JAMA | Review

Diagnosis and Treatment of Myelodysplastic Syndromes
A Review

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IMPORTANCE Myelodysplastic neoplasms (MDS), formerly known as myelodysplastic syndromes, are clonal hematopoietic malignancies that cause morphologic bone marrow dysplasia along with anemia, neutropenia, or thrombocytopenia. MDS are associated with an increased risk of acute myeloid leukemia (AML). The yearly incidence of MDS is approximately 4 per 100 000 people in the United States and is higher among patients with advanced age.

OBSERVATIONS MDS are characterized by reduced numbers of peripheral blood cells, an increased risk of acute myeloid leukemia transformation, and reduced survival. The median age at diagnosis is approximately 70 years, and the yearly incidence rate increases to 25 per 100 000 in people aged 65 years and older. Risk factors associated with MDS include older age and prior exposures to toxins such as chemotherapy or radiation therapy. MDS are more common in men compared with women (with yearly incidence rates of approximately 5.4 vs 2.9 per 100 000). MDS typically has an insidious presentation, consisting of signs and symptoms associated with anemia, thrombocytopenia, and neutropenia. MDS can be categorized into subtypes that are associated with lower or higher risk for acute myeloid leukemia transformation and that help with therapy selection. Patients with lower-risk MDS have a median survival of approximately 3 to 10 years, whereas patients with higher-risk disease have a median survival of less than 3 years. Therapy for lower-risk MDS is selected based on whether the primary clinical characteristic is anemia, thrombocytopenia, or neutropenia. Management focuses on treating symptoms and reducing the number of required transfusions in patients with low-risk disease. For patients with lower-risk MDS, erythropoiesis stimulating agents, such as recombinant humanized erythropoietin or the longer-acting erythropoietin, darbepoetin alfa, can improve anemia in 15% to 40% of patients for a median of 8 to 23 months. For those with higher-risk MDS, hypomethylating agents such as azacitidine, decitabine, or decitabine/cedazuridine are first-line therapy. Hematopoietic cell transplantation is considered for higher-risk patients and represents the only potential cure.

CONCLUSIONS AND RELEVANCE MDS are diagnosed in approximately 4 per 100 000 people in the United States and are associated with a 5-year survival rate of approximately 37%. Treatments are tailored to the patient's disease characteristics and comorbidities and range from supportive care with or without erythropoiesis-stimulating agents for patients with low-risk MDS to hypomethylating agents, such as azacitidine or decitabine, for patients with higher-risk MDS. Hematopoietic cell transplantation is potentially curative and should be considered for patients with higher-risk MDS at the time of diagnosis.

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Multimedia

Supplemental content

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The myelodysplastic neoplasms (MDS), formerly known as myelodysplastic syndromes, are a group of cancers characterized by failure of bone marrow stem cells to mature into normal-functioning blood cells. MDS are characterized by reduced numbers of peripheral blood cells, an increased risk of acute myeloid leukemia transformation, and reduced survival, with a 5-year survival rate of approximately 37%.[1,2] The yearly incidence of MDS is approximately 4 per 100 000 people.[3] MDS are more common in men (with yearly incidence rates of approximately 5.4 per 100 000 vs 2.9 per 100 000 for women) and are more common among people who are White compared with people who are Asian/Pacific Islander (4.0 per 100 000), Black (2.7 per 100 000), or Hispanic (2.9 per 100 000), and among people who are older.[3] The median age of diagnosis is approximately 70 years, and the yearly incidence rate increases to 25 per 100 000 in people aged 65 years and older.[3] Older age is associated with clonal hematopoiesis of indeterminate potential, which is considered a precursor to MDS.[4] Additional risk factors

include prior exposure to chemotherapy or radiation therapy for other malignancies[5]; antecedent hematologic conditions such as aplastic anemia or paroxysmal nocturnal hemoglobinuria[6]; autoimmune disorders such as rheumatoid arthritis[7]; environmental exposures to toxins such as organic solvents[8]; and congenital predisposition syndromes such as Fanconi anemia or germline variants in hematopoietic stem cells.[9] This review summarizes current evidence regarding diagnosis and treatment of MDS.

Methods

We searched PubMed and the Cochrane databases for English-language studies published from January 1, 1995, through June 22, 2022, for randomized clinical trials, meta-analyses, systematic reviews, epidemiologic studies, and observational studies (search terms are reported in the eAppendix in the Supplement). We manually searched the references of selected articles, reviews, meta-analyses, and practice guidelines. Randomized clinical trials and large observational studies were prioritized for inclusion. Of 345 reports retrieved, a total of 77 were included, consisting of 1 meta-analysis, 15 randomized clinical trials, 10 nonrandomized trials, 11 cross-sectional cohort studies, 6 guidelines, 12 reviews, 1 database,[3] and 21 retrospective cohort studies.

