Statement of Editorial Purpose

The Hospital Physician Hematology Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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The Myelodysplastic Syndromes

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Cover Illustration by Christine Armstrong
The Myelodysplastic Syndromes

Gregory A. Abel, MD, MPH

INTRODUCTION

The myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis and a tendency to transform to acute myelogenous leukemia (AML). These disorders range in clinical severity from incidentally found disease manifesting as mild anemia, to highly symptomatic MDS characterized by severe anemia, neutropenia, and/or thrombocytopenia and their sequelae (hemorrhage and infection). In general, the syndromes are distinguishable from de novo AML by the relative stability of the constituent blood counts over time,\(^1\) which provides a sizable window for treatment. However, MDS can be extremely difficult to manage given its predilection for elderly patients who often harbor symptomatic comorbid conditions and have difficulty tolerating chemotherapy.

Despite these challenges, there have been recent improvements in the way that MDS is diagnosed, classified, and treated. Although supportive care (eg, treatment of infections, red blood cell [RBC] and platelet transfusions, hematopoietic growth factors) has long been the standard for management of MDS,\(^2\) there are now 3 medications specifically approved for its treatment, several others that are routinely used as part of its comprehensive management, and many others currently under investigation. For younger patients with high-risk disease, hematopoietic stem cell transplantation is also an option. This manual will review the clinical evaluation, diagnosis, and treatment options for patients with MDS.

EPIDEMIOLOGY AND PATHOGENESIS

Although rare, MDS is thought to be underreported due to its indolent nature and predilection for elderly patients who may die of other causes before the syndrome is diagnosed. Incidence rates for MDS first became reportable to the National Cancer Institute’s Surveillance Epidemiology and End Results Program (SEER) in 2001; in 2003, there were an estimated 10,300 cases per 100,000 persons per year.\(^3\) The incidence of MDS increases with age: age-specific incidence rates are thought to be about 5 per 100,000 for persons aged 50 to 59 years as compared to 49 per 100,000 for persons aged 70 to 79 years.\(^4\)

- Are there any known predisposing factors that cause MDS?

Most cases of MDS are thought to be idiopathic, although some predisposing risk factors have been indentified. These include age, male gender, excessive alcohol use, exposure to radiation, exposure to immunosuppressive therapy, certain genetic syndromes (eg, Down syndrome, Fanconi anemia), and occupational chemical exposures (eg, lead, benzene).\(^2\) When a clear association is found, the syndrome is called secondary MDS (s-MDS). Radiotherapy and medications used to treat malignancy (eg, alkylating agents) have also been implicated in the etiology of a subset of s-MDS called therapy-related MDS (t-MDS).\(^5,6\) t-MDS is even more difficult to treat than spontaneously occurring MDS and has a higher likelihood of transformation to AML.\(^6,7\)

A multistep genetic progression model has been proposed for MDS, given that older age and certain types of radiation/chemotherapy are associated with the development of clinically significant disease, and that MDS has a tendency to progress to AML. In this model, inherited or acquired genetic defects conspire with additional environmentally caused genetic events to cause gains and/or losses of specific chromosome regions or functionality in hematopoietic stem cells.\(^8\) As with other types of malignancy, defective clones predominate through competitive survival advantage and excessive proliferation.\(^9\) Thus, disease-altering treatments for MDS are focused on either replacing the defective clone with a healthy one (eg, stem cell transplantation) or regulating genetic and epigenetic events that contribute to the maintenance of that clone (eg, DNA methyltransferase inhibitors, histone deacetylase inhibitors).

In MDS, malignant clones have a survival advantage but are defective in completing normal hematopoiesis. The syndrome is unique among hematologic malignancies in that it possesses a seemingly contradictory state of a normocellular or hypercellular bone marrow that coexists with progressive peripheral cytopenias.\(^10\)
However, MDS sometimes presents with a more hypoplastic marrow, which some authors suggest may be caused by immune dysregulation (perhaps associated with human leukocyte antigen [HLA]-DR, younger age, and the presence of paroxysmal nocturnal hemoglobinuria [PNH] clones) rather than cumulative genetic defects.10–12

CLINICAL EVALUATION AND DIAGNOSIS OF MDS

CASE PRESENTATION

A 74-year-old man closely followed by his primary care physician for adult-onset diabetes mellitus is found to have a mild normocytic anemia on routine laboratory work-up (hematocrit, 33% [normal, 41%–50%]). He is asymptomatic. A complete blood count (CBC) performed 2 years earlier during a hospital admission for pneumonia was notable for an elevated total white blood cell (WBC) count with neutrophilia, but WBC differential, hemoglobin, mean corpuscular volume (MCV), and platelet count were normal.

The patient’s medical history is notable for well-controlled diabetes, mild hypercholesterolemia, and an appendectomy at age 22 years. His medications include a statin, an oral antihyperglycemic, low-dose angiotensin–converting enzyme inhibitor, and a baby aspirin. His family history is notable for diabetes and coronary artery disease in his father and diabetes in his 1 sibling, a half-brother. He is a retired accountant in a monogamous, long-term relationship, has never smoked, admits to only social drinking, and reports no unusual chemical or infectious exposures or travel. He feels completely well and denies fatigue, abdominal pain, melena, hemosiderin, hematemesis, fevers, or night sweats. Physical examination is normal except for mild pallor; specifically, he exhibits no evidence of hepatosplenomegaly or lymphadenopathy.

