Myelodysplastic Syndromes: Diagnosis and Treatment

David P. Steensma, MD

CME Activity

Target Audience: The target audience for Mayo Clinic Proceedings is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. Mayo Clinic Proceedings aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine designates this journal-based CME activity for a maximum of 1.0 AMA PRA Category 1 Credit(s). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Learning Objectives: On completion of this article, you should be able to (1) diagnose myelodysplastic syndrome in a patient with unexplained cytopenias; (2) describe the role of molecular testing in evaluation of patients with suspected myelodysplastic syndromes; and (3) apply risk stratification tools to choose appropriate initial therapy for patients with myelodysplastic syndromes.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity.

Abstract

In the past few years, new biological insights into the myelodysplastic syndromes (MDS) resulting from molecular genetic analysis have improved pathologic understanding, but treatment advances have not kept pace. More than 40 genes are now known to be recurrently mutated in MDS. However, because most of these genes encode spliceosome components, chromatic remodeling factors, epigenetic pattern modulators, or transcription factors rather than more easily inhibited activated tyrosine kinases, there are as of yet few narrowly targeted therapies available for MDS. Three drugs—aazacitidine, decitabine, and lenalidomide—were approved by the US Food and Drug Administration for MDS indications a decade ago, and these agents can improve hematopoiesis, delay disease progression, and improve survival and quality of life for a subset of patients. However, only a few patients with MDS respond to these agents, and their benefit is temporary. The only potentially curative therapy for MDS is allogeneic hematopoietic stem cell transplant, but owing to the advanced age of many patients with MDS and the frequency of serious comorbid conditions, less than 10% of patients currently undergo stem cell transplant. This narrative review summarizes the current understanding of MDS and treatment options for these challenging disorders.
may progress over time, including evolution to acute myeloid leukemia (AML). Acute myeloid leukemia is currently defined by the World Health Organization (WHO) as at least 20% blasts in the marrow or blood or the presence of either myeloid sarcomas or certain AML-defining karyotypes, such as t(15;17) and t(8;21). Therefore, all patients with MDS have less than 20% marrow blasts, by definition.4

EPIDEMIOLOGIC PROFILE
Owing to the use of ambiguous diagnostic terminology, the exclusion of MDS cases from most cancer registries, and the incomplete evaluation of many older patients with cytopenias, the incidence and prevalence of MDS have been difficult to estimate accurately.5 Data from the US National Cancer Institute’s Surveillance, Epidemiology, and End Results Program (which has captured MDS cases since 2001) suggest that 10,000 to 12,000 new cases are diagnosed in the United States each year (ie, ~3-4 cases per 100,000 persons per year).6 However, analysis of Medicare claims in conjunction with Surveillance, Epidemiology, and End Results data indicates that the actual incidence of MDS in the United States may be closer to 30,000 to 40,000 new cases per year—several times higher than the incidence of AML.7

Aging is the most important risk factor for the development of MDS. Owing to errors in DNA replication and spontaneous mutations from normal metabolic by-products (eg, conversion of cytosine to thymidine by oxidative deamination from reactive oxygen species), coding mutations accumulate in hematopoietic stem cells at a mean ± SD rate of 0.13±0.02 exonic mutations per year of life.8 When an acquired DNA mutation or combination of mutations promotes growth or generates a survival advantage to a hematopoietic stem or progenitor cell, clonal hematopoiesis emerges. Approximately 10% of individuals older than 70 years have clonal mutations in genes associated with myeloid neoplasia, such as DNMT3A, TET2, and SF3B1, and these persons have a 0.5% to 1% chance per year of acquiring additional mutations that lead to progression to MDS or another hematologic neoplasm, similar in magnitude to the risk of monoclonal gamopathy of undetermined significance progressing to myeloma.9,10

In the United States and Western Europe, the median age at diagnosis of MDS is approximately 70 years, and the incidence increases steadily with age. In Eastern Europe and parts of Asia, the median age at diagnosis is younger than in the West, for unclear reasons. Although MDS have a modest male predominance, a specific MDS subtype—MDS associated with isolated deletion of the long arm of chromosome 5, hypolobated megakaryocytes, and erythroid hypoplasia (so-called 5q—syndrome)—is more common in women.11

Approximately 85% to 90% of MDS cases are idiopathic and result from aging-related hematopoietic stem cell injury. Secondary or therapy-related MDS (t-MDS) represents 10% to 15% of cases.12 Myelodysplastic syndrome can be induced by exogenous DNA-damaging agents, including DNA alkylating drugs (eg, cyclophosphamide and melphalan), inhibitors of topoisomerase II (eg, etoposide), ionizing radiation, and volatile hydrocarbons (eg, benzene). Although it can be difficult to prove a direct link between an exposure and subsequent MDS development, features supporting t-MDS rather than de novo MDS include complex karyotype (defined as ≥3 acquired chromosome abnormalities), abnormalities of chromosomes 5 and 7, and TP53 mutation.

