transfusion)
- RBC folate and vitamin B12 evaluation[c]
- Serum ferritin, iron, total iron-binding capacity (TIBC)
- Documentation of transfusion history
- Thyroid-stimulating hormone (TSH)
- Lactate dehydrogenase (LDH)
- Genetic testing for somatic mutations (ie, acquired mutations) in genes associated with myelodysplastic syndromes (MDS)[d]
- Recommend additional molecular and genetic testing for heritable hematologic malignancy predisposition in a subset of patients, particularly in patients[e] <50 years of age
- Human immunodeficiency virus (HIV) testing if clinically indicated
- Consider evaluation of copper deficiency in patients with gastrointestinal (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] → Additional Testing and Classification (MDS-3)

Diagnostic criteria for MDS not met but cytopenias present → Spectrum of Indolent Myeloid Hematopoietic Disorders (MDS-2)

Footnotes on MDS-1A

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

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, et al. Blood 2016;128:2096-2097. For diagnostic features of primary and therapy-related MDS that require cytopenia(s) and hematopoietic cell dysplasia, see MDS-A (1 of 5).

[b] If standard cytogenetics (with ≥20 metaphases) cannot be obtained, a chromosome microarray analysis (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 and is mandatory to the vitamin B12 evaluation, particularly for patients with possible pernicious anemia.

[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] A heritable 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). Functional laboratory studies and constitutional (germline) genetic testing using large next-generation sequencing (NGS) panels to include genes listed on MDS-E, whole exome or whole genome sequencing complemented with in silico copy number variant (CNV) calling, and/or laboratory analysis for CNVs, such as microarray testing are recommended for patients as shown on MDS-D (1 of 6). See Genetic Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes (MDS-D) and Gene Mutations Associated with Hereditary Myeloid Malignancy Predisposition Syndromes (MDS-E).

[f] In patients <40 years of age, CSA is due to disordered mitochondrial heme synthesis, often with distinctive mutational and clinical features. Some of these patients will have disease that responds to pyridoxine or thiamine. CSA is not MDS (Fleming MD. Hematology Am Soc Hematol Educ Program 2011;2011:525-531). CSA may appear late due to lyonization in X-linked sideroblastic anemia.

[g] Confirm diagnosis of MDS according to WHO/International Consensus Classification (ICC) criteria for classification (MDS-A) with application of International Prognostic Scoring System (IPSS) or revised IPSS (IPSS-R) (MDS-B 1 of 4). 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 (FCM) 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 AML-Defining Genetic Abnormalities: WHO 2022 and ICC (MDS-A 4 of 5) and NCCN Guidelines for Acute Myeloid Leukemia.

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

SPECTRUM OF INDOLENT MYELOID HEMATOPOIETIC DISORDERS[i-o,1-4]

Feature	CHIP	ICUS	Lower-Risk CCUS	High-Risk CCUS
Cytopenia(s)	-	+	+	+
Dysplasia	-	-	-	-
Clonality	+	-	+	+
Risk of transformation	+	+/-	++	+++
Clinical approach	Observation; Monitor based on clinical change	Observation; Monitor yearly	Observation; Monitor yearly	Observation; Monitor 2–4x/year CBC; consider clinical trial

CHIP: clonal hematopoiesis of indeterminate potential; ICUS: idiopathic cytopenia of unknown significance; CCUS: clonal cytopenia of undetermined significance

[i] Regular monitoring of blood counts in these patients should be instituted after evaluation as in MDS-1 (generally at least every 3–6 months). Monitoring is ultimately at clinical discretion, but these frequencies are reasonable based on risk of transformation. Molecular evidence (testing suggested on MDS-1) of clonal hematopoiesis provides information to allow earlier identification of predisposition states for myeloid neoplasms.

[j] For patients with MDS, see MDS-4, MDS-5, MDS-C, and MDS-D.

[k] 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 [VAF]). Evaluation of mutations should include sequencing or panels incorporating the 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.

[l] Patients with pathogenic mutations with >10% VAF 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 ASXL*1 have less predictive value.

[m] *DNMT3A, TET2, ASXL1, RUNX1, JAK2, PPM1D, TP53*, and splicing factor genes are the most frequently mutated genes associated with CHIP.

[n] Myeloid neoplasm risk is increased 3-, 37-, and 348-fold in low-risk, intermediate-risk, and high-risk CHIP/CCUS, respectively, compared to unmutated controls.[1]

[o] To facilitate clonal hematopoiesis risk score (CHRS) adoption, an online calculator is available and should be considered by the clinician evaluating the patient:[1] http://www.chrsapp.com. The calculator returns a score with its corresponding risk category as low (CHRS ≤9.5), intermediate (CHRS 10–12), and high (CHRS ≥12.5). The three risk strata significantly differ in the 10-year probabilities of myeloid neoplasms and overall survival for relevant clinical discussions and follow-up.

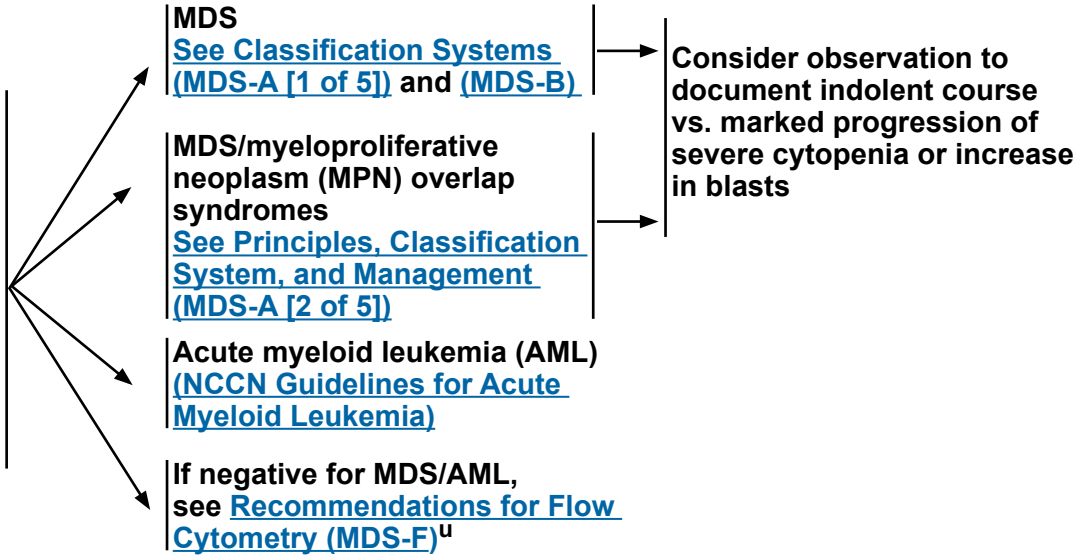
[1] Weeks LD, et al. NEJM Evid 2023;2:EVIDoa2200310.
[2] Malcovati L, et al. Blood 2017;129:3371-3378.
[3] Galli A, et al. Blood 2021;138:965-976.
[4] Kwok B, et al. Blood 2015;126:2355-2361.

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

ADDITIONAL TESTING

- **Consider flow cytometry (FCM) for MDS as a diagnostic aid[p] and consider FCM and *TCR* polymerase chain reaction (PCR) and *STAT3* mutation testing to evaluate for large granular lymphocyte (LGL)[q] and paroxysmal nocturnal hemoglobinuria (PNH) clone[r]**
- **Perform human leukocyte antigen (HLA) typing if hematopoietic cell transplant (HCT) candidate[s]**
- **Consider evaluating patients with chronic myelomonocytic leukemia (CMML) for *PDGFRβ* gene rearrangements at 5q32[t]**
- **Cytomegalovirus (CMV)-safe (CMV-negative or leukopheresed) blood products are recommended whenever possible for CMV-negative transplant candidates**

CLASSIFICATION



[p] See Recommendations for Flow Cytometry (MDS-F) and Discussion.

[q] 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-cell LGL (T-LGL) disease. Morgan EA, et al. Blood Adv 2017;1:1786-1789. Chan WC, Foucar K, Morice WG, Matutes E. T-cell large granular lymphocytic leukemia. In: Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC Press; 2017:348-350.

[r] FCM analysis of granulocytes and monocytes from blood with FLAER (fluorescent aerolysin) and at least one glycophosphatidylinositol-anchored protein to assess the presence of a PNH clone. DeZern AE, et al. Cytometry B Clin Cytom 2018;94:16-22.

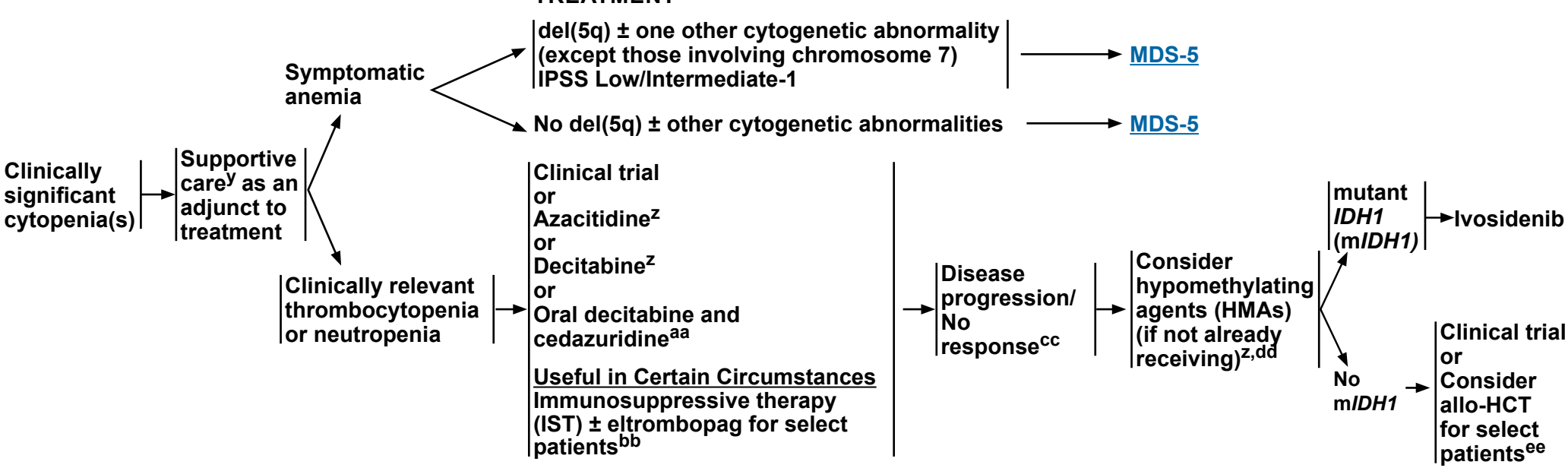
[s] Donors should be evaluated by high-resolution allele-level typing for HLA-A, -B, -C, -DR, and -DQ. All full siblings should be evaluated for HLA match prior to unrelated donor match.

[t] Patients with CMML with *PDGFRB* rearrangement may have disease that responds well to tyrosine kinase inhibitors such as imatinib mesylate. Some patients may have somatic copy-neutral loss of heterozygosity (cnLOH), especially those encompassing *JAK2* mutations.

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

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

MANAGEMENT OF LOWER-RISK DISEASE (IPSS-R VERY-LOW-, LOW-, INTERMEDIATE-RISK DISEASE)[v,w,x]



[v] Presence of comorbidities should also be considered for evaluation of prognosis (see *Comorbidity Indices* in the Discussion).
[w] Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate-Risk MDS may be managed as lower risk if their score is ≤3.5 vs. higher risk if their score is >3.5. Pfeilstöcker M, et al. Blood 2016;128:902-910.
[x] If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.
[y] See Supportive Care (MDS-8).
[z] Some studies have demonstrated clinical benefit with low doses of azacitidine or decitabine for lower-risk MDS. Sasaki K, et al. NEJM Evid 2022;EVIDoa2200034.
[aa] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. Garcia-Manero G, et al. Blood 2020;136:674-683.
[bb] Patients generally ≤60 y and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or *STAT3*-mutant cytotoxic T-cell clones. IST includes equine antithymocyte globulin (ATG) ± cyclosporin A. Additionally, for severe thrombocytopenia, eltrombopag alone could be considered.
[cc] Treatment failure would be considered if no response within 3–6 months. Response should be evaluated based on International Working Group (IWG) criteria: Cheson BD, et al. Blood 2006;108:419-425; Platzbecker U, et al. Blood 2019;133:1020-1030.
[dd] For patients with severe or refractory thrombocytopenia, eltrombopag or romiplostim can be considered. Oliva EN, et al. Lancet Hematol 2017;4:e127-e136. Fenaux P, et al. Br J Haematol 2017;178:906-913. See Discussion.
[ee] Patients with IPSS Intermediate-1, IPSS-R Intermediate, and WHO-Based Prognostic Scoring System (WPSS) Intermediate-Risk MDS with severe cytopenias would also be considered candidates for HCT. Matched sibling, unrelated donor, haploidentical donor, or cord blood donor, including standard and reduced-intensity preparative approaches, may be considered.

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

MANAGEMENT OF LOWER-RISK DISEASE (IPSS-R VERY-LOW-, LOW-, INTERMEDIATE-RISK DISEASE)[v,w,x]

EVALUATION OF RELATED ANEMIA

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

→
- Treat coexisting causes
- Replace iron, folate, B12 if needed
- RBC transfusions (CMV-safe)
- Supportive care[y]

TREATMENT OF SYMPTOMATIC ANEMIA[ff]

MDS-5q (low blasts)
del(5q) ± one other cytogenetic abnormality (except those involving chromosome 7)
IPSS Low/ Intermediate-1

- Serum EPO ≤500 mU/mL → **Preferred** Lenalidomide[hh]; **Other Recommended** Erythropoiesis-stimulating agent (ESA) (epoetin alfa[ii,jj] or darbepoetin alfa[ii])
- Serum EPO >500 mU/mL → **Preferred** Lenalidomide (category 1)[hh]

MDS-*SF3B1* (low blasts)
No del(5q) ± other cytogenetic abnormalities with RS ≥15% (or RS ≥5% with an *SF3B1* mutation)[gg]

- Luspatercept-aamt[kk] (category 1) → No response[nn]
- or
- Imetelstat[ll] (if serum EPO >500 mU/mL [ineligible for ESAs]) → No response[nn]

No del(5q) ± other cytogenetic abnormalities with ring sideroblasts (RS) <15% (or RS <5% with an *SF3B1* mutation) → MDS-6

FOLLOW-UP

- Response[mm] → Continue lenalidomide or ESA, decrease dose to tolerance
- No response to lenalidomide[nn] or ESA[oo] → See Serum EPO >500 mU/mL (poor probability to respond to IST) (MDS-6)

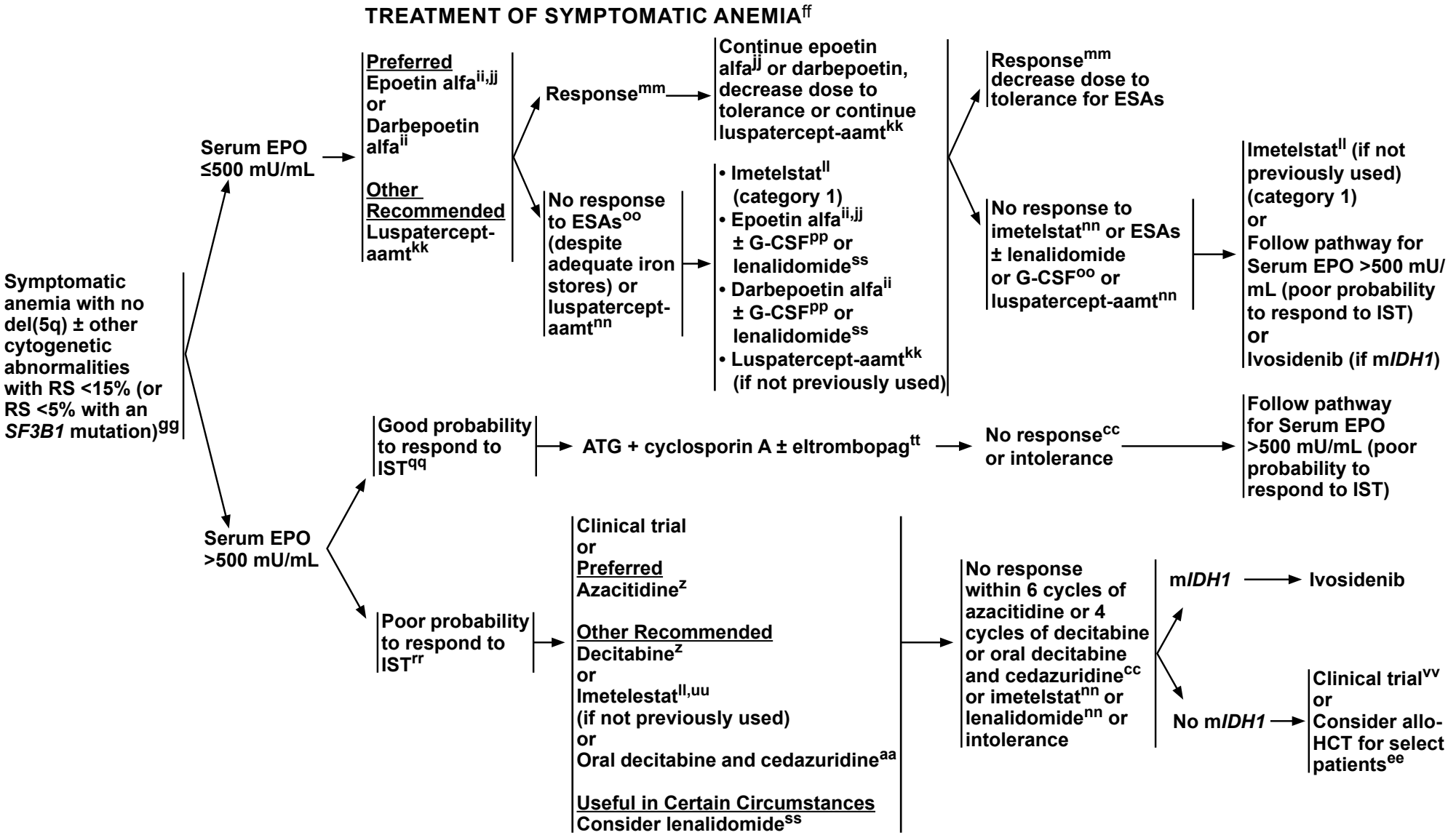
Serum EPO ≤500 mU/mL → Imetelstat (category 1)[ll] or Epoetin alfa[ii,jj] ± granulocyte colony-stimulating factor (G-CSF)[pp] or Darbepoetin alfa[ii] ± G-CSF[pp]
→ No response to imetelstat[nn] or ESAs ± G-CSF[oo]
→ See Serum EPO >500 mU/mL (poor probability to respond to IST) (MDS-6) or Ivosidenib (if m*IDH1*)

Serum EPO >500 mU/mL → Imetelstat[uu] or Consider lenalidomide[hh]
→ No response[nn]
→ See Serum EPO >500 mU/mL (poor probability to respond to IST) (MDS-6) or Ivosidenib (if m*IDH1*)

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

Footnotes on MDS-6A

MANAGEMENT OF LOWER-RISK DISEASE (IPSS-R VERY-LOW-, LOW-, INTERMEDIATE-RISK DISEASE)[v,w,x]



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

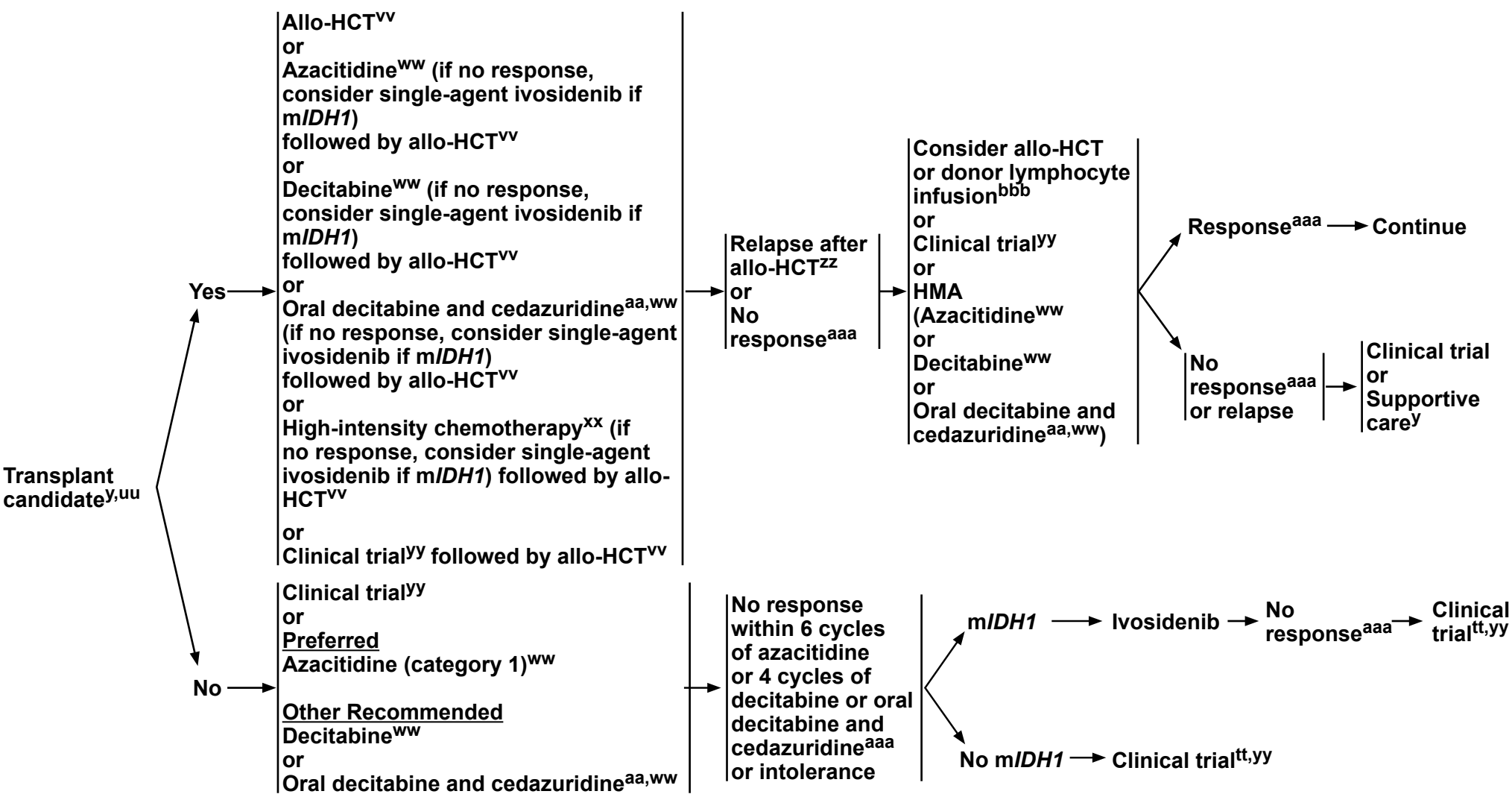
Footnotes on MDS-6A

FOOTNOTES FOR MDS-5 AND MDS-6

[v] Presence of comorbidities should also be considered for evaluation of prognosis (see *Comorbidity Indices* in the Discussion).
[w] Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate-Risk MDS may be managed as lower risk if their score is ≤3.5 vs. higher risk if their score is >3.5. Pfeilstöcker M, et al. Blood 2016;128:902-910.
[x] If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.
[y] See Supportive Care (MDS-8).
[z] Some studies have demonstrated clinical benefit with low doses of azacitidine or decitabine for lower-risk MDS. Sasaki K, et al. NEJM Evid 2022;EVIDoa2200034.
[aa] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. Garcia-Manero G, et al. Blood 2020;136:674-683.
[cc] Treatment failure would be considered if no response within 3–6 months. Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425; Platzbecker U, et al. Blood 2019;133:1020-1030.
[ee] Patients with IPSS Intermediate-1, IPSS-R Intermediate, and WHO-Based Prognostic Scoring System (WPSS) Intermediate-Risk MDS with severe cytopenias would also be considered candidates for HCT. Matched sibling, unrelated donor, haploidentical donor, or cord blood donor, including standard and reduced-intensity preparative approaches, may be considered.
[ff] Refers predominantly to patients with lower-risk IPSS-R and IPSS MDS.
[gg] Per WHO 2022, this entity is now noted as MDS-*SF3B1* (low blasts) (Khoury JD, et al. Leukemia 2022;36:1703-1719). See MDS-A, 1 of 5.
[hh] Recommended lenalidomide initial dose is: 10 mg/day for 21 out of 28 days or 28 days monthly for 2–4 months to assess response (Discussion). Use caution for patients with low platelet and neutrophil counts; consider modifying lenalidomide dose. Sekeres MA, et al. J Clin Oncol 2008;26:5943-5949. Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category (MDS-7). Lenalidomide exposure has been associated with a selective expansion of *TP53*-mutated clones (Sperling AS, et al. Blood 2022;140:1753-1763). Additional consideration for and/or closer monitoring of particular patients is warranted.
[ii] Dosing is 40,000–60,000 U 1–2 times per week subcutaneously (SC) for epoetin alfa and 150–300 mcg every other week SC for darbepoetin alfa. For lack of response, escalate the dose. At some institutions, darbepoetin alfa has been administered using doses up to 500 mcg every other week.
[jj] An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.
[kk] Data have demonstrated the effectiveness of luspatercept for treating the anemia of patients with ring sideroblastic lower-risk MDS. Fenaux P, et al. N Engl J Med 2020;382:140-151. Data have emerged for patients with non-sideroblastic lower-risk MDS with anemia indicating similar but more prolonged responses with luspatercept compared to ESAs (Platzbecker U, et al. Lancet 2023;402:373-385). The starting dose of luspatercept-aamt is 1 mg/kg every 3 weeks, which may be increased to 1.33 mg/kg every 3 weeks if not RBC transfusion-free after at least two consecutive doses (6 weeks) at the 1 mg/kg starting dose. The dose may be further increased to 1.75 mg/kg every 3 weeks if not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose.
[ll] Initial dosing is 7.1 mg/kg IV monthly with potential dose decrements since frequent transient thrombocytopenia and neutropenia may occur. Starting platelet and neutrophil levels should be ≥75,000 and ≥1,500, respectively (Platzbecker U, et al. Lancet 2024;403:249-260).
[mm] Target hemoglobin range 10 to 12 g/dL; not to exceed 12 g/dL.
[nn] Lack of ≥1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 3 to 6 months of treatment.
[oo] 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.
[pp] Dosing is 1–2 mcg/kg 1–2 times per week SC for G-CSF.
[qq] Patients generally ≤60 years and with ≤5% marrow blasts, or those with hypocellular marrows, PNH clone positivity, or *STAT3*-mutant cytotoxic T-cell clones.
[rr] Patients lack features listed in footnote qq.
[ss] Lenalidomide 10 mg daily if absolute neutrophil count >0.5, platelets >50,000; Toma A, et al. Leukemia 2016;30:897-905.
[tt] ATG may be omitted when clinically indicated.
[uu] This does not apply to patients with MDS-5q, since this patient population was not studied.
[vv] Emerging data are demonstrating effectiveness of enasidenib for patients with MDS with *IDH2* mutations (Medeiros BC, et al. Leukemia 2017;31:272-281).

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

MANAGEMENT OF HIGHER-RISK DISEASE (IPSS-R INTERMEDIATE-, HIGH-, VERY-HIGH-RISK DISEASE)[v,w]



Footnotes on MDS-7A

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

FOOTNOTES FOR MDS-7

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

[w] Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate-Risk MDS may be managed as lower risk if their score is ≤3.5 vs. higher risk if their score is >3.5. Pfeilstöcker M, et al. Blood 2016;128:902-910.

[y] See Supportive Care (MDS-8).

[aa] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. Garcia-Manero G, et al. Blood 2020;136:674-683.

[tt] Emerging data are demonstrating effectiveness of enasidenib for patients with MDS with *IDH2* mutations (Medeiros BC, et al. Leukemia 2017;31:272-281).

[uu] Based on age (including up to at least 75 years old), 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. Nakamura R, et al. J Clin Oncol 2021;39:3328-3339.

[vv] Allogeneic HCT from the most suitable donor (ie, HLA-matched sibling or unrelated donor, HLA-haploidentical family member or cord blood). Early referral for transplant evaluation is recommended to allow moving to transplant efficiently. Pre-transplant debulking therapy to reduce marrow blasts to <5% with the goal of reducing post-transplant relapse (see footnote yy and Discussion) is recommended, although the optimum strategy (ie, azacitidine, decitabine, induction-type chemotherapy) has not been determined. To reduce the disease burden pre-transplant is particularly important in patients who will receive a reduced-intensity conditioning regimen (Festuccia M, et al. Biol Blood Marrow Transplant 2016;22:1227-1233). At some centers, failure to achieve <5% blasts with cytoreduction should not preclude patients from proceeding to transplant, as these patients appeared to derive survival benefit from transplant (Nakamura R, et al. J Clin Oncol 2021;39:3328-3339; Schroeder T, et al. Biol Blood Marrow Transplant 2019:25;1550-1559). Strategies for patients with specific mutations are under investigation. Patients with *TP53* mutations, particularly biallelic, have a poor prognosis even with transplantation. These cases should be discussed with a transplant physician and patients should be enrolled in a clinical trial whenever possible.

[ww] Azacitidine, decitabine, or oral decitabine and cedazuridine 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 HMA as maintenance therapy. 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.

[xx] 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.