Pathophysiology

MDS are characterized by clonal proliferation of malignant hematopoietic stem cells, dysregulated cellular differentiation, and compromised tissue function.[10] MDS with lower risk of transformation to AML are typically characterized by low myeloblast percentages, fewer genetic variants, or by genetic variants associated with a better prognosis such as *SF3B1*, less severe anemia, thrombocytopenia, or neutropenia.[11] MDS with higher risk of transformation to AML are typically characterized by a higher percentage of myeloblasts; more genetic variants or genetic variants associated with a worse prognosis, such as *TP53*; and greater degrees of anemia, neutropenis, or thrombocytopenia.

The pathophysiology underlying MDS is heterogeneous. The MDS cell of origin is a hematopoietic stem cell that proliferates and escapes apoptosis.[12,13] Similar to other neoplasms, MDS progresses with serial acquisition of somatic variants, which may occur over decades and result in progressive dysplasia (**Figure**). The bone marrow microenvironment and inflammatory signaling can also determine the rate of development and progression of MDS.[9,14]

The recent discovery of the more common phenomenon of clonal hematopoiesis (CH) related to aging (more commonly referred to as CH of indeterminate potential or CHIP)[15-17] suggests that clonal outgrowth of HSCs is not specific to MDS. Among people with CH (recognized by the World Health Organization (WHO) as a category of precursor myeloid disease state), the incidence of MDS or AML is 0.5% to 1% per year, but not all people with CH will develop MDS or AML.[4] Rather, approximately 90% of people with CH will die from other causes, and CH has been associated with increased risk for cardiovascular disease.[16] Underlying factors contributing to progression of CH to MDS or AML remain unclear.