• What is the typical presentation for patients with MDS?

Most patient with MDS present with anemia, which can be symptomatic (eg, fatigue, malaise, pallor, dyspnea on exertion) or found incidentally. Laboratory findings of leukopenia and thrombocytopenia are less common; presentations associated with symptomatic deficiencies in these cell lines (eg, clinically significant bruising, bleeding, infection) are uncommon.13,14 Patients with chronic myelomonocytic leukemia (CMML) may present with asymptomatic monocytosis. Rarely (~15%), patients present with associated autoimmune phenomena (eg, cutaneous vasculitis, relapsing polychondritis).15 More commonly, symptomatic presentations represent an exacerbation of underlying comorbidities (eg, congestive heart failure, chronic obstructive pulmonary disease) by the presence of ineffective hematopoiesis.

• If MDS is suspected, what details should be sought on history and physical examination?

The clinical history obtained from a patient with suspected MDS should focus on the severity and pace of the associated cytopenias, the patient’s current transfusion requirements, history of recent infections, and possible bleeding episodes. In addition, a detailed assessment of comorbidities; a history of recent exposures (including sexual history with the goal of ruling out HIV); and a review of new medications, current performance status, and presence of possible sibling donors should be undertaken. The physical examination is seldom revealing, except for evidence of anemia and thrombocytopenia. In 1 series, 60% of patients had pallor and 26% had purpura and/or petechiae.13 Hepatosplenomegaly is uncommon in MDS with the exception of CMML, where patients may present with splenomegaly, hepatomegaly, lymphadenopathy, and cutaneous infiltrates.16 Patients with proliferative CMML can also present with clinically apparent periocular effusion and ascites, most often associated with marked monocytosis.17

CASE CONTINUED

The patient’s current CBC is normal except for the low hematocrit (32%) and a mildly elevated MCV (101 fl [normal, 80–100 fl]). Additional laboratory studies reveal normal electrolytes, renal function, vitamin B12, methylmalonic acid (MMA), folate, iron, total iron-binding capacity (TIBC), and lactate dehydrogenase (LDH); normal serum protein electrophoresis; and a negative Coombs’ test. Both ferritin and erythropoietin levels are slightly elevated at 220 ng/mL (normal, 15–200 ng/mL) and 42 IU/L (normal, 5–36 IU/L), respectively. Urine shows moderate microalbuminuria. A reticulocyte count is in the low normal range when adjusted for the level of anemia. A chest radiograph following the patient’s recovery from pneumonia 2 years prior is within normal limits. He is referred for endoscopy and colonoscopy, which are both unrevealing.

• Which diagnostic studies should be undertaken in patients with suspected MDS?

Patients with suspected MDS require a full anemia work-up, as the etiology of anemia may be multifactorial. Appropriate laboratory studies include CBC with
Table 1. Baseline Work-up for Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination including documentation of transfusion history</td>
</tr>
<tr>
<td>Complete blood count including platelet, differential, and reticulocyte count</td>
</tr>
<tr>
<td>Examination of peripheral smear</td>
</tr>
<tr>
<td>Bone marrow aspiration with iron stain, biopsy, and cytogenetics</td>
</tr>
<tr>
<td>Serum erythropoietin level (prior to transfusion)</td>
</tr>
<tr>
<td>Folate, vitamin B₁₂, and methylmalonic acid levels</td>
</tr>
<tr>
<td>Iron, total iron-binding capacity, and ferritin levels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sometimes helpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human leukocyte antigen (HLA) typing if hematopoietic stem cell transplant candidate</td>
</tr>
<tr>
<td>HLA typing if indicated for platelet support</td>
</tr>
<tr>
<td>HLA-DR, DQ typing</td>
</tr>
<tr>
<td>HIV testing</td>
</tr>
<tr>
<td>Evaluation for 5q31–33 translocations and/or platelet-derived growth factor receptor β gene rearrangements (in chronic myelomonocytic leukemia)</td>
</tr>
<tr>
<td>Flow cytometry for paroxysmal nocturnal hemoglobinuria clones</td>
</tr>
<tr>
<td>Flow cytometry for large granular lymphocytic disease</td>
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</tbody>
</table>


differential and MCV (elevated MCV is a hallmark of MDS); reticulocyte count to evaluate for ineffective erythropoiesis; vitamin B₁₂, folate, and MMA levels to rule out nutritional deficiency as a cause of anemia; serum erythropoietin (prior to transfusion if possible); serum protein electrophoresis to rule out myeloma; serum iron, ferritin, and TIBC to assess for baseline iron overload or deficiency; and Coombs’ test, haptoglobin, and LDH levels to rule out hemolysis as a cause of anemia. In addition, some suggest RBC folate levels be measured, and in younger patients, a hemoglobin electrophoresis may be performed to rule out congenital anemia. Blood urea nitrogen and creatinine levels should be obtained to rule out anemia of chronic renal insufficiency. A peripheral smear should be examined, as it may reveal misshapen macrocytic RBCs, hypogranular granulocytes with pseudo-Pelger-Huët cells, and giant platelets. Testing for viral infections including HIV and for toxicities (eg, medication levels or lead exposure) and flow cytometry for PNH (especially in younger patients) also may be appropriate, depending on the patient’s history, to assess for alternative causes of anemia. In patients with thrombocytopenia who may be candidates for bone marrow transplantation, cytomegalovirus status and full HLA typing (A, B, C, DR, and DQ) should be performed on the patient and full siblings.