[yy] Some emerging data have shown efficacy of novel agents, including venetoclax in combination with HMAs or targeted IDH1/2 inhibitors for cytoreduction for patients with high-risk MDS (DiNardo C, et al. N Engl J Med 2018;378:2386-2398) who have HMA-refractory disease. When used as cytoreduction for MDS in combination with HMA, venetoclax has been effectively given in monthly courses of 14 days (Garcia JS, et al. Blood 2023;142:Abstract 319). Emerging data have also shown utility of olutasidenib for treating patients with *IDH1* mutations (Cortes J, et al. Blood 2023;142:Abstract 1872). Repeat of marrow evaluation after 1–2 cycles is important to clarify recovery of hematopoiesis and potential requirement for further therapy. Clinical trials are preferred (Discussion). A 20% blast cut-off for AML evolving out of MDS (AML-MDS) and MDS-EB2 may be arbitrary in some clinical scenarios. AML-style therapies may be considered for appropriate patients with MDS-EB2, especially at younger ages of presentation. Furthermore, a diagnosis of AML may be made with less than 20% in patients with certain cytogenetic abnormalities (NCCN Guidelines for Acute Myeloid Leukemia). Some clinical trials designed for high-grade MDS may allow enrollment of patients with AML-MDS (Estey E, et al. Blood 2022;139:323-332, DiNardo CD, et al. Cancer 2022;128:1568-1570). Per recent communications, some patients with higher risk disease with WHO 2022 MDS-IB2 could be considered for AML-type therapy (Khoury JD, et al. Leukemia 2022;36:1703-1719; Arber DA, et al. Blood 2022;140:1200-1228).

[zz] It is recommended to repeat molecular testing to identify targetable mutations.

[aaa] Treatment failure would be considered if no response within 3–6 months. Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425; Zeidan AM, et al. Blood 2023;141:2047-2061.

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

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

SUPPORTIVE CARE[ccc]

- **Clinical monitoring**
  - **Psychosocial support (NCCN Guidelines for Survivorship)**
  - **Quality-of-life assessment**
  - **Transfusions:[ddd]**
    - ◊ **RBC transfusions (CMV-safe) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they are generally not 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, and prophylaxis may be considered when starting patients on therapy, consistent with local hospital guidelines.**
- **Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.**

- **Iron chelation:[eee]**
  - **If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine SC 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 (Discussion). Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox or deferoxamine.**

- **Cytokines:**
  - **ESAs: See Anemia Pathway (MDS-5)**
    - ◊ **ESAs refer to the following agents: epoetin alfa[jj] and darbopoetin alfa.**
  - **G-CSF:**
    - ◊ **G-CSF refers to the following agents: filgrastim[fff] and tbo-filgrastim. Not recommended for routine infection prophylaxis.**
    - ◊ **Consider use in patients with neutropenia with recurrent or resistant infections.**
    - ◊ **Combine with ESAs 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.[ggg]**
- **Post-transplant:**
  - **Patients should receive antibiotic prophylaxis at least as long as they are on IST.**
  - **Detailed recommendations are provided in the Guidelines generated by the American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT). See NCCN Guidelines for Hematopoietic Cell Transplantation (HCT).**

[jj] An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.
[ccc] NCCN Guidelines for Supportive Care.
[ddd] 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, et al. Blood 2013;122:3879-3883.
[eee] Hoeks M, et al. Haematologica 2020;105:640-651; Yang S, et al. Br J Haematol 2022;197:e9-e11; Angelucci E, et al. Ann Intern Med 2020;172:513-522.
[fff] An FDA-approved biosimilar is an appropriate substitute for filgrastim.
[ggg] Giagounidis A, et al. Cancer 2014;120:1838-1846. Platzbecker U, et al. Lancet Haematol 2015;2:e417-e426. Oliva EN, et al. Lancet Haematol 2017;4:e127-e136.

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

PATHOLOGIC-MORPHOLOGIC CLASSIFICATIONS OF MYELODYSPLASTIC NEOPLASMS 2023[a,b]

Transition from Clinically Based Classifications to New Systems Including Genomic Features in 2022

WHO 2016[1]	WHO 2022[2]	ICC 2022[3]	Bone Marrow Blasts
	MDS, genetically defined		
MDS-del(5q)	MDS-5q[d]	MDS-del(5q)[d]	<5%
MDS-RS	MDS-*SF3B1*[e]	MDS-*SF3B1*[e,h]	<5%
—	MDS-bi*TP53*[f]	Myeloid neoplasms with m*TP53*[i]	<20%
	MDS, morphologically defined		
MDS-SLD, MDS-MLD	MDS-LB	MDS-NOS[j]	<5%
—	MDS-hypoplastic[g]	—	<5%
MDS-EB1	MDS-IB1	MDS-EB	5%–9%
MDS-EB2	MDS-IB2[c]	MDS/AML[c]	10%–19%
—	MDS with fibrosis	—	5%–19%
AML[c]	AML[c]	AML[c]	≥20%[c]

[a] Defined by dysplasia (≥10% for any hematopoietic lineage) and cytopenia(s). In general, clinical evidence should indicate that the blood count abnormality is chronic in duration (typically ≥2–4 months) and not explained by drug, toxin, or comorbid condition.

[b] This table compares specific aspects of the WHO 2016, WHO 2022, and ICC MDS classifications for definitions only. Care should be taken in the clinic as classifications alone do not imply therapeutic choice. AML remains a separate entity (NCCN Guidelines for Acute Myeloid Leukemia) with therapeutic options distinct from MDS or MDS/AML in the majority of patients without rational prognostication until interventions have been rigorously studied in this entity.

[c] ≥20% marrow blasts or ≥10% blasts with AML-defining molecular abnormalities. See MDS-A 4 of 5.

[d] Sole genetic abnormality (or allowable 1 other cytogenetic lesion other than chromosome 7 abnormality).

[e] ≥15% RS only if molecular analysis not available; no del(5q), multi*TP53*, -7/del(7q), abn(3q), or complex cytogenetics.

[f] WHO: Biallelic mutation status determined by VAF ≥50%, >1 distinct mutations, *TP53* locus.

[g] ≤25% bone marrow cellularity, age-adjusted.

[h] No *RUNX1* mutation.

[i] ICC: Biallelic mutation status determined by VAF >50%, >1 distinct mutations, TP53 locus loss of heterozygosity (LOH); single *TP53* mutation and complex karyotype (presumptive).

[j] With -7/del(7q) or complex.

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

References on MDS-A 5 of 5

CLINICAL PRINCIPLES OF MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASM (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 5).**
- **Prognostic classification systems have been developed for patients with CMML with features similar to those for MDS. Proliferative CMML (white blood cell [WBC] count >12,000/mm^3) has a worse prognosis than the dysplastic subtype.**
- **Mutational findings are listed in the table on MDS-A (3 of 5) 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 HMA ± venetoclax treatment for patients with intermediate- and higher-risk disease, 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* D816V 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.**
  - **Next-generation sequencing (NGS) has low sensitivity for *KIT* D816V mutation, and allele-specific PCR is more sensitive and recommended in patients with high clinical suspicion of mast cell disease. Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia 2015;29:1223-1232. See the NCCN Guidelines for Systemic Mastocytosis.**
  - **cKIT-directed therapy should be considered for systemic mastocytosis (Bose P, Verstovsek S. Avapritinib for systemic mastocytosis. Expert Rev Hematol 2021;14:687-696).**
- **About 10%–20% of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) skin lesions are associated with or develop into other myeloid neoplasms, including CMML, MDS, or AML (Facchetti F, et al. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, et al. Revised 4th ed. Lyon: IARC Press; 2017:173-177). Therefore, an accurate pathologic diagnosis is important for patients to receive the best care. Tagraxofusp has been demonstrated to be a potentially useful therapy for these patients (Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2019;380:1628-1637).**

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

MDS/MPN CLASSIFICATION

WHO 2016[1]	WHO 2022[2]	ICC[3]	Features	Frequent Mutations	Treatment
Chronic myelomonocytic leukemia (CMML)	CMML-1[k] CMML-2[l]	CMML-myelodysplastic (CMML-MD)[m] CMML-myeloproliferative (CMML-MP)[m]	≥0.5 absolute monocyte count (AMC) ≥10% monocytes Clonality[p]	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[4,5]	CMML-1: Consider HMA[t] or hydroxyurea[s,u,v,13-23] CMML-2: HMA[t,w] ± venetoclax[x] and/or allogeneic HCT[s,u,v,13-26]
Atypical chronic myeloid leukemia (aCML) (*BCR::ABL* negative)	MDS/MPN and neutrophilia	aCML	WBC ≥13K, dysplastic granulocytosis, ≥10% granulocytic precursor cells[q] m*SETBP1* ± m*ASXL1*	*SETBP1, ETNK1*,[6] *BCR::ABL1* negative	• Consider HMA[t] and/or ruxolitinib[y] and/or allogeneic HCT[v,27,28]
MDS/MPN with ring sideroblasts (RS) and thrombocytosis (T)	MDS/MPN with m*SF3B1* and thrombocytosis	MDS/MPN-T-*SF3B1*[n] MDS/MPN-RS-T, NOS	Platelets ≥450K	*SF3B1, JAK2*[7,8] *MPL, CALR*	• Consider HMA[t] and/or lenalidomide[v,29] or • Consider luspatercept-aamt[v,z,30]
MDS/MPN unclassifiable (MDS/MPN-U)	MDS/MPN not otherwise specified (NOS)	MDS/MPN NOS	Platelets ≥450K or WBC ≥13K	*TET2, NRAS, RUNX1, CBL, SETBP1, ASXL1*[9]	• Consider HMA[t] and/or allogeneic HCT[v]
—	—	MDS/MPN with i(17q)[o]	WBC ≥13K, dysgranulopoiesis	*SETBP1, SRSF2*[10]	Allogeneic HCT[v,10,31]
Juvenile myelomonocytic leukemia (JMML)	JMML (now MPN)	Pediatric disorder and/or germline mutation-associated disorders	>90% RAS pathway activation abnormality[r]	*PTPN11, NF1, N/KRAS, CBL, SETBP1, JAK3*[11,12]	Allogeneic HCT[v]

[k] <10% bone marrow blasts or blast equivalents.
[l] <20% bone marrow blasts or blast equivalents.
[m] CMML-MD=WBC ≤13K, CMML-MP=WBC >13K.
[n] VAF >10%.
[o] Provisional.
[p] 80%–90% with ≥1 mutation in *SRSF2, TET2*, and/or *ASXL1*. Substantial frequency of *SETBP1, NRAS/KRAS, RUNX1, CBL*, and *EZH2* mutations.
[q] <10% eosinophilia.
[r] Canonical RAS pathway mutations in *NRAS, KRAS, PTPN11, NF1, CBL*, or *RAS*-related genes in >95% patients; no *KMT2A* rearrangement or -7 cytogenetic abnormality.
[s] Patients with CMML may have disease that responds to ruxolitinib for symptomatic disease. Padron E, et al. Clin Cancer Res 2016;22:3746-3754. Padron E, et al. Blood 2022;140:1101-1103. Patients with a t(5;12) translocation associated with the *ETV6::PDGFRβ* fusion gene may have disease that responds to imatinib mesylate. See NCCN Guidelines for Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions. Patients with CMML may have associated systemic mastocytosis (SM-AHN) and *KIT* D816V mutation responsive to midostaurin.
[t] Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. Garcia-Manero G, et al. Blood 2020;136:674-683.
[u] Avapritinib was recently approved by the FDA in SM-AHN including CMML. DeAngelo DJ, et al. Nat Med 2021;27:2183-2191. Gotlib J, et al. Nat Med 2021;27:2192-2199.
[v] Hydroxyurea may be helpful in decreasing excessive leukocytosis or thrombocytosis (Itzykson R, et al. Blood 2020;136:53-54).
[w] Ruxolitinib may be added to HMAs for symptom management or splenomegaly.
[x] In non-transplant candidates, the risk of cytopenias with the addition of venetoclax should be carefully considered.
[y] Rare patients with *CSF3R* or *JAK2* mutations may have disease that responds to ruxolitinib therapy due to their JAK-STAT pathway activation.
[z] Luspatercept-aamt is an option for the treatment of anemia.

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

References on MDS-A 5 of 5

AML-DEFINING GENETIC ABNORMALITIES: WHO 2022 AND ICC[2,3,32]

AML	Acute promyelocytic leukemia (APL)
• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Other *KMT2A* rearrangements • t(6;9)(p22.3;q34.1)/*DEK::NUP214* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM(EVI1)* • Other *MECOM* rearrangements • Mutated *NPM1* • *CEBPA* (WHO only), in-frame bZIP *CEBPA* mutations (ICC only) • *RBM15::MRTFA* fusion (WHO only) • *NUP98* rearrangement (WHO only)	• t(15;17)(q24.1;q21.2)/*PML::RARA* • Other *RARA* rearrangements

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

References on
MDS-A 5 of 5

REFERENCES

1 Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.
2 Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumors: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.
3 Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.
4 Valent P, Orazi A, Savona MR, et al. Proposed diagnostic criteria for classical CMML, CMML variants and pre-CMML conditions. Haematologica 2019;104:1935-1949.
5 Meggendorfer M, Roller A, Haferlach T, et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). Blood 2012;120:3080-3088.
6 Mughal TI, Cross NC, Padron E, et al. An International MDS/MPN Working Group's perspective and recommendations on molecular pathogenesis, diagnosis and clinical characterization of myelodysplastic/myeloproliferative neoplasms. Haematologica 2015;100:1117-1130.
7 Malcovati L, Della Porta MG, Pietra D, et al. Molecular and clinical features of refractory anemia with ringed sideroblasts associated with marked thrombocytosis. Blood 2009;114:3538-3545.
8 Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood 2015;126:233-241.
9 Zoi K, Cross NC. Molecular pathogenesis of atypical CML, CMML and MDS/MPN-unclassifiable. Int J Hematol 2015;101:229-242.
10 Kanagal-Shamanna R, Orazi A, Hasserjian RP, et al. Myelodysplastic/myeloproliferative neoplasms-unclassifiable with isolated isochromosome 17q represents a distinct clinico-biologic subset: a multi-institutional collaborative study from the Bone Marrow Pathology Group. Mod Pathol 2022;35:470-479.
11 Calvo KR, Price S, Braylan RC, et al. JMML and RALD (Ras-associated autoimmune leukoproliferative disorder): common genetic etiology yet clinically distinct entities. Blood 2015;125:2753-2758.
12 Sakaguchi H, Okuno Y, Muramatsu H, et al. Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leukemia. Nat Genet 2013;45:937-941.
13 Adès L, Sekeres MA, Wolfromm A, et al. Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. Leuk Res 2013;37:609-613.
14 Santini V, Allione B, Zini G, et al. A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. Leukemia 2018;32:413-418.
15 Padron E, Komrokji R, List AF. The clinical management of chronic myelomonocytic leukemia. Clin Adv Hematol Oncol 2014;12:172-178.
16 Onida F, Barosi G, Leone G, et al. Management recommendations for chronic myelomonocytic leukemia: consensus statements from the SIE, SIES, GITMO groups. Haematologica 2013;98:1344-1352.
17 Padron E, Garcia-Manero G, Patnaik MM, et al. An international data set for CMML validates prognostic scoring systems and demonstrates a need for novel prognostication strategies. Blood Cancer J 2015;5:e333.
18 Hunter AM, Zhang L, Padron E. Current management and recent advances in the treatment of chronic myelomonocytic leukemia. Curr Treat Options Oncol 2018;19:67.
19 Savona MR, Malcovati L, Komrokji R, et al; MDS/MPN International Working Group. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood 2015;125:1857-1865.
20 Sperr WR, Horny HP, Valent P. Spectrum of associated clonal hematologic non-mast cell lineage disorders occurring in patients with systemic mastocytosis. Int Arch Allergy Immunol 2002;127:140-142.
21 Sotlar K, Fridrich C, Mall A, et al. Detection of c-kit point mutation Asp-816 --> Val in microdissected pooled single mast cells and leukemic cells in a patient with systemic mastocytosis and concomitant chronic myelomonocytic leukemia. Leuk Res 2002;26:979-984.
22 Patnaik MM, Vallapureddy R, Lasho TL, et al. A comparison of clinical and molecular characteristics of patients with systemic mastocytosis with chronic myelomonocytic leukemia to CMML alone. Leukemia 2018;32:1850-1856.
23 Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-2541.
24 Eissa H, Gooley TA, Sorror ML, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia: relapse-free survival is determined by karyotype and comorbidities. Biol Blood Marrow Transplant 2011;17:908-915.
25 de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood 2017;129:1753-1762.
26 Padron E, Dezern A, Andrade-Campos M, et al. A multi-institution phase I trial of ruxolitinib in patients with CMML. Clin Can Res 2016;22:3746-3754.
27 Dao KT, Tyner JW, Gotlib J. Recent progress in chronic neutrophilic leukemia and atypical chronic myeloid leukemia. Curr Hematol Malig Rep 2017;12:432-441.
28 Kanagal-Shamanna R, Hodge JC, Tucker T, et al. Assessing copy number aberrations and copy neutral loss of heterozygosity across the genome as best practice: An evidence based review of clinical utility from the cancer genomics consortium (CGC) working group for myelodysplastic syndrome, myelodysplastic/myeloproliferative and myeloproliferative neoplasms. Cancer Genet 2018;228-229:197-217.
29 Huls G, Mulder AB, Rosati S, et al. Efficacy of single-agent lenalidomide in patients with JAK2 (V617F) mutated refractory anemia with ring sideroblasts and thrombocytosis. Blood 2010;116:180-182.
30 Komrokji RS, Platzbecker U, Fenaux P, et al. Luspatercept for myelodysplastic syndromes/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis. Leukemia 2022;36:1432-1435.
31 Ganguly S, Uvodich M, Dias A, McGuirk JP. Clinical characteristics and treatment outcome of patients with isochromosome 17q (i17q) abnormality and myeloid neoplasms: A single center experience. Leuk Res Rep 2018;10:55-56.
32 Zeidan AM, Bewersdorf JP, Buckstein R, et al. Finding consistency in classifications of myeloid neoplasms: a perspective on behalf of the International Workshop for Myelodysplastic Syndromes. Leukemia 2022;36:2939-2946.

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

PROGNOSTIC SCORING SYSTEMS

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	—	—	—

PROGNOSIS ACCORDING TO IPSS RISK SCORE[1]

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-4 through MDS-6
For IPSS: Intermediate-2/High, see MDS-7

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	—	Intermediate	Poor	Very poor
Marrow blasts (%)	≤2	—	>2–<5	—	5–10	>10	—
Hemoglobin	≥10	—	8–<10	<8	—	—	—
Platelets	≥100	50–<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

PROGNOSIS ACCORDING TO IPSS-R RISK SCORE[2]

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-4 through MDS-6
For IPSS-R: Intermediate/High/Very High, see MDS-7

[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.

[1] Adapted with permission from: Greenberg PL, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088; Erratum. Blood 1998;91:1100.
[2] Adapted with permission from: Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120:2454-2465. Websites for accessing the IPSS-R calculator tool: http://www.ipss-r.com or http://mds-foundation.org/calculator/index.php. A mobile app for the calculator tool is also available.

Continued

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

PROGNOSTIC SCORING SYSTEMS

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[c]	Good	Intermediate	Poor	—
Severe anemia (hemoglobin <9 g/dL in males or <8 g/dL in females)	Absent	Present	—	—

PROGNOSIS ACCORDING TO WPSS RISK SCORE[3,4]

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

For WPSS: Very Low, Low, Intermediate, see MDS-4 through MDS-6
For WPSS: High, Very High, see MDS-7

[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.]

[3] Adapted with permission from: Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndromes and its integration into the WHO classification-based Prognostic Scoring System (WPSS). Haematologica 2011;96:1433-1440.
[4] Della Porta MG, Tuechler H, Malcovati L, et al. Validation of WHO classification-based Prognostic Scoring System (WPSS) for myelodysplastic syndromes and comparison with the revised International Prognostic Scoring System (IPSS-R). A study of the International Working Group for Prognosis in Myelodysplasia (IWG-PM). Leukemia 2015;29:1502-1513.

Continued

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

PROGNOSTIC SCORING SYSTEMS

INTERNATIONAL PROGNOSTIC SCORING SYSTEM MOLECULAR (IPSS-M)[f,5]

IPSS-M	Very Low VL	Low L	Moderate Low ML	Moderate High MH	High H	Very High VH
Patients, % (n = 2701)	14% (381)	33% (889)	11% (302)	11% (281)	14% (379)	17% (469)
Risk score	≤ –1.5	> –1.5 to –0.5	> –0.5 to 0	> 0 to 0.5	> 0.5 to 1.5	> 1.5
Hazard ratio[g] (95% CI)	0.51 (0.39–0.67)	1.0 reference	1.5 (1.2–1.8)	2.5 (2.1–3.1)	3.7 (3.1–4.4)	7.1 (6.0–8.3)
Median LFS, y 25%–75% LFS range, y	9.7 5.0–17.4	5.9 2.6–12.0	4.5 1.6–6.9	2.3 0.91–4.7	1.5 0.80–2.8	0.76 0.33–1.5
Median OS, y 25%–75% OS range, y	10.6 5.1– 7.4	6.0 3.0–12.8	4.6 2.0–7.4	2.8 1.2–5.5	1.7 1.0–3.4	1.0 (0.5–1.8)
AML-t by 1 y, % 2 y 4 y	0.0 1.2 2.8	1.7 3.4 5.1	4.9 8.8 11.4	9.5 14.0 18.9	14.3 21.2 29.2	28.2 38.6 42.8
Death w/o AML, by 1 y, % 2 y 4 y	2.2 7.0 15.9	8.5 16.2 29.5	12.0 19.8 33.6	18.0 31.1 51.1	19.3 39.8 54.2	30.6 45.6 51.3

Abbreviations: LFS, leukemia-free survival; OS, overall survival; AML-t, AML transformation

[f] The IPSS-M may have a role in clinical decision-making but requires confirmatory evidence to help assess its efficacy.
[g] Hazard ratio for risk of AML-t or death.

[5] With permission from: Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognosis Scoring System for Myelodysplastic Syndromes. NEJM Evid 2022;1:Evidoa2200008. IPSS-M Web calculator: https://mds-risk-model.com.

Continued

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

PROGNOSTIC SCORING SYSTEMS

GENE MUTATIONS FOR THE IPSS-M PROGNOSTIC RISK SCHEMA[5]

Main Effect Genes (n=16)[h]	Residual Genes (Nres) (n=15)
TP53^{multi}	*BCOR*
MLL^{PTD}	*BCORL1*
FLT3	*CEBPA*
SF3B1^{5q}	*ETNK1*
NPM1	*GATA2*
RUNX1	*GNB1*
NRAS	*IDH1*
ETV6	*NF1*
IDH2	*PHF6*
CBL	*PPM1D*
EZH2	*PRPF8*
U2AF1	*PTPN11*
SRSF2	*SETBP1*
DNMT3A	*STAG2*
ASXL1	*WT1*
KRAS	
SF3B1$^{\alpha}$	

***SF3B1*^{5q}, *SF3B1* mutation with isolated *del(5q)* or with one additional aberration excluding *-7/del(7q)*.**

***SF3B1*$^{\alpha}$, *SF3B1* mutation without co-mutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*, or *del(5q)*.**

[h] In statistically weighted order.

[5] With permission from: Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognosis Scoring System for Myelodysplastic Syndromes. NEJM Evid 2022;1:Evidoa2200008. IPSS-M Web calculator: https://mds-risk-model.com

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

GENES FREQUENTLY SOMATICALLY MUTATED IN MDS[a,b]

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[c]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[e]	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 CHIP and CCUS.
DNMT3A	Nonsense or Frameshift or Splice Site Missense in codons G543, R635, A741, R736, H739, 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 RS 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] 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.

[c] 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 chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL). Mutations should not be used as presumptive evidence of MDS when diagnostic criteria for MDS have not been met.

[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] 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.

Continued

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

GENES FREQUENTLY SOMATICALLY MUTATED IN MDS[a,b]

This table lists gene mutations likely to be somatic (acquired, not congenital) and MDS-related. 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[c]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[e]	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 aCML (24%); CMML (5%–10%) and JMML (7%).
PHF6	Nonsense or Frameshift or Splice Site	<5%	More frequent in cases with excess blasts (EBs), 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 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.
UBA1	Missense: exon 3 M41T, M41V, M41L	~5%	VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) associated with systemic autoinflammatory and hematologic diseases, mainly MDS.

[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] 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.

[c] 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 chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL). Mutations should not be used as presumptive evidence of MDS when diagnostic criteria for MDS have not been met.

[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] 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.

Continued

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

GENES FREQUENTLY SOMATICALLY MUTATED IN MDS
REFERENCES

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

- Bejar R. Prognostic models in myelodysplastic syndromes. Hematology Am Soc Hematol Educ Program 2013;504-510.
- Tothova Z, Steensma DP, Ebert BL. New strategies in myelodysplastic syndromes: application of molecular diagnostics to clinical practice. Clin Cancer Res 2013;19:1637-1643.
- Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. Blood 2013;122:4021-4034.
- Kohlmann A, Bacher U, Schnittger S, Haferlach T. Perspective on how to approach molecular diagnostics in acute myeloid leukemia and myelodysplastic syndromes in the era of next-generation sequencing. Leuk Lymphoma 2014;55:1725-1734.
- Greenberg PL. The multifaceted nature of myelodysplastic syndromes: clinical, molecular, and biological prognostic features. J Natl Compr Canc Netw 2013;11:877-884.

1 Bejar R, Papaemmanuil E, Haferlach T, et al. Somatic mutations in MDS patients are associated with clinical features and predict prognosis independent of the IPSS-R: Analysis of combined datasets from the International Working Group for prognosis in MDS- molecular committee [abstract]. Blood 2015;126: Abstract 907.

2 Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med 2011;364:2496-2506.

3 Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 2013;122:3616-3627.

4 Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 2014;28:241-247.

5 Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. Blood 2013;122:4021-4034.

6 Lindsley RC, Ebert BL. Molecular pathophysiology of myelodysplastic syndromes. Annu Rev Pathol 2013;8:21-47.

7 Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature 2011;478:64-69.

8 Malcovati L, Papaemmanuil E, Bowen DT, et al. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood 2011;118:6239-6246.

9 Sakaguchi H, Okuno Y, Muramatsu H, et al. Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leukemia. Nat Genet 2013;45:937-941.

10 Bejar R, Stevenson KE, Caughey BA, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. J Clin Oncol 2012;30:3376-3382.

11 Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol 2013;31:2428-2436.

12 Patnaik MM, Itzykson R, Lasho TL, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia 2014;28:2206-2212.

13 Walter MJ, Ding L, Shen D, et al. Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. Leukemia 2011;25:1153-1158.

14 Graubert TA, Shen D, Ding L, et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. Nat Genet 2011;44:53-57.

15 Thol F, Kade S, Schlarmann C, et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood 2012;119:3578-3584.

16 Makishima H, Yoshida K, Nguyen N, et al. Somatic SETBP1 mutations in myeloid malignancies. Nat Genet 2013;45:942-946.

17 Patnaik MM, Lasho TL, Hodnefield JM, et al. SF3B1 mutations are prevalent in myelodysplastic syndromes with ring sideroblasts but do not hold independent prognostic value. Blood 2012;119:569-572.

18 Sebaa A, Ades L, Baran-Marzack F, et al. Incidence of 17p deletions and TP53 mutation in myelodysplastic syndrome and acute myeloid leukemia with 5q deletion. Genes Chromosomes Cancer 2012;51:1086-1092.

19 Jadersten M, Saft L, Smith A, et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. J Clin Oncol 2011;29:1971-1979.

20 Mallo M, Del Rey M, Ibanez M, et al. Response to lenalidomide in myelodysplastic syndromes with del(5q): influence of cytogenetics and mutations. Br J Haematol 2013;162:74-86.

21 Jadersten M, Saft L, Pellagatti A, et al. Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression. Haematologica 2009;94:1762-1766.

22 Meggendorfer M, Roller A, Haferlach T, et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). Blood 2012;120:3080-3088.

23 Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood 2014;124:2705-2712.

24 Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia 2011;25:1147-1152.

25 Damm F, Chesnais V, Nagata Y, et al. BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. Blood 2013;122:3169-3177.

26 Jerez A, Clemente MJ, Makishima H, et al. STAT3 mutations indicate the presence of subclinical T-cell clones in a subset of aplastic anemia and myelodysplastic patients. Blood 2013;122:2453-2459.

27 Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med 2017;376:536-547.

28 Kanagal-Shamanna R, Hodge J, Tucker T, et al. Assessing copy number aberrations and copy neutral loss of heterozygosity across the genome as best practice: An evidence based review of clinical utility from the cancer genomics consortium (CGC) working group for myelodysplastic syndrome, myelodysplastic/myeloproliferative and myeloproliferative neoplasms. Cancer Genetic 2018;228-229:197-217.

29 Linder K, Iragavarapu C, Liu D. *SETBP1* mutations as a biomarker for myelodysplasia/myeloproliferative neoplasm overlap syndrome. Biomark Res. 2017;5:33.

30 Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in *UBA1* and severe adult-onset autoinflammatory disease. N Engl J Med 2020;383:2628-2638.

31 Georgin-Lavialle S, Terrier B, Guedon AF, et al. Further characterization of clinical and laboratory features in VEXAS syndrome: Large-scale analysis of a multicentre case series of 116 French patients. Br J Dermatol 2022;186:564-574.

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

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

Evaluation for Suspected Hereditary Myeloid Malignancy Predisposition Syndromes (HMMPS)

WHOM TO TEST?

- Allogeneic related donor HCT candidate of patients with suspected HMMPS
- All patients with MDS and adults <50 y with AML[b]
- Clinically suspected genetic predisposition syndrome at any age[a]
- "Hypocellular MDS"[c,1]
- Newly diagnosed aplastic anemia
- Personal history of MDS or AML (including therapy-related) and ≥1 additional cancer(s)[2]

→

INITIAL TESTING

Peripheral blood testing
- FCM for PNH
- Telomere length by flow FISH
- Chromosomal breakage study[d]
- Consider syndrome-specific testing based on clinical suspicion[e]

Skin biopsy for fibroblast culture[f] (for DNA for germline genetic testing)
- Consider upfront to avoid unnecessary delay
- In select settings

Additional bone marrow testing
- CGAT/CMA

→

SUBSEQUENT STEPS

- The presence of a PNH clone[3,4] or 6p[4,5,6] loss of heterozygosity (LOH) are associated with acquired diseases. These findings have not been rigorously established to exclude a germline disorder.
- If abnormally short telomere length and clinically suspected short telomere syndrome, consider panel-based multigene sequencing of germline DNA (eg, fibroblast DNA or remission sample)[g] (Note: telomere length in patients with short telomere syndromes presenting as adults may not be markedly short)
- If chromosomal breakage studies are positive, consider panel-based multigene sequencing or whole exome or genome sequencing of germline DNA[g]
- If initial testing is negative, consider panel-based sequencing of germline DNA or whole exome or genome sequencing of germline DNA[g]

Potential pathogenic germline variant found on "somatic" mutation panels →

- If somatic NGS panel is suggestive of germline mutation, send confirmatory sequencing or whole exome or genome sequencing of germline DNA. Peripheral blood telomere length and chromosomal breakage studies may also be relevant[g]

[a] Suggestive features:
Personal history of congenital anomalies and/or other manifestations concerning for an HMMPS, including so-called inborn errors of immunity (eg, early-onset and/or multiple cancers, excessive toxicity with chemotherapy or radiation, hypocellular marrow, poor stem cell mobilizer, unexplained cytopenias or macrocytosis, pulmonary and/or liver fibrosis, immune deficiency/dysregulation ± laboratory findings of humoral and/or cellular immunodeficiency).
Relative with one or more of the following: acute leukemia or MDS or other manifestations (see above bullet) concerning for an HMMPS.
Member of a family with a genetically defined HMMPS.