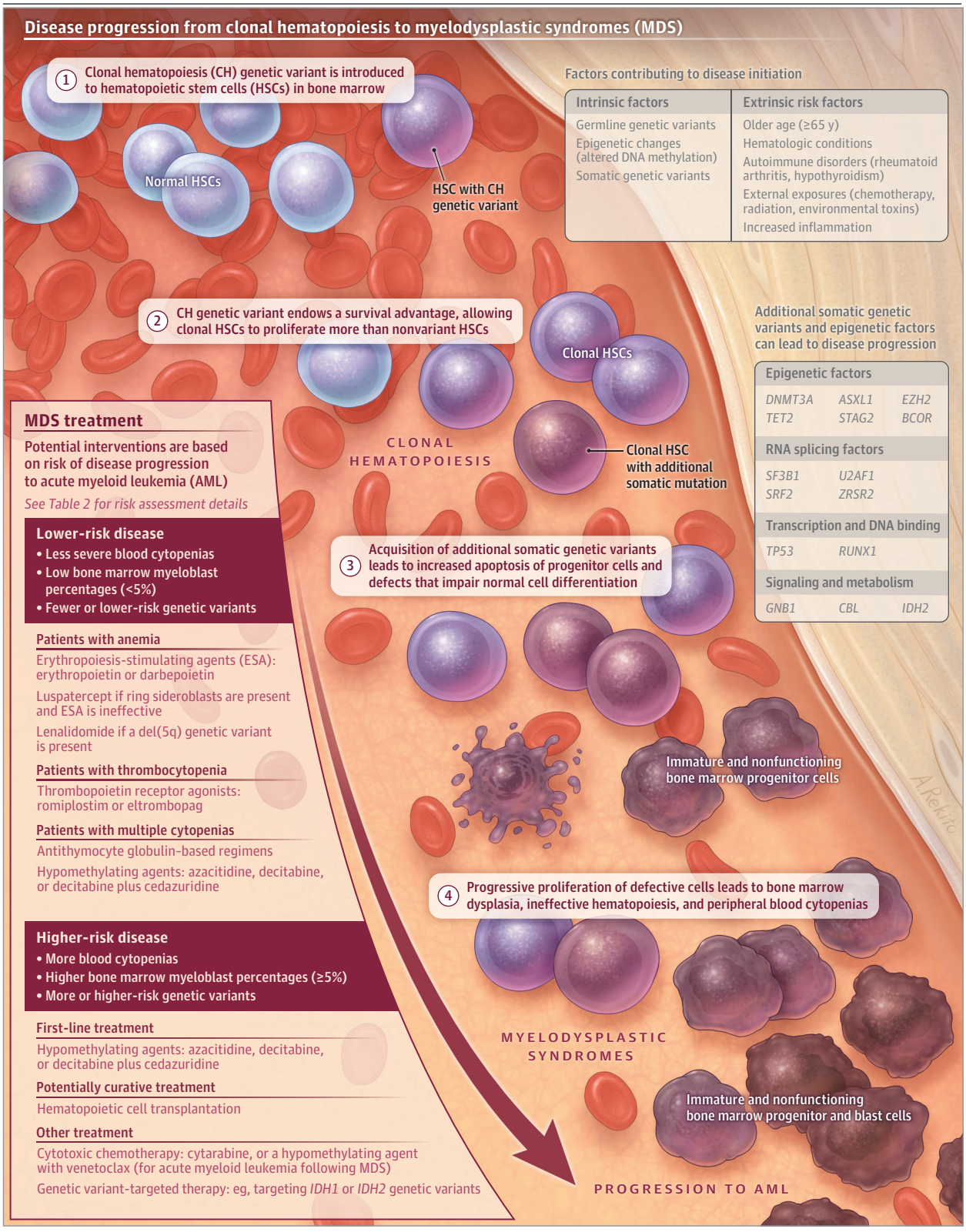
Clinical Presentation

Typical presenting symptoms of MDS are nonspecific and include fatigue or diminished appetite stemming from normocytic or macrocytic anemia. Additionally, gingival bleeding, epistaxis, or bruising from thrombocytopenia may occur less frequently. Patients may present with recurrent bacterial infections due to neutropenia (with infections occurring in approximately 2% to >50% of patients with established MDS diagnoses).[18,19] Among 7012 patients from 11 countries with newly diagnosed MDS, the median age was 71 years, 40% had a platelet count of less than 100×10^9/L, and 52% of patients had a hemoglobin level of less than 10 g/dL. Approximately one-third of patients had received red blood cell transfusions at the time of diagnosis. Only 18% had a neutrophil count of less than 800×10^9/L.[2] The prevalence of typical signs and symptoms at the time of MDS diagnosis is summarized in **Table 1**. These should be differentiated from signs and laboratory results associated with a myeloproliferative neoplasm, such as splenomegaly, elevated monocyte counts, or a *JAK2* variant.[20] Anemia, thrombocytopenia and/or neutropenia, typical in patients with MDS, also occur in patients with bone marrow failure due to other conditions such as aplastic anemia, paroxysmal nocturnal hemoglobinuria, autoimmune conditions, iron or vitamin deficiencies, blood loss, and autoimmune or endocrine abnormalities. Patients with normocytic or macrocytic anemia, and those with 2 or more of these cytopenias or with the previously mentioned risk factors, are more likely to have MDS than an alternative diagnosis. After other causes of abnormal blood counts are excluded, a bone marrow aspirate and biopsy should be obtained to diagnose MDS along with karyotype and myeloid next-generation sequencing of the bone marrow aspirate for further characterization.

Diagnosis and Risk Stratification

The WHO criteria for the diagnosis of MDS consist of anemia, thrombocytopenia or neutropenia that persists for 6 months or longer, dysplasia greater than 10% in at least 1 bone marrow cell lineage, and MDS-associated clonal cytogenetic abnormalities or molecular markers (**Box**).[1] In contrast with conditions associated with bone marrow failure, such as aplastic anemia with hypocellular marrow, typical bone marrow findings of MDS are a hypercellular marrow for a person's age (normal cellularity is calculated approximately as 100% minus age [eg, an 80-year old person should only have 20% cellularity in the bone marrow]), dysplasia in 1 to 3 lineages (eg, pseudo-Pelger-Huet nuclei, hypogranular neutrophils, micromegakaryocytes, and/or ring sideroblasts), and increased myeloblasts in a subset of patients.[21] In patients with unexplained anemia, thrombocytopenia, or neutropenia, who do not have morphologic bone marrow dysplasia, the presence of monosomy 5, 7, or 13; 5q, 7q, and 13q deletions; i(17p) and t(17p); 11q deletion; 9q or 12p deletion; or t(12p), idic (X)(q13) is consistent with an MDS diagnosis, even in the absence of dysplastic changes, but occurs in less than 10% of patients with MDS. Unexplained anemia, thrombocytopenia, or neutropenia without significant bone marrow dysplasia but with a clonal variant that does not meet criteria for MDS is considered clonal cytopenia of undetermined significance (CCUS).[22,23]

Figure. The Evolution From Clonal Hematopoiesis to Myelodysplastic Syndromes and Potential Points of Intervention



The discovery of age-related clonal hematopoiesis has shown that genetic variants associated with MDS can occur years prior to diagnosis in bone marrow HSCs. Genetic, epigenetic, and immune-related changes including inflammation, as well as external exposures, then influence the expansion of these clonal hematopoietic stem cells. Acquisition of additional variants leads to further expansion of cells with defective differentiation and ultimate phenotypes of ineffective hematopoiesis, anemia, thrombocytopenia or neutropenia, and bone marrow dysplasia that is diagnosed as myelodysplastic syndromes. Multiple potential points of intervention are shown.