Pediatric MDS, which are rare, are frequently associated with inborn disorders such as Fanconi anemia, Down syndrome, and congenital neutropenia.13 Germline mutations in RUNXI and GATA2 transcription factors also predispose to MDS. Germline RUNXI mutations are associated with a prodiome of thrombocytopenia that is often mistaken for immune thrombocytopenia, and GATA2 mutations may be associated with monocytopenia, mycobacterial infections, and lymphedema (MonoMAC syndrome).14,15

CLASSIFICATION
The fourth edition of the WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues, published in 2008, is currently the most widely used MDS classification (Table 1).4 The 2008 WHO MDS classification is similar to the earliest formal MDS classification, the 1982 MDS classification of the French-American-British Cooperative Group. In 2016, a revision of the WHO classification will be published that will simplify classification and formally address the role of molecular genetic testing in myeloid neoplasia diagnosis. The current WHO classification has limited prognostic
value, so other risk stratification tools have been developed, as described further herein.

The 2008 WHO classification considers marrow and blood blast proportion, which myeloid cell lineages exhibit greater than 10% of dysplastic cells, whether ring sideroblast erythroid precursors or Auer rods are present, and, to a limited extent, karyotype results. Therapy-related MDS is grouped with therapy-related AML because outcomes in these patients are poor regardless of the blast count. For cases that exhibit both MDS and myeloproliferative features such as leukocytosis and thrombocytosis—a group that includes chronic myelomonocytic leukemia (defined by \( >1 \times 10^9/L \) blood monocytes) and refractory anemia with ring sideroblasts and marked thrombocytosis (which requires a platelet count \( >450 \times 10^9/L \))—the WHO classification includes a separate MDS/myeloproliferative neoplasm (MPN) overlap category. The genetics, biology, and clinical approach to MDS/MPN are distinct from those of MDS without proliferative features and are not discussed further herein.\(^ {16} \)

### DIAGNOSTIC EVALUATION

Anemia is the most commonly observed cytopenia in MDS, but most patients present with multiple cytopenias. The median hemoglobin level of patients at diagnosis is 9.5 g/dL (to convert to g/L, multiply by 10.0), and 75% of patients have a hemoglobin level less than 11 g/dL; 80% of patients have a platelet count less than \( 100 \times 10^9/L \) (to convert to \( \text{g/L} \), multiply by 10.0), and 75% of patients have a platelet count less than \( 100 \times 10^9/L \). Anemia associated with MDS is usually macrocytic or normocytic but rarely can be microcytic owing to acquired alpha-thalassemia from somatic mutation of ATRX, a chromatin remodeling factor that alters alpha-globin expression.\(^ {18} \) Patients with MDS may seek medical attention because of fatigue, dyspnea, poor exercise tolerance, bruising, bleeding, or an infection, but some patients are asymptomatic at diagnosis and are discovered to have MDS only when a complete blood cell count is performed to evaluate another condition.

Currently, the observation of dysplastic blood and marrow cell morphologic features in more than 10% of examined cells is considered important for MDS diagnosis.\(^ {19} \) Commonly observed dysplastic features include megaloblastoid erythroid maturation, binucleate erythroid...
precursor cells and other nucleation abnormalities, ring sideroblasts, neutrophil hypolobulation or hypogranulation, and small megakaryocytes with abnormally segmented nuclei. The diagnostic requirement for morphologic dysplasia may evolve with more routine use of molecular genetic testing in diagnostic evaluation.

Dysplastic morphologic features are often accompanied by cellular dysfunction. For example, hypogranular neutrophils have impaired bactericidal activity, which increases neutropenia-associated infection risk, and platelets in MDS often express abnormally low levels of procoagulant cell surface markers or lack intracellular granules, which exacerbates bleeding from thrombocytopenia. Increased reticulin levels of procoagulant cell surface markers or platelets in MDS often express abnormally low levels of procoagulant cell surface markers or lack intracellular granules, which exacerbates bleeding from thrombocytopenia. As a result of such functional defects, infection and bleeding risks in MDS correlate poorly with the circulating neutrophil and platelet count.

Although the bone marrow in MDS usually is normocellular or hypercellular for age, 10% to 20% of cases are accompanied by a hypocellular marrow. These hypoplastic or hypocellular MDS cases may be difficult to distinguish from aplastic anemia and may have an increased likelihood of response to immunosuppressive drug therapy. Increased reticulin fibrosis is frequently present in the marrow in MDS; severe fibrosis is associated with poorer prognosis. Occasionally, patients with MDS present with immune dysregulation, paraneoplastic syndromes, or other clonal disorders, such as a small B-cell clone, paroxysmal nocturnal hemoglobinuria clone, and monoclonal gammopathy of undetermined significance. The influence of paroxysmal nocturnal hemoglobinuria clones on clinical behavior is unpredictable, but these clones are usually small, clinically irrelevant, and not associated with hemolysis. Leukocytosis and splenomegaly are rare in MDS, and their presence suggests the possibility of chronic myelomonocytic leukemia or another MDS/MPN overlap syndrome, or an alternative diagnosis.