[b] The precise age cut-off for risk of inherited predisposition is not known. Note DDX41 may present above this age. Some syndromes are particularly enriched among children and young adults with chromosome 7 abnormalities. See Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[c] "Hypocellular MDS" is currently not a distinct entity recognized by the WHO and presents a diagnostic challenge. Bennett JM, et al. Haematologica 2009:94:264-268.

[d] If testing returns negative and clinical suspicion of Fanconi anemia (FA) persists, repeat on cultured skin fibroblasts to exclude somatic reversion.

[e] Serum pancreatic isoamylase (pediatric and adult patients) and serum isoamylase (pediatric patients) for Shwachman-Diamond syndrome and erythrocyte adenosine deaminase for Diamond-Blackfan anemia.

[f] Skin fibroblast culture and DNA isolation are available at select centers and commercially.

[g] Genetic counseling is needed prior to testing and consultation with an HMMPS expert may be helpful.

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

Continued

References on MDS-D 6 of 6

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

- **Recognition of these predisposition syndromes is clinically relevant for active therapeutic decisions, familial screening, and further investigations.**
  - **Patients may require surveillance for disease-specific serious extra-hematopoietic complications and malignant clonal hematopoiesis evaluation.**
  - **In the setting of HCT consideration, specialized evaluations of a familial donor are warranted as well as potential use of a modified conditioning regimen.**
  - **The recognition of a familial genetic disorder also allows for appropriate genetic counseling and follow-up of affected family members.[7,8]**

- **Increased treatment-related toxicity and prolonged post-treatment aplasia have been observed in patients with MDS/AML with these hereditary syndromes. Early referral to a transplant center and early HCT donor identification should be considered.**

- **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. Additionally, as there can be genetic anticipation in the short telomere syndromes, a child may be clinically affected, and the genetically affected parent clinically unaffected or less severely affected.**

- **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.[9] Patients <50 years with MDS and those with therapy-related myeloid malignancies may be more likely to harbor germline variants in these cancer predisposition genes.[10,11,12]**

Continued
References on
MDS-D 6 of 6

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

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

Below is tailored to heritable hematologic malignancy predisposition syndromes; for a broad and more detailed discussion of cancer risk assessment and counseling, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

- **Principles of Cancer Risk Assessment and Counseling. Consultation with a heritable hematologic malignancy predisposition syndrome expert may be helpful at all stages below:**
  1. **Pre-test counseling prior to ordering testing**
  2. **Appropriate DNA source for germline genetic testing**
  3. **Consideration of the appropriate genetic testing methodologies and other diagnostic testing**
  4. **Testing results disclosure and post-test counseling**
  5. **Limitations of the proposed approach**
  6. **Surveillance**

1. Pre-test counseling includes the following elements:

- **Evaluation of patient's needs and concerns regarding:**
  - **Knowledge of genetic testing for cancer and/or other inherited bone marrow failure risks, including risks, benefits, and limitations of testing and the implications of test results for family members**
    - ◊ **Specific issues to discuss:**
      - **Mutations identified in blood or marrow for somatic mutations associated with MDS can identify constitutional (germline) mutations providing rationale to test a constitutional tissue.**
      - **Distinguishing constitutional versus somatic mutations may require sequencing DNA from a non-hematopoietic tissue in blood-based cancers.**
  - **Goals for cancer family risk assessment**
- **Detailed family history (including cancers and age at diagnosis and multiple cancers in a single individual, cytopenias, immune deficiency/dysregulation, congenital malformations, short stature, developmental delays, pulmonary or liver fibrosis, and ancestry with notation if any consanguinity)**
- **Detailed past medical history and review of systems, including:**
  - **Documentation of prior genetic testing results of patient and family members**
  - **Personal cancer history (age of diagnosis, treatment-related toxicities, and attention to solid and liquid malignancies in the same individual)**
  - **Personal history of cytopenias, immune deficiency/dysregulation, congenital malformations, short stature, developmental delays, and pulmonary or liver fibrosis**
  - **Reproductive history**
- **Complete physical examination**
- **Generation of a differential diagnosis and educating the patient on inheritance pattern, penetrance, variable expressivity, and the possibility of genetic heterogeneity**
- **Discussion of possible genetic testing result outcomes, including positive (pathogenic or likely pathogenic), negative, variants of undetermined significance, and mosaic results**
- **Obtaining written informed consent from patient for testing**
- **Discussion of the clinical implications of testing results to the patient**
- **Discussion of the clinical implications of testing results to potentially affected family members and their available options for risk assessment, testing, and management**
- **Cost of genetic testing**
- **Current legislation regarding genetic discrimination and the privacy of genetic information**

Continued

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

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

2. Appropriate DNA source for germline genetic testing

- 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 or somatic genetic reversion events.[13,14,15]
  - Utilizing skin fibroblasts 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.
  - Buccal samples can be considered, acknowledging the risk of peripheral blood contamination.
  - Peripheral blood during disease remission may be considered with the limitation that acquisition of a dominant revertant clone can occur in individuals with germline mutations. In this setting, genetic testing of blood/marrow-derived DNA could miss the germline mutation (eg, germline mutations in *SAMD9*[16] or *SAMD9L*).[14,16,17]
  - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for information about constitution mismatch repair deficiency.
  - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for information about Li-Fraumeni syndrome.

3. Consideration of the appropriate genetic testing methodologies and other diagnostic testing

- Multigene testing (aka NGS-based panel testing)
- Accurate interpretation of germline (or somatic) mutation testing is essential for effective medical care.
- As commercially available tests differ in the specific genes analyzed, variant classification, and other factors, it is important to consider the indication for testing and the expertise of the laboratory when choosing the specific laboratory and test panel.
  - The interpretation of genetic testing remains subjective and complex. Interpretations may differ by laboratory. Mutations may be reclassified as additional data emerge in the field (ie, mutations initially deemed pathogenic may be reconsidered and reclassified as nonpathogenic or vice versa).
- Mutations identified in testing blood or marrow for somatic mutations associated with MDS can identify constitutional (germline) mutations, but somatic panels are often not comprehensive and so a negative somatic panel does not rule out a constitutional mutation.[18,19]
- 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 heritable hematologic malignancy predisposition syndrome. Specifically, somatic mutation panels may not target the relevant genomic locus and/or detect relevant copy number aberrations implicated in inherited disorders.[18]
- NGS and chromosome genomic array testing (CGAT) are complementary in detecting both mutations and copy number aberrations and copy-neutral LOH (cnLOH) in genes associated with these disorders.
- Additional laboratory testing can assist in diagnosing these disorders.
  - Fanconi anemia (FA) 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.
  - Short telomere syndromes, such as dyskeratosis congenita, demonstrate shortened telomere lengths, which can be measured by fluorescence in situ hybridization (FISH) assays using leukocyte subsets, although in older patients telomere length results may not be sensitive or specific and may require complementary genetic evaluation to aid in interpretation.[20,21]
  - Erythrocyte adenosine deaminase is often elevated in Diamond-Blackfan anemia.[22]

Continued

References on
MDS-D 6 of 6

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

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

4. Post-test counseling done when the test results are disclosed

- Discuss results and associated medical risks.
- Interpret results in context of patient's presentation.
- Discuss recommended medical management.
- Discuss and help to facilitate education and testing of family members at risk for heritable malignancy predisposition syndrome.
- Discuss available resources such as high-risk clinics, disease-specific support groups, and research studies.
- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic testing.
- Consider carrier status implications of autosomal recessive disorders.

5. Limitations of the proposed approach

- The current criteria are focused on known genetic predisposition syndromes for MDS or AML. The proposed age threshold of 50 years at diagnosis is arbitrary and may miss some patients with underlying heritable risk. A notable example of this is *DDX41*. Germline DDX41 variants have been reported in ~2% to 6% of unselected adult patients with myeloid malignancy,[23,24,25] which makes DDX41 one of the most common predisposition genes for myeloid malignancy in adult patients. These patients are commonly diagnosed with their AML/MDS after 50 years of age. Additionally, likely not all genetic predisposition syndromes have been defined and so the current criteria for testing may change over time. Any clinical suspicion of hereditary predisposition warrants a referral to an institution with expertise in the field.
- Initial testing: Telomere length measurement by flow-FISH to assess the risk of telomere-mediated disease in patients with hematologic malignancies where there are circulating malignant cells may be confounded or falsely shortened secondarily due to the malignancy itself. In such cases, germline genetic assessment should be performed in lieu of telomere length measurement and telomere length measurement should be assessed during remission where possible. In some cases of familial disease, assessment of telomere length in a relative with an identical variant in a telomere gene could also be used for interpreting the significance of the variant (optional). Additionally, if there are circulating malignant cells or the malignant cell composition in peripheral blood is unknown, the finding of abnormally short telomere length measurement alone should be interpreted with caution and additional evidence of a telomere-mediated process is needed including the presence of a germline variant of clinical features including a family history of pulmonary fibrosis.
- In the absence of a genetically confirmed heritable hematologic malignancy predisposition syndrome, a concerning personal/or family history may warrant consideration of an unrelated over a related donor for allogeneic HCT.

6. Surveillance

- Individuals who fulfill the clinical diagnostic criteria for a myeloid neoplasm with a germline predisposition should undergo surveillance, even if the pathogenic genetic variant is undetermined.
- Individuals with a deleterious or likely deleterious genetic variant associated with a germline predisposition should undergo surveillance, regardless of clinical presentation.

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

References on
MDS-D 6 of 6

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES
REFERENCES

[1] Bennett JM, Orazi A. Diagnostic criteria to distinguish hypocellular acute myeloid leukemia from hypocellular myelodysplastic syndromes and aplastic anemia: recommendations for a standardized approach. Haematologica 2009:94:264-268.
[2] Singhal D, Hahn CN, Feurstein S, et al. Targeted gene panels identify a high frequency of pathogenic germline variants in patients diagnosed with a hematological malignancy and at least one other independent cancer. Leukemia 2021:35:3245-3256.
[3] DeZern AE, Sekeres MA. The challenging world of cytopenias: distinguishing myelodysplastic syndromes from other disorders of marrow failure. Eur J Hematol 2014;92:467-470.
[4] Shah YB, Priore SF, Li Y, et al. The predictive value of PNH clones, 6p CN-LOH, and clonal TCR gene rearrangement for aplastic anemia diagnosis. Blood Adv 2021:5:3216-3226.
[5] Katagiri T, Sato-Otsubo A, Kashiwase K, et al. Frequent loss of HLA alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. Blood 2011;118:6601-6609.
[6] Babushok DV, Xie HM, Roth JJ, et al. Single nucleotide polymorphism array analysis of bone marrow failure patients reveals characteristic patterns of genetic changes. Br J Haematol 2014;164:73-82.
[7] DiNardo CD, Bannon SA, Routbort M, et al. Evaluation of patients and families with concern for predispositions to hematologic malignancies within the Hereditary Hematologic Malignancy Clinic (HHMC). Clin Lymphoma Myeloma Leuk 2016;16:417-428.e2.
[8] Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. Blood 2017;130:424-432.
[9] Sebert M, Passet M, Raimbault A, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood 2019;134:1441-1444.
[10] Churpek JE, Marquez R, Neistadt B, et al. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. Cancer 2016;122:304-311.
[11] Wlodarski MW, Collin M, Horwitz MS. GATA2 deficiency and related myeloid neoplasms. Semin Hematol 2017;54:81-86.
[12] Feurstein S, Churpek JE, Walsh T, et al. Germline variants drive myelodysplastic syndrome in young adults. Leukemia 2021;35:2439-2444.
[13] Tan S, Kermasson L, Hilcenko C, et al. Somatic genetic rescue of a germline ribosome assembly defect. Nat Commun 2021;12:5044.
[14] Sahoo SS, Pastor VB, Goodings C, et al. Clinical evolution, genetic landscape and trajectories of clonal hematopoiesis in SAMD9/SAMD9L syndromes. Nat Med 2021;27:1806-1817.
[15] Schratz KE, Gaysinskaya V, Cosner ZL, et al. Somatic reversion impacts myelodysplastic syndromes and acute myeloid leukemia evolution in the short telomere disorders. J Clin Invest 2021;131:e147598.
[16] Wong JC, Bryant V, Lamprecht T, et al. Germline SAMD9 and SAMD9L mutations are associated with extensive genetic evolution and diverse hematologic outcomes. JCI Insight 2018;3:e121086.
[17] Tesi B, Davidsson J, Voss M, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood 2017;129:2266-2279.
[18] Trottier AM, Cavalcante de Andrade Silva M, Li Z, Godley LA. Somatic mutation panels: Time to clear their names. Cancer Genet 2019;235-236:84-92.
[19] Kraft IL, Godley LA. Identifying potential germline variants from sequencing hematopoietic malignancies. Blood 2020;136:2498-2506.
[20] Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. Proc Natl Acad Sci USA 2018;115:E2358-E2365.
[21] Schratz KE, Haley L, Danoff SK, et al. Cancer spectrum and outcomes in the Mendelian short telomere syndromes. Blood 2020;135:1946-1956.
[22] Fargo JH, Kratz CP, Giri N, et al. Erythrocyte adenosine deaminase: diagnostic value for Diamond-Blackfan anaemia. Br J Haematol 2013;160:547-554.
[23] Sébert M, Passet M, Raimbault A, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood 2019;134:1441-1444.
[24] Qu S, Li B, Qin T, et al. Molecular and clinical features of myeloid neoplasms with somatic DDX41 mutations. Br J Haematol 2021;192:1006-1010.
[25] Choi EJ, Cho YU, Hur EH, et al. Unique ethnic features of DDX41 mutations in patients with idiopathic cytopenia of undetermined significance, myelodysplastic syndrome, or acute myeloid leukemia. Haematologica 2022;107:510-518.

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

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES[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] with or without cytopenias	*DDX41*	AML, MDS, CML	Late age of onset of hematologic malignancies; non-Hodgkin lymphoma, Hodgkin lymphoma.[5] Patients with germline *DDX41* may present with cytopenias prior to myeloid malignancy development.[6]
14q32.2 genomic duplication[7]	Includes *ATG2B* and *GSKIP*	AML, MPN, CMML (highly penetrant)	Familial MPN. Earlier age of onset compared to sporadic MPN.
Xeroderma pigmentosum C (XPC)[8,9]	*XPC*^{delTG}	Increased myeloid malignancies and T-cell ALL in people aged 7–29 years	Sensitivity to ultraviolet light, experiencing severe sunburns within minutes of exposure, dry skin (xeroderma), freckling (pigmentosum), hearing loss, poor coordination, loss of intellectual function, seizures, and development of squamous cell carcinomas and melanomas often as early as 10 years old in sun-exposed areas.
ERCC6L2[10,11,12]	*ERCC6L2*	Marrow failure, MDS, AML	Skeletal/cardiac abnormalities, neurological defects also associated with somatic *TP53* mutations and erythroleukemia. Pre-existing cytopenias, microcephaly, developmental delay, and other congenital abnormalities.

[a] The list of genes associated with heritable hematologic malignancy predisposition syndromes is continually evolving. Not all of the listed individual genes under the Gene column have been reported in myeloid malignancies.

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

Continued
References on MDS-E 5 of 6

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

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[13]	*ANKRD26*	Moderate thrombocytopenia with mild bleeding manifestations; platelet size is usually not enlarged; dysmegakaryopoiesis[14]/AML, MDS	
ETV6[15,16]	*ETV6*	Thrombocytopenia and mild bleeding manifestations; platelet size is usually not enlarged[17]/AML, MDS	ALL (typically precursor B-cell ALL)[15,17]
GATA2 deficiency syndrome[18,19]	*GATA2*	Bone marrow failure; B-/NK-/CD4-cell lymphocytopenia, monocytopenia[20] AML/ MDS (highly penetrant)	Immune deficiency (ie, viral infections, warts, disseminated nontuberculous mycobacterial infections), wide range of extra-hematopoietic manifestations (eg, lymphedema, sensorineural hearing loss, pulmonary alveolar proteinosis)[21]; megakaryocyte atypia; pediatric MDS w/-7/del(7q), trisomy 8, or der(1;7).
Familial platelet disorder with associated myeloid malignancy[b,22,23]	*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.
LIG-4 syndrome[24]	*LIG4*	Marrow failure, lymphoid malignancy	Short stature, microcephaly, combined immunodeficiency.
SAMD9/SAMD9L syndromes[25, 26, 27,28]	*SAMD9* *SAMD9L*	Transient or permanent cytopenias and hypocellular marrow failure/AML, MDS	MIRAGE (SAMD9): MDS, 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.[25] Ataxia-pancytopenia syndrome (SAMD9L): cerebellar atrophy and white matter hyperintensities, gait disturbance, nystagmus, immune deficiency; MDS with monosomy 7/-7q; somatic genetic aberrations in hematopoietic cells often occur that result in loss of the mutant *SAMD9L* allele.[26] Can have overlap in phenotype between SAMD9 and SAMD9L disorders.
SRP72[29]	*SRP72*	Marrow failure/MDS	Congenital sensorineural deafness.

[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).

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

Continued

References on MDS-E 5 of 6

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES[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, FANCE, FANCF, FANCG, FANCI, FANCJ/BRIP1/BACH1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANQ/ERCC4, FANCR/RAD51, FANCS/BRCA1, FANCT/UBE2T, FANCU/XRCC2, FANCV/REV7/MAD2L2*	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; somatic mutations in *EIF6* & *TP53*.[31]
Short telomere syndromes[g]	*ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RTEL1, TERC, TERT, TINF2, WRAP53, ZCCHC8*[30]	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	*G6PC3* mutations can be associated with congenital anomalies.[32] *HAX1* mutations can be associated with neurologic manifestations including seizures.[33]
Myeloid neoplasms associated with Down syndrome	*Trisomy 21, GATA1*	Transient abnormal myelopoiesis/AML, MDS	Down syndrome; acute megakaryoblastic leukemia.

[c] Additional laboratory testing: Erythrocyte adenosine deaminase is often elevated.
[d] Some FA 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 FA 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 FA 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.

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

Continued

References on MDS-E 5 of 6

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

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, XPC*[8]	AML, *MBD4:* early-onset AML with a high somatic mutation burden characterized by CG>TG changes including biallelic CG>TG mutations in *DNMT3A*[34]	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.

[d] Some FA genes overlap with inherited breast and ovarian cancer genes.

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

Continued

References on
MDS-E 5 of 6

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES
REFERENCES

Data for the table are derived from the references listed below and the following reviews and primary manuscripts:

- Furutani E, Shimamura A. Germline genetic predisposition to hematologic malignancy. J Clin Oncol 2017;35:1018-1028.
- Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. Blood 2017;130:424-432.
- Wlodarski MW, Collin M, Horwitz MS. GATA2 deficiency and related myeloid neoplasms. Semin Hematol 2017;54:81-86.
- Churpek JE, Marquez R, Neistadt B, et al. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop chemotherapy-related leukemia. Cancer 2016;122:304-311.
- Keel SB, Scott A, Sanchez-Bonilla M, et al. Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients. Haematologica 2016;101:1343-1350.

[1] Smith ML, Cavenagh JD, Lister TA, Fitzgibbon J. Mutation of CEBPA in familial acute myeloid leukemia. N Engl J Med 2004;351:2403-2407.
[2] Tawana K, Wang J, Renneville A, et al. Disease evolution and outcomes in familial AML with germline CEBPA mutations. Blood 2015;126:1214-1223.
[3] Taskesen E, Bullinger L, Corbacioglu A, et al. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. Blood 2011;117:2469-2475.
[4] Polprasert C, Schulze I, Sekeres MA, et al. Inherited and somatic defects in DDX41 in myeloid neoplasms. Cancer Cell 2015;27:658-670.
[5] Lewinsohn M, Brown AL, Weinel LM, et al. Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. Blood 2016;127:1017-1023.
[6] Sebert M, Passet M, Raimbault A, et al. Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood 2019;134:1441-1444.
[7] Saliba J, Saint-Martin C, Di Stefano A, et al. Germline duplication of ATG2B and GSKIP predisposes to familial myeloid malignancies. Nat Genet 2015;47:1131-1140.
[8] Sarasin A, Quentin S, Droin N, et al. Familial predisposition to TP53/complex karyotype MDS and leukemia in DNA repair-deficient xeroderma pigmentosum. Blood 2019;133:2718-2724.
[9] Oetjen KA, Levoska MA, Tamura D, et al. Predisposition to hematologic malignancies in patients with xeroderma pigmentosum. Haematologica 2020;105:e144-e146.
[10] Tummala H, Dokal AD, Walne A, et al. Genome instability is a consequence of transcription deficiency in patients with bone marrow failure harboring biallelic ERCC6L2 variants. Proc Natl Acad Sci U S A 2018;115:7777-7782.
[11] Tummala H, Kirwan M, Walne AJ, et al. ERCC6L2 mutations link a distinct bone-marrow-failure syndrome to DNA repair and mitochondrial function. Am J Hum Genet 2014;94:246-256.
[12] Douglas SPM, Siipola P, Kovanen PE, et al. ERCC6L2 defines a novel entity within inherited acute myeloid leukemia. Blood 2019;133:2724-2728.
[13] Pippucci T, Savoia A, Perrotta S, et al. Mutations in the 5' UTR of ANKRD26, the ankirin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia, THC2. Am J Hum Genet 2011;88:115-120.
[14] Noris P, Perrotta S, Seri M, et al. Mutations in ANKRD26 are responsible for a frequent form of inherited thrombocytopenia: analysis of 78 patients from 21 families. Blood 2011;117:6673-6680.
[15] Noetzli L, Lo RW, Lee-Sherick AB, et al. Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia. Nat Genet 2015;47:535-538.
[16] Zhang MY, Churpek JE, Keel SB, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. Nat Genet 2015;47:180-185.
[17] Melazzini F, Palombo F, Balduini A, et al. Clinical and pathogenic features of ETV6-related thrombocytopenia with predisposition to acute lymphoblastic leukemia. Haematologica 2016;101:1333-1342.
[18] Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). Nat Genet 2011;43:929-931.
[19] Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat Genet 2011;43:1012-1017.

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

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES
REFERENCES

Data for the table are derived from the references listed below and the following reviews and primary manuscripts:

- Furutani E, Shimamura A. Germline genetic predisposition to hematologic malignancy. J Clin Oncol 2017;35:1018-1028.
- Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. Blood 2017;130:424-432.
- Wlodarski MW, Collin M, Horwitz MS. GATA2 deficiency and related myeloid neoplasms. Semin Hematol 2017;54:81-86.
- Churpek JE, Marquez R, Neistadt B, et al. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop chemotherapy-related leukemia. Cancer 2016;122:304-311.
- Keel SB, Scott A, Sanchez-Bonilla M, et al. Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients. Haematologica 2016;101:1343-1350.

[20] Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. Blood 2014;123:809-821.
[21] Wlodarski MW, Collin M, Horwitz MS. GATA2 deficiency and related myeloid neoplasms. Semin Hematol 2017;54:81-86.
[22] Song WJ, Sullivan MG, Legare RD, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. Nat Genet 1999;23:166-175.
[23] Weiss HJ, Chervenick PA, Zalusky R, Factor A. A familial defect in platelet function associated with impaired release of adenosine diphosphate. N Engl J Med 1969;281:1264-1270.
[24] Chistiakov DA, Voronova NV, Chistiakov AP. Ligase IV syndrome. Eur J Med Genet 2009;52:373-378.
[25] Narumi S, Amano N, Ishii T, et al. SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet 2016;48:792-797.
[26] Tesi B, Davidsson J, Voss M, et al. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood 2017;129:2266-2279.
[27] Chen DH, Below JE, Shimamura A, et al. Ataxia-pancytopenia syndrome is caused by missense mutations in SAMD9L. Am J Hum Genet 2016;98:1146-1158.
[28] Sahoo SS, Pastor VB, Goodings C, et al. Clinical evolution, genetic landscape and trajectories of clonal hematopoiesis in SAMD9/SAMD9L syndromes. Nat Med 2021;27:1806-1817.
[29] Kirwan M, Walne AJ, Plagnol V, et al. Exome sequencing identifies autosomal-dominant SRP72 mutations associated with familial aplasia and myelodysplasia. Am J Hum Genet 2012;90:888-892.
[30] Gable DL, Gaysinskaya V, Atik CC, et al. ZCCHC8, the nuclear exosome targeting component, is mutated in familial pulmonary fibrosis and is required for telomerase RNA maturation. Genes Dev 2019:33;1381-1396.
[31] Kennedy AL, Myers KC, Bowman J, et al. Distinct genetic pathways define pre-malignant versus compensatory clonal hematopoiesis in Shwachman-Diamond syndrome. Nat Commun 2021;12:1334.
[32] Boztug K, Appaswamy G, Ashikov A, et al. A syndrome with congenital neutropenia and mutations in G6PC3. N Engl J Med 2009;360:32-43.
[33] Germeshausen M, Grudzien M, Zeidler C, et al. Novel HAX1 mutations in patients with severe congenital neutropenia reveal isoform-dependent genotype-phenotype associations. Blood 2008;111:4954-4957.
[34] Sanders MA, Chew E, Flensburg C, et al. MBD4 guards against methylation damage and germ line deficiency predisposes to clonal hematopoiesis and early-onset AML. Blood 2018;132:1526-1534.

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

RECOMMENDATIONS FOR FLOW CYTOMETRY

Initial Evaluation (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 MDS.[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 a 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.**

[1] Bellos F and Kern W. Flow cytometry in the diagnosis of myelodysplastic syndromes and the value of myeloid nuclear differentiation antigen. Cytometry B Clin Cytom 2017;92:200-206.
[2] Cremers EM, Westers TM, Alhan C, et al. Multiparameter flow cytometry is instrumental to distinguish myelodysplastic syndromes from non-neoplastic cytopenias. Eur J Cancer 2016;54:49-56.
[3] Della Porta MG and Picone C. Diagnostic utility of flow cytometry in myelodysplastic syndromes. Mediterr J Hematol Infect Dis 2017;9:e2017017.
[4] Westers TM, Ireland R, Kern W, et al. Standardization of flow cytometry in MDS: a report from an international consortium and the EuLeuNet Working Group. Leukemia 2012;26:1730-1741.
[5] Porwit A, van de Loosdrecht AA, Bettelheim P, et al. Revisiting guidelines for integration of flow cytometry results in the WHO classification of myelodysplastic syndromes-proposal from the International/European LeukemiaNet Working Group for Flow Cytometry in MDS. Leukemia 2014;28:1793-1798.
[6] Selimoglu-Buet D, Wagner-Ballon O, Saada V, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukemia. Blood 2015;125:3618-3626.
[7] Alhan C, Westers TM, Cremers EM, et al. Application of flow cytometry for myelodysplastic syndromes: Pitfalls and technical considerations. Cytometry B Clin Cytom 2016;90:358-367.