Specific molecular characteristics can be used to refine diagnostic classifications. MDS subtyptes can be defined entirely by specific genetic variants (such as *SF3B1*) or morphologically defined based on dysplasia in bone marrow cells.[24] The current WHO diagnostic classification (5th Edition) distinguishes MDS from AML based on the percentage of blasts (MDS, <20% blasts and AML, ≥20% blasts), although the criteria include that MDS patients with greater than 10% bone marrow myeloblasts may be classified as having AML for treatment purposes (ie, MDS with >10% blasts could be treated similarly to AML).[25]

After an MDS diagnosis is made, MDS is staged using risk classification schemas. Although WHO diagnostic criteria include subclassification of patients with MDS based on genetic and morphologic criteria for diagnostic purposes, the highly variable outcomes within these subgroups limit their prognostic value, and the WHO categorization has recently been simplified to distinguish patients with defining genetic abnormalities (such as *SF3B1*, deletion 5q, or *TP53*) or morphologically defined subtypes, stratified by low bone marrow blast count (<5%) or increased bone marrow blast counts (5%-19%).[23,26] The most well-studied and widely adopted prognostic systems are the International Prognostic Scoring System (IPSS)[27] and the revised IPSS (IPSS-R),[2] which is the current standard. Both the IPSS and IPSS-R stratify newly diagnosed untreated patients based on the presence and degree of anemia, thrombocytopenia or neutropenia, myeloblast percentage, and karyotypic abnormalities.

The IPSS-R defines 5 risk groups based on a numbered point value for each prognostic variable that is summed to attain a total score ranging from 0 to 10 (**Table 2**). Patients are often classified with either lower- or higher-risk MDS, with one analysis identifying the optimal raw score cut point as 3.5 or less (lower-risk) or greater than 3.5 (higher-risk), with the very high risk defined as score greater than 6.[28] More recent studies have used artificial intelligence and machine-learning platforms to incorporate molecular abnormalities, pathologic variables, and clinical variables to provide more accurate prognostic estimates that are dynamic, with the ability to estimate survival at any time point in a patient's disease course, and that offer predictions that do not depend on the type of therapy received.[29,30] MDS prognostic scoring systems also help in selecting the most appropriate therapy.

Table 1. Common Presenting Signs and Symptoms of Myelodysplatic Syndromes

Symptom or sign	Prevalence, %[a]
Fatigue	55
Fever/infection	15
Bleeding	8
Loss of appetite	Not available
Bruising	Not available
Anemia, hemoglobin <10 g/dL	52
Thrombocytopenia, platelet count $<100 \times 10^9$/L	40
Neutropenia, neutrophil count $<800 \times 10^9$/L	18

[a] Values have been rounded and are therefore approximate.

Box. Commonly Asked Questions

How Are the Myelodysplastic Syndromes (MDS) Diagnosed?
Answer: A bone marrow biopsy and aspirate are necessary to make the diagnosis of MDS. The WHO criteria for the diagnosis of MDS consist of anemia, thrombocytopenia or neutropenia that persists for 6 months or longer, greater than 10% bone marrow dysplasia in at least 1 cell lineage, and MDS-associated clonal cytogenetic abnormalities or molecular markers.

How Is MDS Staged?
Answer: After an MDS diagnosis is made, MDS is staged using risk classification schemas. The most well-studied and widely adopted prognostic systems are the International Prognostic Scoring System (IPSS) and the revised IPSS (IPSS-R), which is the current standard. Both the IPSS and IPSS-R stratify newly diagnosed, untreated patients based on the number and degree of anemia, thrombocytopenia, or neutropenia, myeloblast percentage, and karyotypic abnormalities.

What Is First-line Therapy for Patients With Higher-Risk MDS?
Answer: First-line initial therapy for patients with higher-risk MDS is use of the hypomethylating agents azacitidine, decitabine, or decitabine/cedazuridine. Patients with higher-risk MDS should be considered for hematopoietic cell transplantation soon after diagnosis.