- Should all patients suspected of having MDS undergo bone marrow examination?

Whether or not a bone marrow examination is indicated in all cases of suspected MDS is controversial. The procedure can be difficult in elderly patients who may not tolerate it, and confirming the diagnosis through visualization of the marrow often does not change management in early-stage disease (which is largely supportive). Protecting patients from the discomfort and possible morbidity of a procedure that will not alter management seems reasonable. However, pathologic examination of the bone marrow is the only way to classify the type of MDS and determine the prognosis; it also may aid in selecting the appropriate therapy. For example, therapy with lenalidomide is most appropriate if a patient has the 5q–chromosomal abnormality, which can only be determined with bone marrow cytogenetics. Indeed, cytogenetic studies are increasingly guiding both prognosis and treatment for MDS. Thus, the National Comprehensive Cancer Network’s (NCCN) practice guidelines recommend a baseline bone marrow aspiration and biopsy for all patients with suspected MDS (Table 1). When ordering bone marrow aspiration and biopsy, iron staining, cytogenetic testing, and, in the case of CMML, assessments of 5q31–33 translocations and/or platelet-derived growth factor receptor β (PDGFRβ) gene rearrangements should be specifically requested.

In MDS, the bone marrow usually demonstrates normal or increased cellularity as well as several morphologic abnormalities (Figure). These abnormalities may include megaloblastic erythroid precursors with multiple or misshapen nuclei and cytoplasmic blebbing, ringed sideroblasts (RBC precursors laden with iron-rich mitochondria), and granulocytic precursors with asynchronous maturation of the nucleus and cytoplasm. Megakaryocytes are often small and have few nuclear lobes, sometimes in the so-called triple “pawnpiece” shape. Foci of immature myeloid elements may be located far away from the bone trabeculae, referred to as abnormal localization of immature precursors (ALIP). In advanced cases, the number of bone marrow blasts can be significantly increased. Cytogenetic abnormalities, their prevalence, and significance as single defects are listed in Table 2.

CLASSIFICATION OF MDS

MDS was first reported in 1953 by Block et al, who
The Myelodysplastic Syndromes

described a phase of bone marrow failure in a cohort of patients who subsequently developed AML. Several names were suggested for this condition, including the oxymoronic phrase “smoldering acute leukemia.”

In the late 1970s and early 1980s, an international consensus conference of hematologists and hema-topathologists created the French-American-British (FAB) classification system, which includes 5 categories of MDS based on light microscopic morphology of bone marrow aspirates: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and CMML (Table 3). The FAB system has been used in clinical practice and for research purposes and also has become a crude measure of prognosis (with RA being unlikely to progress to AML, and RAEB-T being most likely). Problems with the FAB classification include its inability to account for new molecular diagnostic techniques, the wide range of bone marrow blasts (5%–20%) associated with RAEB, and its inability to clearly distinguish RAEB-T from AML (eg, RAEB-T class was permitted to have Auer rods, the hallmark of AML).

To address these issues, the World Health Organization (WHO) created a new classification scheme, reorganizing MDS into 8 categories and placing CMML into a new group of overlapping myelodysplastic/myeloproliferative syndromes (Table 4). Several other differences exist between the FAB and the WHO classification systems. First, the WHO system distinguishes between unilineage dysplasia with low blast count (RA in the WHO system) and multilineage dysplasias with low blast count (refractory cytopenia with multilineage dysplasia [RCMD] in the WHO system; both were RA in the FAB system), as many providers believe that the latter has a worse prognosis. The WHO system also created a new category called 5q− syndrome (isolated deletion of 5q and < 5% blasts) as well as another called MDS unclassified (for unilineage dysplasias that do not include the erythroid line). Next, the WHO system classifies all syndromes with inversion 16, translocation 8/21, translocation 15/17, or 11q23 abnormalities as AML regardless of the blast count. Finally, the WHO system classifies patients with greater than 20% bone marrow blasts as having AML (21%–30% in the FAB system was considered to be RAEB-T). Although some authors still suggest reporting and using both systems, the WHO system has become increasingly accepted as the standard and has been shown to correlate more closely with prognosis than the FAB system.
CASE CONTINUED

The patient is referred to a hematologist who performs a bone aspiration and biopsy. Pathology reveals a moderately hypercellular marrow showing trilineage hematopoiesis with mild dysgranulopoiesis, including hypersegmented and occasional hyposegmented forms, some small megakaryocytes, and some abnormal localization of precursors. However, a definitive morphologic diagnosis of MDS is not made, and the consulting pathologists suggest that either transient nutritional deficiency or infection may be responsible for the patient’s anemia. Cytogenetics are normal, and there are 2% blasts (normal). At this point, the patient’s only hematologic abnormality is a hematocrit of 32%. He continues to feel well. A watchful waiting strategy, with blood counts obtained once per month, is initiated.