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

ABBREVIATIONS

aCML	atypical chronic myeloid leukemia
ALL	acute lymphoblastic leukemia
AMC	absolute monocyte count
AML	acute myeloid leukemia
AML-t	AML transformation
APL	acute promyelocytic leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
ATG	antithymocyte globulin
BPDCN	blastic plasmacytoid dendritic cell neoplasm
CBC	complete blood count
CCUS	clonal cytopenia of undetermined significance
CGAT	chromosome genomic array testing
CHIP	clonal hematopoiesis of indeterminate potential
CHRS	clonal hematopoiesis risk score
CMA	chromosome microarray analysis
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CMV	cytomegalovirus
cnLOH	copy-neutral loss of heterozygosity
CNV	copy number variant
CSA	congenital sideroblastic anemia
EB	excess blasts
ESA	erythropoiesis-stimulating agent
FA	Fanconi anemia
FAB	French American British
FCM	flow cytometry
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
H&P	history and physical
HCT	hematopoietic cell transplant
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMA	hypomethylating agent
HMMPS	hereditary myeloid malignancy predisposition syndromes
IB	increased blasts
ICC	International Consensus Classification
ICUS	idiopathic cytopenia of unknown significance
IPSS	International Prognostic Scoring System
IPSS-M	International Prognostic Scoring System Molecular
IPSS-R	Revised International Prognostic Scoring System
IST	immunosuppressive therapy
IWG	International Working Group
JMML	juvenile myelomonocytic leukemia
LB	low blasts
LDH	lactate dehydrogenase
LFS	leukemia-free survival
LGL	large granular lymphocyte
LOH	loss of heterozygosity
MD	myelodysplastic
MDS	myelodysplastic syndromes(s)
m*IDH1*	mutant *IDH1*
MLD	multilineage dysplasia
MP	myeloproliferative
MPN	myeloproliferative neoplasm(s)
NGS	next-generation sequencing
NOS	not otherwise specified
OS	overall survival
PCR	polymerase chain reaction
PNH	paroxysmal nocturnal hemoglobinuria

Continued

ABBREVIATIONS

RAEB	**refractory anemia with excess blasts**
RARS	**refractory anemia with ring sideroblasts**
RCMD	**refractory cytopenia with multilineage dysplasia**
RCUD	**refractory cytopenia with unilineage dysplasia**
RBC	**red blood cell**
RS	**ring sideroblasts**
RS-T	**ring sideroblasts and thrombocytosis**
SLD	**single lineage dysplasia**
SM-AHN	**systemic mastocytosis with associated hematologic neoplasm**
TIBC	**total iron-binding capacity**
T-LGL	**T-cell large granular lymphocyte**
VAF	**variant allele frequency**
WBC	**white blood cell**
WPSS	**World Health Organization-Based Prognostic Scoring System**
XPC	**xeroderma pigmentosum C**

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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 Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

Discussion

This discussion corresponds to the NCCN Guidelines for Myelodysplastic Syndromes. Last updated: July 25, 2024

Table of Contents

Overview **MS-2**

Guidelines Update Methodology **MS-2**

Literature Search Criteria **MS-2**

Sensitive/Inclusive Language Usage **MS-2**

Diagnostic Classification **MS-3**

- Myelodysplastic Syndromes MS-3
- Myelodysplastic/Myeloproliferative Neoplasms MS-5
- Indolent Myeloid Hematopoietic Disorders MS-7
- Childhood MDS MS-8

Evaluation **MS-10**

- Initial Evaluation MS-10
- Additional Testing MS-12
- Evaluation of Related Anemia MS-14

Prognostic Stratification **MS-15**

- Prognostic Scoring Systems MS-15

Molecular Abnormalities in MDS **MS-19**

Comorbidity Indices **MS-20**

Therapeutic Options **MS-20**

- Supportive Care MS-21
- Treatment of Related Anemia MS-25
- Low-Intensity Therapy MS-29
- High-Intensity Therapy MS-34
- Targeted Therapy MS-36

Recommended Treatment Approaches **MS-37**

- Therapy for Lower-Risk Disease (IPSS Low, Intermediate-1; IPSS-R Very Low, Low, Intermediate; or WPSS Very Low, Low, Intermediate) MS-37
- Therapy for Higher-Risk Disease (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High) MS-40

Summary **MS-42**

References **MS-44**

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Myelodysplastic Syndromes

Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with a relatively heterogeneous spectrum of presentation. Diagnosis and disease stratification are based on multiple factors that may include clinical data, morphology of peripheral blood and bone marrow, fluorescence in situ hybridization (FISH), cytogenetics, flow cytometry, and next-generation sequencing myeloid mutation studies. 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 addition, there are complications that may arise from chronic transfusions, treatment toxicity, and in some cases, secondary phenomena such as systemic inflammatory conditions.[1] In the general population, the incidence rate of MDS is approximately 4.5 per 100,000 people per year.[2] MDS is rare among children/adolescents and young adults. Accounting for 1.6% of patients diagnosed with MDS, individuals <40 years of age have an incidence of 0.1 per 100,000 people per year. However, among individuals between ages 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.[2]

The management of MDS is complicated by the generally advanced age of the patients, median age 77 years,[3] the non-hematologic comorbidities commonly seen in this cohort, 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.[4]

The multidisciplinary Panel of experts for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes 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 biologic factors that may have prognostic significance in MDS.

Guidelines Update Methodology

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

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Myelodysplastic Syndromes, an electronic search of the PubMed database was performed to obtain key literature in MDS published since the previous Guidelines update, using the search term: myelodysplastic syndrome. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[5]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update 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.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[6] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and

inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

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 human immunodeficiency virus [HIV] infection) can cause morphologic changes in marrow cells that are similar to MDS.[4,7] The NCCN Guidelines for Myelodysplastic Syndromes include the World Health Organization (WHO) 2016 and 2022 and the International Consensus Classification (ICC) 2022 classification systems for diagnostic evaluations.[8,9]

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% to 19%; and 3) a specific MDS-associated karyotype [eg, del(5q), del(20q), +8, or -7/del(7q)]. Furthermore, several co-criteria may help confirm the diagnosis of MDS. These co-criteria include 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).[10]

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.[11] 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.[12]

In 2001, WHO proposed an alternative classification for MDS that was modified from the original French-American-British (FAB) definitions.[13-15] The 2022 WHO classification uses the abbreviation "MDS" for

myelodysplastic neoplasms instead of myelodysplastic syndromes.[8] As such, when referring to the 2022 WHO classification in this discussion, "MDS" refers to myelodysplastic neoplasms. However, the abbreviation "MDS/MPN" refers to myelodysplastic/myeloproliferative neoplasm. The 2022 WHO guidelines identify multiple entities of MDS classified as genetically defined MDS: MDS with low blasts and isolated 5q deletion (MDS-5q; previously MDS-del(5q)), MDS with low blasts and *SF3B1* mutation (MDS-*SF3B1*; previously MDS with ring sideroblasts [MDS-RS]), MDS with biallelic *TP53* inactivation (MDS-bi*TP53*); or classified as morphologically defined MDS: MDS with low blasts (MDS-LB; previously MDS with single lineage dysplasia [MDS-SLD] and MDS with multilineage dysplasia [MDS-MLD]), MDS-hypoplastic, MDS with increased blasts 1 (MDS-IB1; previously MDS with excess blasts 1 [MDS-EB1]), MDS with increased blasts 2 (MDS-IB2; previously MDS-EB2), and MDS with fibrosis (see *Pathologic-morphologic classifications of myelodysplastic neoplasms 2023* in the algorithm).[8] The ICC system identifies the following MDS entities: MDS-del(5q), MDS-*SF3B1*, myeloid neoplasms with *TP53* mutation, MDS not otherwise specified (MDS-NOS), MDS with excess blasts (MDS-EB), and MDS/AML. The Panel cautions that classifications alone do not imply therapeutic choice.

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]

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 >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, patients who have 20% to 29% marrow blasts may be considered to have MDS or AML. A 20% blast cut off for AML evolving out of MDS and MDS-EB2 may be arbitrary in some clinical scenarios. AML-style therapies may be considered for appropriate patients with MDS-EB2, especially at younger ages of presentation. Furthermore, a diagnosis of AML may be made with <20% in patients with certain cytogenetic abnormalities (See NCCN Guidelines for Acute Myeloid Leukemia). Some clinical trials designed for high-grade MDS may allow the enrollment of patients with AML-MDS.[24,25] Some patients with higher-risk disease with MDS-IB2 could be considered for AML-type therapy.[8,9] 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.[26-30]

The WHO classifications were revised to improve both the diagnostic and prognostic capabilities of these entities. MDS with del(5q) generally has a relatively good prognosis[16] and is highly responsive to lenalidomide therapy.[31] With a moderate degree of variability, patients with MDS-EB or

MDS-EB in transformation (MDS-EB-T) generally have a relatively poor prognosis, with a median survival ranging from 5 to 12 months. In contrast, patients with MDS-RS-SLD (RA) or MDS-RS have a median survival of approximately 3 to 6 years. The proportion of these individuals with disease that transforms to AML ranges from 5% to 15% in the low-risk MDS-RS-SLD/MDS-RS group to 40% to 50% in the relatively high-risk MDS-EB/MDS-EB-T group. In a study evaluating time-to-disease evolution, 25% of MDS-EB cases and 55% of MDS-EB-T cases underwent transformation to AML in the first year, increasing to 35% of MDS-EB cases and 65% of MDS-EB-T cases within 2 years.[4] In contrast, the incidence of transformation for RA was 5% in the first year and 10% within 2 years. None of the patients with MDS-RS developed leukemia within 2 years.

Biologic evidence indicates that similar clinical phenotypes, including lower blast counts, older age, lower 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[32,33] 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,[33] which arises without *a* known antecedent hematologic disorder. High-risk MDS, AML-MDS, and some older 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[33] differently than patients with indolent MDS (see NCCN Guidelines for Acute Myeloid Leukemia).

Myelodysplastic/Myeloproliferative Neoplasms

The category of MDS/MPN was added to the 2008 update of the WHO classification of myeloid neoplasms.[34] In the 2022 update, this category includes chronic myelomonocytic leukemia (CMML)-1 and CMML-2, MDS/MPN and neutrophilia (previously aCML), MDS/MPN with *SF3B1* mutation and thrombocytosis (previously MDS/MPN with ring sideroblasts and thrombocytosis), and MDS/MPN NOS (previously MDS/MPN unclassifiable).[8] (See *MDS/MPN, Classification* in the algorithm). Juvenile myelomonocytic leukemia (JMML) is classified as a myeloproliferative neoplasm.

In the ICC, CMML has been subdivided into two groups based on molecular and clinical differences: CMML-myelodysplastic (WBC count ≤13 x 10^9/L) and CMML-myeloproliferative (WBC count >13 x 10^9/L).[9] In addition to the WBC count, the percentage of blasts plus monocytes in the peripheral blood and bone marrow has demonstrated prognostic significance. Two blast-based groups are included in the WHO 2022 classification: CMML-1 for patients with <10% bone marrow blasts or blasts equivalents; and CMML-2 for patients with 10 to <20% bone marrow blasts or blasts equivalents.[8] 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] In patients with CMML-1 and CMML-2, 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 cell transplantation (HCT).[37,39,43,44] Patients with CMML may have disease that responds to ruxolitinib for symptomatic disease.[42,45]

Patients with a t(5;12) translocation associated with the *ETV6::PDGFRβ* fusion gene may respond to imatinib mesylate.[37,46,47] Patients with CMML may also have systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and *KIT*816V mutation responsive to midostaurin.[48,49] Hypomethylating agents (HMAs) or hydroxyurea may be considered for patients with CMML-1. HMAs, with or without venetoclax, and/or allogeneic HCT, is recommended for patients with CMML-2. In non-transplant candidates, the risk of cytopenias with the addition of venetoclax should be carefully considered. Ruxolitinib may be added to HMAs for symptom management or splenomegaly for CMML-2.

MDS/MPN and neutrophilia (termed aCML in the ICC), is rare and has similar neutrophilia as the chronic neutrophilic leukemia (CNL) subtype of MPN. However, molecular characterization may distinguish the two entities. The presence of *CSF3R* mutations is strongly associated with CNL but is present in <10% of cases.[50,51] Other MPN-associated driver mutations (ie, *JAK2, CALR, MPL*) are uncommon. The presence of *SETBP1* or *ETNK1* mutations (or both) is reported in up to one third of patients.[52-56] The use of HMAs in MDS/MPN and neutrophilia is a rational application of their established activity in MDS and CMML.[57-59] Emerging data suggest that rare patients with *CSF3R* or *JAK2* mutations may respond to ruxolitinib therapy due to their JAK-STAT pathway activation.[58,60,61] Although the data on HCT procedures are limited, allogeneic HCT is the only treatment modality that can induce long-term remissions in aCML.[54,57,58,62] HMAs and/or ruxolitinib and/or allogeneic HCT may be considered for patients with MDS/MPN and neutrophilia.[57,61]

MDS-RS-T includes patients who present with clinical and morphologic features consistent with MDS and thrombocytosis (platelet counts ≥450 x 10^9/L).[63] The morphology 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 (termed MDS/MPN-T-*SF3B1* or MDS/MPN-RS-T, NOS in the ICC) as a full entity.[64-67] *SF3B1* mutations are associated with the presence of ring sideroblasts and frequently have the *JAK2* V617F mutation or *MPL* W515K/L mutation.[63] In contrast to MDS-RS, *SF3B1* mutations do not change the required percentage of ring sideroblasts for diagnostic classification. *CALR* mutations have also been reported.[68] Case reports suggest efficacy of lenalidomide at alleviating the need for red blood cell (RBC) transfusions in patients with MDS/MPN-RS-T.[68-70] HMAs and/or lenalidomide[69]; or luspatercept-aamt[71] may be considered. In one study, out of 14 patients with MDS/MPN-RS-T randomized to receive luspatercept, 64.3% achieved RBC-TI of ≥8 weeks during weeks 1 to 24, compared to 22.2% out of 9 patients randomized to receive placebo (P = .028).[71]

MDS/MPN-U (termed MDS/MPN NOS in the ICC) is a rare diagnosis, making up <5% of all myeloid disorders.[72] 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.[73] The diagnostic criteria include: clinical and morphologic features consistent with MDS and thrombocytosis (platelet counts ≥450 x 10^9/L), and WBC count ≥13 x 10^9/L. The most frequently mutated genes associated with this subtype include *TET2*, *NRAS*, *RUNX1*, *CBL*, *SETBP1*, and *ASXL1*.[51,53,73,74] There is no optimal treatment consensus for patients with MDS/MPN-U who are not eligible for allogeneic HCT.[54] In a series of 85 patients with WHO-defined MDS/MPN-U, most of the patients received HMAs, which was associated with improved overall survival (OS) compared to other treatment approaches (16.4 vs. 11.5 months).[54,72] These alternate non-transplant approaches included interferon alpha, thalidomide, and lenalidomide.[72] HMAs and/or allogeneic HCT may be considered.

MDS/MPN with i(17q) is a provisional entity in the ICC and is characterized by a WBC count ≥13 x 10^9/L and dysgranulopoiesis.[9] Frequent mutations include those in the *SETBP1* and *SRSF2* genes.[75] The recommended treatment approach is allogeneic HCT.

JMML is a rare childhood cancer that presents in infants and young children. In the 2022 WHO update, it is now classified as an MPN. In the ICC, this is classified as a pediatric disorder and/or germline mutation-associated disorder. Clinical and hematologic criteria for the diagnosis of JMML include: peripheral blood monocyte count ≥1 x 10^9/L; blast percentage in the peripheral blood and bone marrow <20%; splenomegaly; and the absence of *BCR::ABL1* rearrangement.[73] Although no mutations 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%).[76,77] Secondary mutations in the *SETBP1* and *JAK3* genes were also reported.[77] 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*)*. In patients who do not have genetic features of JMML, with at least two of the following must be present: 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*.[8,73] Allogeneic HCT is the main treatment option for JMML.[54,78]

In patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) skin lesions, approximately 10% to 20% of cases are associated or develop into other myeloid neoplasms, including CMML, MDS, or AML.[79] Therefore, an accurate pathologic diagnosis is important for patients to receive the best care. Tagraxofusp has been shown to be a potentially useful therapy for these patients.[80]

Hydroxyurea may be helpful in decreasing excessive leukocytosis or thrombocytosis for the subtypes described above (except for BPDCN).[81] For patients with MDS or MDS/MPN overlap syndromes, observation may be considered to document indolent course versus marked progression of severe cytopenia or increase in blasts.

Indolent Myeloid Hematopoietic Disorders

The spectrum of indolent myeloid hematopoietic disorders encompasses four groups: clonal hematopoiesis of indeterminate potential (CHIP); idiopathic cytopenia of undetermined significance (ICUS); lower-risk clonal cytopenia of undetermined significance (CCUS); and higher-risk CCUS. Based on cytopenia(s), dysplasia, clonality, and risk of transformation, 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, although 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.[82,83] Additionally, shorter survival in these patients compared with aged-matched controls has been demonstrated and may be attributed to non-hematologic causes.[83] The most frequently mutated genes associated with CHIP include *DNMT3A*, *TET2*, *ASXL1*, *RUNX1*, *JAK2*, *PPM1D*, *TP53*, and SF genes.[83-85] 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).[86] Isolated mutations of *DNMT3A*, *TET2*, and *ASXL1* have less predictive value.[86] The risk for myeloid neoplasm is increased 3-, 37-, and 348-fold in low-risk, intermediate-risk, and high-risk CHIP/CCUS, respectively, compared to unmutated controls.[87] ICUS has no known cause, lack somatic mutations or clonal karyotypic abnormalities. There is significant heterogeneity within ICUS, with some patients experiencing spontaneous resolution of disease and others developing a myeloid neoplasm.[88] Data are limited regarding natural history and disease progression for these two disorders. An online calculator should be considered to obtain a clonal hematopoiesis risk score with a corresponding risk category (low, intermediate, or high), as these risk groups significantly differ in the 10-year probabilities of developing myeloid neoplasms, as well as OS.[87]

Two studies have focused on the role of mutational analysis in indolent malignant disease. In a prospective analysis of 144 patients, Kwok and colleagues[89] used a 22-gene panel to determine the frequency of MDS-associated mutations. Among these patients, 17% were categorized as MDS, 15% as ICUS with mild dysplasia, and 69% as ICUS without dysplasia. Further analysis showed that 35% of patients with ICUS had a somatic mutation or chromosomal abnormality similar to MDS; these patients were characterized as CCUS. The similar mutational features may have a role in the diagnostic value of these disorders.[89]

Cargo et al[88] evaluated mutational features associated with ICUS in patients with disease that developed into progressive dysplasia or AML. Although this study was not designed to evaluate the diagnostic role of mutations, detection of mutational features predicted progression to high-risk disease and 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 3 to 6 months. More frequent monitoring may be recommended based on clinical expertise. Observation is the recommended clinical approach. Monitoring is recommended for CHIP (based on clinical change), ICUS (yearly), lower-risk CCUS (yearly), and high-risk CCUS (CBC 2 to 4 times yearly). Enrollment in a clinical trial should be considered for high-risk CCUS.

Childhood 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.[90-92] MDS in children is strongly associated with congenital disorders.[93] Genetic syndromes are evident in 50% of cases, including Down syndrome,[94-96] trisomy 8 syndrome,[97] Fanconi anemia,[98,99] congenital neutropenia (Kostmann syndrome),[100,101] Diamond-Blackfan anemia,[102] Shwachman-Diamond syndrome,[103] dyskeratosis congenita (DC),[104] neurofibromatosis type 1,[105] Bloom syndrome,[106,107] Noonan syndrome,[108] and Dubowitz syndrome.[109] Prior exposure to cytotoxic therapy (eg, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors)[110-113] or radiation[114,115] increases the risk for MDS.

The 2022 WHO classification identifies 2 childhood myelodysplastic neoplasms: Childhood MDS with low blasts (previously termed refractory cytopenia of childhood [RCC]) and childhood MDS with increased blasts.[8] RCC is the most common subtype of MDS found in children, accounting for approximately 50% of cases.[92] Abnormal karyotypes are found in 30% to 50% of children with MDS,[116] most common are numerical anomalies with <10% showing structural abnormalities. Monosomy 7 is the most common cytogenetic abnormality, occurring in 30% of cases,[117,118] followed by trisomy 8[119,120] and trisomy 21.[121] The del(5q) abnormality is rarely seen in children.[122] 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 of MDS-related cytogenetic abnormalities can also help differentiate MDS from AA.[123] 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 <20% also suggests MDS, but biologic 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.[124] Dysplasia in bone marrow cells may also be due to other etiologies including infection (eg, Parvo virus,[125,126] herpes viruses,[127] HIV), deficiencies of B_{12} and copper,[128] drug therapy, and chronic disease.[129] 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), and are usually categorized as having acute megakaryoblastic leukemia (AMKL, M7).[94,96,130,131] This commonly has a prodromal phase of cytopenia(s) similar to MDS and may be considered a spectrum of the same disease. Prognosis of patients with Down syndrome and AMKL is quite good with an 80% cure rate when treated with intensive chemotherapy. HCT is not indicated in first complete remission for these children. Newborns with Down syndrome can develop abnormal myelopoiesis with leukocytosis, circulating blasts, anemia, and thrombocytopenia, but this resolves spontaneously within weeks to months. Approximately 20% of children with Down syndrome, who have transient abnormal myelopoiesis, will subsequently develop AMKL.[95]

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%.[132-134] 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.[118]

Patients with RCC have a median time to progression to advanced MDS of 1.7 years,[118] but the time to progression is highly variable, depending on the underlying cause of MDS and standard prognostic factors.[135] 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.[136] Children diagnosed before age 2 years have the best prognosis. Poor prognostic features include high hemoglobin F, older age, and thrombocytopenia.

Pediatric AML or MDS with monosomy 7 has a poor prognosis with conventional therapies. A 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%.[137] Four of the five deaths occurred in patients transplanted with active leukemia. Seven of eight patients with MDS were alive without

evidence of disease (six in first complete remission, one in second complete remission, and one death due to complications).[137]

Although MDS can occur in both 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.[12] 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, chromosome microarray analysis (CMA)/ chromosome genomic array testing (CGAT)[61] or MDS-related FISH panel should be performed. If karyotype is normal, the CMA should be considered. However, CMAs detect both somatic and germline or constitutional changes.

Bone marrow biopsy staining for reticulin is recommended for evaluating the presence and degree of bone marrow fibrosis.[138] Increased reticulin fibers in the marrow at diagnosis are seen in approximately 5% to 10% of MDS cases.[139-142] MDS with fibrosis is considered a distinct subtype of MDS in the 2022 WHO classification.[8] These patients frequently present with severe pancytopenia and decreased survival in these patients has been reported.[139,140]

Other useful recommended 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, although clinicians should be advised of the limitations. Serum ferritin levels may be nonspecific, particularly in 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.[143] 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 with disease categorized as IPSS-R intermediate. Patients with LDH levels ≥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).[144]

There have been reports that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.[145-147] Copper deficiency is an etiology of anemia, neutropenia, and bone marrow dysplasia that may be under-recognized. There are rare cases of patients with clinical presentation consistent with MDS who 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.[148] Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,[145-147] prior GI surgery,[145,146] a history of vitamin B_{12} deficiency,[146,149] 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-*SF3B1*, and CMML compared to other myeloid neoplasms. Approximately 40% of patients with MDS will carry a mutation in one of the three most frequently mutated splice factors: *SF3B1*, *SRSF2*, and *U2AF1*.[150] 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%).[65] Mutations of *JAK2* are found in 50% of patients with MDS-RS-T, although 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*.[77] 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).[86] 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 for heritable hematologic malignancy predisposition is recommended in a subset of patients, particularly in patients <50 years of age. Diseases, syndromes, and mutations that may potentially be associated include GATA2 deficiency syndrome, Shwachman-Diamond syndrome, short telomere syndromes, *DDX41* mutations (usually present at older ages), and others (see *Genetic Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes* and see *Gene Mutations Associated with Hereditary Myeloid Malignancies* in the algorithm). Shortened telomere length has been associated with diseases of bone marrow failure, including inherited disorders such as dyskeratosis congenita, particularly in the presence of mutations in the *DKC1*, *TERT,* or *TERC* genes that encode for components of the telomere complex.[151,152] Telomere length can be measured by FISH assays using leukocyte (or leukocyte subset) samples.[151,153] 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.[154,155] 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.[156] 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.[156] 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.[157] Identification of Fanconi anemia is clinically important, because it is associated with chromosomal fragility that results in variability of disease response to HMAs.

The *GATA2* gene codes for a transcription factor involved in gene regulation during the development and differentiation of hematopoietic cells and its expression was shown to correlate with severe dysplasia in patients with primary MDS.[158] Heritable mutations in *GATA2* were identified in families with highly penetrant, early-onset MDS and/or AML.[159] 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.[159] 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 cell surface expression of CD34) 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. Flow cytometry may be considered as a diagnostic aid for MDS and may be considered along with *TCR* polymerase chain reaction and *STAT3* mutation testing to evaluate for LGL and paroxysmal nocturnal hemoglobinuria (PNH) clone.

The screening for 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[160-162] (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.[163-166] Deficiency in GPI-anchored proteins such as those involved in complement inhibition (eg, CD55, CD59) leads to complement sensitivity of RBCs and subsequent hemolysis.[163,164] 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.[167] For evaluation of PNH clonogenicity, multiparameter flow cytometry analysis of granulocytes and monocytes using FLAER, and at least one GPI-anchored protein, should be considered.[163,164,167] It should be emphasized that although evidence of a minor PNH clone may be present in approximately 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.[168-171] In one of these studies, three out of nine patients responded to IST as indicated by improved blood counts.[168] Although patients with both MDS and LGL did not respond as well as patients with LGL (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 patients with MDS with LGL clonogenicity receiving anti-thymocyte globulin (ATG).[169] Moreover, the MDS-SLD refractory anemia (RA) subtype was determined as a favorable predictor of response compared to patients with non-MDS-SLD RA (odds ratio [OR], 0.15; 95% CI, 0.04–0.59; $P = .005$).[169]

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.[172-176] Flow analysis should use appropriate antibody combinations with four fluorescence channel instrumentation.[172-176] 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.[177] 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).[177] 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.[177] Using this flow cytometric score in the learning cohort, a correct diagnosis of MDS was made with 70% sensitivity and 93% specificity. Among patients with MDS 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.[177] 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.[178] In addition, *STAT3* mutations are commonly found in T-LGL disease.[179]

Determination of platelet-derived growth factor receptor beta (*PDGFRβ*) gene rearrangements at 5q32 may be helpful to evaluate in patients with CMML.[180] The activation of this gene encoding a receptor tyrosine kinase for *PDGFRβ* has been identified in some of these patients.[181,182] Data have shown that patients with CMML/MPD with *PDGFRβ* rearrangement may respond well to treatment with the tyrosine kinase inhibitor imatinib mesylate.[46,183,184]

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.[4,185] 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 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.[186,187]

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.[16,186] 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.[188]

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) <5%; 2) 5% to 10%; 3) 11% to 20%; and 4) 21% to 30%.

Cytopenias were defined for the IPSS as a hemoglobin level <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]

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.[189] 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.[189] 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 HMAs.[190-195]

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).[196] 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.[196]

In a retrospective analysis of data from lower-risk MDS (IPSS low or int-1) patients in a large multicenter registry (N = 2373) in Spain, the IPSS-R could identify three 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.[194] Within the IPSS int-1–risk group, the IPSS-R further stratified patients into four risk categories (very low, low, intermediate, high) with only one patient categorized as very high risk. 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. Within the IPSS int-1 risk group, median survival based on the IPSS-R risk categories was 113.7 months for very low, 61.3 months for low, 30.4 months for intermediate, and 21.2 months for high risk. This study also applied the refined WPSS to further stratify the IPSS low and int-1 risk groups, and identified a group of patients (refined WPSS high-risk group) within the IPSS int-1 group who had poorer prognosis. However, the IPSS-R identified a larger proportion of patients with poor-risk IPSS int-1 MDS than the refined WPSS (47% vs. 17%).

In a retrospective database analysis of patients with MDS 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 ($P < .005$).[193] 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 HMAs (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.[193] The IPSS-R may therefore provide a tool for therapeutic decision-making.

One study applied the IPSS-R to a series of patients with t-MDS and oligoblastic t-AML (ot-AML).[197] Although some IPSS-R cutpoints were

suboptimal for patients with t-MDS/ot-AML, the overall IPSS-R scores separated patients with t-MDS/ot-AML 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 patients with t-MDS compared to the IPSS, the global MD Anderson risk model, or the t-MDS MD Anderson model.[198] Further studies are warranted to better evaluate the impact of specific therapies and more refined variables and their cut points for analysis of this heterogeneous group of patients.

Other studies have confirmed the value of the IPSS-R in treated as well as untreated patients.[195,199-201] Since more accurate risk stratification by the IPSS-R compared to the IPSS and WPSS has been demonstrated,[199] 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. An 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 MDS was obtained by a dichotomization based on 3.5 scoring points of the IPSS-R raw score (ie, ≤3.5 vs. >3.5).[202]

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.[203] 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.[204] 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,[203] there have been confirmatory studies demonstrating the usefulness of the WPSS.[205-207] 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 <9 g/dL for males and <8 g/dL for females.[208] 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).[208]

IPSS-M

The international prognostic scoring system molecular (IPSS-M) is a prognostic model that takes into account blood counts, marrow blasts, IPSS-R cytogenetic risk categories, 16 main effect genes, and 15 residual genes and provides times estimates for OS, LFS, and AML transformation.[209] Data from 2957 patients with MDS, including those with secondary or therapy-related MDS and MDS/MPN overlap syndromes, were used to identify six risk categories (very low, low, moderate low,

moderate high, high, very high). The median OS was 10.6 years for the very low risk category, 6.0 for low risk, 4.6 for moderate low risk, 2.8 years for moderate high risk, 1.7 for high risk, and 1.0 for very high risk. The median LFS was 9.7 (very low risk), 5.9 (low risk), 4.5 (moderate low risk), 2.3 (moderate high risk), 1.5 (high risk), and 0.76 years (very high risk) respectively. The model was validated in a cohort of 754 Japanese patients. The Panel notes that the IPSS-M may have a role in improving clinical decision-making but requires confirmatory evidence to help assess its efficacy.

LR-PSS

The Lower-Risk Prognostic Scoring System (LR-PSS), 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.[210] 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 x 10^9/L), and higher percentage of bone marrow blasts (≥4%). Importantly, the cytogenetic categories in this system were derived from the previously defined IPSS categories rather than from the more refined IPSS-R. Each of these factors was given a weighted score, and the sum of the scores (range, 0–7 points) was used to generate three 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 three risk categories for both the IPSS low-risk and IPSS int-1–risk subgroups. The LR-PSS may be useful in identifying patients with lower-risk disease who have poorer prognosis and require earlier treatment.

The prognostic value of the LR-PSS has been validated in several independent studies.[66,194,211-213] In a retrospective analysis of data from patients with lower-risk MDS (IPSS low or int-1) in the multicenter Spanish registry (N = 2373), the LR-PSS was able to further stratify patients with lower-risk disease into three risk categories.[194] 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 (30%) 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).

Data from a cohort of patients with lower-risk MDS 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.[213] 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.

Molecular Abnormalities in MDS

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 >80% of patients harboring at least one mutation.[66,214-216] The most frequently mutated genes were *TET2*, *SF3B1*, *ASXL1*, *DNMT3A*, *SRSF2*, *RUNX1*, *TP53*, *U2AF1*, *EZH2*, *ZRSR2*, *STAG2*, *CBL*, *NRAS*, *JAK2*, *SETBP1*, *IDH1, IDH2,* and *ETV6*, although no single mutated gene was found in more than one third of patients. Several of these gene mutations are associated with adverse clinical features such as complex karyotypes (*TP53*), excess bone marrow blast proportion (*RUNX1*, *NRAS*, and *TP53*), and severe thrombocytopenia (*RUNX1*, *NRAS*, and *TP53*). See the IPSS-M section above and *Prognostic Scoring Systems in* the algorithm for a discussion of mutational changes in MDS as noted in the IPSS-M.[209]

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.[214,216] 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 patients with int-1–risk disease with an adverse gene mutation was similar to that of patients assigned to the int-2–risk group by the IPSS).[214] 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.[216] 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.[217,218] Other mutated genes have been associated with decreased OS, including *DNMT3A*, *U2AF1*, *SRSF2*, *CBL*, *PRPF8*, *SETBP1*, and *KRAS*.[214,216,219-223] 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.[216,224,225]

TET2 mutations have been shown to impact the response to HMAs.[226,227] 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.[226] Another study identified 39 genes that were mutated in 213 patients with MDS treated with AzaC or decitabine.[227] A higher response to HMAs 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 HMAs nor be used to influence the selection of HMAs.