Treatment

Treatment of Patients With Lower-Risk MDS

For patients with lower-risk MDS, no therapeutic intervention has been shown in a randomized clinical trial to improve overall survival compared with receiving no therapy. Therefore, treatment goals consist of reducing disease-related symptoms, lessening or eliminating transfusions, and minimizing morbidity associated with chronic anemia, thrombocytopenia, or neutropenia.[31,32] Because patients are often older and diagnosed with comorbid diseases, treatment toxicities must be balanced with any potential treatment benefits.[33]

Treatment selection for patients with lower-risk disease depends on whether the predominating bone marrow abnormality is anemia, thrombocytopenia, or neutropenia (**Table 3**). Most MDS patients have anemia, which is associated with a variety of adverse events including increased risk of falls, cardiopulmonary and cognitive decline, and reduced overall survival.[50,51] Erythropoiesis-stimulating agents (ESAs), such as recombinant humanized erythropoietin or the long-acting erythropoietin darbopoietin alfa, have been used for decades to treat anemia in patients with MDS. Compared with the doses used to treat anemia in patients with chronic kidney disease, higher doses of erythropoietin are typically used for MDS (eg, 60 000 units of recombinant humanized erythropoietin administered weekly or 500 µg of darbepoetin alfa administered every 3 weeks).[34,35] One pooled analysis of 1587 patients with lower-risk MDS randomized in clinical trials of ESAs, in which response criteria consisted of hematologic improvements of 1g/dL hemoglobin or greater or achievement of transfusion independence, demonstrated that erythropoietin was associated with a response in 39.5% of patients.[36] A more recent randomized, blind trial of 147 patients with lower-risk MDS with hemoglobin levels of less than 10 g/dL and serum erythropoietin levels less than 500 IU/L

Table 2. Risk Categories, Scores, and Survival for the International Prognostic Scoring System Revised[a]

Risk group	Very low	Low	Intermediate	High	Very high
Risk score	≤1.5	>1.5-3	>3-4.5	>4.5-6	>6
Median survival, y	8.8	5.3	3.0	1.6	0.8

[a] Based on additive scores (total score range, 0-10) from the Revised International Prognostic Scoring System.[2] Scores for cytogenetic risk groups are indicated by 0 (very good: −Y, del[11q]); 1 (good or normal: del[5q], del[12p], del[20q], double including del[5q]); 2 (intermediate: del[7q], +8, +19, i[17q], any other single or double independent clones); 3 (poor: −7, inv[3]/t[3q]/del[3q], double including −7/del[7q], complex of 3 abnormalities); and or 4 (very poor or complex: >3 abnormalities). Scores for bone marrow blasts are indicated by 0 (≤ 2%), 1 (>2%-<5%), 2 (5%-10%), and 3 (>10%). Scores for hemoglobin are indicated by 0 (≥10 g/dL), 1 (8 g/dL-<10 g/dL), or 1.5 (<8 g/dL). Scores for platelets are indicated by 0 (≥100/mL^3), 0.5 (50/mL^3-<100/mL^3), or 1 (<50/mL^3). Scores for absolute neutrophil count are indicated by 0 (≥0.8/mL^3) or 0.5 (<8/mL^3).

reported that darbepoetin attained a hematologic improvement response rate of 14.7% compared with 0% in the placebo group (P = .02)[35] Patients with lower baseline serum erythropoietin levels (<200 IU/L) and minimal or absent history of blood transfusion had a higher rate of benefiting from ESAs.[52] Mean duration of response to ESAs ranged from 8 to 23 months.[35,53]

Patients with lower-risk MDS with ring sideroblasts (often associated with the *SF3B1* variant)[54] and anemia with disease either refractory to ESA or unlikely to respond to ESA can be treated with the drug luspatercept. Luspatercept is a recombinant fusion protein that binds transforming growth factor B superfamily ligands to reduce SMAD2 and SMAD3 signaling in late stages of erythropoiesis.[37] In a randomized, blind, placebo-controlled study of 229 lower-risk patients with MDS and ring sideroblasts who were dependent on red blood cell transfusions, luspatercept significantly improved transfusion independence lasting at least 8 weeks compared with placebo (38% vs 13%; P < .001).[55] The median duration of response was 30.6 weeks. This study highlighted the importance of placebo control groups in clinical trials of MDS, as transfusion needs vary over time and can be reduced for limited time periods without intervention, potentially suggesting or augmenting apparent efficacy of a drug.

