Myelodysplastic Syndromes

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Myelodysplastic Syndromes

Jasleen Randhawa, MD, and Ehab Atallah, MD

INTRODUCTION

Myelodysplastic syndromes (MDS) are a spectrum of clonal myeloid disorders characterized by ineffective hematopoiesis, cytopenias, qualitative disorders of blood cells, clonal chromosomal abnormalities, and the potential for clonal evolution to acute myeloid leukemia (AML).1 In this review, we discuss the various pathogenic conditions included in the spectrum of MDS and the associated risk stratification for these conditions. We further discuss the treatment recommendations based on the risk status and the expected prognosis.

EPIDEMIOLOGY, ETIOLOGY, AND PATHOGENESIS

In the western population, the onset of MDS usually occurs after age 50 years, except in cases where the individual has undergone radiation therapy or chemotherapy for a prior malignancy.2,3 The annual incidence of MDS increases in a logarithmic fashion after the age of 40 years. According to National Cancer Institute data, the annual incidence of MDS increases from 2 per 1 million persons at age 40 years to more than 40 per 100,000 persons in the septuagenarian population. Males are affected 1.5 times as often as females.2

The etiologic factors that have been associated with increased incidence of MDS are similar to those that have been associated with increased AML incidence. These factors include prolonged exposure to high levels of benzene, alkylating agents, topoisomerase inhibitors, and radiation.4,5

The major pathogenic mechanism in MDS is ineffective hematopoiesis, causing defective maturation and death of marrow precursors.9 More recently, significant strides have been made in understanding MDS at a molecular and cytogenetic level.7,8 Hopefully, this information will help improve the prognostication of MDS and help individualize therapy to each patient for the best possible outcomes.

CLINICAL FEATURES

Clinically, MDS is usually suspected when a patient undergoes evaluation for cytopenias. A bone marrow biopsy is essential to establish the diagnosis of MDS, which is confirmed by the presence of dysplasia. Biopsy also helps to determine the marrow cellularity and architecture, including morphology, and allows for detailed evaluation of blasts. Cytogenetic evaluation of 20 metaphases is required to determine the cytogenetic patterns. At this time, there is no definitive data showing that flow cytometry or fluorescence in situ hybridization (FISH) analysis is better at establishing the phenotype than conventional cytogenetics.9

Fatigue and other symptoms secondary to anemia may be seen. The patient may have repeated infections due to severe neutropenia or neutrophil dysfunction and bleeding due to thrombocytopenia or platelet dysfunction. Fever may occur as a result of the disease itself, irrespective of infection. Hepatomegaly and splenomegaly can occur in 5% to 10% of cases.10

Less common manifestations of MDS may include diabetes. Hypothalamic-posterior pituitary insufficiency in clonal myeloid states has been associated with monosomy 7 in the hematopoietic cells, and these patients experience polyuria, polydipsia, and decreased libido.11 Immune or inflammatory syndromes have been reported in up to 10% of cases.10

Some patients may exhibit a syndrome suggestive of systemic lupus erythematosus with fever, pleurisy, arthritis, and positive plasma antinuclear antibodies preceding progression to AML.12,13 Behçet’s disease, systemic vasculitis, inflammatory bowel disease, seronegative arthritis, and glomerulonephritis have also been reported with MDS.14-17

Several laboratory abnormalities can be seen with MDS. Iron and ferritin levels may be elevated due to anemia and transfusions. Lactate dehydrogenase and uric acid concentrations may be elevated due to a high death ratio of the marrow precursors. Other abnormalities include monoclonal gammopathy, hyper-/hypogammaglobulinemia, and increased β2 microglobulin levels.18,19
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### Classification and Risk Stratification

The World Health Organization (WHO) has devised a classification to overcome disparities in the nomenclature defining MDS. Prior to the WHO classification, the FAB (French-American-British) classification was used to classify MDS. The most important difference between the FAB and the WHO classifications was the lowering of the threshold of the blasts to 20% from 30% for the diagnosis of AML. In addition, a new category was introduced to define dysplasia involving 2 or more cell lines, refractory cytopenias with multilineage dysplasia (RCMD). Two subtypes of refractory anemias with excess blasts (RAEB) were defined, and MDS associated with del(5q) was identified as a distinct entity. This WHO classification was further refined in 2008, when unilineage dysplasia was more precisely defined and the definition of RAEB-1 and RAEB-2 was revised. The blood and marrow findings in MDS as defined by the 2008 WHO classification are shown in Table 1.