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.[214] 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.[228,229] These

mutations are associated with diminished response or relapse after treatment with lenalidomide.[230,231] 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.[232]

Comorbidity Indices

Patients with MDS predominantly comprise an older adult population, posing potential challenges in terms of treatment tolerability and outcomes due to the presence of comorbid conditions. Approximately 50% of patients with newly diagnosed MDS present with one or more comorbidities, with cardiac disease and diabetes among the most frequently observed conditions.[233-237] Assessment of the presence and degree of comorbidities using tools such as the Charlson Comorbidity Index (CCI) or the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) has demonstrated the significant prognostic influence of comorbidities on the survival outcome of patients with MDS.[233,235-237] Some studies have shown that comorbidity (as measured by HCT-CI or Adult Comorbidity Evaluation-27 [ACE-27]) was a significant prognostic factor for survival, independent of IPSS.[234,237] In these studies, comorbidity indices provided additional prognostic information for survival outcomes in patients with MDS 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.[235] 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.[238] Improved risk stratification has also been demonstrated with the incorporation of the Myelodysplastic Syndromes Comorbidity Index with the IPSS-R.[201] 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 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. In addition, factors such as patient age, performance status, and presence of comorbidities have a major influence on the patient's ability to tolerate certain intensive treatments and play a major role in selecting the optimal management strategy. 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, targeted agents, 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.[239-244]

For the MDS therapeutic algorithm, all patients should receive relevant supportive care. Following that, the MDS Panel has proposed stratifying patients with clinically significant cytopenia(s) into two major risk groups: 1) patients with lower-risk MDS (ie, IPSS low, int-1; IPSS-R very low, low, intermediate; WPSS very low, low, intermediate); and 2) patients with higher-risk MDS (ie, IPSS int-2, high; IPSS-R intermediate, high, very high; WPSS high, very high). Patients with IPSS-R intermediate risk may be treated as lower risk if their score is ≤3.5 versus higher risk if their score is >3.5.[202] In addition, patients with intermediate-risk 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. This disease is generally managed as 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. Prior to transplant, transplant patients should receive support.

Supportive care should include RBC transfusions for symptomatic anemia as needed (CMV-safe [CMV-negative or leukopheresed]) or platelet transfusions for bleeding events; however, platelet transfusions are generally not used routinely in patients with thrombocytopenia in the absence of bleeding. CMV-safe blood products are recommended whenever possible for recipients who are CMV-negative. Both the number of transfusions as well as the number of packed RBCs per transfusion should be kept to a minimum in patients who are classified as non-cardiac 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.[245] 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 patients who are potential transplant candidates should be irradiated. Additionally, CMV-safe (CMV-negative or leukopheresed) blood products are recommended whenever possible for recipients who are CMV-negative. Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy, consistent with local hospital guidelines. 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.[246] For example, recombinant human granulocyte colony-stimulating factor (G-CSF) treatment could be considered for patients with MDS with neutropenia with recurrent or resistant bacterial infections.

Post-transplantation, patients should receive antibiotic prophylaxis at least as long as they are on immunosuppressive therapy. Detailed recommendations are provided in the Guidelines generated by the American Society of Transplantation and Cellular Therapy[247] and the NCCN Guidelines for Hematopoietic Cell Transplantation.

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.[248,249] Increased endogenous TPO levels have been reported among patients with MDS compared with healthy individuals.[249] At the same time, TPO receptor sites per platelet were decreased among patients with MDS compared to healthy individuals. The RA subgroup (as defined by Bennett et al[250]) appeared to have the highest TPO levels compared with patients with MDS-EB or MDS-EB-T, while the number of TPO receptor sites remained similar across subtypes.[249] Studies have reported that high endogenous TPO levels correlated with decreased platelet counts in patients with RA, but not in patients with MDS-EB or MDS-EB-T.[249,251] 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.[249,251]

Several studies are investigating the role of the TPO receptor agonist romiplostim in the treatment of thrombocytopenia in patients with lower-risk MDS.[252-257] Phase I/II studies with romiplostim showed promising rates of platelet response (46%–65%) in patients with lower-risk MDS.[253,255] 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 HMAs,[252,254] and decreased frequency of dose reductions or delays in patients receiving lenalidomide therapy.[256] 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).[258] However, due to the early drug discontinuation, interpretation of these data is limited. Following up on previous studies,[253,258] 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.[259] 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.[257]

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.[260,261] 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. A phase II study enrolled patients with low-risk or IPSS int-1 risk MDS with severe thrombocytopenia who were randomized 2:1 to receive eltrombopag or placebo.[262] At the time of the interim analysis, in the intention-to-treat population, 47% of patients receiving eltrombopag demonstrated a platelet response, as opposed to 3% of patients in the placebo group (P < .0001; OR, 27.1 [95% CI, 3.5–211.9; P = .0017]). Forty-six percent of patients in the eltrombopag arm had grade 3–4 adverse events compared to 16% in the placebo group (P = .0053). Fewer bleeding events were reported in the eltrombopag arm compared to the placebo arm (14% vs. 42%, respectively; P = .0025). The results from another phase II trial determined that eltrombopag monotherapy in patients with lower-risk MDS with cytopenia, including anemia, thrombocytopenia, or neutropenia, led to a 44% rate of hematologic response at 16 to 20 weeks.[263] A few patients acquired chromosomal abnormalities. A study by Fan et al[264] found that 50% of patients with moderate aplastic anemia or unilineage cytopenias (platelet count <30 x 10^9/L or dependence on platelet transfusions or hemoglobin count <8.5 g/dL or dependence on

RBC transfusions) treated with eltrombopag achieved a clinically meaningful response at 16 to 20 weeks. Out of 34 patients, two patients acquired cytogenetic abnormalities.

A phase II trial evaluated eltrombopag monotherapy or eltrombopag in combination with HMAs in adults who have had >4 cycles of HMAs but who have disease that fails to respond to treatment or disease that continues to have ongoing cytopenias.[265,266] Out of 28 evaluable patients, three of those who received the combination treatment showed platelet improvement and three had progressive disease. The median OS was 12 months. The phase II ASPIRE trial evaluated eltrombopag monotherapy for thrombocytopenia in adult patients with intermediate-2 or high-risk MDS and AML.[267] Patients on eltrombopag monotherapy experienced significantly fewer clinically relevant thrombocytopenic events compared to those on placebo. However, there was no improvement in hematologic parameters or in platelet transfusion independence.

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.[268,269] 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 is currently approved for use in patients with MDS.

Management of Iron Overload

RBC transfusions are a key component in the supportive care of patients with MDS. Although the specific therapies patients receive may alleviate RBC transfusion need, a substantial proportion of patients with MDS may not respond to these treatments and may develop iron overload and its consequences.[270] Thus, effective treatment of transfusional siderosis in patients with MDS 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.[271,272]

Although limited, there is evidence suggesting that organ dysfunction can result from iron overload in patients with MDS.[273-275] Retrospective data indicate that transfusional iron overload might be a contributor of increased mortality and morbidity in early-stage MDS.[276] The WPSS has shown that the requirement for RBC transfusion is a negative prognostic factor for patients with MDS.[203] A few studies have reported an improvement in OS for patients receiving iron chelation therapy compared to those who did not.[277-279] However, prospective studies are required to substantiate the value of iron chelation in these patients.

A randomized prospective trial with 225 patients with lower-risk MDS (IPSS low or int-1) and serum ferritin levels >2247 pmol/L demonstrated the benefit of iron chelation therapy.[280] Compared to patients in the placebo arm (n = 76), patients in the deferasirox arm (n = 149) had a higher median event-free survival (3.9 years [95% CI, 3.2–4.3 years] vs. 3.0 years [95% CI, 2.2–3.7 years]; hazard ratio [HR] = .64 [95% CI, 0.42–0.96]). The median OS was 5.2 years (95% CI, 3.9 years–not evaluable) and 4.1 years (3.0–4.9 years) for the deferasirox arm and the placebo arm respectively (HR = .83; 95% CI, .54–1.28). Per the IWG 2006 response criteria, the hematologic improvement in erythroid response was achieved in 39.6% (95% CI, 31.4%–47.8%) of patients treated with deferasirox compared to 27.6% (95% CI, 16.9%–38.3%) of patients treated with placebo.

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 <1000 mcg/L. Beyond this level, serum ferritin can negatively impact the OS of patients with MDS.[281] It is recognized that such measurements, although useful, are less precise than Superconducting Quantum Interference Device (SQUID), or T2* MRI, to provide a specific measurement of hepatic iron content.[282,283]

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.[241,272] This included transfusion independence (TI) in a subset of the small group of patients with MDS who had undergone effective deferoxamine chelation for 1 to 4 years.[284] In addition, improvement in cardiac iron content was demonstrated in these patients after chelation.[285] Such findings have major implications for altering the morbidity of patients with MDS, particularly those with pre-existing cardiac or hepatic dysfunction.

The availability of iron chelators, such as deferoxamine[286] and deferasirox,[287-289] 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.[286] Deferasirox (given orally) is indicated for the treatment of chronic iron overload due to blood transfusions.[287] Deferasirox has been evaluated in multiple phase II clinical trials in patients with TD-MDS.[290-292] A randomized phase II study evaluated the outcomes of deferasirox compared to placebo in patients with low- to intermediate-1–risk MDS.[280] The results demonstrated that deferasirox prolonged the median event-free survival by approximately 1 year.[280] 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.[293] The U.S. Food and Drug Administration (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.[293] Controversy remains regarding the use of this agent. The NCCN Task Force report, *Transfusion and Iron Overload in Patients with Myelodysplastic Syndromes*, provides detailed evidence regarding iron chelation in patients with MDS.[294]

The NCCN Guidelines Panel recommends consideration of once-daily deferoxamine SC or deferasirox/ICL670 orally to decrease iron overload in patients who have received >20 to 30 RBC transfusions, particularly for those who have lower-risk MDS or who are potential transplant candidates (with Low/int-1 MDS). For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL.

As mentioned above, a black-box warning was added to the prescribing information for deferasirox.[287] 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 <40 mL/min.[287] A recent phase IV study with 61 patients with MDS or AA determined that the adverse events noted within a 3-year period were largely mild or moderate.[295]

Treatment of Related Anemia

Erythropoiesis-stimulating agents (ESAs) such as epoetin alfa 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 patients with lower-risk MDS have demonstrated erythroid response rates of 40% and 60% (combined major and minor responses using IWG response criteria) in the initial trials.[296,297] Clinical trial results in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than epoetin.[296-299] 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%).[300] Epo and G-CSF appeared to have synergistic activity. Lower sEPO levels (<500 mU/mL) and a lower pretreatment RBC transfusion requirement (<2 units per month) were associated with a higher response rate; response rates were not significantly different across IPSS risk groups. Median survival, including 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.

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.[301] 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 (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.

Similar findings were reported in a study from the French myelodysplasia group, which analyzed outcomes with ESAs (epoetin or darbepoetin), with or without G-CSF, in patients with MDS with anemia (N = 403).[302] 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. 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.[303] 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.[303]

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 patients with lower-risk MDS 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.[304] 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.[302,305] Duration of response in these patients was significantly decreased compared with patients without del(5q) (mean duration, 25–27 months). Based on multivariate analysis, del(5q) was a significant predictor of a shorter response duration with treatment (see *Prognostic Category Very Low, Low, Intermediate-1 Treatment* in the algorithm).[302]

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 >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 patients undergoing orthopedic surgery. However, ESAs have been used safely in large numbers of adult patients with MDS and have become important for symptomatic improvement of anemia caused by this disease, often with a decrease in RBC transfusion requirements. Studies assessing the long-term use of Epo with or without G-CSF in patients with MDS have shown no negative impact of such treatment on survival or AML evolution when compared to either randomized controls[306] or historical controls.[301,302]

Jadersten et al[301] reported improved survival in patients with low-risk MDS with low transfusion need following treatment with these agents. In another study, improved survival and decreased AML progression of patients with IPSS low or int-1 following Epo treatment, with or without G-CSF, compared to the historical control IMRAW database patients were reported.[302] 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 patients with MDS, with a target hemoglobin range of 10 to 12 g/dL but not exceeding 12 g/dL.

The phase III randomized COMMANDS trial evaluated the use of luspatercept in patients with no del(5q) with very-low risk, low-risk, or

intermediate-risk IPSS-R MDS (73% of whom had ring sideroblasts), with no prior ESAS treatment and who needed RBC transfusions.[307] Data from an interim efficacy analysis revealed that 59% of patients receiving luspatercept achieved the primary endpoint of RBC transfusion independence for 12 weeks or longer and a mean hemoglobin increase of ≥1.5 g/dL, compared to 31% of patients receiving epoetin alfa (P < .0001). In patients with ring sideroblasts, responses were 65% with luspatercept versus 26% with epoetin alfa but in those with ring sideroblast-negative disease, responses were similar, 41% with luspatercept versus 46% for epoetin alfa. The median duration of responses was 127 weeks for luspatercept versus 77 weeks for epoetin alfa. Occurring in ≥3% of patients, fatigue, asthenia, nausea, dyspnea, hypertension, and headache were the most frequent suspected treatment-related adverse events in patients receiving luspatercept. No treatment-related adverse events occurred in ≥3% of patients receiving epoetin alfa.

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.[308] 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 QOL and survival.[189,309-311] 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.[312] In April 2020, based on encouraging phase III data,[311] the FDA approved luspatercept for the treatment of anemia in patients with lower-risk MDS with ring sideroblasts that failed treatment with ESAs. In the phase III MEDALIST trial, 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).[311] In this trial, eligible patients 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. 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 endpoint of transfusion independence for 8 weeks or longer (P < .001). The median duration of the longest single continuous period of response to luspatercept was 30.6 weeks. The most common adverse events associated with luspatercept included fatigue, diarrhea, asthenia, nausea, and dizziness, which decreased over time. Additionally, 81.0% of patients in the luspatercept group met the secondary endpoint of a mean absolute increase in neutrophil count of ≥0.5 x 10^9/L from baseline compared to 51.3% of patients in the placebo group. 70.6% and 42.1% of patients in the luspatercept and placebo groups, respectively, met the secondary

endpoint of a mean absolute increase in platelet count of ≥30 x 10^9/L.[313] In the overall population, 4.6% and 7.9% of patients in the luspatercept and placebo groups, respectively, had treatment-emergent grade 3 or 4 neutropenia.

In a phase II multicenter, open-label, dose-finding study (PACE-MDS), patients 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).[314] 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 to 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 to 1.75 mg/kg, and patients could be treated for up to 5 years.[314] 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 patients with low transfusion burden, 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 patients with high transfusion burden.[314]

Long-term efficacy and safety data of the PACE-MDS study support the use of lusptercept.[315] Of the 108 patients who received treatment with luspatercept, 44 patients had non-ring sideroblastic disease and 48 had received prior treatment with ESAs. The hematologic improvement in erythroid response was 54% in the overall group and 36% in patients with non-ring sideroblastic MDS. Among 73 evaluable patients, 44% of the overall group achieved RBC-TI ≥8 weeks, compared to 35% of the subgroup with non-ring sideroblastic MDS. The most common treatment-emergent adverse occurrences were headache, bone pain and hypertension in patients with non-ring sideroblastic MDS.

In a phase II trial comprising 57 patients with lower-risk MDS that had relapsed or was refractory to ESAs and who were RBC transfusion dependent, treatment with imetelstat, a telomerase inhibitor, resulted in a 37% and 23% RBC TI rates, at 8 and 24 weeks respectively.[316] At the same time points, RBC TI rates of 42% and 29% respectively were observed in a subgroup of 38 patients without del(5q) and who were not previously treated with an HMA or lenalidomide. The median duration for TI was 65 weeks for the overall group compared to 86 weeks in the subgroup. Hematologic improvement, in terms of erythroid response per the IWG 2006 response criteria, was achieved in 65% of patients in the overall group and 68% of patients in the subgroup. Overall, the most common grade ≥3 hematologic adverse events were neutropenia (60%), thrombocytopenia (54%), and anemia (19%). At 5%, the most common grade ≥3 nonhematologic adverse events were back pain, increased alanine aminotransferase, increased aspartate aminotransferase, and bronchitis.

In the phase III IMerge study, patients with IPSS low or intermediate-1 risk MDS with disease that relapsed or that was refractory to ESAs or who were ineligible (with sEPO >500 mU/mL) for ESAs were randomized 2:1 to receive treatment with imetelstat or placebo.[317] A higher percentage of patients treated with imetelstat achieved the primary endpoint of RBC-TI for at least 8 weeks (40% vs. 15% in the placebo arm; P = .0008) and the secondary endpoint of RBC-TI for at least 24 weeks (28% vs. 3% in the placebo arm; P = .0001). Out of those who achieved the primary endpoint, the median RBC-TI duration was 51.6 weeks with imetelstat and 13.3 weeks with placebo. Hematologic improvement-erythroid was observed in 64% of patients in the imetelstat arm (vs. 52% in the placebo arm) when assessed by the IWG 2006 response criteria. When assessed by the IWG

2018 criteria, hematologic improvement-erythroid was 42% in the imetelstat arm and 13% in the placebo arm. The results of a subgroup analysis showed that among patients with sEPO >500 mU/mL, 26.9% (vs. 9.1% for placebo; *P* = .107) and 15.4% (vs. 0.0% for placebo; *P* = .050) achieved TI with imetelstat at 8 weeks and 24 weeks, respectively. Ninety-one percent of patients treated with imetelstat experienced a grade 3–4 treatment emergent adverse event, compared to 47% of patients receiving placebo, with neutropenia (68% vs. 3% in the placebo arm) and thrombocytopenia (62% vs. 8% in the placebo arm) being reported as the most frequent events in those patients.

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) HMAs 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.[318-321] 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.[321] 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[322] provided a summary of three AzaC studies in a total of 306 patients with high-risk MDS.[322] 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 patients treated with AzaC 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.[322] 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.[318] 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 is a recommended option for progressive MDS 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 six 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.[323] 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.[323] 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.[323]

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)[324] and as an IV regimen (75 mg/m^2/day IV for 5 days every 28 days).[325] Although response rates with the 5-day regimens appeared similar to the approved 7-day dosing schedule,[324,325] 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,[326] with an overall response rate of 49%, and a 64% response rate was seen in patients with a high-risk IPSS score[327]; results were similar to those seen in AzaC studies.[319,328]

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.[319] 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 patients receiving supportive care than for patients receiving decitabine. Based on this study and three supportive phase II trials,[329] the drug has also been approved by the FDA for treating patients with MDS.

In another phase III randomized trial with this regimen, decitabine was compared with best supportive care (BSC) in patients ≥60 years of age (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.[320] 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).[320] 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 European Organization for Research and Treatment of Cancer [EORTC] QOL Questionnaire C30) for the dimensions of fatigue and physical functioning.[320]

In 2007, Kantarjian and colleagues[330] provided an update to their study of 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens.[330] Patients received one of three different schedules of decitabine, including both SC and IV administration with a mean of seven 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.[331] 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.

A phase I dose-escalation study evaluated the combination of decitabine with cedazuridine in 44 patients with intermediate to high-risk MDS or CMML.[332] The clinical responses were comparable to those obtained with a 5-day treatment with IV decitabine. These results were confirmed in a phase II study documenting bioequivalence for this combination in patients with IPSS int-1 and above with 60% of patients achieving a clinical response and 21% of patients having a complete response.[333] Results from the phase III ASCERTAIN randomized trial with a crossover design showed that the combination treatment had an equivalent decitabine exposure to IV decitabine.[334] A clinical response was obtained in 70% of evaluable patients. Occurring in 61%, 57%, and 50% of patients, respectively, thrombocytopenia, neutropenia, and anemia were the most common ≥3 adverse events.

Several retrospective studies have evaluated the role of cytoreductive therapy with HMAs prior to allogeneic HCT (with both myeloablative and reduced-intensity conditioning [RIC] regimens).[335-338] These studies suggest that HMAs may provide a feasible alternative to induction chemotherapy regimens prior to transplant, and may serve as a beneficial bridge to allogeneic HCT. The VidazaAllo study, which enrolled patients with higher-risk MDS aged 55 to 70 years, reported a higher event-free survival rate in patients who underwent transplant following a reduced-intensity conditioning regimen after pretreatment with AzaC, compared to those who received continuous AzaC therapy.[339] One meta-analysis found that the use of HMAs before HCT did not improve OS compared to chemotherapy, except in older patients.[340] However, these agents should not be used in lieu of early transplantation or to delay transplantation until loss of response or disease progression.[341]

AzaC and decitabine are considered to be therapeutically similar, although the improved survival of patients with higher-risk MDS treated with AzaC compared to control in a phase III trial, as indicated above, supports the preferred use of AzaC as a first-line treatment option for patients with high-risk MDS who are not transplant candidates 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 HMAs. The minimum number of courses prior to discontinuing treatment should be four courses for decitabine or six courses for AzaC. As discussed earlier, the optimal duration of therapy with HMAs 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 HMAs, 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 with disease that is not expected to respond to (or with disease relapse 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.[4,342-347]

Use of IST with ATG, with or without cyclosporine,[345,347] has been shown in several studies to be most efficacious in patients with MDS with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a PNH clone.[160,348] Researchers from the National Institutes of Health (NIH) have updated their analysis of 129 patients treated with IST with equine ATG alone, cyclosporine alone, or in combination.[162] This study demonstrated markedly improved response rates in the subgroup of patients aged ≤60 years with IPSS int-1 risk or patients with high response probability characteristics as indicated by their prior criteria (ie, age, number of transfusions, possibly HLA-DR15 status).[162]

Although equine ATG has been found to be more effective than rabbit ATG for treating AA,[349] 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.[350] 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.[351,352]

A phase I–II trial examined the combination of IST with eltrombopag in patients with aplastic anemia (not MDS).[353] Three cohorts were used that differed by the schedule for the start of treatment and the duration of treatment. The most common grade 3 or above adverse event attributed to eltrombopag was an abnormality in a liver test (18%), specifically transaminase elevation and/or hyperbilirubinemia. The complete hematologic response and overall response rate (ORR) for the combined cohorts at 6 months, when compared to a historical cohort of 102 patients who were treated with IST, were 39% (95% CI, 29%–49%) versus 10% and 87% (95% CI, 80%–94%) versus 66%, respectively. The rate of clonal evolution was not increased in patients who received eltrombopag compared to a historical cohort at the 2-year time point. A phase II trial with patients with aplastic anemia reported an ORR of 76% in patients receiving the combination treatment compared to 71% in patients treated with IST only.[354] The complete remission rate, median time to response, and the survival rate at 2 years were similar in both groups. One study showed that STAT3-mutant cytotoxic T-lymphocyte clones are present in a small proportion (5%) of patients with MDS (including those lacking LGLs), which is associated with HLA-DR15 positivity, marrow hypocellularity, and neutropenia.[161] Despite lack of a survival difference in the STAT3-mutated versus patients with non-mutated MDS treated with IST in this small cohort, these findings suggest that STAT3-mutant cytotoxic T-lymphocyte clones may facilitate persistently dysregulated autoimmune activation akin to that present in other patients with MDS responsive to IST.[161]

Lenalidomide (a thalidomide analog) is an immunomodulating agent with activity in patients with lower-risk MDS.[31,355] Beneficial results have been particularly evident for patients with the del(5q) chromosomal abnormality.[31,355,356] A multicenter phase II trial of lenalidomide (10 mg/day for 21 days every 4 weeks or 10 mg daily) in patients with anemic RBC-TD MDS with del(5q), with or without additional cytogenetic abnormalities

(N = 148), demonstrated that the hematologic response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained.[31] RBC-TI (assessed at 24 weeks) occurred in 67% of patients; among patients with IPSS low/int-1 risk (n = 120), 69% achieved TI.[31] 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 patients with IPSS low/int-1–risk MDS 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 patients with RBC-TD (N = 205) lower-risk MDS (IPSS low- and int-1 risks) and del(5q).[357] The primary endpoint of RBC-TI ≥26 weeks was achieved in a significantly greater proportion of patients treated with lenalidomide (5 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.[357] 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 non-responders (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.[357]

A 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]).[358] 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 ($P = .755$).[358] 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.[358]

A phase II study evaluated lenalidomide treatment in patients with RBC-TD (N = 214) low- or int-1–risk MDS without del(5q).[359] Results showed that 26% of the patients with non-del(5q) (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.[342] 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 >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 four 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.[342] Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents for patients with non-del(5q) MDS, particularly addressing the characterization of the subgroup 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 prior therapy.

A phase III randomized trial in patients with lower-risk, ESA-refractory, non-del(5q) MDS compared lenalidomide alone (10 mg/day for 21 days every 28 days) with patients receiving lenalidomide in conjunction with epoetin alfa (60,000 U/wk).[360] 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 patients with heavy RBC transfusion dependence (defined as receiving greater than 4 RBC units per 8 weeks) a statistically significant improvement was seen with the addition of epoetin alfa (47% vs. 16%; *P* = .04), suggesting that lenalidomide may restore sensitivity of MDS erythroid precursors to Epo.[360] Another phase III trial also reported a significantly higher major erythroid response in patients with lower-risk MDS lacking del(5q) treated with 4 cycles of lenalidomide in conjunction with epoetin alfa compared to lenalidomide monotherapy (28.3% vs. 11.5%; *P* = .004).[361] The median duration of the major erythroid response for the combination treatment was 23.8 months versus 13.0 months for the lenalidomide arm.

High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy or HCT.[4,362] 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.[363]

A high degree of multi-drug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS[364] 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[365,366] and negative[367] studies have been published.

Allogeneic HCT from an HLA-matched sibling, unrelated donor, haploidentical donor, or cord blood donor is a preferred approach for treating select patients with MDS, particularly those with high-risk disease.[368-378] This includes both standard and RIC strategies.

A multicenter study investigating the outcomes of patients with IPSS int-2 or high MDS who were eligible for RIC allo-transplant found a survival advantage for patients who underwent transplantation.[379] At 3 years, an intention-to-treat analysis revealed that the adjusted OS rate in patients aged 50 to 75 years was 47.9% (95% CI, 41.3%–54.1%) and 26.6% (95% CI, 18.4%–35.6%; *P* = .0001) for those in the donor arm (expected to undergo reduced-intensity conditioning HCT, n = 260) and the no-donor arm (expected to receive HMA therapy or best supportive care, n = 124), respectively. In addition, at the same time point, the leukemia-free survival rate was 35.8% (95% CI, 29.8%–41.8%) versus 20.6% (95% CI, 13.3%–29.1%; *P* = .003), respectively. Subgroup analyses showed that there were no differences in outcomes by age ≤65 years versus age >65 years. However, since ~34% of patients in both arms had disease that did not respond to HMAs, it is not surprising that the donor arm results appeared better.

Another study examined retrospectively the outcomes of patients with high-risk MDS or secondary AML who underwent transplantation without prior cytoreductive therapy (n = 67) compared to those who received cytoreductive therapy in the form of induction chemotherapy (n = 64) or HMAs (n = 34) prior to transplantation.[380] Patients had a blast count of ≥5% in the bone marrow. Reduced-intensity conditioning was applied before stem cell infusion in 68% of patients. Compared to the other groups, a higher percentage of patients in the HMA group (85%) were treated with a reduced-intensity conditioning regimen, which is likely due to the difference in age. Multivariate analyses revealed that the type of pretransplant treatment did not impact the OS, relapse-free survival (RFS), and non-relapse mortality. However, cytogenetics, reduced-intensity conditioning and the use of an unrelated donor were found to be predictors of negative outcomes. At 5 years, there was no difference in OS (61%, 50%, and 45% respectively; *P* = .116) and relapse-free survival (38%, 41%, and 38% respectively; *P* = .926) between the 3 groups. The OS (*P* = .971) and RFS (*P* = .883) were similar in patients with blasts <10% or with blasts ≥10% in the bone marrow who underwent transplantation without prior cytoreductive therapy.

A randomized trial in patients with MDS or AML determined that myeloablative conditioning resulted in a higher rate of transplanted-related mortality at 4 years (25.1% vs. 9.9% for reduced-intensity conditioning; *P* < .001).[381] However, as the risk of relapse is greater in those who received reduced-intensity conditioning (HR, 4.06; *P* < .001), patients in the myeloablative conditioning arm fared better in terms of OS (HR, 1.54; *P* = .03).

Early referral for transplant evaluation is recommended to allow moving to transplant efficiently. Pre-transplant debulking therapy to reduce marrow

blasts to < 5% blasts with the goal of reducing post-transplant relapse is recommended, although the optimum strategy has not been determined. To reduce the disease burden pre-transplant is particularly important in patients who will receive a reduced-intensity conditioning regimen.[341] At some centers, failure to achieve <5% blasts with cytoreduction did not preclude from proceeding to transplant, as these patients appeared to derive survival benefit from transplant.[379,380]

An argument in favor of pre-transplant cytoreduction was provided by Festuccia et al[341] who showed that the presence of minimal identifiable disease (MID) prior to transplantation in patients with MDS or AML arising from MDS impacted prognosis following transplantation. In patients with MID positive by cytogenetics, irrespective of positivity by flow cytometry, the overall mortality risk was higher in those who underwent low-intensity conditioning compared to those who underwent high-intensity conditioning. However, in patients with MID negative status, as determined by both cytogenetics and flow cytometry, the risk of mortality with low- and high-intensity conditioning regimens was similar. It is important to note that this study did not specifically examine outcomes in patients who proceeded to transplant without cytoreductive therapy. In patients with a MID positive status, as assessed by both cytogenetics and flow cytometry, the risk of relapse was higher in those who underwent low-intensity conditioning, as opposed to those who underwent high-intensity conditioning. As the MID classification can help to identify patient subgroups who may have better outcomes with high- or low-intensity conditioning, the authors propose to consider the presence of MID to help determine the intensity of the conditioning regimen for patients being considered for transplant.