Diagnostic evaluation of the patient with suspected MDS includes medical history and physical examination, complete blood cell count, review of the blood smear, bone marrow aspirate and biopsy, and laboratory tests to rule out other disorders that mimic MDS. Not all that is dysplastic is MDS, and nutritional deficiency (iron, vitamin B₁₂, folate, and copper), medication effect (eg, antimetabolites, such as methotrexate and azathioprine), alcohol abuse, human immunodeficiency virus infection, and immune-mediated cytopenias need to be excluded. Although the blood smear may suggest MDS, marrow aspiration is essential to establish the diagnosis. Bone marrow core (trephine) biopsy provides complementary information on cellularity and architecture, megakaryocyte morphology, and the presence of fibrosis—useful information that may inform therapeutic decisions.

Flow cytometric analysis is often used by pathologists to evaluate patients suspected of having MDS. Flow cytometry may detect aberrant antigen expression by hematopoietic cells or abnormal cell populations, such as increased blasts, but flow cytometry is currently a complementary assay that is best interpreted in the context of marrow morphology. Because flow cytometric enumeration of marrow blasts is subject to various technical artifacts, it should not replace a marrow aspirate manual differential count.

In contrast to flow cytometry, cyogenetic studies of the marrow are essential in evaluation of suspected MDS. Abnormal cytogenetic results can provide confirmation of the diagnosis when the morphologic profile is ambiguous. Specific karyotypes correlate with prognosis and response to treatment (Tables 2 and 3), such as deletion of chromosome arm 5q and high response rate to lenalidomide. Rarely, fluorescence in situ hybridization (FISH) analysis with probes directed toward common MDS-associated abnormalities reveals specific chromosomal translocations and gains or losses of large DNA segments not detected using standard cytogenetic methods. The yield of FISH is low if karyotyping is successful, and the clinical relevance of small clones detectable only by FISH and not by karyotyping is unclear. Although the WHO classification allows labeling patients with cytogenetic abnormalities but bland morphologic features as having unclassifiable MDS, certain karyotypes (trisomy 8, loss of the Y chromosome, and deletion 20q) are not specific enough to diagnose unclassifiable MDS.

Almost all patients who develop t-MDS secondary to exposure to mutagenic agents have chromosomal abnormalities. Therapy-related MDS that is associated with previous treatment with alkylating agents or exposure to ionizing radiation frequently demonstrates...
losses involving chromosomes 5 and 7 and emerges 3 to 7 years after exposure. Patients treated with epipodophyllotoxins may exhibit translocations at the chromosome 11q23 locus involving the \textit{MLL} gene; the latency period between exposure and diagnosis with this form of t-MDS/AML is typically 1 to 3 years.

Increasingly, molecular genetic profiling is used to evaluate patients suspected of having MDS. Molecular genetic profiling can augment prognostic assessment and predict outcomes after allogeneic stem cell transplant.\textsuperscript{31,32} Molecular genetic profiling may also be useful diagnostically, especially in cases that lack another explanation for cytopenias but do not meet the diagnostic criteria for MDS or another disorder. The term \textit{idiopathic cytopenia(s) of undetermined significance} (ICUS) has been used for such patients, and although some individuals with ICUS will eventually be diagnosed as having MDS or AML, others will resolve or be found to have a nonneoplastic diagnosis.\textsuperscript{33} Several commercial vendors offer MDS molecular genetic panels, and a homegrown clinically validated 96-gene panel that returns results in 72 hours is now routinely used for evaluating patients with ICUS or suspected MDS in the author’s practice.\textsuperscript{34} Because more than 80% of patients with MDS have a somatic mutation in 1 of the more than 40 most commonly mutated MDS-associated genes, the negative predictive value of a normal result on an MDS mutation panel is relatively high, and nonneoplastic causes of cytopenias should be carefully excluded when mutation results are normal.\textsuperscript{35} However, because clonal hematopoiesis is present in more than 10% of healthy people older than 70 years, clinicians must be cautious in interpreting mutations in patients with a normal karyotype and without morphologic changes of dysplasia.

## PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.

### PROGNOSIS

Risk assessment in MDS is important for therapy selection and for counseling patients. Although the natural history of MDS includes a risk of progression to AML in 25% to 30% of patients, most patients with MDS do not develop AML and instead die of complications of cytopenias or of unrelated conditions that are common in geriatric populations, such as cardiovascular disease.\textsuperscript{36} This observation led to a change in the name of these disorders in the 1970s from the simpler but incomplete designation preleukemia to MDS.
number of cytopenias, and proportion of marrow blasts. Patients younger than 60 years with a low IPSS score have median survival of more than 5 years, and older patients with a high IPSS score have median survival of only less than 6 months, if treated with supportive care alone. For each IPSS risk group, outcomes tend to be better for younger patients than for older patients.