After approximately 5 months of stable blood counts, the patient is admitted to the hospital with a non-ST elevation inferior myocardial infarction. His hematocrit is 31% at the time (with slightly elevated WBC and platelet counts), and his MCV has risen to 105 fL; repeat vitamin B12, folate, and MMA levels are normal. β-Blocker therapy is initiated, and the patient tolerates cardiac rehabilitation well. The following month after rehabilitation, his hematocrit is only 29%, so he is initiated on darbepoetin alfa (a repeat serum erythropoietin is 90 IU/L). He responds well to erythropoietin therapy for the next 6 months, maintaining a hematocrit in the 33% to 35% range.

At 1 year from his original presentation, the patient’s monthly laboratory work shows his platelet count has decreased to 120 × 10^9/µL (normal, 150–350 × 10^9/µL). Hematocrit is 33%, and WBC count is within normal limits. The hematologist performs a repeat bone marrow aspiration and biopsy, which shows 4% blasts with trilineage dysplasia consistent with the WHO category RCMD. There are no ringed sideroblasts, and cytogenetics are again normal. Within a month, the patient develops atrial fibrillation and is started on warfarin. His monthly blood counts show his hematocrit to be 29% despite continued erythropoietin therapy. His platelet count has also dropped to 85 × 10^9/µL. Now that the patient has a definitive diagnosis of MDS, he wants to know what his prognosis is.

- **What are the criteria for determining prognosis for patients with MDS?**

**The International Prognostic Scoring System (IPSS)**

Although a sizable percentage of patients with MDS will progress to AML or die of infections or bleeding, variable clinical outcomes have been observed.² Of the several prognostic scoring systems that have been developed, the IPSS has had the widest success (Table 5). The IPSS was developed at an international MDS risk analysis workshop in 1996 that pooled data from 7 MDS studies (n = 816).¹³ It should be noted that the IPSS used survival data specifically assessed from the time of presentation to a tertiary center and thus may underestimate survival for indolent disease that was suspected but not immediately referred.

The IPSS focuses on the percentage of bone marrow blasts (< 5%, 5%–10%, 11%–20%, and 21%–30%; note that this system was developed before the WHO classification system considered this last category AML),

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**Table 2. Common Cytogenetic Abnormalities in the Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Incidence (%)</th>
<th>Prognostic Significance as Single Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of all or part of chromosome 5</td>
<td>13</td>
<td>Favorable</td>
</tr>
<tr>
<td>Loss of all or part of chromosome 7</td>
<td>5</td>
<td>Poor</td>
</tr>
<tr>
<td>Trisomy 8</td>
<td>5</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Deletion of 17p</td>
<td>&lt; 1</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Deletion of 20q</td>
<td>2</td>
<td>Favorable</td>
</tr>
<tr>
<td>Loss of Y</td>
<td>10</td>
<td>Favorable</td>
</tr>
</tbody>
</table>


**Table 3. French-American-British (FAB) Cooperative Group Classification of the Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>FAB Subtype</th>
<th>Peripheral Blasts (%)</th>
<th>Bone Marrow Blasts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>&lt; 1</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>&lt; 1</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts (RAEB)</td>
<td>&lt; 5</td>
<td>5–20</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts in transformation (RAEB-T)</td>
<td>≥ 5</td>
<td>21–30</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia (CMML; &gt; 1000 monocytes/µL)</td>
<td>&lt; 5</td>
<td>5–20</td>
</tr>
</tbody>
</table>

**Table 4. World Health Organization Classification of the Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Erythroid dysplasia only; &lt; 5% blasts; &lt; 15% ringed sideroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>Anemia; no or rare blasts</td>
<td></td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenias (bicytopenia or pan cytopenia); no or rare blasts; no Auer rods; &lt; 1 × 10⁹/L monocytes</td>
<td>Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; &lt; 5% blasts; no Auer rods; &lt; 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>Anemia; no blasts</td>
<td>Erythroid dysplasia only; &lt; 5% blasts; &lt; 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)</td>
<td>Cytopenias (bicytopenia or pan cytopenia); no or rare blasts; no Auer rods; &lt; 1 × 10⁹/L monocytes</td>
<td>Dysplasia in ≥ 10% of cells in ≥ 2 myeloid cell lines; &lt; 5% blasts; no Auer rods; ≥ 15% ringed sideroblasts</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenias; &lt; 5% blasts; no Auer rods; &lt; 1 × 10⁹/L monocytes</td>
<td>Unilineage or multilineage dysplasia; 5%–9% blasts; no Auer rods</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenias; 5%–19% blasts; Auer rods may be present; &lt; 1 × 10⁹/L monocytes</td>
<td>Unilineage or multilineage dysplasia; 10%–19% blasts; Auer rods may be present</td>
</tr>
<tr>
<td>MDS associated with isolated deletion of 5q</td>
<td>Anemia; &lt; 5% blasts; platelets normal or increased</td>
<td>Normal to increased megakaryocytes with hypolobated nuclei; &lt; 5% blasts; no Auer rods; isolated deletion of 5q</td>
</tr>
</tbody>
</table>

Adapted with permission from Vardiman JW, Harris NL, Bruning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2297. © The American Society of Hematology.