For higher-risk MDS, AzaC, decitabine, oral decitabine and cedazuridine, 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. A clinical trial followed by allo-HCT is another option. In patients with disease relapse after a prolonged remission following the first transplant, a second transplant or donor lymphocyte infusion immuno-based therapy may be considered. Allogeneic HCT may also be considered in select patients with lower-risk MDS (IPSS int-1, IPSS-R, and WPSS intermediate) with severe cytopenias. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been prospectively established.[382] Comparative clinical trials are needed to address these issues.

Targeted Therapy

Emerging data have shown efficacy of novel agents, including venetoclax, a B-cell lymphoma 2 (BCL-2) inhibitor, in combination with HMAs or targeted IDH1/2 inhibitors for cytoreduction for patients with high-risk MDS.[383-386] When used as cytoreduction for MDS in combination with an HMA, venetoclax has been effectively given for 14 days in monthly courses.[384] Repeating the bone marrow evaluation after 1 to 2 cycles is important to clarify the recovery of hematopoiesis and potential requirement for further therapy. Clinical trials are preferred (NCT04401748).

As overexpression of the BCL-2 protein has been linked to disease progression in MDS, studies are ongoing to investigate the efficacy and safety of venetoclax in patients with MDS either first-line or refractory or resistant to HMAs.[384,387] Abstract data from a phase Ib study investigating the combination of venetoclax and AzaC for 14 days in a 28-day cycle in upfront higher-risk MDS (IPSS-R intermediate, high, or very-high) resulted in an ORR, median OS, and median complete remission duration of 29.9%, 26 months, and 16.6 months.[384] The most frequent grade ≥3 treatment-emergent adverse events were neutropenia (48.6%), thrombocytopenia (43.0%), febrile neutropenia (42.1%), and anemia (34.6%). In a study exploring venetoclax in combination with AzaC in patients with relapsed/refractory MDS, results showed a modified ORR of

39% and a median OS of 12.6 months.[385] Febrile neutropenia (34%), thrombocytopenia (32%), neutropenia (27%), and anemia (18%) were the most frequent grade ≥3 hematologic adverse events.

Mutations in the isocitrate dehydrogenase 1 (*IDH1*) or 2 (*IDH2*) genes occur in approximately 4% to 12% of patients with MDS.[388-390] Ongoing clinical trials are investigating the efficacy of targeted *IDH1/2* inhibitors in patients with MDS (clinicaltrials.gov NCT03503409, NCT03471260, and NCT03744390).[391-393] Substudy data from a phase I trial investigating the safety and efficacy of ivosidenib in 18 evaluable patients with relapsed or refractory MDS with m*IDH* demonstrated an ORR of 83.3% and an approximate median OS of 36 months.[394] Additionally, 71.4% and 75.0% of patients with RBC-TD and platelet transfusion-dependence, respectively, achieved transfusion independence. Emerging data have also shown the utility of olutasidenib for treatment patients with *IDH1* mutations.[386] In one study, 33% of patients with intermediate-, high-, or very high-risk MDS treated with olutasidenib monotherapy achieved an overall response, while 69% of patients treated with olutasidenib and AzaC achieved an overall response.

A phase II study in patients with higher-risk *IDH-2* mutated MDS determined an ORR and median OS of 74% and 26 months, respectively, in newly diagnosed patients treated with enasidenib and AzaC, compared to 35% and 20 months, respectively, in patients who were previously treated with an HMA.[395] Across both groups, the most frequent adverse events included neutropenia (40%), nausea (36%), and constipation (32%).

Recommended Treatment Approaches

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

Regarding the therapeutic options for patients with lower-risk MDS with clinically significant cytopenias, the NCCN Guidelines Panel recommends stratifying these patients into several groups. For patients without symptomatic anemia who have clinically relevant thrombocytopenia or neutropenia, recommended treatment options include a clinical trial, AzaC, decitabine, oral decitabine and cedazuridine, or IST, with or without eltrombopag (useful in certain circumstances) for select patients. IST is recommended for patients generally aged ≤60 years 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, with or without cyclosporin A. Additionally, for severe thrombocytopenia, eltrombopag alone could be considered. Some studies have shown clinical benefit with low doses of AzaC or decitabine.[396] If there is disease progression or no response following initial treatment, HMAs should be considered, if not previously used. Eltrombopag or romiplostim can be considered for patients with severe or refractory thrombocytopenia.[258,262,397] Ivosidenib is recommended for m*IDH1* MDS. In the absence of m*IDH1*, clinical trial as well as consideration of allogeneic HCT in select patients with lower-risk MDS (IPSS int-1, IPSS-R, and WPSS intermediate MDS) with severe cytopenias are recommended.

For patients with del(5q) chromosomal abnormalities alone or with one other cytogenetic abnormality, except those involving chromosome 7, and symptomatic anemia, lenalidomide is a category 1 preferred option if sEPO is >500 mU/mL. If sEPO is ≤500 mU/mL, lenalidomide is a preferred regimen and epoetin alfa and darbepoetin alfa are other recommended regimens. An FDA-approved biosimilar is an appropriate substitute for epoetin alfa. Studies have shown the relative safety of lenalidomide in

these patients and improved QOL outcomes in randomized clinical trials.[398,399] The recommended initial 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. 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.[357] Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category. Exposure to lenalidomide has been associated with an elevated risk of *TP53*-mutated clones.[400] Additional consideration for and/or closer monitoring of particular patients is warranted. If no response is seen to lenalidomide or ESAs, these patients should follow treatment options (with the exception of imetelstat) for patients without the del(5q) abnormality, with sEPO levels >500 mU/mL, and with poor probability to respond to IST (see *Management of Lower-Risk Disease* in the algorithm).

Patients without the del(5q) abnormality, alone or with one other cytogenetic abnormality and with symptomatic anemia, are categorized on the basis of ring sideroblasts percentage and sEPO levels. In patients with no del(5q), with or without other cytogenetic abnormalities, with ≥15% ring sideroblasts, or ≥5% ring sideroblasts with an *SF3B1* mutation, luspatercept-aamt (category 1); and imetelstat (if sEPO >500 mU/mL [ineligible for ESAs]) are first-line options. The starting dose of luspatercept-aamt is 1 mg/kg every 3 weeks, which may be increased to 1.33 mg/kg every 3 weeks if RBC transfusions are still needed after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose. The dose may be further increased to 1.75 mg/kg every 3 weeks if RBC transfusions are still needed after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose. The initial dosing of imetelstat is 7.1 mg/kg IV monthly with potential dose decrements since frequent transient thrombocytopenia and neutropenia may occur. The starting platelet and neutrophil levels should be ≥75,000 and ≥1,500, respectively.[317] If there is no response by 3 to 6 months of treatment with luspatercept-aamt and the sEPO level is ≤500 mU/mL, imetelstat (category 1), as well as epoetin alfa with or without G-CSF or darbepoetin alfa with or without G-CSF, are recommended options. If the sEPO level is >500 mU/mL, imetelstat or consideration of treatment with lenalidomide is recommended. If there is no response by 3 to 6 months of treatment in patients who received first-line imetelstat, lenalidomide should be considered.

The epoetin alfa 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. For a lack of response, the dose may be escalated. At some NCCN member institutions, darbepoetin alfa has been given at doses up to 500 mcg every other week. Erythroid responses generally occur within 6 to 8 weeks of treatment.[300,401-403] A prompter response may be obtained with a higher starting dose. The above-recommended dose for epoetin alfa 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. 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.[300,401,402,404] This is particularly evident for patients with ≥15% ring sideroblasts in the marrow (and sEPO level ≤500 mU/mL), as the very low response rates to epoetin alfa or darbepoetin alone in this subgroup are markedly enhanced when combined with G-CSF.[300,402] For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in patients who initially have

neutropenia or to double the neutrophil count in patients who do not initially have neutropenia. 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.[300,401,402,404]

If no response is seen by 6 to 8 weeks of treatment with ESAs with or without G-CSF or by 3 to 6 months of treatment with imetelstat or lenalidomide, ivosidenib (if m*IDH1*), a clinical trial, AzaC (preferred), imetelstat if not previously used (other recommended), decitabine (other recommended), oral decitabine and cedazuridine (other recommended), or consideration of lenalidomide (useful in certain circumstances) are recommended. If there is no response within 6 cycles of AzaC or 4 cycles of decitabine or oral decitabine and cedazuridine or intolerance, ivosidenib is recommended for m*IDH1* MDS. A clinical trial or consideration of HCT for select patients are recommended for patients without m*IDH1*.

Epoetin alfa or darbepoetin alfa are preferred options and luspatercept-aamt is an other recommended option for patients with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts <15% (or ring sideroblasts <5% with an *SF3B1* mutation) and sEPO ≤500 mU/mL. Patients with normal cytogenetics, <15% ring sideroblasts, and sEPO levels of ≤500 mU/mL may respond to Epo if relatively high doses are administered.[246,404,405] Iron repletion needs to be verified before instituting epoetin alfa or darbepoetin alfa therapy. If no response occurs with ESAs alone (despite adequate iron stores) after 6 to 8 weeks or with luspatercept-aamt after 3 to 6 months, G-CSF or lenalidomide may be combined with ESAs. Imetelstat (category 1) and luspatercept-aamt (if not previously used) are also options.

If no response occurs following subsequent treatment with ESAs, with or without lenalidomide or G-CSF, within 6 to 8 weeks of treatment, or following subsequent treatment with imetelstat or luspatercept-aamt within 3 to 6 months of treatment, treatment should be discontinued. Patients should follow treatment options for patients without the del(5q) abnormality, with sEPO >500 mU/mL, and with poor probability to respond to IST (see *Management of Lower-Risk Disease* in the algorithm). Imetelstat (category 1), if not previously used, and ivosidenib (for m*IDH1*) are also options. 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.[402,406] This cytokine treatment is not suggested for patients with endogenous sEPO levels >500 mU/mL due to the very low erythroid response rate to these drugs in this patient population.

Patients with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts <15% (or ring sideroblasts <5% with an *SF3B1* mutation) and sEPO levels >500 mU/mL should be evaluated to determine whether they would be good candidates for IST (generally ≤60 years and with ≤5% marrow blasts, or with hypocellular marrows, PNH clone positivity, or STAT3-mutant cytotoxic T-cell clones). For patients with disease that has a good probability to respond to IST, IST options include ATG plus cyclosporin A, with or without eltrombopag. ATG may be omitted when clinically indicated. If there is no response within 3 to 6 months or if the patients have disease that has a poor probability to respond to IST, a clinical trial, treatment with AzaC (preferred), imetelstat if not previously used (other recommended), decitabine (other recommended), oral decitabine and cedazuridine (other recommended), or consideration of lenalidomide (useful in certain circumstances), are recommended. Oral decitabine and cedazuridine could be a substitution for IV decitabine in patients with IPSS Intermediate-1 and above.[332,407] A phase II prospective study of patients with MDS, that is 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 5-day AzaC courses were well-tolerated.[408] 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. In addition, 3-day cycles of HMAs have also been beneficial for patients with lower-risk MDS with anemia.[396]

If there is no response within 6 cycles of AzaC or 4 cycles of decitabine or oral decitabine and cedazuridine or intolerance, ivosidenib is recommended for m*IDH1* MDS. A clinical trial or consideration of HCT for select patients are recommended for patients without m*IDH1*. Emerging data are demonstrating effectiveness of enasidenib for patients with MDS with *IDH2* mutations[409] (see *Targeted Therapy*).

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

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

Treatment for higher-risk disease is dependent on whether patients are possible candidates for intensive therapy (eg, allogeneic HCT, intensive chemotherapy). Clinical features relevant for this determination include patient age (including patients up to 75 years of 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.[379] 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

Allogeneic HCT is recommended for eligible patients. Treatment with AzaC, decitabine, oral decitabine and cedazuridine, high-intensity chemotherapy, or enrollment in a clinical trial prior to allogeneic HCT are also options. Single-agent ivosidenib may be considered for m*IDH1* MDS if there is no response following treatment with HMAs or high-intensity chemotherapy. 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.[410]

To aid therapeutic decision-making regarding the timing and selection of patients with MDS for HCT, a study compared outcomes with HLA-matched sibling HCT in patients with MDS ≤60 years of age to data in patients with MDS who did not undergo transplantation from the IMRAW/IPSS database.[411] Using a Markov decision analysis, this investigation indicated that patients with IPSS int-2 and high-risk MDS ≤60 years of age had the longest life expectancy if transplanted (from HLA-identical siblings) soon after diagnosis, whereas patients with IPSS low risk MDS 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).[411] A retrospective study evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HCT.[205] The data suggest that patients with lower-risk MDS (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).[205]

Based on data regarding RIC for transplantation from two studies[412,413] and two comprehensive reviews of the field,[414,415] patient age and disease status generally dictated the type of conditioning. Patients >55 or 65 years of age, particularly if they had <10% marrow myeloblasts, generally received RIC; if the blast count was high, pre-HCT debulking therapy was often given. Younger patients, regardless of marrow blast burden, most frequently received high-dose conditioning. Variations on these approaches would be considered by the individual transplant physician based on patient features and the specific regimen used at that center. Some general recommendations have been presented in a review article.[416]

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 ages 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.[417] 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.[418,419] 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.[420] It is recognized that there are even fewer data available in regard to patients who are >75 years of age.

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.[421] 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.

Relapse after allo-HCT or No Response

The Panel recommends repeating molecular testing in order to identify targetable mutations. In patients with disease relapse after a prolonged remission following the first transplant or with no response, a second transplant or donor lymphocyte infusion immuno-based therapy may be considered. Enrollment in a clinical trial or HMAs (AzaC, decitabine, oral decitabine and cedazuridine) are also options. If there is no response to treatment or the disease relapses, enrollment in a clinical trial or supportive care is recommended.

Non-Intensive Therapy

For patients with higher-risk MDS who do not have a suitable transplant donor and who are not candidates for intensive therapy, the use of AzaC (preferred regimen), decitabine (other recommended regimen), oral decitabine and cedazuridine (other recommended regimen), or a relevant clinical trial are recommended. Oral decitabine and cedazuridine could be a substitution for IV decitabine in patients with IPSS Intermediate-1 and

above.[332,407] Ivosidenib is recommended for m*IDH1* MDS if there is no response within 6 cycles of azacitidine or 4 cycles of decitabine or oral decitabine and cedazuridine or intolerance. Enrollment in a clinical trial is recommended if there is no response to ivosidenib within 3 to 6 months or for those without m*IDH1*.

In a phase III, international, multicenter, controlled, open-label study (AZA-001), 358 patients with higher-risk MDS were randomly assigned 1:1 to receive azacitidine (75 mg/m^2 daily for 7 days every 28 days) or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy.[318] With a median follow-up of 21.1 months (interquartile range [IQR], 15.1–26.9), treatment with AzaC led to a higher median OS (24.5 months [9.9 months–not reached]) when compared to conventional care (15.0 months [5.6–24.1 months]; HR, 0.58; 95% CI, 0.43–0.77; *P* = .0001). At 2 years, 50.8% (95% CI, 42.1%–58.8%) of patients receiving AzaC were alive compared with 26.2% (18.7%–34.3%) of patients receiving conventional care group (*P* < .0001). The most frequent grade 3–4 adverse events for all treatments were peripheral cytopenias. These data demonstrated that treatment with AzaC increased OS in patients with higher-risk MDS relative to conventional care.

Results from a phase III trial comparing decitabine to BSC in patients with higher-risk disease 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, although they did not reach statistical significance.[319] AzaC, decitabine, or oral decitabine and cedazuridine should be continued for a least 6 cycles of AzaC or 4 cycles of decitabine or oral decitabine and cedazuridine to assess response to these agents. For patients who show clinical benefit, treatment with HMAs should be continued as maintenance therapy.

Two further 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.[422,423] 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).[422] The earlier report from the same trial showed improved OS and tolerability in patients aged ≥75 years with good performance status.[423] 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 or oral decitabine and cedazuridine 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 with the management of MDS. Drugs approved by the FDA for treating specific patients with MDS include lenalidomide for patients with del(5q) cytogenetic abnormalities; AzaC, decitabine, or the oral combination of decitabine and cedazuridine for treating higher-risk MDS or MDS that is non-responsive; deferasirox and deferoxamine for iron chelation in the treatment of iron overload; luspatercept-aamt for treating ring sideroblastic MDS in those with no response to prior ESA treatment or for treating lower-risk MDS; imetelstat for treating lower-risk MDS in patients with no response or loss

of response to ESAs or for those who are ineligible for ESAs; and ivosidenib for m*IDH* MDS. However, as a substantial proportion of subsets of patients with MDS lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents, along with supportive care, remain the hallmark of disease management. Evaluating the role of thrombopoietic cytokines for the management of thrombocytopenia in MDS and determining the effects of therapeutic interventions on QOL are important issues needing investigation.[401,403,406,424,425] 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.

References

1. Beck DB, Ferrada MA, Sikora KA, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med 2020;383:2628-2638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33108101.

2. National Cancer Institute. SEER cancer statistics review 1975-2016: Myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMD), and chronic myelomonocytic leukemia (CMML). 2020. Available at: https://seer.cancer.gov/csr/1975_2016/browse_csr.php?sectionSEL=30&pageSEL=sect_30_intro.01. Accessed January 8, 2020.

3. Zeidan AM, Shallis RM, Wang R, et al. Epidemiology of myelodysplastic syndromes: Why characterizing the beast is a prerequisite to taming it. Blood Rev 2019;34:1-15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30314642.

4. Greenberg P. The myelodysplastic syndromes. In: Hoffman R, Benz E, Shattil S, et al, eds. Hematology: Basic Principles and Practice. 3rd ed. New York: Churchill Livingstone; 2000;1106-1129.

5. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed January 4, 2022.

6. Freedman-Cass DA, Fischer T, Alpert AB, et al. The value and process of inclusion: Using sensitive, respectful, and inclusive language and images in NCCN content. J Natl Compr Canc Netw 2023;21:434-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37156485.

7. Kaloutsi V, Kohlmeyer U, Maschek H, et al. Comparison of bone marrow and hematologic findings in patients with human immunodeficiency virus infection and those with myelodysplastic syndromes and infectious diseases. Am J Clin Pathol 1994;101:123-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8116565.

8. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35732831.

9. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35767897.

10. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: Consensus statements and report from a working conference. Leuk Res 2007;31:727-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17257673.

11. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27069254.

12. Greenberg PL, Tuechler H, Schanz J, et al. Cytopenia levels for aiding establishment of the diagnosis of myelodysplastic syndromes. Blood 2016;128:2096-2097. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27535995.

13. Brunning R, Bennett J, Flandrin G, et al. Myelodysplastic syndromes. In: Jaffe E, Harris N, Stein H, et al, eds. WHO Classification of Tumours: Pathology and Genetics of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press 2001;61-73.

14. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835-3849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10577857.

15. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2292-2302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12239137.

16. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088. Erratum. Blood 1998;2091:1100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9058730.

17. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol 2012;30:820-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22331955.

18. Germing U, Lauseker M, Hildebrandt B, et al. Survival, prognostic factors and rates of leukemic transformation in 381 untreated patients with MDS and del(5q): a multicenter study. Leukemia 2012;26:1286-1292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22289990.

19. Mallo M, Cervera J, Schanz J, et al. Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia 2011;25:110-120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20882045.

20. Arber DA, Brunning RD, Orazi A, et al. Acute myeloid leukaemia with myelodysplastia-related changes. In Swerdlow, SH, Campo, E, Harris, NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC Press; 2008:124-126.

21. Hasserjian RP, Campigotto F, Klepeis V, et al. De novo acute myeloid leukemia with 20-29% blasts is less aggressive than acute myeloid leukemia with ≥30% blasts in older adults: a Bone Marrow Pathology Group study. Am J Hematol 2014;89:E193-199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25042343.

22. Albitar M, Manshouri T, Shen Y, et al. Myelodysplastic syndrome is not merely "preleukemia". Blood 2002;100:791-798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12130488.

23. Greenberg P, Anderson J, de Witte T, et al. Problematic WHO reclassification of myelodysplastic syndromes. Members of the International MDS Study Group. J Clin Oncol 2000;18:3447-3452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11013289.

24. Estey E, Hasserjian RP, Dohner H. Distinguishing AML from MDS: A fixed blast percentage may no longer be optimal. Blood 2022;139:323-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34111285.

25. DiNardo CD, Garcia-Manero G, Kantarjian HM. Time to blur the blast boundaries. Cancer 2022;128:1568-1570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35133004.

26. Germing U, Gattermann N, Strupp C, et al. Validation of the WHO proposals for a new classification of primary myelodysplastic syndromes: a retrospective analysis of 1600 patients. Leuk Res 2000;24:983-992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11077111.

27. Germing U, Strupp C, Kuendgen A, et al. Refractory anaemia with excess of blasts (RAEB): analysis of reclassification according to the WHO proposals. Br J Haematol 2006;132:162-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16398650.

28. Germing U, Strupp C, Kuendgen A, et al. Prospective validation of the WHO proposals for the classification of myelodysplastic syndromes. Haematologica 2006;91:1596-1604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17145595.

29. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005;23:7594-7603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16186598.

30. Muller-Berndorff H, Haas PS, Kunzmann R, et al. Comparison of five prognostic scoring systems, the French-American-British (FAB) and World Health Organization (WHO) classifications in patients with myelodysplastic syndromes: Results of a single-center analysis. Ann Hematol 2006;85:502-513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16715299.

31. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456-1465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17021321.

32. Taskesen E, Havermans M, van Lom K, et al. Two splice-factor mutant leukemia subgroups uncovered at the boundaries of MDS and AML using combined gene expression and DNA-methylation profiling. Blood 2014;123:3327-3335. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24668493.

33. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 2015;125:1367-1376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25550361.

34. Swerdlow SH, Campo E, Harris NL, et al.: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC Press; 2008.

35. Meggendorfer M, Roller A, Haferlach T, et al. SRSF2 mutations in 275 cases with chronic myelomonocytic leukemia (CMML). Blood 2012;120:3080-3088. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22919025.

36. Valent P, Orazi A, Savona MR, et al. Proposed diagnostic criteria for classical chronic myelomonocytic leukemia (CMML), CMML variants and pre-CMML conditions. Haematologica 2019;104:1935-1949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31048353.

37. Onida F, Barosi G, Leone G, et al. Management recommendations for chronic myelomonocytic leukemia: consensus statements from the SIE, SIES, GITMO groups. Haematologica 2013;98:1344-1352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24006407.

38. Ades L, Sekeres MA, Wolfromm A, et al. Predictive factors of response and survival among chronic myelomonocytic leukemia patients treated with azacitidine. Leuk Res 2013;37:609-613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23415110.

39. Hunter AM, Zhang L, Padron E. Current management and recent advances in the treatment of chronic myelomonocytic leukemia. Curr Treat Options Oncol 2018;19:67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30367269.

40. Padron E, Komrokji R, List AF. The clinical management of chronic myelomonocytic leukemia. Clin Adv Hematol Oncol 2014;12:172-178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24927265.

41. Santini V, Allione B, Zini G, et al. A phase II, multicentre trial of decitabine in higher-risk chronic myelomonocytic leukemia. Leukemia 2018;32:413-418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28607470.

42. Padron E, Dezern A, Andrade-Campos M, et al. A multi-institution phase I trial of ruxolitinib in patients with chronic myelomonocytic leukemia (CMML). Clin Cancer Res 2016;22:3746-3754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26858309.

43. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood 2017;129:1753-1762. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28096091.

44. Eissa H, Gooley TA, Sorror ML, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia: relapse-free survival is determined by karyotype and comorbidities. Biol Blood Marrow Transplant 2011;17:908-915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20932924.

45. Padron E, Tinsley-Vance S, DeZern AE, et al. Efficacy and safety of ruxolitinib for treatment of symptomatic chronic myelomonocytic leukemia (CMML): Results of a multicenter phase II clinical trial [abstract]. Blood 2022;140:1101-1103. Available at: https://ashpublications.org/blood/article/140/Supplement%201/1101/491958/Efficacy-and-Safety-of-Ruxolitinib-for-Treatment.

46. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with

rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med 2002;347:481-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181402.

47. Cheah CY, Burbury K, Apperley JF, et al. Patients with myeloid malignancies bearing PDGFRB fusion genes achieve durable long-term remissions with imatinib. Blood 2014;123:3574-3577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24687085.

48. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-2541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27355533.

49. Sotlar K, Fridrich C, Mall A, et al. Detection of c-kit point mutation Asp-816 --> Val in microdissected pooled single mast cells and leukemic cells in a patient with systemic mastocytosis and concomitant chronic myelomonocytic leukemia. Leuk Res 2002;26:979-984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12363464.

50. Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. Blood 2013;122:1707-1711. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23896413.

51. Wang SA, Hasserjian RP, Fox PS, et al. Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. Blood 2014;123:2645-2651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24627528.

52. Gambacorti-Passerini CB, Donadoni C, Parmiani A, et al. Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. Blood 2015;125:499-503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25343957.

53. Meggendorfer M, Bacher U, Alpermann T, et al. SETBP1 mutations occur in 9% of MDS/MPN and in 4% of MPN cases and are strongly associated with atypical CML, monosomy 7, isochromosome i(17)(q10), ASXL1 and CBL mutations. Leukemia 2013;27:1852-1860. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23628959.

54. Mughal TI, Cross NC, Padron E, et al. An International MDS/MPN Working Group's perspective and recommendations on molecular pathogenesis, diagnosis and clinical characterization of myelodysplastic/myeloproliferative neoplasms. Haematologica 2015;100:1117-1130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26341525.

55. Piazza R, Valletta S, Winkelmann N, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. Nat Genet 2013;45:18-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23222956.

56. Linder K, Iragavarapu C, Liu D. SETBP1 mutations as a biomarker for myelodysplasia /myeloproliferative neoplasm overlap syndrome. Biomark Res 2017;5:33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29225884.

57. Dao KT, Tyner JW, Gotlib J. Recent progress in chronic neutrophilic leukemia and atypical chronic myeloid leukemia. Curr Hematol Malig Rep 2017;12:432-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28983816.

58. Gotlib J. How I treat atypical chronic myeloid leukemia. Blood 2017;129:838-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27899359.

59. Tong X, Li J, Zhou Z, et al. Efficacy and side-effects of decitabine in treatment of atypical chronic myeloid leukemia. Leuk Lymphoma 2015;56:1911-1913. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25426665.

60. Assi R, Kantarjian HM, Garcia-Manero G, et al. A phase II trial of ruxolitinib in combination with azacytidine in myelodysplastic syndrome/myeloproliferative neoplasms. Am J Hematol 2018;93:277-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29134664.

61. Kanagal-Shamanna R, Hodge JC, Tucker T, et al. Assessing copy number aberrations and copy neutral loss of heterozygosity across the genome as best practice: An evidence based review of clinical utility from the cancer genomics consortium (CGC) working group for myelodysplastic syndrome, myelodysplastic/myeloproliferative and myeloproliferative neoplasms. Cancer Genet 2018;228-229:197-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30377088.

62. Lim SN, Lee JH, Lee JH, et al. Allogeneic hematopoietic cell transplantation in adult patients with myelodysplastic/myeloproliferative neoplasms. Blood Res 2013;48:178-184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24086937.

63. Vardiman JW, Bennett JM, Bain BJ, et al. Myelodysplastic/myeloproliferative neoplasm, unclassifiable. In: Swerdlow, SH, Campo, E, Harris, NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC Press; 2008;85-86.

64. Papaemmanuil E, Cazzola M, Boultwood J, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med 2011;365:1384-1395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21995386.

65. Malcovati L, Papaemmanuil E, Bowen DT, et al. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. Blood 2011;118:6239-6246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21998214.

66. Bejar R, Stevenson KE, Caughey BA, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. J Clin Oncol 2012;30:3376-3382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22869879.

67. Cazzola M, Rossi M, Malcovati L, Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative. Biologic and clinical significance of somatic mutations of SF3B1 in myeloid and lymphoid neoplasms. Blood 2013;121:260-269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23160465.

68. Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis: "2019 Update on Diagnosis, Risk-stratification, and Management". Am J Hematol 2019;94:475-488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30618061.

69. Huls G, Mulder AB, Rosati S, et al. Efficacy of single-agent lenalidomide in patients with JAK2 (V617F) mutated refractory anemia with ring sideroblasts and thrombocytosis. Blood 2010;116:180-182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20194893.

70. Nicolosi M, Mudireddy M, Vallapureddy R, et al. Lenalidomide therapy in patients with myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). Am J Hematol 2018;93:E27-E30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29067707.

71. Komrokji RS, Platzbecker U, Fenaux P, et al. Luspatercept for myelodysplastic syndromes/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis. Leukemia 2022;36:1432-1435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35220402.

72. DiNardo CD, Daver N, Jain N, et al. Myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN, U): natural history and clinical outcome by treatment strategy. Leukemia 2014;28:958-961. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24492324.

73. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.

74. Zoi K, Cross NC. Molecular pathogenesis of atypical CML, CMML and MDS/MPN-unclassifiable. Int J Hematol 2015;101:229-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25212680.

75. Kanagal-Shamanna R, Orazi A, Hasserjian RP, et al. Myelodysplastic/myeloproliferative neoplasms-unclassifiable with isolated isochromosome 17q represents a distinct clinico-biologic subset: A multi-institutional collaborative study from the Bone Marrow Pathology Group.

Mod Pathol 2022;35:470-479. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34775472.

76. Calvo KR, Price S, Braylan RC, et al. JMML and RALD (Ras-associated autoimmune leukoproliferative disorder): common genetic etiology yet clinically distinct entities. Blood 2015;125:2753-2758. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25691160.

77. Sakaguchi H, Okuno Y, Muramatsu H, et al. Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leukemia. Nat Genet 2013;45:937-941. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23832011.

78. Maguire AM, Vowels MR, Russell S, et al. Allogeneic bone marrow transplant improves outcome for juvenile myelomonocytic leukaemia. J Paediatr Child Health 2002;38:166-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12030999.

79. Facchetti F, Petrella T, Pileri SA. Blastic plasmacytoid dendritic cell neoplasm. In: Swedlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. (ed Revised 4th). Lyon: IARC; 2017.

80. Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2019;380:1628-1637. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31018069.

81. Itzykson R, Santini V, Thepot S, et al. Decitabine versus hydroxyurea for advanced proliferative chronic myelomonocytic leukemia: Results of a randomized phase III trial within the EMSCO network. J Clin Oncol 2023;41:1888-1897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36455187.

82. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med 2014;20:1472-1478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25326804.

83. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371:2488-2498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25426837.

84. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371:2477-2487. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25426838.

85. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 2015;126:9-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25931582.

86. Malcovati L, Galli A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood 2017;129:3371-3378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28424163.

87. Weeks LD, Niroula A, Neuberg D, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. NEJM Evid 2023;2. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37483562.

88. Cargo CA, Rowbotham N, Evans PA, et al. Targeted sequencing identifies patients with preclinical MDS at high risk of disease progression. Blood 2015;126:2362-2365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26392596.

89. Kwok B, Hall JM, Witte JS, et al. MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance. Blood 2015;126:2355-2361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26429975.

90. Hasle H, Kerndrup G, Jacobsen BB. Childhood myelodysplastic syndrome in Denmark: incidence and predisposing conditions. Leukemia 1995;9:1569-1572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7658725.

91. Jackson GH, Carey PJ, Cant AJ, et al. Myelodysplastic syndromes in children. Br J Haematol 1993;84:185-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8338777.

92. Passmore SJ, Chessells JM, Kempski H, et al. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia in the UK: a population-based study of incidence and survival. Br J Haematol 2003;121:758-767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12780790.

93. Alter BP, Giri N, Savage SA, et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. Br J Haematol 2010;150:179-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20507306.

94. Creutzig U, Ritter J, Vormoor J, et al. Myelodysplasia and acute myelogenous leukemia in Down's syndrome. A report of 40 children of the AML-BFM Study Group. Leukemia 1996;10:1677-1686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8892666.

95. Zipursky A, Poon A, Doyle J. Leukemia in Down syndrome: a review. Pediatr Hematol Oncol 1992;9:139-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1388043.

96. Zipursky A, Thorner P, De Harven E, et al. Myelodysplasia and acute megakaryoblastic leukemia in Down's syndrome. Leuk Res 1994;18:163-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8139285.

97. Hasle H, Clausen N, Pedersen B, Bendix-Hansen K. Myelodysplastic syndrome in a child with constitutional trisomy 8 mosaicism and normal phenotype. Cancer Genet Cytogenet 1995;79:79-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7850757.

98. Alter BP. Fanconi's anemia and malignancies. Am J Hematol 1996;53:99-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8892734.

99. Alter BP, Caruso JP, Drachtman RA, et al. Fanconi anemia: myelodysplasia as a predictor of outcome. Cancer Genet Cytogenet 2000;117:125-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10704682.

100. Welte K, Zeidler C, Dale DC. Severe congenital neutropenia. Semin Hematol 2006;43:189-195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16822461.

101. Zeidler C, Welte K. Kostmann syndrome and severe congenital neutropenia. Semin Hematol 2002;39:82-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11957189.

102. Salariu M, Miron I, Tansanu I. [Diamond-Blackfan anemia. Case report]. Rev Med Chir Soc Med Nat Iasi 2010;114:420-423. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20700978.

103. Okcu F, Roberts WM, Chan KW. Bone marrow transplantation in Shwachman-Diamond syndrome: report of two cases and review of the literature. Bone Marrow Transplant 1998;21:849-851. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9603415.

104. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in dyskeratosis congenita. Blood 2009;113:6549-6557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19282459.

105. Maris JM, Wiersma SR, Mahgoub N, et al. Monosomy 7 myelodysplastic syndrome and other second malignant neoplasms in children with neurofibromatosis type 1. Cancer 1997;79:1438-1446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9083167.

106. Aktas D, Koc A, Boduroglu K, et al. Myelodysplastic syndrome associated with monosomy 7 in a child with Bloom syndrome. Cancer Genet Cytogenet 2000;116:44-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10616531.

107. Poppe B, Van Limbergen H, Van Roy N, et al. Chromosomal aberrations in Bloom syndrome patients with myeloid malignancies. Cancer Genet Cytogenet 2001;128:39-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11454428.

108. Derbent M, Oncel Y, Tokel K, et al. Clinical and hematologic findings in Noonan syndrome patients with PTPN11 gene mutations. Am J Med Genet A 2010;152A:2768-2774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20954246.

109. Tsukahara M, Opitz JM. Dubowitz syndrome: review of 141 cases including 36 previously unreported patients. Am J Med Genet 1996;63:277-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8723121.

110. Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's Oncology Group. Blood 2007;109:46-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16985182.

111. Felix CA. Secondary leukemias induced by topoisomerase-targeted drugs. Biochim Biophys Acta 1998;1400:233-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9748598.

112. Krishnan A, Bhatia S, Slovak ML, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood 2000;95:1588-1593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10688812.

113. Le Deley MC, Leblanc T, Shamsaldin A, et al. Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Societe Francaise d'Oncologie Pediatrique. J Clin Oncol 2003;21:1074-1081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12637473.

114. Polishchuk AL, Dubois SG, Haas-Kogan D, et al. Response, survival, and toxicity after iodine-131-metaiodobenzylguanidine therapy for neuroblastoma in preadolescents, adolescents, and adults. Cancer 2011;117:4286-4293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21387264.

115. Weiss B, Vora A, Huberty J, et al. Secondary myelodysplastic syndrome and leukemia following 131I-metaiodobenzylguanidine therapy for relapsed neuroblastoma. J Pediatr Hematol Oncol 2003;25:543-547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12847321.

116. Gohring G, Michalova K, Beverloo HB, et al. Complex karyotype newly defined: the strongest prognostic factor in advanced childhood myelodysplastic syndrome. Blood 2010;116:3766-3769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20802024.

117. Daghistani D, Toledano SR, Curless R. Monosomy 7 syndrome. Clinical heterogeneity in children and adolescents. Cancer Genet Cytogenet 1990;44:263-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2297685.

118. Kardos G, Baumann I, Passmore SJ, et al. Refractory anemia in childhood: a retrospective analysis of 67 patients with particular reference to monosomy 7. Blood 2003;102:1997-2003. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12763938.

119. Paulsson K, Johansson B. Trisomy 8 as the sole chromosomal aberration in acute myeloid leukemia and myelodysplastic syndromes. Pathol Biol (Paris) 2007;55:37-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16697122.

120. Saumell S, Florensa L, Luno E, et al. Prognostic value of trisomy 8 as a single anomaly and the influence of additional cytogenetic aberrations in primary myelodysplastic syndromes. Br J Haematol 2012;159:311-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22958186.

121. Cortes JE, Kantarjian H, O'Brien S, et al. Clinical and prognostic significance of trisomy 21 in adult patients with acute myelogenous leukemia and myelodysplastic syndromes. Leukemia 1995;9:115-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7845005.

122. Pitman SD, Victorio A, Rowsell E, et al. 5q- syndrome in a child with slowly progressive pancytopenia: a case report and review of the literature. J Pediatr Hematol Oncol 2006;28:115-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16679931.

123. Al-Rahawan MM, Alter BP, Bryant BJ, Elghetany MT. Bone marrow cell cycle markers in inherited bone marrow failure syndromes. Leuk Res 2008;32:1793-1799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18606449.

124. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood 2012;120:3187-3205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22879540.

125. Carpenter SL, Zimmerman SA, Ware RE. Acute parvovirus B19 infection mimicking congenital dyserythropoietic anemia. J Pediatr Hematol Oncol 2004;26:133-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14767207.

126. Yetgin S, Cetin M, Yenicesu I, et al. Acute parvovirus B19 infection mimicking juvenile myelomonocytic leukemia. Eur J Haematol 2000;65:276-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11073169.

127. Liu Y, Tang SQ, Liu LZ, et al. [Characteristics of chronic active Epstein-Barr virus infection-associated hematological disorders in children]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2008;16:574-578. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18549632.

128. Angotti LB, Post GR, Robinson NS, et al. Pancytopenia with myelodysplasia due to copper deficiency. Pediatr Blood Cancer 2008;51:693-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18623212.

129. Steensma DP. Dysplasia has A differential diagnosis: distinguishing genuine myelodysplastic syndromes (MDS) from mimics, imitators, copycats and impostors. Curr Hematol Malig Rep 2012;7:310-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23015360.

130. Tandonnet J, Clavel J, Baruchel A, et al. Myeloid leukaemia in children with Down syndrome: report of the registry-based French experience between 1990 and 2003. Pediatr Blood Cancer 2010;54:927-933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20405513.

131. Zubizarreta P, Felice MS, Alfaro E, et al. Acute myelogenous leukemia in Down's syndrome: report of a single pediatric institution using a BFM treatment strategy. Leuk Res 1998;22:465-472. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9652734.

132. Bierings M, Nachman JB, Zwaan CM. Stem cell transplantation in pediatric leukemia and myelodysplasia: state of the art and current challenges. Curr Stem Cell Res Ther 2007;2:53-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18240454.

133. Shaw PJ, Kan F, Woo Ahn K, et al. Outcomes of pediatric bone marrow transplantation for leukemia and myelodysplasia using matched sibling, mismatched related, or matched unrelated donors. Blood 2010;116:4007-4015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20671124.

134. Strahm B, Nollke P, Zecca M, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome in children: results of the EWOG-MDS 98 study. Leukemia 2011;25:455-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21212791.

135. Yin CC, Medeiros LJ, Bueso-Ramos CE. Recent advances in the diagnosis and classification of myeloid neoplasms--comments on the 2008 WHO classification. Int J Lab Hematol 2010;32:461-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20626469.

136. Loh ML. Recent advances in the pathogenesis and treatment of juvenile myelomonocytic leukaemia. Br J Haematol 2011;152:677-687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21623760.

137. Trobaugh-Lotrario AD, Kletzel M, Quinones RR, et al. Monosomy 7 associated with pediatric acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS): successful management by allogeneic hematopoietic stem cell transplant (HSCT). Bone Marrow Transplant 2005;35:143-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15558042.

138. Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. Br J Haematol 1979;43:185-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/508627.

139. Lambertenghi-Deliliers G, Orazi A, Luksch R, et al. Myelodysplastic syndrome with increased marrow fibrosis: a distinct clinico-pathological entity. Br J Haematol 1991;78:161-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1712222.

140. Maschek H, Georgii A, Kaloutsi V, et al. Myelofibrosis in primary myelodysplastic syndromes: a retrospective study of 352 patients. Eur J Haematol 1992;48:208-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1592101.

141. Pagliuca A, Layton DM, Manoharan A, et al. Myelofibrosis in primary myelodysplastic syndromes: a clinico-morphological study of 10 cases. Br J Haematol 1989;71:499-504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2640542.

142. Steensma DP, Hanson CA, Letendre L, Tefferi A. Myelodysplasia with fibrosis: a distinct entity? Leuk Res 2001;25:829-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11532514.

143. Jafarzadeh A, Poorgholami M, Izadi N, et al. Immunological and hematological changes in patients with hyperthyroidism or hypothyroidism. Clin Invest Med 2010;33:E271-279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20926033.

144. Morita K, Arai S, Kogure Y, et al. Serum LDH is useful to predict prognosis for intermediate-risk myelodysplastic syndrome [abstract]. Blood 2015;126:Abstract 5255. Available at: http://www.bloodjournal.org/content/126/23/5255.

145. Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodysplastic syndrome. Blood 2002;100:1493-1495. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149237.

146. Haddad AS, Subbiah V, Lichtin AE, et al. Hypocupremia and bone marrow failure. Haematologica 2008;93:e1-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18166767.

147. Koca E, Buyukasik Y, Cetiner D, et al. Copper deficiency with increased hematogones mimicking refractory anemia with excess blasts. Leuk Res 2008;32:495-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17706281.

148. Fong T, Vij R, Vijayan A, et al. Copper deficiency: an important consideration in the differential diagnosis of myelodysplastic syndrome. Haematologica 2007;92:1429-1430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024379.

149. Prodan CI, Bottomley SS, Vincent AS, et al. Hypocupremia associated with prior vitamin B12 deficiency. Am J Hematol 2007;82:288-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16986134.

150. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature 2011;478:64-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21909114.

151. Du HY, Pumbo E, Ivanovich J, et al. TERC and TERT gene mutations in patients with bone marrow failure and the significance of telomere length measurements. Blood 2009;113:309-316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18931339.

152. Vulliamy TJ, Marrone A, Knight SW, et al. Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. Blood 2006;107:2680-2685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16332973.

153. Alter BP, Baerlocher GM, Savage SA, et al. Very short telomere length by flow fluorescence in situ hybridization identifies patients with dyskeratosis congenita. Blood 2007;110:1439-1447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17468339.

154. Michaud J, Wu F, Osato M, et al. In vitro analyses of known and novel RUNX1/AML1 mutations in dominant familial platelet disorder with

predisposition to acute myelogenous leukemia: implications for mechanisms of pathogenesis. Blood 2002;99:1364-1372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11830488.

155. Song WJ, Sullivan MG, Legare RD, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. Nat Genet 1999;23:166-175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10508512.

156. Liew E, Owen C. Familial myelodysplastic syndromes: a review of the literature. Haematologica 2011;96:1536-1542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21606161.

157. Quentin S, Cuccuini W, Ceccaldi R, et al. Myelodysplasia and leukemia of Fanconi anemia are associated with a specific pattern of genomic abnormalities that includes cryptic RUNX1/AML1 lesions. Blood 2011;117:e161-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21325596.

158. Fadilah SA, Cheong SK, Roslan H, et al. GATA-1 and GATA-2 gene expression is related to the severity of dysplasia in myelodysplastic syndrome. Leukemia 2002;16:1563-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12145700.

159. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. Nat Genet 2011;43:1012-1017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21892162.

160. Dunn DE, Tanawattanacharoen P, Boccuni P, et al. Paroxysmal nocturnal hemoglobinuria cells in patients with bone marrow failure syndromes. Ann Intern Med 1999;131:401-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10498555.

161. Jerez A, Clemente MJ, Makishima H, et al. STAT3 mutations indicate the presence of subclinical T-cell clones in a subset of aplastic anemia and myelodysplastic syndrome patients. Blood 2013;122:2453-2459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23926297.

162. Sloand EM, Wu CO, Greenberg P, et al. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol 2008;26:2505-2511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18413642.

163. Borowitz MJ, Craig FE, Digiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry B Clin Cytom 2010;78:211-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20533382.

164. Dezern AE, 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;94:16-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29236352.

165. Takeda J, Miyata T, Kawagoe K, et al. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell 1993;73:703-711. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8500164.

166. Ware RE, Rosse WF, Howard TA. Mutations within the Piga gene in patients with paroxysmal nocturnal hemoglobinuria. Blood 1994;83:2418-2422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8167330.

167. Battiwalla M, Hepgur M, Pan D, et al. Multiparameter flow cytometry for the diagnosis and monitoring of small GPI-deficient cellular populations. Cytometry B Clin Cytom 2010;78:348-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20533383.

168. Sauntharajah Y, Molldrem JL, Rivera M, et al. Coincident myelodysplastic syndrome and T-cell large granular lymphocytic disease: clinical and pathophysiological features. Br J Haematol 2001;112:195-200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11167802.

169. Molldrem JJ, Leifer E, Bahceci E, et al. Antithymocyte globulin for treatment of the bone marrow failure associated with myelodysplastic syndromes. Ann Intern Med 2002;137:156-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12160363.

170. Kochenderfer JN, Kobayashi S, Wieder ED, et al. Loss of T-lymphocyte clonal dominance in patients with myelodysplastic syndrome responsive to immunosuppression. Blood 2002;100:3639-3645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393644.

171. Dhodapkar MV, Li CY, Lust JA, et al. Clinical spectrum of clonal proliferations of T-large granular lymphocytes: a T-cell clonopathy of undetermined significance? Blood 1994;84:1620-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8068951.

172. Kussick SJ, Fromm JR, Rossini A, et al. Four-color flow cytometry shows strong concordance with bone marrow morphology and cytogenetics in the evaluation for myelodysplasia. Am J Clin Pathol 2005;124:170-181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16040286.

173. van de Loosdrecht AA, Alhan C, Bene MC, et al. Standardization of flow cytometry in myelodysplastic syndromes: report from the first European LeukemiaNet working conference on flow cytometry in myelodysplastic syndromes. Haematologica 2009;94:1124-1134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19546437.

174. Westers TM, Ireland R, Kern W, et al. Standardization of flow cytometry in myelodysplastic syndromes: a report from an international consortium and the European LeukemiaNet Working Group. Leukemia 2012;26:1730-1741. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22307178.

175. Wood BL. Myeloid malignancies: myelodysplastic syndromes, myeloproliferative disorders, and acute myeloid leukemia. Clin Lab Med 2007;27:551-575, vii. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17658407.

176. Wood BL, Arroz M, Barnett D, et al. 2006 Bethesda International Consensus recommendations on the immunophenotypic analysis of hematolymphoid neoplasia by flow cytometry: optimal reagents and reporting for the flow cytometric diagnosis of hematopoietic neoplasia. Cytometry B Clin Cytom 2007;72 Suppl 1:S14-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17803189.

177. Della Porta MG, Picone C, Pascutto C, et al. Multicenter validation of a reproducible flow cytometric score for the diagnosis of low-grade myelodysplastic syndromes: results of a European LeukemiaNET study. Haematologica 2012;97:1209-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22315489.

178. Chan WC, Foucar K, Morice WG, Catovsky D. T-cell large granular lymphocytic leukaemia. In: Swerdlow, SH, Campo, E, Harris, NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC; 2008;272-273.

179. Morgan EA, Lee MN, DeAngelo DJ, et al. Systematic STAT3 sequencing in patients with unexplained cytopenias identifies unsuspected large granular lymphocytic leukemia. Blood Adv 2017;1:1786-1789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29296824.

180. Patnaik MM, Tefferi A. Cytogenetic and molecular abnormalities in chronic myelomonocytic leukemia. Blood Cancer J 2016;6:e393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26849014.

181. Baxter EJ, Kulkarni S, Vizmanos JL, et al. Novel translocations that disrupt the platelet-derived growth factor receptor beta (PDGFRB) gene in BCR-ABL-negative chronic myeloproliferative disorders. Br J Haematol 2003;120:251-256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12542482.

182. Steer EJ, Cross NC. Myeloproliferative disorders with translocations of chromosome 5q31-35: role of the platelet-derived growth factor receptor Beta. Acta Haematol 2002;107:113-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11919393.

183. David M, Cross NC, Burgstaller S, et al. Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. Blood 2007;109:61-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16960151.

184. Magnusson MK, Meade KE, Nakamura R, et al. Activity of STI571 in chronic myelomonocytic leukemia with a platelet-derived growth factor

beta receptor fusion oncogene. Blood 2002;100:1088-1091. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12130532.

185. Jacobs A, Janowska-Wieczorek A, Caro J, et al. Circulating erythropoietin in patients with myelodysplastic syndromes. Br J Haematol 1989;73:36-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2803975.

186. Sanz GF, Sanz MA, Greenberg PL. Prognostic factors and scoring systems in myelodysplastic syndromes. Haematologica 1998;83:358-368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9592987.

187. Padron E, Garcia-Manero G, Patnaik MM, et al. An international data set for CMML validates prognostic scoring systems and demonstrates a need for novel prognostication strategies. Blood Cancer J 2015;5:e333. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26230957.

188. Bennett JM, Catovsky D, Daniel MT, et al. The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Group. Br J Haematol 1994;87:746-754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7986717.

189. Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012;120:2454-2465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22740453.

190. Zeidan AM, Sekeres MA, Garcia-Manero G, et al. Comparison of risk stratification tools in predicting outcomes of patients with higher-risk myelodysplastic syndromes treated with azanucleosides. Leukemia 2016;30:649-657. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26464171.

191. Moon JH, Sohn SK, Ahn JS, et al. Role of hypomethylating agents for patients with lower-risk myelodysplastic syndrome defined by IPSS and IPSS-R. Blood 2013;122:2782-2782. Available at: http://www.bloodjournal.org/content/122/21/2782.

192. de Swart L, Smith A, Johnston TW, et al. Validation of the revised international prognostic scoring system (IPSS-R) in patients with lower-risk myelodysplastic syndromes: a report from the prospective European LeukaemiaNet MDS (EUMDS) registry. British Journal of Haematology 2015;170:372-383. Available at: http://dx.doi.org/10.1111/bjh.13450.

193. Mishra A, Corrales-Yepez M, Ali NA, et al. Validation of the revised International Prognostic Scoring System in treated patients with myelodysplastic syndromes. Am J Hematol 2013;88:566-570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23605934.

194. Valcarcel D, Sanz G, Ortega M, et al. Use of newer prognostic indices for patients with myelodysplastic syndromes in the low and intermediate-1 risk categories: a population-based study. Lancet Haematol 2015;2:e260-266. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26688236.

195. Neukirchen J, Lauseker M, Blum S, et al. Validation of the revised international prognostic scoring system (IPSS-R) in patients with myelodysplastic syndrome: a multicenter study. Leuk Res 2014;38:57-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24238640.

196. Messa E, Gioia D, Evangelista A, et al. High predictive value of the revised International Prognostic Scoring System (IPSS-R): An external analysis of 646 patients from a multiregional Italian MDS registry [abstract]. Blood 2012;120:Abstract 1702. Available at: http://www.bloodjournal.org/content/120/21/1702.

197. Ok CY, Hasserjian RP, Fox PS, et al. Application of the international prognostic scoring system-revised in therapy-related myelodysplastic syndromes and oligoblastic acute myeloid leukemia. Leukemia 2014;28:185-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23787392.

198. Zeidan AM, Al Ali N, Barnard J, et al. Comparison of clinical outcomes and prognostic utility of risk stratification tools in patients with therapy-related vs de novo myelodysplastic syndromes: a report on behalf of the MDS Clinical Research Consortium. Leukemia 2017;31:1391-1397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28111463.

199. Voso MT, Fenu S, Latagliata R, et al. Revised International Prognostic Scoring System (IPSS) predicts survival and leukemic evolution of myelodysplastic syndromes significantly better than IPSS and WHO Prognostic Scoring System: validation by the Gruppo Romano Mielodisplasie Italian Regional Database. J Clin Oncol 2013;31:2671-2677. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23796988.

200. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood 2014;123:2333-2342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24558201.

201. van Spronsen MF, Ossenkoppele GJ, Holman R, van de Loosdrecht AA. Improved risk stratification by the integration of the revised international prognostic scoring system with the myelodysplastic syndromes comorbidity index. Eur J Cancer 2014;50:3198-3205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25454415.

202. Pfeilstocker M, Tuechler H, Sanz G, et al. Time-dependent changes in mortality and transformation risk in MDS. Blood 2016;128:902-910. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27335276.

203. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25:3503-3510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17687155.

204. Kao JM, McMillan A, Greenberg PL. International MDS risk analysis workshop (IMRAW)/IPSS reanalyzed: impact of cytopenias on clinical outcomes in myelodysplastic syndromes. Am J Hematol 2008;83:765-770. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18645988.

205. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood 2008;112:895-902. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18497321.

206. Cermak J, Kacirkova P, Mikulenkova D, Michalova K. Impact of transfusion dependency on survival in patients with early myelodysplastic syndrome without excess of blasts. Leuk Res 2009;33:1469-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19646756.

207. Park MJ, Kim HJ, Kim SH, et al. Is International Prognostic Scoring System (IPSS) still standard in predicting prognosis in patients with myelodysplastic syndrome? External validation of the WHO Classification-Based Prognostic Scoring System (WPSS) and comparison with IPSS. Eur J Haematol 2008;81:364-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18637029.

208. Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). Haematologica 2011;96:1433-1440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21659359.

209. Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evid 2022;1:EVIDoa2200008. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38319256.

210. Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia 2008;22:538-543. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18079733.

211. Pomares H, Sánchez-Ortega I, Alonso E, et al. Validation of the Low Risk Prognostic Scoring System (LR-PSS) in patients with very low, low and intermediate risk IPSS-R myelodysplastic syndrome. Results from a single center [abstract]. Blood 2015;126:Abstract 2902. Available at: http://www.bloodjournal.org/content/126/23/2902.

212. Komrokji R, Ramadan H, Al Ali N, et al. Validation of the lower-risk MD Anderson prognostic scoring system for patients with myelodysplastic syndrome. Clin Lymphoma Myeloma Leuk 2015;15 Suppl:S60-63. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26297280.

213. Sekeres MA, Elson P, Tiu RV, et al. Validating the Lower-Risk MD Anderson Prognostic Scoring System (LR-PSS) and the Revised International Prognostic Scoring System (IPSS-R) for patients with myelodysplastic syndromes [abstract]. Blood 2011;118:Abstract 1720. Available at: https://ashpublications.org/blood/article/118/21/1720/139864/Validating-the-Lower-Risk-MD-Anderson-Prognostic.

214. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med 2011;364:2496-2506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21714648.

215. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 2013;122:3616-3627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24030381.

216. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia 2014;28:241-247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24220272.

217. Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. J Clin Oncol 2013;31:2428-2436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23690417.

218. Patnaik MM, Itzykson R, Lasho TL, et al. ASXL1 and SETBP1 mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-center study of 466 patients. Leukemia 2014;28:2206-2212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24695057.

219. Walter MJ, Ding L, Shen D, et al. Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. Leukemia 2011;25:1153-1158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21415852.

220. Graubert TA, Shen D, Ding L, et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. Nat Genet 2011;44:53-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22158538.

221. Wang H, Zhang N, Wu X, et al. Prognostic value of U2AF1 mutant in patients with de novo myelodysplastic syndromes: a meta-analysis. Ann Hematol 2019;98:2629-2639. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31754743.

222. Thol F, Kade S, Schlarmann C, et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood 2012;119:3578-3584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22389253.

223. Makishima H, Yoshida K, Nguyen N, et al. Somatic SETBP1 mutations in myeloid malignancies. Nat Genet 2013;45:942-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23832012.

224. Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood 2015;126:233-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25957392.

225. Patnaik MM, Lasho TL, Hodnefield JM, et al. SF3B1 mutations are prevalent in myelodysplastic syndromes with ring sideroblasts but do not hold independent prognostic value. Blood 2012;119:569-572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22096241.

226. Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia 2011;25:1147-1152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21494260.

227. Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood 2014;124:2705-2712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25224413.

228. Sebaa A, Ades L, Baran-Marzack F, et al. Incidence of 17p deletions and TP53 mutation in myelodysplastic syndrome and acute myeloid

leukemia with 5q deletion. Genes Chromosomes Cancer 2012;51:1086-1092. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22933333.

229. Jadersten M, Saft L, Smith A, et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. J Clin Oncol 2011;29:1971-1979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21519010.

230. Mallo M, Del Rey M, Ibanez M, et al. Response to lenalidomide in myelodysplastic syndromes with del(5q): influence of cytogenetics and mutations. Br J Haematol 2013;162:74-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23614682.

231. Jadersten M, Saft L, Pellagatti A, et al. Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression. Haematologica 2009;94:1762-1766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19797731.

232. Mohamedali AM, Alkhatabi H, Kulasekararaj A, et al. Utility of peripheral blood for cytogenetic and mutation analysis in myelodysplastic syndrome. Blood 2013;122:567-570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23760614.

233. Della Porta MG, Malcovati L. Clinical relevance of extra-hematologic comorbidity in the management of patients with myelodysplastic syndrome. Haematologica 2009;94:602-606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19407314.

234. Naqvi K, Garcia-Manero G, Sardesai S, et al. Association of comorbidities with overall survival in myelodysplastic syndrome: development of a prognostic model. J Clin Oncol 2011;29:2240-2246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21537048.

235. Sperr WR, Wimazal F, Kundi M, et al. Comorbidity as prognostic variable in MDS: comparative evaluation of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian MDS Study Group. Ann Oncol 2010;21:114-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19605505.

236. Wang R, Gross CP, Halene S, Ma X. Comorbidities and survival in a large cohort of patients with newly diagnosed myelodysplastic syndromes. Leuk Res 2009;33:1594-1598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19324411.

237. Zipperer E, Pelz D, Nachtkamp K, et al. The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. Haematologica 2009;94:729-732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19336740.

238. Della Porta MG, Malcovati L, Strupp C, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. Haematologica 2011;96:441-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21134982.

239. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood 2000;96:3671-3674. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11090046.

240. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16609072.

241. Greenberg P, Baer, M, Bennett, J et al. NCCN Practice Guidelines for Myelodysplastic Syndromes, Version1, 2001, In "The Complete Library of NCCN Guidelines [CD-ROM]," Rockledge, PA; 2001.

242. Platzbecker U, Fenaux P, Ades L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood 2019;133:1020-1030. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30404811.

243. Komrokji RS, Al Ali NH, Sallman D, et al. Validation of International Working Group response criteria in higher-risk myelodysplastic syndromes: A report on behalf of the MDS Clinical Research Consortium. Cancer Med 2021;10:447-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33350168.

244. Zeidan AM, Platzbecker U, Bewersdorf JP, et al. Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes. Blood 2023;141:2047-2061. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36724453.

245. Hicks LK, Bering H, Carson KR, et al. The ASH Choosing Wisely® campaign: five hematologic tests and treatments to question. Blood 2013;122:3879-3883. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24307720.

246. Greenberg P. The role of hemopoietic growth factors in the treatment of myelodysplastic syndromes. Int J Ped Hem-Onc 1997;4:231-238. Available at:

247. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2015;21:1863-1869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26256941.

248. Houwerzijl EJ, Blom NR, van der Want JJ, et al. Increased peripheral platelet destruction and caspase-3-independent programmed cell death of bone marrow megakaryocytes in myelodysplastic patients. Blood 2005;105:3472-3479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15542580.

249. Tamura H, Ogata K, Luo S, et al. Plasma thrombopoietin (TPO) levels and expression of TPO receptor on platelets in patients with myelodysplastic syndromes. Br J Haematol 1998;103:778-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9858230.

250. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6952920.

251. Zwierzina H, Rollinger-Holzinger I, Nuessler V, et al. Endogenous serum thrombopoietin concentrations in patients with myelodysplastic syndromes. Leukemia 1998;12:59-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9436921.

252. Greenberg PL, Garcia-Manero G, Moore M, et al. A randomized controlled trial of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving decitabine. Leuk Lymphoma 2013;54:321-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22906162.

253. Kantarjian H, Fenaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol 2010;28:437-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008626.