The 1997 IPSS had several important limitations. It was validated only for adult patients with de novo disease treated with supportive care or hematopoietic growth factors. It did not weight severity of cytopenias, included a limited repertoire of karyotypes, did not include risk factors such as transfusion dependence, and did not adequately stratify patients with MPN features or those with t-MDS. In addition, in each IPSS risk group there are wide variations in patient outcomes. Several newer MDS prognostic systems have been introduced since 2007 to try to overcome these limitations. The WHO-based Prognostic Scoring System integrates the WHO classification with karyotyping data, the degree of anemia, and the presence or absence of marrow fibrosis; it is used primarily in Europe. A general risk model proposed by investigators at the MD Anderson Cancer Center is valid across a broad spectrum of patients with MDS, including those

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes</th>
<th>Median survival (y)</th>
<th>Time until 25% of patients developed AML (y)</th>
<th>Patients in this group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>5.4</td>
<td>Not reached</td>
<td>4</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
<td>4.8</td>
<td>9.4</td>
<td>72</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), i17q, +19, any other single or double abnormality not listed, 2 or more independent clones</td>
<td>2.7</td>
<td>2.5</td>
<td>13</td>
</tr>
<tr>
<td>Poor</td>
<td>Abnormal 3q, -7, double abnormality include -7/del(7q), complex with 3 abnormalities</td>
<td>1.5</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt;3 abnormalities</td>
<td>0.7</td>
<td>0.7</td>
<td>7</td>
</tr>
</tbody>
</table>

**IPSS-R**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cytogenetic risk group</th>
<th>Marrow blasts (%)</th>
<th>Hemoglobin (g/dL)</th>
<th>Absolute neutrophil count (×10⁹/L)</th>
<th>Platelet count (×10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&lt;2</td>
<td>2-&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
<td>50-100</td>
<td>&lt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IPSS-R (see: http://www.mds-foundation.org/ipss-r-calculator/)**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% patients in this risk group (n=7012; AML data on 6485)</th>
<th>Median survival, years</th>
<th>Median survival for pts under 60 years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>2.0-3.0</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3.5-4.5</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>5.0-6.0</td>
<td>13%</td>
<td>1.5</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;6.0</td>
<td>10%</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*AML = acute myeloid leukemia.

1SI conversion factors: To convert hemoglobin values to g/L, multiply by 10.0.

*Possible range of summed scores: 0-10.

Adapted from Blood.35

### TABLE 3. 2012 Revised International Prognostic Scoring System (IPSS-R)*<sup>35</sup>

Updated cytogenetic classification for use in the IPSS-R (n=7012)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Included karyotypes</th>
<th>Median survival (y)</th>
<th>Time until 25% of patients developed AML (y)</th>
<th>Patients in this group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>del(11q), -Y</td>
<td>5.4</td>
<td>Not reached</td>
<td>4</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)</td>
<td>4.8</td>
<td>9.4</td>
<td>72</td>
</tr>
<tr>
<td>Intermediate</td>
<td>+8, del(7q), i17q, +19, any other single or double abnormality not listed, 2 or more independent clones</td>
<td>2.7</td>
<td>2.5</td>
<td>13</td>
</tr>
<tr>
<td>Poor</td>
<td>Abnormal 3q, -7, double abnormality include -7/del(7q), complex with 3 abnormalities</td>
<td>1.5</td>
<td>1.7</td>
<td>4</td>
</tr>
<tr>
<td>Very poor</td>
<td>Complex with &gt;3 abnormalities</td>
<td>0.7</td>
<td>0.7</td>
<td>7</td>
</tr>
</tbody>
</table>
with t-MDS and those who previously have been treated with a disease-modifying drug. A risk model for IPSS lower-risk MDS also was developed at the MD Anderson Cancer Center. A revised IPSS (IPSS-R) based on analysis of more than 7000 patients from more than 10 countries was published in 2012 (Table 3). The major changes in the IPSS-R from the IPSS are that the IPSS-R includes a broader range of cytogenetic abnormalities than those included in the 1997 IPSS, and the IPSS-R also weights cytogenetic findings more heavily than other variables, such as cytopenias, whereas the IPSS weighted blasts most heavily. In addition, blast cutoff points are different in the IPSS-R, which has 5 risk categories compared with 4 for the IPSS, and the degree of cytopenias is considered in the IPSS-R, whereas the IPSS considered only the number of cytopenias. Despite these improvements, the IPSS-R is still valid only in patients with de novo MDS at the time of diagnosis. In addition, other prognostically important variables, such as the presence of comorbid conditions, kinetics of clonal evolution, and molecular genetic findings, are not accounted for by the IPSS-R or by any of the other MDS risk stratification tools.

In the future, molecular genetic data will be increasingly used for risk stratification. For example, in 1 study, mutations in EZH2, ETV6, ASXL1, RUNX1, and TP53 retained prognostic significance independent of the IPSS in a multivariable analysis, and the overall mutation burden was also prognostic, with a higher risk of AML progression and death in those with more detected mutations.

BIOLOGY
A detailed discussion of MDS biology is beyond the scope of this review. Cytogenetic and molecular genetic abnormalities indicate that MDS are clonal disorders. The neoplastic clone in MDS includes stem/progenitor cells and more differentiated myeloid, erythroid, and megakaryocytic cells; B cells are also sometimes part of the clonal process, but T cells are rarely involved, although T-cell clones similar to those seen in large granular lymphocyte leukemia can be detected in some patients. Most marrow and blood cells in MDS are clonal, even if blast counts are not increased.