The number of cytopenias (0/1 or 2/3), and the type of cytogenetics (good, intermediate, or poor). Cytopenias are defined as hemoglobin less than 10 g/dL, absolute neutrophil count less than 1800/µL, and platelet count less than 100 × 10⁹/µL. Scores are combined to assign patients to 1 of 4 categories (low, intermediate-1, intermediate-2, and high), as these categories were shown through survival analysis to correlate with both overall survival and risk of transformation to AML. Additionally, some authors have found that the IPSS might be made more useful by adding additional cytogenetic findings not detailed in the original (eg, deletion of 12p from the good category).²⁷

**Other MDS Prognostic Systems**

Despite the success and subsequent demonstrated reliability of the IPSS,³⁰ 3 other prognostic scoring systems deserve mention. The first, developed because cytogenetics are not always readily available at every center and due to the observation that the 2 intermediate IPSS groups may not be significantly different,³¹ focuses on bone marrow blast count (< 5% or ≥ 5%) and MCV (< 100 fl or ≥ 100 fl). In their analysis of 162 patients with MDS, Tannant and colleagues³¹ were able to classify patients into 3 predictive groups: low-risk (blasts < 5% and MCV > 100 fl; median survival, 4.9 yr), high-risk (blasts > 5% and MCV < 100 fl; median survival 0.5 yr), and intermediate risk (all others, median survival about 1.9 yr).

The second scoring system involves CMML, as proliferative type CMML (WBC count > 12.0 × 10⁹/µL) was excluded altogether from the IPSS analysis. In their review of 107 patients with CMML, Fenaux et al³² found that several factors predicted poor prognosis, such as excess bone marrow blasts, high peripheral blood monocytes, cytogenetic abnormalities, thrombocytopenia, and splenomegaly. Additionally, the most important predictive factors for survival at 1 year seemed to be absence of anemia and absence of elevated bone marrow blasts.

Finally, a WHO classification–based prognostic scoring system (WPSS) was recently proposed, partially because the IPSS is weighted heavily toward blast count and cytopenias at levels that may not be clinically significant (eg, platelets < 100 × 10⁹/µL).³³ The model, validated in 467 Italian patients with MDS, includes 3 variables: WHO subtype (replacing the blast percentage in IPSS), transfusion requirements (replacing the number of cytopenias in IPSS), and cytogenetics (as defined by IPSS). Based on points given for each of those variables, a patient is categorized into 1 of 5 groups (from very low risk to very high risk), with median survival of 138, 63, 44, 19, and 8 months, respectively. If further validated, the WPSS could replace the IPSS, as it makes better use of the WHO classification.²⁵
The patient is classified by his hematologist as being in the IPSS intermediate-1 risk group. The hematologist explains that given his current age of 75 years, he would be expected to have a median survival of 2.4 years and a 25% chance of progressing to AML within 3.3 years. At that visit, the patient’s hematocrit is 28%, and he has his first RBC transfusion to maintain the hematocrit at approximately 30%, per the patient’s cardiologist. A repeat ferritin is within normal limits. The patient is becoming increasingly thrombocytopenic (platelet count, $60 \times 10^3/\mu L$), and warfarin and aspirin are stopped. Darbepoetin therapy is also stopped, as it has become ineffective in this patient. The patient decides to defer any treatment decisions until after the holidays but needs to be transfused with RBCs another time before his next visit with the hematologist. At this visit, 14 months after his initial presentation with anemia, the patient and his hematologist consider treatment with a low-intensity agent.

### Hematopoietic Growth Factors

Most authors include the use of hematopoietic growth factors (eg, recombinant erythropoietin) as part of the supportive care strategy.35–37 Initiating such treatment may coincide with the onset of transfusion dependence or precede that state if a patient is symptomatic despite transfusion independence. Before commencing treatment, it is important to check the erythropoietin level. Although it is still reasonable to treat patients with either epoetin alfa or darbepoetin alfa if the native erythropoietin level is elevated (there can be a supraphysiologic effect of adding more), treatment of patients with levels greater than 500 IU/L is discouraged.1,38 If ferritin levels are low, iron should be repleted before beginning therapy. The iron balance should also be periodically monitored during therapy, as a therapy-related increase in the effective hematopoiesis may deplete iron stores.

If there is no response to recombinant erythropoietin alone, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor may be added for a synergistic effect, especially if the blast count is low.39 In patients who have more than 15% ringed sideroblasts (FAB system class RARS or WHO system classes RARS and RCMD-RS), G-CSF should be added upfront to recombinant erythropoietin.40 Use of growth factors has been shown not only to reduce transfusion requirements but also to improve quality of life for patients with MDS.41,42 Finally, treatment with growth factors should be terminated if they do not appear to have an effect; many MDS patients have growth factors added early in their course but needlessly continue on them even when the patients have become heavily transfusion dependent.