### Table 1. World Health Organization Classification of Myelodysplastic Syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peripheral Blood Findings</th>
<th>Bone Marrow Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia (RCUD): refractory anemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (RT)</td>
<td>Single lineage cytopenia, no or rare blasts (&lt;1%), bicitopenia may be occasionally observed</td>
<td>Unilineage dysplasia (≥10% of the cells in 1 myeloid lineage) &lt;5% blasts, &lt;15% ring sideroblasts within erythroid precursors</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts (RARS)</td>
<td>Anemia, no blasts</td>
<td>Erythroid dysplasia only, &lt;5% blasts, ≥15% ringed sideroblasts within erythroid precursors</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenia(s), no or rare blasts (1%), no Auer rods, &lt;1x10⁹/L monocytes</td>
<td>Dysplasia in ≥10% of cells in 2 or more myeloid cell lineages, &lt;5% blasts, no Auer rods</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-1 (RAEB-1)</td>
<td>Cytopenia(s), &lt;5% blasts, no Auer rods, &lt;1x10⁹/L monocytes (cases with Auer rods and &lt;5% blasts in the peripheral blood and &lt;10% blasts in the marrow should be classified as RAEB-2)</td>
<td>Unilineage or multilineage dysplasia, 5% to 9% blasts, no Auer roads (cases with Auer rods and &lt;5% blasts in the peripheral blood and &lt;10% blasts in the marrow should be classified as RAEB-2)</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts-2 (RAEB-2)</td>
<td>Cytopenia(s), 5%–19% blasts, occasional Auer rods, &lt;1x10⁹/L monocytes</td>
<td>Unilineage or multilineage dysplasia, 10%–19% blasts, occasional Auer roads</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, unclassified (MDS-U)</td>
<td>Cytopenias, no or rare blasts (≤1%)</td>
<td>Unequivocal dysplasia in &lt;10% of cells in 1 or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS, &lt;5% blasts</td>
</tr>
<tr>
<td><em>Cases of RCUD with pancytopenia</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cases of RCUD and RCMD with 1% myeloblasts in peripheral blood</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Several prognostic systems have been devised for the risk stratification of patients with MDS. These include the International Prognostic Scoring System (IPSS, Table 2), the revised IPSS (R-IPSS, Table 3), WHO classification–based prognostic scoring system (WPSS, Table 4), the MD Anderson Cancer Center (MDACC) classification for patients with low-risk MDS (Table 5), and the MDACC classification for patients with high-risk MDS (Table 6). In the IPSS, patients are classified into 4 risk groups based on the blast percentage in the bone marrow, cytogenetic abnormalities, and number of cytopenias. The median survival for patients in the low, intermediate-1, intermediate-2, and high-risk groups was 5.7, 3.5, 1.2, and 0.4 years, respectively. Survival did not appear to differ according to age in the intermediate-2 and high-risk groups. However, in the low-risk group, the median survival was 9.0 versus 4.4 years for patients ≤70 years and >70 years, respectively. Similarly, in the intermediate-1 risk group, the median survival was 4.4 versus 2.4 years for patients ≤70 years and >70 years, respectively. The R-IPSS was developed to further refine the IPSS scoring system. The main differences between
Myelodysplastic Syndromes

Table 2. International Prognostic Scoring System (IPSS)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Score Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow blasts (%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Scores for risk groups are as follows: Low 0; Intermediate-1 0.5–1.0; Intermediate-2 1.5–2.0; and High ≥2.5.

*Good: normal, −Y, del(5q), del(20q); Poor: complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate: other abnormalities.


Table 3. Revised International Prognostic Scoring System (R-IPSS)

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics*</td>
<td>Very good</td>
<td>—</td>
<td>Good</td>
<td>—</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very poor</td>
</tr>
<tr>
<td>BM blasts (%)</td>
<td>≤2</td>
<td>—</td>
<td>&gt;2% – &lt;5%</td>
<td>—</td>
<td>5%–10%</td>
<td>&gt;10%</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>—</td>
<td>8 – &lt;10</td>
<td>&lt;8</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50 – &lt;100</td>
<td>&lt;50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Scores for risk groups are as follows: Very low ≤1.5; Low >1.5–3; Intermediate >3–4.5; High >4.5–6; Very high >6.