Recurrent MDS-associated DNA mutations cluster in genes that encode biological pathways for messenger RNA splicing, DNA methylation, and chromatin remodeling (Figure 1). Cell culture studies with primary MDS samples have found reduced growth of multilineage colony-forming unit progenitors. Experimental evidence also implicates inhibitory cytokines and increased intramedullary apoptosis as contributors to ineffective hematopoiesis in early MDS. The role of the marrow microenvironment and hematopoietic niche in MDS continues to undergo scrutiny as stromal support of the growth and maturation of normal hematopoietic progenitors is impaired in MDS, and in a murine model, mutation of a gene in osteoprogenitor cells resulted in an MDS-like phenotype.

TREATMENT
Other than allogeneic hematopoietic stem cell transplant (HSCT), which is currently used in less than 10% of patients and is successful 20% to 50% of the time, there is no cure for MDS. Three medications have specific US Food and Drug Administration (FDA) approval for MDS-related indications: azacitidine, a DNA methyltransferase inhibitor and nucleoside analogue that was approved in 2004; lenalidomide, a modulator of cereblon and ubiquitin ligase activity that was approved in 2005; and decitabine, another DNA methyltransferase inhibitor that was approved in 2006. Several other drugs, such as hematopoietic growth factors, are commonly used off label in the MDS setting.

Risk stratification systems, such as the IPSS-R, supplemented by molecular genetic testing and clinical assessment, can aid treating physicians in therapeutic decision making. The goals of MDS therapy depend on prognostic assessment and the individual patient profile. For lower-risk patients, common goals of therapy include symptom control and quality of life, improvement of hematopoiesis, and delay of disease progression. For higher-risk patients, extension of survival has been reported with azacitidine therapy. Figure 2 displays a general treatment algorithm for MDS. Experimental compounds currently undergoing testing in patients with MDS were recently reviewed elsewhere.

Supportive Care: Transfusions and Iron Chelation
The proportion of patients with MDS receiving red blood cell transfusion is approximately 40% in lower-risk patients and 60% to 80% in higher-risk patients. Patients receiving regular
Transfusions have inferior survival compared with those who do not require transfusions, either because transfusions indicate more severe hematopoietic failure or because transfusions themselves cause harm via iron overload, immunomodulation, or another mechanism.54 There is controversy about the magnitude of risk from transfusion-related hemosiderosis in patients with MDS and the importance of hemosiderosis compared with other disease-associated risks.55,56 Lower-risk patients with MDS who have a ferritin level greater than 1000 ng/mL (to convert to pmol/L, multiply by 2.247) have worse survival than patients with lower ferritin levels, and patients with ferritin levels greater than 2500 ng/mL have inferior survival with HSCT.54,57 However, serum ferritin is an acute phase reactant that has only moderate correlation with iron burden, so newer magnetic resonance imaging techniques have been developed for noninvasively measuring hepatic, cardiac, and other organ iron concentrations. Quantitative R2*/T2* magnetic resonance imaging of the liver or heart may be useful in determining which patients are appropriate candidates for iron chelation therapy. T2* signals in the heart are usually normal until patients have received at least 80 to 100 U of blood.58 Measurement of reactive oxygen species (non-transferrin-bound iron) suggests that these volatile species are elevated in transfused patients with MDS and decrease rapidly during chelation therapy, but the clinical significance is unclear.59

Iron chelation therapy with oral deferasirox or parenteral deferoxamine can be considered in patients with a relatively good MDS prognosis who have evidence of tissue iron overload. There are currently no controlled prospective data indicating benefit from iron chelation in MDS, and chelation therapy is expensive (deferasirox), is...
MDS initial diagnosis (using WHO 2008 diagnostic criteria, supplemented by novel genomics approaches)

Individualized risk assessment, using IPSS-R or other tools

High-risk

Is there a need for treatment now?

Lower-risk

Is the patient a transplant candidate?

Azacitidine or decitabine (ie, HMA) until disease progression, relapse, or drug intolerance

AlloSCT, perhaps with HMA or chemotherapy as bridging therapy

Relapse

Enrollment in a clinical trial, or supportive/palliative care

Donor lymphocyte infusion or second alloSCT, possibly after cytoreductive therapy

Failure

Optimal approach is unclear consider G-CSF or TPO agonist, HMA, IST, clinical trial

Failure

Optimal therapy unclear consider HMA, IST, androgens, lenalidomide (if not already used), or clinical trial

Failure

AlloSCT, enrollment in a clinical trial, or palliative/supportive care

Enrollment in a clinical trial, or supportive/palliative care

Clinical monitoring

Development of a need for therapy

Is anemia isolated, or the major problem?

Yes

No

Is del5q present?

Yes

No

sEPO <500 U/L?