Anemia is the most common cytopenia in lower-risk MDS patients with a del(5q) cytogenetic abnormality.[56] Lenalidomide is an immunomodulatory derivative of thalidomide that acts through a defect in ribosomal protein function, via ubiquitination and degradation of CK1 alpha, to achieve cell apoptosis.[57,58] One double-blind study randomized 205 red blood cell transfusion–dependent del(5q) patients with MDS to receive lenalidomide at 2 different doses or to placebo.[38] More patients in the lenalidomide groups became transfusion independent for at least 26 weeks (the primary end point) vs those receiving placebo (lenalidomide at 1 dose [56.1%] and at a different dose [42.6%] vs placebo [5.9%]; both P < .001).[38] A separate study reported a median duration of response of greater than 2 years. Grade 3 or 4 neutropenia occurred in more than 70% of treated patients and thrombocytopenia (which is predictive of erythroid response)[59] occurred in more than one-third. Like thalidomide, lenalidomide is teratogenic.

As many as two-thirds of patients with MDS have thrombocytopenia prior to treatment.[60] Romiplostim and eltrombopag bind and activate the thrombopoietin receptor on megakaryocyte precursors, promoting cell proliferation.[61] Both drugs have been studied in randomized trials in patients with lower-risk MDS and thrombocytopenia.[39,40] In a clinical trial in which 250 patients with lower-risk MDS and baseline platelet counts of less than 20 000/mL^3 were randomized to receive romiplostim or placebo, romiplostim significantly reduced platelet transfusions compared with placebo (1250.5 compared with 1778.6 platelet transfusions per 100 patient-years (P < .0001).[39] In a clinical trial of 90 patients with lower-risk MDS and platelet counts of less than 30 000/mL^3, eltrombopag improved platelet counts significantly more than placebo at a median of 11 weeks follow-up (47% vs 3%; P = .0017).[40] In both clinical trials, rates of transformation to AML were higher in patients who received treatment than in patients who did not—particularly in patients who had MDS with excess myeloblasts prior to starting therapy, though rates of AML were not significantly different between patients treated with romiplostim and placebo with 5 years of follow-up (10 of 167 patients (6%) in the romiplostim-treated group vs 4 of 83 patients (4.9%) in patients receiving placebo, hazard ratio (HR, 1.20 [95% CI, 0.38-3.84]).[41] Therefore, thrombopoietin receptor agonists are often avoided in patients with excess blasts, except in palliative settings.[62]

Patients with multiple cytopenias, defined as combinations of anemia, thrombocytopenia, and neutropenia, are commonly treated with a hypomethylating agent such as intravenous or subcutaneous azacitidine, decitabine, or the oral decitabine-cedazuridine. These drugs work through multiple mechanisms including DNA methyltransferase inhibition, differentiation, and direct cytotoxicity.[63] While few randomized trials of these agents have been completed in patients with lower-risk MDS, uncontrolled clinical trials reported response rates similar to those seen in patients with higher-risk disease (see next section) for a median of 12 to 18 months.[44,45] Similar efficacy may be seen with shorter dosing schedules (eg, 3 days of treatment rather than 5 or7 days in a 28-day cycle).[64] For a select group of patients, such as those with MDS that may in part be autoimmune mediated or for those with a hypocellular bone marrow similar to aplastic anemia, immunosuppressive therapies, such as antithymocyte globulin-based regimens, may be effective in as many as one-third of patients, with a duration of response of approximately 1.5 years.[42,43]

Treatment of Patients With Higher-Risk MDS

For patients with higher-risk MDS, for whom median survival is approximately 6 months, treatment should be initiated promptly with goals of delaying transformation to AML, prolonging survival, and improving quality of life through improvement of peripheral blood counts.[65]

First-line initial therapy for patients with advanced MDS are the hypomethylating agents. In an open-label, phase 3 trial, 358 patients with higher-risk MDS were randomized to receive either azacitidine or conventional care. Of those randomized to conventional care, 59% received best supportive care, 27% received low-dose