### SUPPORTIVE CARE

The standard of care for MDS has largely been supportive.1,2,34,35 Such supportive measures include clinical observation, regular monitoring of blood counts, RBC and platelet transfusions as needed, antibiotics for infections, and aminocaproic acid or other antifibrinolytic agents for uncontrolled bleeding. Ferritin levels should be periodically checked, as patients who are receiving transfusions may additionally need iron chelation. For lower-risk patients who are not symptomatic and do not need transfusions, supportive care makes sense as part of a watchful waiting strategy.

### What are the treatment approaches for patients with MDS?

### Hematopoietic Growth Factors

Most authors include the use of hematopoietic growth factors (eg, recombinant erythropoietin) as part of the supportive care strategy.35–37 Initiating such treatment may coincide with the onset of transfusion dependence or precede that state if a patient is symptomatic despite transfusion independence. Before commencing treatment, it is important to check the erythropoietin level. Although it is still reasonable to treat patients with either epoetin alfa or darbepoetin alfa if the native erythropoietin level is elevated (there can be a supraphysiologic effect of adding more), treatment of patients with levels greater than 500 IU/L is discouraged.1,38 If ferritin levels are low, iron should be repleted before beginning therapy. The iron balance should also be periodically monitored during therapy, as a therapy-related increase in the effective hematopoiesis may deplete iron stores.

If there is no response to recombinant erythropoietin alone, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor may be added for a synergistic effect, especially if the blast count is low.39 In patients who have more than 15% ringed sideroblasts (FAB system class RARS or WHO system classes RARS and RCMD-RS), G-CSF should be added upfront to recombinant erythropoietin.40 Use of growth factors has been shown not only to reduce transfusion requirements but also to improve quality of life for patients with MDS.41,42 Finally, treatment with growth factors should be terminated if they do not appear to have an effect; many MDS patients have growth factors added early in their course but needlessly continue on them even when the patients have become heavily transfusion dependent.

### What is the role of iron chelation for patients with MDS?

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**Table 5.** The International Prognostic Scoring System (IPSS) Risk-Based Classification System

<table>
<thead>
<tr>
<th>Overall IPSS risk score based on:</th>
<th>IPSS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blast (%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>0</td>
</tr>
<tr>
<td>5–10</td>
<td>0.5</td>
</tr>
<tr>
<td>11–20</td>
<td>1.5</td>
</tr>
<tr>
<td>21–30</td>
<td>2.0</td>
</tr>
<tr>
<td>Karyotype</td>
<td>IPSS score</td>
</tr>
<tr>
<td>Good prognosis (−Y, 5q−, 20q−)</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate prognosis</td>
<td>0.5</td>
</tr>
<tr>
<td>Poor prognosis (abn. 7; complex)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>IPSS score</td>
</tr>
<tr>
<td>None or 1 type</td>
<td>0</td>
</tr>
<tr>
<td>2 or 3 types</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall IPSS score and survival rate:</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0)</td>
<td>5.7 yr</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>1 (0.5 or 1.0)</td>
<td>3.5 yr</td>
</tr>
<tr>
<td>2 (1.5 or 2.0)</td>
<td>1.2 yr</td>
</tr>
<tr>
<td>High (≥ 2.5)</td>
<td>0.4 yr</td>
</tr>
</tbody>
</table>


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**TREATMENT**

**CASE CONTINUED**

The patient is classified by his hematologist as being in the IPSS intermediate-1 risk group. The hematologist explains that given his current age of 75 years, he would be expected to have a median survival of 2.4 years and a 25% chance of progressing to AML within 3.3 years. At that visit, the patient’s hematocrit is 28%, and he has his first RBC transfusion to maintain the hematocrit at approximately 30%, per the patient’s cardiologist. A repeat ferritin is within normal limits. The patient is becoming increasingly thrombocytopenic (platelet count, $60 \times 10^3/\mu L$), and warfarin and aspirin are stopped. Darbepoetin therapy is also stopped, as it has become ineffective in this patient. The patient decides to defer any treatment decisions until after the holidays but needs to be transfused with RBCs another time before his next visit with the hematologist. At this visit, 14 months after his initial presentation with anemia, the patient and his hematologist consider treatment with a low-intensity agent.
Iron Overload

Due to their need for chronic RBC transfusions, patients with MDS have a high risk for iron overload and its potential for damage to the liver, heart, and endocrine system. Removal of iron by chelation—in low-risk patients with a long expected survival—may not only reverse some of the secondary end-organ damage but also have a beneficial effect on the MDS course itself. Jensen and associates treated 11 MDS patients with deferasoxamine for up to 60 months, given subcutaneously for 5 to 7 nights weekly. Five patients became transfusion independent, and platelet and neutrophil counts increased in an additional 7 patients. The authors concluded that treatment with deferasoxamine itself might abate the progression of MDS. They subsequently demonstrated that cardiac iron was decreased as well, which indicates that chelation likely has true benefits in terms of end-organ damage.