Yes

No

Lenalidomide if sEPO <500 U/L, ESA trial before or after

ESA ± G-CSF

Failure

Failure

Failure

Failure

FIGURE 2. A general approach to myelodysplastic syndromes (MDS) therapy. All the patients should receive supportive care with transfusions and antimicrobial agents as needed. Iron chelation therapy can be considered for selected red blood cell transfusion—requiring lower-risk patients. For lower-risk patients in whom the clinical picture is dominated by anemia, the initial therapeutic choice depends on the karyotype and the serum erythropoietin (sEPO) level. For patients with del(5q), lenalidomide is an appropriate first choice and is Food and Drug Administration approved for that indication. For patients without del(5q) but with sEPO levels less than 500 U/L, the erythropoiesis-stimulating agents (ESAs) epoetin and darbepoetin are recommended. The most appropriate therapy for lower-risk patients with anemia with sEPO levels greater than 500 U/L and without del(5q), pancytopenia, or a clinical picture dominated by individual cytopenias other than anemia (ie, neutropenia or thrombocytopenia) is unclear. Hypomethylating agents can be beneficial in some patients with lower-risk disease, although their effect on survival in this group is unclear, and some reports indicate the potential for inferior survival. Patients with isolated thrombocytopenia may overlap with immune thrombocytopenia and may benefit from corticosteroids, romiplostim or eltrombopag, intravenous gamma globulin or other immune thrombocytopenia—directed therapies. Immunosuppressive therapy, lenalidomide, supportive care alone, and hematopoietic stem cell transplant (HSCT) are all reasonable choices in the other patient groups, depending on patient-specific factors. For higher-risk patients, the treatment approach differs depending on whether the patient is an HSCT candidate. Higher-risk patients who are HSCT candidates should proceed with definitive HSCT therapy as soon as feasible. The HSCT may be preceded by a few treatment cycles of a hypomethylating agent as a “bridging” therapy to try to cytoreduce or at least keep the disease stable until a donor is identified and pretransplant screening tests are completed. Patients who are not HSCT candidates can be treated with a hypomethylating agent until disease progression or intolerance. Some investigators prefer azacitidine over decitabine because of the demonstrated survival advantage in this setting. Once initial therapy fails, no optimal second-line therapy is defined, and the choice depends on clinical circumstances. Clinical trial enrollment is always appropriate if a well-designed study is available for which the patient is eligible. alloSCT = allogeneic stem cell transplant; G-CSF = granulocyte colony-stimulating factor; HMA = hypomethylating agent (azacitidine or decitabine); IPSS-R = 2012 Revised International Prognostic Scoring System; IST = immunosuppressive therapy; TPO = thrombopoietin; WHO = World Health Organization. Partly based on European LeukemiaNet and National Comprehensive Cancer Network guidelines; see Malcovati et al48 and http://www.nccn.org. Adapted from Blood.52
cumbersome (defereroxamine), and can have adverse effects. In elderly patients with MDS, a dose of deferasirox high enough to cause a negative iron balance (ie, ≥20-30 mg/kg per day) often results in elevated creatinine levels or intolerable gastrointestinal symptoms.60,63

Bleeding is the second most common non-AML cause of death in MDS, after infection.61 Platelet transfusions can decrease bleeding risk, but the development of alloimmunization is common with repeated platelet transfusions.

**Hematopoietic Growth Factors**

Recombinant erythropoiesis-stimulating agents (ESAs; epoetin and darbepoetin) induce erythroid response rates in 20% to 50% of patients.62-64 Combinations of an ESA and granulocyte colony-stimulating factor (G-CSF) may be more effective than an ESA alone in ameliorating anemia, especially in patients with refractory anemia with ring sideroblasts, for unclear reasons.62 Although several retrospective studies suggest that ESAs may improve life expectancy in MDS, no prospective studies have found increased survival. For patients with serum erythropoietin levels less than 500 U/L, an 8- to 12-week trial of an ESA is appropriate; patients with higher serum erythropoietin levels rarely respond.65

The myeloid growth factors G-CSF (filgrastim and tbo-filgrastim) and granulocyte-macrophage CSF (sargramostim and molgramostim) increase the neutrophil count in many patients but do not increase survival. In one study of 102 patients, progression to AML was similar between G-CSF–treated patients and the control group, but survival was shorter in patients with excess blasts who received G-CSF.66 Patients with recurrent infections are the best candidates for myeloid growth factors but may not be helped by these agents if the increased circulating neutrophils are dysfunctional. There are reports of spontaneous splenic rupture and leukemoid reactions in MDS with pegfilgrastim, so this agent should be used only with caution.67

One of the major shifts in clinical practice in the past few years is the increased use of thrombopoietin (TPO) receptor agonists in MDS.68 Although romiplostim and eltrombopag are currently not approved for use in MDS, their label includes immune thrombocytopenia, which some patients with MDS also have. These agents can improve platelet counts and reduce bleeding events, especially in patients who have an endogenous TPO level less than 500 pg/mL and are not heavily dependent on platelet transfusions.69 One important safety concern is that blasts can have functional TPO receptors, so patients treated with romiplostim or eltrombopag may experience an increase in blood or marrow blasts. In a placebo-controlled study of romiplostim, AML progression was observed in 6% of romiplostim-treated patients and in 2.4% who received placebo, and most patients who progressed to AML had excess blasts before therapy.70 Romiplostim combined with azacitidine, decitabine, or lenalidomide has also been used to ameliorate thrombocytopenia. The anti-fibrinolytic drug epsilon–aminocaproic acid can decrease bleeding in thrombocytopenic patients who have mucosal hemorrhage, but it increases thrombosis risk when used systemically.71