Table 3. Commonly Used Treatments for Lower- and Higher-Risk MDS

Drug name[a]	Indication[b]	Mechanism of action	Typical dose	Efficacy from RCTs[c]	Adverse effects, %
Erythropoiesis-stimulating agents (erythropoietin, darbepoietin)[34-36]	Lower-risk MDS, anemia	Binds to erythropoietin receptor on red blood cells, activating signal transduction pathways to stimulate division and differentiation of erythroid progenitors	Erythropoietin, 60 000 units/wk Darbepoietin, 500 µg every 2-3 wk	Of 147 participants, 14.7% treated with darbepoetin attained hematologic improvement compared with 0% for those randomized to placebo at 24-wk follow-up. Improvement was defined as an increase in hemoglobin of 1.5g/dL or red blood cell transfusion independence. During a 48-wk open-label study period, hematologic improvement rates increased to 35% for those treated with darbepoetin, lasting a mean of 235 d.[35]	Fatigue, 17 Pyrexia, 9 Back pain, 8 Headache, 7
Luspatercept[37]	Lower-risk MDS, anemia in patients with ring sideroblasts	Binds transforming growth factor B superfamily ligands to promote late stages of erythropoiesis	1.0-1.75 mg/kg every 3 wk	Of 229 participants, 38% treated with luspatercept attained red blood cell transfusion independence compared with 13% for those receiving placebo, lasting a median of 31 wk.	Fatigue, 27 Diarrhea, 22 Nausea, 20 Dizzyness, 20 Back pain, 19
Lenalidomide[38]	Lower-risk MDS, anemia in patients with the deletion 5q cytogenetic abnormality	Works through a defect in ribosomal protein function via ubiquitination and degradation of casein kinase 1 alpha	10 mg/d for 21 days of a 28-d cycle	Of 205 participants, 56% treated with lenalidomide (10 mg) attained red blood cell transfusion independence compared with 43% treated with lenalidomide (5 mg) and 3% treated with placebo, for those receiving placebo, lasting for a median duration that was not reached.	Neutropenia, 75 Thrombocytopenia, 41 Deep venous thrombosis, 6 Teratogenicity[d]
Thrombopoietin receptor agonists (romiplostim, eltrombopag)[39]	Lower-risk MDS without excess blasts, thrombocytopenia	Binds to and activates the thrombopoietin receptor on megakaryocyte precursors, promoting cell proliferation	Eltrombopag, 50-300 mg/d Romiplostim, 750-1000 µg/wk[40]	Of 250 participants, the clinically significant bleeding event rate/100 patient-years for those receiving romiplostim with baseline platelet counts >20 × 10^9/L was 79.5 compared with 226.4 for those receiving placebo. Platelet transfusion event rates/100 patient-years for those receiving romiplostim with baseline platelet counts <20 × 10^9/L were 1251 compared with 1779 for those receiving placebo. No response duration data were available.[39]	AML transformation in 6-7 (rates became similar between romiplostim and placebo groups over time)[41]
ATG-based regimens such as ATG + cyclosporine[42,43]	Lower-risk MDS, multiple cytopenias	T-cell depletion through complement-dependent lysis and T-cell activation and apoptosis	2.5 mg/kg daily for 4 doses	Of 88 participants, 31% treated with ATG + cyclosporine attained hematolopgic improvement compared with 9% treated with best supportive care, lasting for a median of 16.4 mo.[43]	Neutropenia, 38 Thrombocytopenia, 53 Anemia, 47 Febrile reaction, 11
Hypomethylating agents (azacitidine, decitabine, decitabine-cedazuridine)[44-49]	Lower-risk MDS, multiple cytopenias, higher-risk MDS	DNA methyltransferase inhibition, differentiation, and direct cytotoxicity	Azacitidine, 75 mg/m^2 daily for 3-7 days of a 28-d cycle Decitabine, 20 mg/m^2 daily for 3-5 days of a 28-d cycle[49] Decitabine-cedazuridine, 35 mg-100 mg/d for 5 days of a 28-d cycle[45]	Of 358 participants, 29% treated with azacitidine attained a complete or partial response compared with 12% of those treated with conventioal care regimens (low-dose cytarabine, cytarabine + daunorubicin, or best supportive care). Median overall survival was 24 mo for those receiving azacitidine compared with 15 mo for those receiving conventional care regimens.[47]	Neutropenia, 91 Thrombocytopenia, 85 Anemia, 57[46]

Abbreviations: ATG, antithymocyte globulin; MDS, myelodysplastic syndromes; RCT, randomized clinical trial.

[a] For some drugs, multiple studies are cited in addition to the study from which RCT efficacy results are shown.

[b] Lower-risk MDS is defined as patients with a Revised International Prognistic Scoring System (IPSS-R) score of 3.5 or less, higher-risk as having a score greater than 3.5 to less than 6, and very high risk is indicated by a score greater than 6 (score range, 0-10)6. Primary end points in trials for lower-risk MDS include hematologic improvement (as defined). For higher-risk MDS, primary end points include complete and partial response rates, hematologic improvement, and overall survival.

[c] Column 4 cites the specific study associated with the RCT efficacy results.