The availability of oral chelators (eg, deferasirox) makes iron chelation much more attractive for patients with MDS. Although the NCCN guidelines recommend considering iron chelation with an oral agent, they also provide a few caveats. First, patients should have received 20 to 30 units of RBC transfusions before starting, and serum ferritin levels should be greater than 2500 µg/L. Second, serum ferritin levels should be monitored, with the goal of attaining a level less than 1000 µg/L. Finally, chelation therapy should be considered only for those patients with low-risk disease who are expected to enjoy a prolonged survival because therapy is associated with side effects, such as gastrointestinal upset. As with other noncurative therapies for MDS, the patient’s quality of life must be heavily considered in the treatment decision process.

LOW-INTENSITY THERAPY

For symptomatic patients with lower-risk disease (IPSS low and intermediate-1 groups), low-intensity therapy (eg, lenalidomide, azacytidine, decitabine) should be considered after therapy with recombinant growth factors has failed. As low-risk disease is relatively indolent, the goals of therapy are hematologic improvement and improvement in quality of life, although therapy also may affect a change in the disease course. Low-intensity therapy also may be an option for patients presenting with clinically significant thrombocytopenia or neutropenia, as hematopoietic growth factors often have little effect in such presentations.

5q− MDS and Lenalidomide

Lenalidomide, an analogue of thalidomide, possesses anti-angiogenic and immunomodulatory properties, such as the ability to alter T-lymphocyte responses. After finding that it had some moderate efficacy in reducing transfusion dependence in 42 patients with various types of MDS, List and associates further investigated whether lenalidomide could reduce the transfusion requirement and suppress the abnormal 5q− clone in 148 patients with this abnormality. Patients received 10 mg of lenalidomide orally for either 21 days per month for 6 months or continuously for 6 months. The results were impressive: 76% of treated patients had a reduced need for transfusions, and 67% no longer required transfusions. Among 85 patients evaluated with bone marrow examination, 62 had cytogenetic improvement, 38 of whom had a complete cytogenetic remission. The number of concomitant karyotype abnormalities did not affect the decrease in transfusion dependence or cytogenetic improvement. Moderate-to-severe neutropenia and thrombocytopenia were the most common toxicities but seemed to abate with time. These results have made lenalidomide the first-line treatment for MDS patients who harbor deletion of 5q, whether or not it is an isolated abnormality (the 5q− syndrome).

DNA Methyltransferase Inhibitors (DMTIs)

The DMTIs are cytidine analogues that are thought to cause hypomethylation of DNA as well as direct toxicity to malignant bone marrow cells. The first to be approved was azacytidine, which is a subcutaneous injection (75 mg/m²/day) that is traditionally given for 7 consecutive days per month. A Cancer and Leukemia Group B (CALGB) randomized controlled trial of 191 patients with MDS compared treatment with azacytidine with supportive care. Patients represented all 4 IPSS groups but were concentrated in the 2 intermediate prognostic groups. Responses occurred in 60% of patients on the treatment arm (7% complete, 16% partial, 37% improved) as compared with 5% (improved only) receiving supportive care (P = 0.001). Median time to AML transformation or death was 21 months for treatment versus 13 months for supportive care (P = 0.007). A rigorous quality-of-life assessment also found major advantages to treatment. Based on these results, azacytidine was approved by the US Food and Drug Administration (FDA) for RA, RARS, RAEB, RAEB-T, and CMML.

Decitabine (5-aza-2′ deoxycytidine) is another cytidine analogue that was recently approved by the FDA for the treatment of all MDS FAB subgroups intermediate-1 and higher on the IPSS. After promising preliminary research by a German group that showed modest cytogenetic responses could be achieved in high-risk MDS patients treated with decitabine, the MD Anderson...
Cancer Center completed a phase III trial of 170 patients randomized to receive either decitabine (given intravenously in the hospital 3 days/mo) or supportive care. Patients treated with decitabine achieved a significantly higher overall response rate (17%), including complete responses (9%), as compared with supportive care (0%; \( P < 0.001 \)). An additional 12 patients who were treated with decitabine (13%) achieved hematologic improvement. Patients treated with decitabine also had a trend toward a longer median time to progress to AML or death compared with patients who received supportive care alone, most pronounced in those with IPSS intermediate-2/high-risk disease (12.0 mo versus 6.8 mo; \( P = 0.03 \)). As one of the difficult issues with decitabine is the need for hospitalization, more convenient dosing schedules are currently being investigated.

- **Is there a role for an alternative DMTI if the first fails?**

  Although standard treatment guidelines, such as the NCCN guidelines, stipulate that the 2 approved DMTIs can be used essentially interchangeably, an interesting question is whether it is useful to switch to the other DMTI if the first fails to have an effect or stops having an effect. In a preliminary study, 14 adults with MDS who had progressed or failed to respond after at least 3 courses of azacitidine were then treated with decitabine. Five patients achieved some response (including complete response in 3 patients) by standard criteria. Improvement of thrombocytopenia was noted in 2 of 5 patients who had pretreatment platelet counts less than \( 50 \times 10^3/\mu \text{L} \) at entry. This study, which is ongoing, provides evidence that trying an alternative DMTI may be reasonable if the first fails.