**Immunosuppressive and Immunomodulatory Drugs**

Autoreactive T cells, either clonal or polyclonal, can contribute to suppressed hematopoiesis in some patients with MDS.72 This has prompted studies with anti–T-cell immunosuppressive treatment approaches similar to those used for aplastic anemia, such as antithymocyte globulin with a calcineurin inhibitor such as cyclosporine or tacrolimus. The most difficult task is selection of patients most likely to respond.73 Benefits are primarily seen in younger patients (<60 years) with lower-risk disease who are not transfusion dependent and have either normal cytogenetics or trisomy 8.74 In some studies, marrow hypocellularity and HLA-DR15 have predicted a higher likelihood of response to immunosuppression.

In the 1990s, thalidomide was used as an immunomodulatory agent and as an inhibitor of neoangiogenesis. Favorable responses were seen in 15% to 25% of patients, but adverse events were problematic, especially sedation, constipation, and neuropathy.75,76 Lenalidomide is a drug that is a minor chemical modification of thalidomide and has an improved safety profile. It is now known that the pleiotropic biological effects of thalidomide and lenalidomide are mediated by modulation of the activity of cereblon, a component of an E3 ubiquitin ligase complex that targets cellular proteins for degradation.77 Lenalidomide specifically alters the degradation rate of casein kinase 1, a serine-threonine kinase encoded on chromosome arm 5q that modulates Wnt/β-catenin signaling.78
Lenalidomide is most effective in patients with IPSS low-risk or intermediate-1 risk disease who have deletion of chromosome 5q31. In this group, 67% achieve transfusion independence, with a median time to response of 4.6 weeks, a median increase in hemoglobin level of 5.4 g/dL, and a median duration of response of more than 2 years. Cytogenetic remissions are seen in up to one-half of patients, but del(5q) hematopoietic stem cells are still detectable even in patients in remission. For patients who lack del(5q), responses are less frequent—approximately 25% become transfusion free during lenalidomide therapy— and less durable, with a median response of 40 weeks. The most common adverse effect with lenalidomide is myelosuppression. Patients with a low platelet count (especially <50×10^9/L), excess blasts, or a complex karyotype are less likely to respond to lenalidomide therapy.

**Hypomethylating Agents (DNA Methyltransferase Inhibitors)**

Epigenetic changes are those such as DNA methylation or histone acetylation that alter gene expression without changing the DNA sequence. Methylated cytidine residues cluster in CpG islands, which are located near the promoter regions of many genes. DNA methylation is a dynamic process that affects transcription rates of adjacent genes; when CpG islands are hypermethylated, expression of nearby genes is silenced. The aza-substituted cytosine nucleoside analogues azacitidine and decitabine are inhibitors of DNA methyltransferase 1, the enzyme that maintains cytidine methylation patterns. Azacitidine and decitabine treatment decreases methylation of DNA and reverses gene silencing. These agents also induce DNA damage similar to cytarabine and other nucleoside analogues, and it remains unclear whether epigenetic changes or other activities are responsible for clinical activity. Patients with TET2 or DNMT3A mutations have a higher likelihood of response to DNA methyltransferase 1 inhibitor therapy.

AZA-001 was a multicenter trial in which 358 patients with IPSS intermediate-2 or high-risk MDS were randomized to receive either azacitidine, 75 mg/m² subcutaneously for 7 consecutive days every 28 days, or conventional care (best supportive care alone, low-dose cytarabine, or AML-like induction chemotherapy using infusional cytarabine and an anthracycline). Median survival was 24 months in patients receiving azacitidine and 15 months in patients receiving conventional care; thus, azacitidine was the first choice. The complete response rate in the azacitidine-treated group was less than 20%, but subsequent analysis found that a complete response was not necessary for patients to achieve a survival benefit. Azacitidine is FDA approved for either intravenous administration or subcutaneous dosing. Intravenous administration avoids injection site reactions but necessitates venous access.

Decitabine is also clinically active in MDS, but neither an American nor a European multicenter study of decitabine reported a survival benefit. It is unclear whether this is because decitabine is an inferior molecule to azacitidine or because the studies enrolled different patient populations than AZA-001. The latter is suggested by the short (<10 months) survival of the control arms in decitabine studies. Decitabine is given most commonly intravenously for 5 consecutive days every 4 to 6 weeks.

Clinical response to hypomethylating agents may be slow, and an adequate therapeutic trial of either agent requires at least 4 treatment cycles with decitabine or 6 treatment cycles with azacitidine. The most common adverse events associated with these drugs are neutropenia and thrombocytopenia, which may improve with time as the MDS clones are suppressed and normal hematopoiesis recovers. The optimal maintenance dosing once patients achieve a response is unknown, but some maintenance therapy seems to be required to maintain responses. Thus far, no therapy has been found to improve survival for patients with lower-risk MDS, although azacitidine or decitabine can reduce transfusions and improve counts in some patients.