[d] Teratogenicity (birth defect) rates are not available, as they were demonstrated in preclinical animal models.

cytarabine, and 14% received intensive chemotherapy.[46] At a median follow-up of 21.1 months comparing patients randomized to azacitidine vs conventional care, complete and partial responses occurred in 29% vs 12%, and median survival was 24.5 months vs 15 months (HR, 0.58 [95% CI, 0.43-0.77]; P = .0001). Multiple subsequent randomized trials that compared azacitidine-based combinations with azacitidine alone showed more modest median gains in overall survival (ie, typically 15-18 months) in patients treated with either azacitidine alone or azacitidine combinations.[47,48] More favorable response rates to azacitidine-based regimens may be associated with treating on schedule (ie, without delaying any treatments) without reduction in dose for at least 6 cycles of therapy.[66]

In a randomized clinical trial, decitabine had similar overall survival rates in 233 patients with higher-risk MDS compared with best

supportive care (10.1 months vs 8.5 months(HR, 0.88 [95% CI, 0.66-1.17]; $P = .38$). A subsequent analysis of SEER (Surveillance, Epidemiology, and End Results Program)-Medicare data for 2025 patients treated with azacitidine or decitabine, however, showed no difference in survival for patients treated with either drug (median survival for azacitidine-treated patients was 15 months compared with 13 months for decitabine-treated patients; in multivariate analyses, HR, 1.06 [95% CI, 0.94-1.19]).[67] Thus, both agents are used in this patient population. Multiple clinical trials of hypomethylating agent-based combinations of drugs have not demonstrated a survival benefit when compared with a single therapy, likely due to greater toxicities and dosing modifications that limit drug exposure in patients treated with combinations of drugs.[47,48,68] Once hypomethylating agents have been determined to be ineffective for a particular patient, no standard therapies for patients with higher-risk MDS are available, although cytotoxic chemotherapy such as cytarabine (in combination with venetoclax in patients with AML following MDS) may be used, and variant-targeted treatments are being explored.[69,70] Median survival for these patients is typically less than 6 months.[71]

The only potentially curative treatment for MDS is hematopoietic cell transplantation (HCT). Patients with higher-risk MDS should be considered for HCT at the time of diagnosis. Patients with lower-risk MDS are considered for HCT with certain higher-risk features (such as poor-risk molecular variants) or after non-HCT therapies have failed. Two decision analyses, one including younger patients who underwent ablative conditioning HCT and the other consisting of older patients who received a reduced intensity conditioning HCT, demonstrated that transplant soon after an MDS diagnosis was associated with better survival in patients with higher-risk MDS but not lower-risk MDS.[72,73] A recent biologic assignment trial in which patients received a transplant only if they had a matched donor compared outcomes in 384 patients with higher-risk MDS receiving reduced-intensity HCT with patients treated with hypomethylating agents or best supportive care.[74] The adjusted overall survival rate at 3-year follow up was 47.9% in those undergoing HCT compared with 26.6% in patients who received hypomethylating agents or best supportive care (P <.001). Illustrating the complexity of interpreting biologic randomization trials of HCT in MDS, which are intended to compare patients undergoing HCT with those receiving another therapy, more than 50% of patients in the transplant group of the trial also received a hypomethylating agent, while only 58% of patients who did not receive an HCT were confirmed to have been treated with hypomethylating agents despite this being the standard of care for higher-risk patients with MDS. A separate observational study from the Center for International Bone Marrow Transplant Research reported similar overall survival for patients aged 55 to 64 years compared with those aged 65 years and older, indicating that older age should not preclude consideration of HCT.[75] The potential risks and benefits of transplant should be discussed with patients who have higher-risk MDS soon after diagnosis, and individual treatment goals must be considered.

Prognosis

Prognostic scores such as the IPSS-R are calculated soon after diagnosis and help with therapy selection. Patients with lower-risk MDS have a median survival of 3 to 10 years, while patients with higher-risk disease have a median survival less than 3 years.[2] Given the poor overall prognosis of MDS, similar to more aggressive cancers, discussion of prognosis and patient goals of care is essential. Only treatment with azacitidine and HCT have been shown to alter the natural history of the disease in patients with higher-risk MDS.

Limitations

This review has several limitations. First, the quality of included articles was not evaluated. Second, some relevant references may have been missed. Third, relatively few randomized clinical trials were identified in the literature search.

Conclusions

MDS are diagnosed in approximately 4 per 100 000 people in the United States and are associated with decreased survival. Treatments are tailored to the patient's disease characteristics and comorbidities and range from supportive care with or without erythropoiesis-stimulating agents for patients with low-risk MDS to hypomethylating agents, such as azacitidine or darbopoeitin, for patients with high-risk MDS. HCT is potentially curative and should be considered for patients with higher risk MDS at the time of diagnosis.

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