254. Kantarjian HM, Giles FJ, Greenberg PL, et al. Phase 2 study of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving azacitidine therapy. Blood 2010;116:3163-3170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20631375.

255. Sekeres MA, Kantarjian H, Fenaux P, et al. Subcutaneous or intravenous administration of romiplostim in thrombocytopenic patients with lower risk myelodysplastic syndromes. Cancer 2011;117:992-1000. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20945323.

256. Wang ES, Lyons RM, Larson RA, et al. A randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate-1 risk myelodysplastic syndrome receiving lenalidomide. J Hematol Oncol 2012;5:71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23190430.

257. Sekeres MA, Giagounidis A, Kantarjian H, et al. Development and validation of a model to predict platelet response to romiplostim in patients with lower-risk myelodysplastic syndromes. Br J Haematol 2014;167:337-345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25039607.

258. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24706489.

259. Fenaux P, Muus P, Kantarjian H, et al. Romiplostim monotherapy in thrombocytopenic patients with myelodysplastic syndromes: long-term safety and efficacy. Br J Haematol 2017;178:906-913. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28616874.

260. Mavroudi I, Pyrovolaki K, Pavlaki K, et al. Effect of the nonpeptide thrombopoietin receptor agonist eltrombopag on megakaryopoiesis of patients with lower risk myelodysplastic syndrome. Leuk Res 2011;35:323-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20688394.

261. Will B, Kawahara M, Luciano JP, et al. Effect of the nonpeptide thrombopoietin receptor agonist Eltrombopag on bone marrow cells from patients with acute myeloid leukemia and myelodysplastic syndrome. Blood 2009;114:3899-3908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19710504.

262. 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:e127-e136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28162984.

263. Vicente A, Patel BA, Gutierrez-Rodrigues F, et al. Eltrombopag monotherapy can improve hematopoiesis in patients with low to intermediate risk-1 myelodysplastic syndrome. Haematologica 2020;105:2785-2794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33256377.

264. Fan X, Desmond R, Winkler T, et al. Eltrombopag for patients with moderate aplastic anemia or uni-lineage cytopenias. Blood Adv 2020;4:1700-1710. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32330244.

265. Swaminathan M, Borthakur G, Kadia TM, et al. A phase 2 clinical trial of eltrombopag for treatment of patients with myelodysplastic syndromes after hypomethylating-agent failure. Leuk Lymphoma 2019;60:2207-2213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30773968.

266. Khan M, Kristy B, Kadia T, et al. Efficacy and safety of eltrombopag for treatment of patients with myelodysplastic syndromes after hypomethylating-agent failure: A phase 2 clinical trial. Blood 2015;126:1691-1691. Available at: http://www.bloodjournal.org/content/126/23/1691.

267. Mittelman M, Platzbecker U, Afanasyev B, et al. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. Lancet Haematol 2018;5:e34-e43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29241762.

268. Hashimoto S, Toba K, Fuse I, et al. Thrombopoietin activates the growth of megakaryoblasts in patients with chronic myeloproliferative disorders and myelodysplastic syndrome. Eur J Haematol 2000;64:225-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10776693.

269. Luo SS, Ogata K, Yokose N, et al. Effect of thrombopoietin on proliferation of blasts from patients with myelodysplastic syndromes. Stem Cells 2000;18:112-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10742383.

270. Greenberg PL. Myelodysplastic syndromes: iron overload consequences and current chelating therapies. J Natl Compr Canc Netw 2006;4:91-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16403408.

271. Farquhar MJ, Bowen DT. Oxidative stress and the myelodysplastic syndromes. Int J Hematol 2003;77:342-350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12774921.

272. Hershko C, Link G, Cabantchik I. Pathophysiology of iron overload. Ann N Y Acad Sci 1998;850:191-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9668540.

273. Jaeger M, Aul C, Sohngen D, et al. [Secondary hemochromatosis in polytransfused patients with myelodysplastic syndromes]. Beitr Infusionsther 1992;30:464-468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1284762.

274. Schafer AI, Cheron RG, Dluhy R, et al. Clinical consequences of acquired transfusional iron overload in adults. N Engl J Med 1981;304:319-324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6777701.

275. Jensen PD, Jensen FT, Christensen T, et al. Relationship between hepatocellular injury and transfusional iron overload prior to and during iron chelation with desferrioxamine: a study in adult patients with acquired anemias. Blood 2003;101:91-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393528.

276. Malcovati L. Impact of transfusion dependency and secondary iron overload on the survival of patients with myelodysplastic syndromes. Leuk Res 2007;31 Suppl 3:S2-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18037415.

277. Mainous AG, 3rd, Tanner RJ, Hulihan MM, et al. The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome. Br J Haematol 2014;167:720-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25048454.

278. Hoeks M, Yu G, Langemeijer S, et al. Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes participating in the European MDS registry. Haematologica 2020;105:640-651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31278207.

279. Yang S, Zhang MC, Leong R, et al. Iron chelation therapy in patients with low- to intermediate-risk myelodysplastic syndrome: A systematic review and meta-analysis. Br J Haematol 2022;197:e9-e11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34927248.

280. Angelucci E, Li J, Greenberg P, et al. Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: A randomized trial. Ann Intern Med 2020;172:513-522. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32203980.

281. Yang Y, Tang Z, An T, Zhao L. The impact of iron chelation therapy on patients with lower/intermediate IPSS MDS and the prognostic role of elevated serum ferritin in patients with MDS and AML: A meta-analysis. Medicine (Baltimore) 2019;98:e17406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31577751.

282. Brittenham GM, Badman DG. Noninvasive measurement of iron: report of an NIDDK workshop. Blood 2003;101:15-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393526.

283. St Pierre TG, Clark PR, Chua-anusorn W, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood 2005;105:855-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15256427.

284. Jensen PD, Heickendorff L, Pedersen B, et al. The effect of iron chelation on haemopoiesis in MDS patients with transfusional iron overload. Br J Haematol 1996;94:288-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8759889.

285. Jensen PD, Jensen FT, Christensen T, et al. Evaluation of myocardial iron by magnetic resonance imaging during iron chelation therapy with deferrioxamine: indication of close relation between myocardial iron content and chelatable iron pool. Blood 2003;101:4632-4639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12576333.

286. Prescribing information for deferoxamine mesylate for injection USP. 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016267s050lbl.pdf. Accessed October 12, 2016.

287. Prescribing information for deferasirox tablets for oral suspension. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021882s019lbl.pdf. Accessed October 12, 2016.

288. Nisbet-Brown E, Olivieri NF, Giardina PJ, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet 2003;361:1597-1602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12747879.

289. Piga A, Galanello R, Forni GL, et al. Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassemia patients with transfusional iron overload. Haematologica 2006;91:873-880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16818273.

290. Gattermann N, Finelli C, Porta MD, et al. Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: Results from the large 1-year EPIC study. Leuk Res 2010;34:1143-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20451251.

291. Greenberg PL, Koller CA, Cabantchik ZI, et al. Prospective assessment of effects on iron-overload parameters of deferasirox therapy in patients with myelodysplastic syndromes. Leuk Res 2010;34:1560-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20615548.

292. List AF, Baer MR, Steensma DP, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. J Clin Oncol 2012;30:2134-2139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22547607.

293. Prescribing information for deferiprone tablets for oral use. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021825s001lbl.pdf. Accessed October 12, 2016.

294. Greenberg PL, Rigsby CK, Stone RM, et al. NCCN Task Force: Transfusion and iron overload in patients with myelodysplastic syndromes. J Natl Compr Canc Netw 2009;7 Suppl 9:S1-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20064286.

295. Ko BS, Chang MC, Chiou TJ, et al. Long-term safety and efficacy of deferasirox in patients with myelodysplastic syndrome, aplastic anemia and other rare anemia in Taiwan. Hematology 2019;24:247-254. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30558522.

296. Mannone L, Gardin C, Quarre MC, et al. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. Br J Haematol 2006;133:513-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16681638.

297. Musto P, Lanza F, Balleari E, et al. Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. Br J Haematol 2005;128:204-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15638854.

298. Giraldo P, Nomdedeu B, Loscertales J, et al. Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. Cancer 2006;107:2807-2816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17115424.

299. Stasi R, Abruzzese E, Lanzetta G, et al. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. Ann Oncol 2005;16:1921-1927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16166176.

300. Hellstrom-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood 1998;92:68-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9639501.

301. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol 2008;26:3607-3613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559873.

302. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-

CSF: the GFM experience. Blood 2008;111:574-582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17940203.

303. Kelaidi C, Beyne-Rauzy O, Braun T, et al. High response rate and improved exercise capacity and quality of life with a new regimen of darbepoetin alfa with or without filgrastim in lower-risk myelodysplastic syndromes: a phase II study by the GFM. Ann Hematol 2013;92:621-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23358617.

304. Tehranchi R, Fadeel B, Schmidt-Mende J, et al. Antiapoptotic role of growth factors in the myelodysplastic syndromes: concordance between in vitro and in vivo observations. Clin Cancer Res 2005;11:6291-6299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16144933.

305. Kelaidi C, Park S, Brechignac S, et al. Treatment of myelodysplastic syndromes with 5q deletion before the lenalidomide era; the GFM experience with EPO and thalidomide. Leuk Res 2008;32:1049-1053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18191202.

306. Greenberg PL, Sun Z, Miller KB, et al. Treatment of myelodysplastic syndromes patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase III trial by the Eastern Cooperative Oncology Group (E1996). Blood 2009;114:2393-2400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19564636.

307. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): Interim analysis of a phase 3, open-label, randomised controlled trial. Lancet 2023;402:373-385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37311468.

308. Phurrough S, Jacques L, Ciccanti M, et al. Decision memo for erythropoiesis stimulating agents (ESAs) for non-renal disease indications (CAG-00383N). Centers for Medicare and Medicaid Services 2007. Available at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=203&ver=12&NcaName=Erythropoiesis+Stimulating+Agents+&bc=BEAAAAAAIAAA&.

309. Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. Blood 2013;121:4280-4286. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23575446.

310. Fenaux P, Kiladjian JJ, Platzbecker U. Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis. Blood 2019;133:790-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30602619.

311. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med 2020;382:140-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31914241.

312. Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-beta superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med 2014;20:408-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24658078.

313. Garcia-Manero G, Mufti GJ, Fenaux P, et al. Neutrophil and platelet increases with luspatercept in lower-risk MDS: Secondary endpoints from the MEDALIST trial. Blood 2022;139:624-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34758066.

314. Platzbecker U, Germing U, Gotze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol 2017;18:1338-1347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28870615.

315. Platzbecker U, Gotze KS, Kiewe P, et al. Long-term efficacy and safety of luspatercept for anemia treatment in patients with lower-risk myelodysplastic syndromes: The phase II PACE-MDS study. J Clin Oncol 2022;40:3800-3807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35998303.

316. Steensma DP, Fenaux P, Van Eygen K, et al. Imetelstat achieves meaningful and durable transfusion independence in high transfusion-burden patients with lower-risk myelodysplastic syndromes in a phase II

study. J Clin Oncol 2021;39:48-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33108243.

317. Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): A multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2024;403:249-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38048786.

318. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19230772.

319. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer 2006;106:1794-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16532500.

320. Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 2011;29:1987-1996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21483003.

321. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002;20:2429-2440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12011120.

322. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol 2006;24:3895-3903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921040.

323. Silverman LR, Fenaux P, Mufti GJ, et al. Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes. Cancer 2011;117:2697-2702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21656747.

324. Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. J Clin Oncol 2009;27:1850-1856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255328.

325. Martin MG, Walgren RA, Procknow E, et al. A phase II study of 5-day intravenous azacitidine in patients with myelodysplastic syndromes. Am J Hematol 2009;84:560-564. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19650118.

326. Lubbert M, Wijermans P, Kunzmann R, et al. Cytogenetic responses in high-risk myelodysplastic syndrome following low-dose treatment with the DNA methylation inhibitor 5-aza-2'-deoxycytidine. Br J Haematol 2001;114:349-357. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11529854.

327. Wijermans P, Lubbert M, Verhoef G, et al. Low-dose 5-aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients. J Clin Oncol 2000;18:956-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10694544.

328. van den Bosch J, Lubbert M, Verhoef G, Wijermans PW. The effects of 5-aza-2'-deoxycytidine (decitabine) on the platelet count in patients with intermediate and high-risk myelodysplastic syndromes. Leuk Res 2004;28:785-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15203276.

329. Saba HI, Lubbert M, Wijermans PW. Response rates of phase 2 and phase 3 trials of decitabine (DAC) in patients with myelodysplastic syndromes (MDS) [Abstract]. Blood 2005;106:Abstract 2515. Available at: http://www.bloodjournal.org/content/106/11/2515.

330. Kantarjian HM, O'Brien S, Shan J, et al. Update of the decitabine experience in higher risk myelodysplastic syndrome and analysis of prognostic factors associated with outcome. Cancer 2007;109:265-273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17133405.

331. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood 2007;109:52-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16882708.

332. Savona MR, Odenike O, Amrein PC, et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicentre, open-label, dose-escalation, phase 1 study. Lancet Haematol 2019;6:e194-e203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30926081.

333. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood 2020;136:674-683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32285126.

334. Garcia-Manero G, McCloskey J, Griffiths EA, et al. Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): A registrational, randomised, crossover, pharmacokinetics, phase 3 study. Lancet Haematol 2024;11:e15-e26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38135371.

335. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-Francophone des Myelodysplasies. J Clin Oncol 2012;30:4533-4540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23109707.

336. Field T, Perkins J, Huang Y, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2010;45:255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19543327.

337. Gerds AT, Gooley TA, Estey EH, et al. Pretransplantation therapy with azacitidine vs induction chemotherapy and posttransplantation outcome in patients with MDS. Biol Blood Marrow Transplant 2012;18:1211-1218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22252125.

338. Lubbert M, Bertz H, Ruter B, et al. Non-intensive treatment with low-dose 5-aza-2'-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. Bone Marrow Transplant 2009;44:585-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19363531.

339. Kröger N, Sockel K, Wolschke C, et al. Comparison between 5-azacytidine treatment and allogeneic stem-cell transplantation in elderly patients with advanced MDS according to donor availability (VidazaAllo study). J Clin Oncol 2021;39:3318-3327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34283629.

340. Qin Y, Kuang P, Zeng Q, et al. Hypomethylating agents for patients with myelodysplastic syndromes prior to hematopoietic stem cell transplantation: a systematic review and meta-analysis. Ann Hematol 2019;98:2523-2531. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31637485.

341. Festuccia M, Deeg HJ, Gooley TA, et al. Minimal identifiable disease and the role of conditioning intensity in hematopoietic cell transplantation for myelodysplastic syndrome and acute myelogenous leukemia evolving from myelodysplastic syndrome. Biol Blood Marrow Transplant 2016;22:1227-1233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27064057.

342. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol 2016;34:2988-2996. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27354480.

343. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood 2011;118:3765-3776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21753188.

344. Deeg HJ, Jiang PY, Holmberg LA, et al. Hematologic responses of patients with MDS to antithymocyte globulin plus etanercept correlate with improved flow scores of marrow cells. Leuk Res 2004;28:1177-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15380342.

345. Molldrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. Br J Haematol 1997;99:699-705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9401087.

346. Garg R, Faderl S, Garcia-Manero G, et al. Phase II study of rabbit anti-thymocyte globulin, cyclosporine and granulocyte colony-stimulating factor in patients with aplastic anemia and myelodysplastic syndrome. Leukemia 2009;23:1297-1302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19242494.

347. Passweg JR, Giagounidis AA, Simcock M, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: a prospective randomized multicenter phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care--SAKK 33/99. J Clin Oncol 2011;29:303-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21149672.

348. Sauntharajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood 2002;100:1570-1574. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12176872.

349. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med 2011;365:430-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21812672.

350. Stadler M, Germing U, Kliche KO, et al. A prospective, randomised, phase II study of horse antithymocyte globulin vs rabbit antithymocyte globulin as immune-modulating therapy in patients with low-risk myelodysplastic syndromes. Leukemia 2004;18:460-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14712285.

351. Alsultan A, Goldenberg NA, Kaiser N, et al. Tacrolimus as an alternative to cyclosporine in the maintenance phase of immunosuppressive therapy for severe aplastic anemia in children. Pediatr Blood Cancer 2009;52:626-630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19148946.

352. Macartney C, Freilich M, Odame I, et al. Complete response to tacrolimus in a child with severe aplastic anemia resistant to cyclosporin A. Pediatr Blood Cancer 2009;52:525-527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19058202.

353. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med 2017;376:1540-1550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28423296.

354. Assi R, Garcia-Manero G, Ravandi F, et al. Addition of eltrombopag to immunosuppressive therapy in patients with newly diagnosed aplastic anemia. Cancer 2018;124:4192-4201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30307606.

355. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med 2005;352:549-557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15703420.

356. Nimer SD. Clinical management of myelodysplastic syndromes with interstitial deletion of chromosome 5q. J Clin Oncol 2006;24:2576-2582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16735711.

357. Giagounidis A, Mufti GJ, Mittelman M, et al. Outcomes in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with isolated deletion 5q treated with lenalidomide: a subset analysis from the MDS-004 study. Eur J Haematol

2014;93:429-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24813620.

358. Kuendgen A, Lauseker M, List AF, et al. Lenalidomide does not increase AML progression risk in RBC transfusion-dependent patients with Low- or Intermediate-1-risk MDS with del(5q): a comparative analysis. Leukemia 2013;27:1072-1079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23257782.

359. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood 2008;111:86-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17893227.

360. Toma A, Kosmider O, Chevret S, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. Leukemia 2016;30:897-905. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26500139.

361. List AF, Sun Z, Verma A, et al. Lenalidomide-epoetin alfa versus lenalidomide monotherapy in myelodysplastic syndromes refractory to recombinant erythropoietin. J Clin Oncol 2021;39:1001-1009. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33439748.

362. Tricot G, Boogaerts MA. The role of aggressive chemotherapy in the treatment of the myelodysplastic syndromes. Br J Haematol 1986;63:477-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3730285.

363. Estey EH, Thall PF, Cortes JE, et al. Comparison of idarubicin + ara-C-, fludarabine + ara-C-, and topotecan + ara-C-based regimens in treatment of newly diagnosed acute myeloid leukemia, refractory anemia with excess blasts in transformation, or refractory anemia with excess blasts. Blood 2001;98:3575-3583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11739159.

364. Sonneveld P, van Dongen JJ, Hagemeijer A, et al. High expression of the multidrug resistance P-glycoprotein in high-risk myelodysplasia is associated with immature phenotype. Leukemia 1993;7:963-969. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8100604.

365. Advani R, Saba HI, Tallman MS, et al. Treatment of refractory and relapsed acute myelogenous leukemia with combination chemotherapy plus the multidrug resistance modulator PSC 833 (Valspodar). Blood 1999;93:787-795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9920827.

366. Wattel E, Solary E, Hecquet B, et al. Quinine improves results of intensive chemotherapy (IC) in myelodysplastic syndromes (MDS) expressing P-glycoprotein (PGP). Updated results of a randomized study. Groupe Francais des Myelodysplasies (GFM) and Groupe GOELAMS. Adv Exp Med Biol 1999;457:35-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10500778.

367. Greenberg PL, Lee SJ, Advani R, et al. Mitoxantrone, etoposide, and cytarabine with or without valspodar in patients with relapsed or refractory acute myeloid leukemia and high-risk myelodysplastic syndrome: a phase III trial (E2995). J Clin Oncol 2004;22:1078-1086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15020609.

368. Anderson JE, Appelbaum FR, Fisher LD, et al. Allogeneic bone marrow transplantation for 93 patients with myelodysplastic syndrome. Blood 1993;82:677-681. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8329721.

369. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood 2005;105:1343-1347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15466923.

370. De Witte T, Zwaan F, Hermans J, et al. Allogeneic bone marrow transplantation for secondary leukaemia and myelodysplastic syndrome: a survey by the Leukaemia Working Party of the European Bone Marrow Transplantation Group (EBMTG). Br J Haematol 1990;74:151-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2180469.

371. Demuynck H, Verhoef GE, Zachee P, et al. Treatment of patients with myelodysplastic syndromes with allogeneic bone marrow transplantation from genotypically HLA-identical sibling and alternative donors. Bone Marrow Transplant 1996;17:745-751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8733692.

372. Jurado M, Deeg HJ, Storer B, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome after conditioning with busulfan and fractionated total body irradiation is associated with low relapse rate but considerable nonrelapse mortality. Biol Blood Marrow Transplant 2002;8:161-169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11939606.

373. Kerbauy DM, Chyou F, Gooley T, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia. Biol Blood Marrow Transplant 2005;11:713-720. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16125642.

374. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med 2004;351:2265-2275. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15564543.

375. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 2008;14:641-650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18489989.

376. Nevill TJ, Fung HC, Shepherd JD, et al. Cytogenetic abnormalities in primary myelodysplastic syndrome are highly predictive of outcome after allogeneic bone marrow transplantation. Blood 1998;92:1910-1917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9731047.

377. Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia 2006;20:128-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16270037.

378. Wallen H, Gooley TA, Deeg HJ, et al. Ablative allogeneic hematopoietic cell transplantation in adults 60 years of age and older. J Clin Oncol 2005;23:3439-3446. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15824415.

379. Nakamura R, Saber W, Martens MJ, et al. Biologic assignment trial of reduced-intensity hematopoietic cell transplantation based on donor availability in patients 50-75 years of age with advanced myelodysplastic syndrome. J Clin Oncol 2021;39:3328-3339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34106753.

380. Schroeder T, Wegener N, Lauseker M, et al. Comparison between upfront transplantation and different pretransplant cytoreductive treatment approaches in patients with high-risk myelodysplastic syndrome and secondary acute myelogenous leukemia. Biol Blood Marrow Transplant 2019;25:1550-1559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30880268.

381. Scott BL, Pasquini MC, Fei M, et al. Myeloablative versus reduced-intensity conditioning for hematopoietic cell transplantation in acute myelogenous leukemia and myelodysplastic syndromes-long-term follow-up of the BMT CTN 0901 clinical trial. Transplant Cell Ther 2021;27:483 e481-483 e486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33775615.

382. Fukumoto JS, Greenberg PL. Management of patients with higher risk myelodysplastic syndromes. Crit Rev Oncol Hematol 2005;56:179-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15979321.

383. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 2018;378:2386-2398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29860938.

384. Garcia JS, Platzbecker U, Odenike O, et al. Efficacy and safety of venetoclax in combination with azacitidine for the treatment of patients with treatment-naive, higher-risk myelodysplastic syndromes [abstract]. Blood 2023;142:319. Available at:

https://ashpublications.org/blood/article/142/Supplement%201/319/504371/Efficacy-and-Safety-of-Venetoclax-in-Combination.

385. Zeidan AM, Borate U, Pollyea DA, et al. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes. Am J Hematol 2023;98:272-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36309981.

386. Cortes J, Yang J, Lee S, et al. Olutasidenib alone or in combination with azacitidine induces durable complete remissions in patients with *mIDH1* myelodysplastic syndromes/neoplasms (MDS) [abstract]. Blood 2023;142:1872. Available at: https://ashpublications.org/blood/article/142/Supplement%201/1872/505413/Olutasidenib-Alone-or-in-Combination-with.

387. Zeidan AM, Pollyea DA, Garcia JS, et al. A phase 1b study evaluating the safety and efficacy of venetoclax as monotherapy or in combination with azacitadine for the treatment of relapsed/refractory myelodysplastic syndrome [abstract]. Blood 2019;134:Abstract 565. Available at: https://ashpublications.org/blood/article/134/Supplement_1/565/426344/A-Phase-1b-Study-Evaluating-the-Safety-and.

388. Thol F, Weissinger EM, Krauter J, et al. IDH1 mutations in patients with myelodysplastic syndromes are associated with an unfavorable prognosis. Haematologica 2010;95:1668-1674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20494930.

389. Kosmider O, Gelsi-Boyer V, Slama L, et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. Leukemia 2010;24:1094-1096. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20376084.

390. Patnaik MM, Hanson CA, Hodnefield JM, et al. Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic study of 277 patients. Leukemia 2012;26:101-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22033490.

391. Sebert M, Cluzeau T, Rauzy OB, et al. Ivosidenib monotherapy is effective in patients with IDH1 mutated myelodysplastic syndrome (MDS): The Idiome phase 2 study by the GFM group [abstract]. Blood 2021;138:Abstract 62. Available at: https://ashpublications.org/blood/article/138/Supplement%201/62/477527/Ivosidenib-Monotherapy-Is-Effective-in-Patients.

392. Lachowiez CA, Loghavi S, Zeng Z, et al. A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in IDH1-mutated myeloid malignancies. Blood Cancer Discov 2023;4:276-293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37102976.

393. Ades L, Dimicoli-Salazar S, Sebert M, et al. Enasidenib (ENA) is effective in patients with IDH2 mutated myelodysplastic syndrome (MDS): The Ideal phase 2 study by the GFM group [abstract]. Blood 2021;138:Abstract 63. Available at: https://ashpublications.org/blood/article/138/Supplement%201/63/477536/Enasidenib-ENA-Is-Effective-in-Patients-with-IDH2.

394. DiNardo CD, Roboz GJ, Watts JM, et al. Final phase I substudy results of ivosidenib in patients with mutant IDH1 relapsed/refractory myelodysplastic syndrome Blood Adv 2024:Online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38640348.

395. DiNardo CD, Venugopal S, Lachowiez C, et al. Targeted therapy with the mutant IDH2 inhibitor enasidenib for high-risk IDH2-mutant myelodysplastic syndrome. Blood Adv 2023;7:2378-2387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35973199.

396. Sasaki K, Jabbour E, Montalban-Bravo G, et al. Low-dose decitabine versus low-dose azacitidine in lower-risk MDS. NEJM Evid 2022;1:EVIDoa2200034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38319837.

397. 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:e417-426. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26686043.

398. Revicki DA, Brandenburg NA, Muus P, et al. Health-related quality of life outcomes of lenalidomide in transfusion-dependent patients with Low- or Intermediate-1-risk myelodysplastic syndromes with a chromosome 5q deletion: results from a randomized clinical trial. Leuk Res 2013;37:259-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23273538.

399. Oliva EN, Latagliata R, Lagana C, et al. Lenalidomide in International Prognostic Scoring System Low and Intermediate-1 risk myelodysplastic syndromes with del(5q): an Italian phase II trial of health-related quality of life, safety and efficacy. Leuk Lymphoma 2013;54:2458-2465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23432724.

400. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. Nat Rev Cancer 2017;17:5-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27834397.

401. Casadevall N, Durieux P, Dubois S, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. Blood 2004;104:321-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15054036.

402. Hellstrom-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol 1997;99:344-351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9375752.

403. Spiriti MA, Latagliata R, Niscola P, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. Ann Hematol 2005;84:167-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15592833.

404. Negrin RS, Stein R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. Blood 1996;87:4076-4081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8639764.

405. Hellstrom-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol 1995;89:67-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7833279.

406. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol 2003;120:1037-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12648074.

407. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine: A phase 2, pharmacokinetic/pharmacodynamic, randomized, crossover study in MDS and CMML. Blood 2020;136:674-683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32285126.

408. Fili C, Malagola M, Follo MY, et al. Prospective phase II Study on 5-days azacitidine for treatment of symptomatic and/or erythropoietin unresponsive patients with low/INT-1-risk myelodysplastic syndromes. Clin Cancer Res 2013;19:3297-3308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23596104.

409. Medeiros BC, Fathi AT, DiNardo CD, et al. Isocitrate dehydrogenase mutations in myeloid malignancies. Leukemia 2017;31:272-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27721426.

410. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. Blood 2005;105:1810-1814. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15459007.

411. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is

associated with improved outcome. Blood 2004;104:579-585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15039286.

412. Laport GG, Sandmaier BM, Storer BE, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. Biol Blood Marrow Transplant 2008;14:246-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18215785.

413. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol 2010;28:1878-1887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20212255.

414. Kindwall-Keller T, Isola LM. The evolution of hematopoietic SCT in myelodysplastic syndrome. Bone Marrow Transplant 2009;43:597-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19252532.

415. Oliansky DM, Antin JH, Bennett JM, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. Biol Blood Marrow Transplant 2009;15:137-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19167676.

416. Deeg HJ, Sandmaier BM. Who is fit for allogeneic transplantation? Blood 2010;116:4762-4770. Available at: http://bloodjournal.hematologylibrary.org/cgi/content/abstract/bloodjournal;116/23/4762.

417. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. JAMA 2011;306:1874-1883. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22045765.

418. Kroger N. Allogeneic stem cell transplantation for elderly patients with myelodysplastic syndrome. Blood 2012;119:5632-5639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22504927.

419. Bokhari SW, Watson L, Nagra S, et al. Role of HCT-comorbidity index, age and disease status at transplantation in predicting survival and non-relapse mortality in patients with myelodysplasia and leukemia undergoing reduced-intensity-conditioning hemopoeitic progenitor cell transplantation. Bone Marrow Transplant 2012;47:528-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21743502.

420. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol 2013;31:2662-2670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23797000.

421. Beran M, Shen Y, Kantarjian H, et al. High-dose chemotherapy in high-risk myelodysplastic syndrome: covariate-adjusted comparison of five regimens. Cancer 2001;92:1999-2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11596013.

422. Gore SD, Fenaux P, Santini V, et al. A multivariate analysis of the relationship between response and survival among patients with higher-risk myelodysplastic syndromes treated within azacitidine or conventional care regimens in the randomized AZA-001 trial. Haematologica 2013;98:1067-1072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23585522.

423. Seymour JF, Fenaux P, Silverman LR, et al. Effects of azacitidine compared with conventional care regimens in elderly (≥ 75 years) patients with higher-risk myelodysplastic syndromes. Crit Rev Oncol Hematol 2010;76:218-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20451404.

424. Kornblith AB, Herndon JE, 2nd, Silverman LR, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol 2002;20:2441-2452. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12011121.

425. Thomas M. Health-Related Quality of Life for those with myelodysplastic syndrome: Conceptualization, measurement and

implications. In: Greenberg PL, Editor, Myelodysplastic Syndromes: Clinical and Biological Advances: Cambridge University Press, Cambridge, England; 2006:263-295.