**IMMUNOSUPPRESSIVE THERAPY**

Somewhere between low- and high-intensity therapy lies immunosuppressive therapy, which has been effective in some cases of “hypoplastic MDS.” Popular agents are cyclosporine A and antithymocyte globulin, and therapy should be considered if hematopoietic growth factors are not likely to be helpful due to an elevated erythropoietin level (\( > 500 \text{IU/L} \)). In addition to having hypoplastic morphology, good candidates for response to immunosuppressive therapy have been shown to be younger than 60 years, to be HLA-DR15 positive, and/or to possess PNH clones in their bone marrow.

**HIGH-INTENSITY THERAPY**

For patients who are in the higher-risk groups (IPSS intermediate-2 and high groups), the paramount goal is avoiding the risk of transformation to AML, which, when arising out of MDS, can be extremely difficult to manage. The goal is to alter the disease course with high-intensity therapy (eg, hematopoietic stem cell transplant, intensive chemotherapy), with a possible by-product being hematologic improvement and improvement in quality of life. Unfortunately, these treatments are also more likely to cause significant morbidity and mortality. Thus, low-intensity therapy remains an option for high-risk patients in 2 circumstances: first, as a bridge to high-intensity therapy; and second, if age, comorbidities, or other factors (eg, unavailability of a suitable donor) make high-intensity therapy not feasible. High-intensity therapy for MDS includes traditional hospital-based induction chemotherapy as well as hematopoietic stem cell transplantation.

Despite reasonable first complete response rates, several traditional chemotherapy regimens (eg, idarubicin-, cytarabine- and fludarabine-based regimens) have been shown to convey little ultimate benefit. Although the magnitude and duration of response are less than for AML, induction chemotherapy should be considered in high-risk cases where there is no suitable donor. Alternatively, supportive care alone is always reasonable to consider for treating elderly MDS patients with high-risk disease and comorbid conditions.

Allogeneic stem cell transplant from an HLA-matched sibling is the preferred (and potentially curative) approach for eligible MDS patients, especially in younger patients with high-risk disease. Reduced-intensity and unrelated donor programs are options at some centers, while auto transplantation remains rare. Several issues particular to transplant for MDS are vexing, especially given the relatively low numbers of transplantations performed. For example, it is unclear whether or not to reserve transplantation only for patients who are in remission—and whether or not the DMTIs are the optimal agents to achieve that state.

- **Should MDS patients who are candidates for transplantation undergo transplantation upfront or wait until the disease progresses?**

  Another issue is whether low-risk patients who are candidates for transplantation should receive upfront transplantation and thus take advantage of the relatively healthy marrow. Cutler and colleagues utilized a national database of transplant patients and their outcomes to perform a decision analysis to address this question. They found that delayed transplantation for IPSS low and intermediate-1 groups was associated with better overall survival. In contrast, transplantation at diagnosis maximized overall survival for IPSS intermediate-2 and high groups.
CHRONIC MYELOMONOCYTIC LEUKEMIA

As noted earlier, CMML has both myelodysplastic and myeloproliferative properties. Recent studies have shown that it, too, responds well to therapy with DMTIs. For example, Jabbour et al treated 19 CMML patients with decitabine, and found that 13 achieved clinically significant responses: complete remission in 11, and hematologic improvement in 2. Improvement of thrombocytopenia was noted in 7 out of 8 patients (88%) with pretreatment platelets less than $5 \times 10^9/\mu L$ at entry. Median survival was 19 months. Among 6 patients with pretreatment chromosomal abnormalities who achieved response, 1 had disappearance and 2 had greater than 50% reduction of cytogenetic abnormalities.

A small proportion of patients with chronic myeloproliferative diseases and CMML have constitutive activation of the gene for PDGFRβ, which encodes a receptor tyrosine kinase. Recent research has shown that this gene is located on chromosome 5q33, and that its activation can be caused by a translocation associated with an ETV6-PDGFRβ fusion gene. In patients with CMML who can be demonstrated to have this PDGFRβ fusion, a trial of imatinib mesylate is suggested.

CLINICAL TRIALS AND NEW DIRECTIONS

At any step in the treatment pathway but especially after conventional treatments have failed, it may be appropriate to offer patients with MDS participation in a clinical trial, although their ability to do so may be limited by age and comorbidity. Some trials are focusing on more convenient administration of FDA-approved agents (eg, decitabine) and combination therapies, whereas others are assessing new agents (eg, histone deacetylase inhibitors, farnesyltransferase inhibitors).

CASE CONCLUSION

After a discussion with the patient of the risks, benefits, and costs of treatment, therapy with azacitidine is initiated at a dose of 75 mg/m²/day subcutaneously for 7 days each month. During the first few months, the patient’s transfusion interval decreases to every 21 days. After an additional 3 months, the interval increases to approximately 28 days. By month 7, he has not received a transfusion in approximately 45 days. His platelets stabilize at around $100 \times 10^9/\mu L$. The WBC count is acceptable, with a neutrophil count of 2000/µL. His serum ferritin is mildly elevated (900 ng/dL), but as his transfusion needs are decreasing (only about 10 so far overall), a decision is made to hold off on iron chelation therapy. During the patient’s eighth month of treatment (~22 months after first presenting with anemia), he experiences another myocardial infarction and dies.

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