Deacetylase inhibitors maintain chromatin in a transcriptionally active state by inhibiting deacetylation of histone tails on chromatin. In vitro, these agents reverse transcription repression and gene silencing and are synergistic with hypomethylating agents. However, although several deacetylase inhibitors have been FDA approved for lymphoma (panobinostat and vorinostat), in 3 randomized cooperative group trials, the combination of azacitidine plus a deacetylase inhibitor (entinostat [MS-275] in E1905, vorinostat in S1117, and valproic acid in Aza-Plus) was not superior to azacitidine monotherapy.
Once hypomethylating agents fail the patient, the prognosis is grim, with median survival of less than 6 months.\(^93,94\) Switching from one failed hypomethylating agent to the other agent or adding lenalidomide or a deacetylase inhibitor is rarely helpful. Responses are seen in some patients with clofarabine use, AML-type induction chemotherapy, or low-dose cytarabine therapy, but patients in whom hypomethylating agents are failing should instead be referred for HSCT or enrolled in clinical trials if possible.

**Allogeneic HSCT**

Treatment of choice for children and young adults with MDS is HSCT. Younger patients (ie, ≤ 40 years) without excess blasts at the time of transplant may have long-term disease-free survival exceeding 50% after an HLA-matched HSCT. Unless the patient has t-MDS, it is imperative to perform a chromosome breakage assay to exclude Fanconi anemia before transplant in a child or young adult because patients with Fanconi anemia cannot tolerate conventional conditioning regimens. Although most patients with Fanconi anemia have short stature, radial ray anomalies, or other dysmorphic features, many do not.

Advanced age, the presence of comorbidities, clinical inertia, and lack of a suitable donor limit the availability of allogeneic HSCT, but the growing use of reduced-intensity conditioning approaches and alternative stem cell sources such as cord blood and mismatched donors (including haploidentical donors) are expanding the roster of potentially transplant-eligible patients.\(^66\) Therefore, patients with MDS who are potentially candidates for transplant should be evaluated early in the disease course by a physician with expertise in stem cell transplant. In many centers, reduced-intensity stem cell transplant is routinely performed for patients aged up to the early 70s. Patients with high IPSS scores or treatment-resistant disease (including persistence of excess blasts despite a hypomethylating agent) have lower survival rates after HSCT. Patients with a complex monosomal karyotype, defined as 2 or more autosomal monosomies or 1 monosity plus additional structural chromosomal abnormalities, have especially poor outcomes, as do those with t-MDS; when patients with complex karyotype also have a TP53 mutation, survival with HSCT is less than 10%.\(^32,95,96\)

The optimal time to refer patients for transplant is unclear, but mathematical modeling suggests that the best strategy is to perform transplant early in the disease course in patients with higher-risk disease and to defer transplant in patients with lower-risk disease (ie, IPSS low and intermediate-1 risk or IPSS-R very low and low risk) until the time of progression.\(^97,98\) It is unclear what the best strategy is with IPSS-R intermediate-risk patients, and this is a group where molecular genetic typing may assist in treatment selection.

No clear benefit has been found for the administration of 1 or more courses of cytotoxic chemotherapy or hypomethylating agent therapy before HSCT, although pretransplant therapy may be useful to reduce the burden of marrow blasts and clonal cells before HSCT.\(^99\) Most patients with higher-risk disease relapse after HSCT, and a variety of strategies to reduce relapse rates are being studied.\(^100\)

**CONCLUSION**

The MDS are among the most common and serious hematologic disorders diagnosed in older adults. Treatment options are limited, but HSCT offers the possibility of cure, and hematopoietic growth factors, azacitidine, lenalidomide, decitabine, and supportive care can provide palliative benefit. New insights into pathogenesis will, hopefully, lead to novel therapies and improved patient outcomes.

**Abbreviations and Acronyms:** alloSCT = allogeneic stem cell transplant; AML = acute myeloid leukemia; ESA = erythropoiesis-stimulating agent; FDA = Food and Drug Administration; FISH = fluorescence in situ hybridization; G-CSF = granulocyte colony stimulating factor; HSCT = hematopoietic stem cell transplant; ICUS = idiopathic cytopenia(s) of undetermined significance; IPSS = International Prognostic Scoring System; IPSS-R = revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; RCDU = refractory cytopenias with unilineage dysplasia; t-MDS = therapy-related myelodysplastic syndrome; TPO = thrombopoietin; WHO = World Health Organization

**Potential Competing Interests:** Dr. Steensma is a consultant for Celgene, MEI Pharma, Astex, and H3/Eisai and serves on the Data Safety Monitoring Committee for Amgen and Novartis.

**Statement About Off-label Drug Use:** Only azacitidine, decitabine, and lenalidomide are FDA approved for MDS. All other agents and uses are off label or experimental.

**Correspondence:** Address to David P. Steensma, MD, Adult Leukemia Program, Division of Hematological Malignancies, Department of Medical Oncology, Dana-Farber Cancer Institute, Brigham and Women’s Hospital, 450 Brookline Ave, D2037, Boston, MA 02215 (David_Steensma@DFCI. 

---

REFERENCES

11. Van den Berghe H, Michaux L. 5q-, twenty-.