ANC = absolute neutrophil count; BM = bone marrow.

*Cytogenetics: Very good: −Y, del(11q); Good: normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones; Poor: −7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities; Very poor: complex: ≥3 abnormalities.


Table 4. World Health Organization Classification–Based Prognostic Scoring System

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO category</td>
<td>RA, RARS, 5q−</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-I</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>—</td>
</tr>
<tr>
<td>Transfusion requirement†</td>
<td>No</td>
<td>Regular</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Risk groups: Very low (score = 0), Low (score = 1), Intermediate (score = 2), High (score = 3 to 4), and Very high (score = 5 to 6).

RA = refractory anemia; RAEB = refractory anemia with excess blasts; RARS = refractory anemia with ring sideroblasts; RCMD = refractory cytopenia with multilineage dysplasia.

*Karyotype: Good: diploid, −Y, del(5q), del(20q); Poor: complex (≥3 abnormalities), chromosome 7 anomalies; and Intermediate: other abnormalities.

†Red blood cell (RBC) transfusion dependency was defined as having at least 1 RBC transfusion every 8 weeks over a period of 4 months.


the IPSS and the R-IPSS are different marrow blast categories, 5 cytogenetic risk groups (compared to 3 with IPSS), and incorporation of the depth of the cytopenias (compared to a cytopenia present/absent categorization in the IPSS). The median survival for patients was 9.3, 6.3, 3.4, 1.2, and 0.6 years for the 5 R-IPSS risk categories very low, low, intermediate, high, and very high, respectively. Both the IPSS and the R-IPSS were designed to classify patients at the time of their diagnosis. The WPSS, however, is a time-independent prognostic
system that can be used at any time during the patient’s illness. The WPSS incorporates the WHO classification, cytogenetic categories, and red cell transfusion dependence. Five risk groups were identified, very low, low, intermediate, high, and very high, with a median survival of 141, 66, 48, 26, and 9 months, respectively.25

**MOLECULAR BASIS OF MDS**

As more is uncovered about the molecular basis of MDS, efforts are being made to determine the clinical implications of the molecular abnormalities and pathogenesis of MDS. Bejar and colleagues described 18 somatic mutations in MDS patients using the polymerase chain reaction (PCR) technique.8 This group showed that mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 are poor prognostic indicators for survival, after adjustment for the IPSS risk group.8 At least 1 of these mutations was present in 51.5% of the 439 patient samples that were analyzed. Mutations of TET2 were noted to be associated more with normal cytogenetic features (P = 0.005), whereas TP53 mutations showed an association with a complex karyotype. The RUNX1, TP53, and NRAS mutations each had a strong association with severe thrombocytopenia (P<0.001 for each gene). TET2 mutations were the most prevalent abnormality identified in this patient population, but patients with these mutations did not show any particular predilection to cytopenias or blast proportion. Itzykson et al showed that the presence of TET2 mutations predicts a favorable response to azacitidine therapy in MDS patients and in AML patients with a low blast count.26 Patients with TET2 mutations had a higher response rate to azacitidine (82%) than the wild phenotype (45%, P = 0.007). The duration of response and overall survival (OS), however, were similar in both groups.

The presence of spliceosome mutations has also been reported in MDS patients. Makishima et al reported that mutations in the U2AF1, SF3B1, and SRSF2 genes were the most frequent spliceosomal mutations noted in a cohort of 310 patients with MDS.29 Mutations of any 1 of these 3 genes were found in 39% of patients with low-risk MDS, and mutations in SF3B1 were highly associated with refractory anemia with ring sideroblasts (RARS). The presence of ring sideroblasts was found to correlate strongly with SF3B1 mutations, irrespective of other clinical or morphologic features. Furthermore, the SF3B1 mutations were less commonly found in advanced MDS, suggesting that this mutation does not contribute to disease progression. The U2AF1 mutations were most frequently noted in high-risk MDS/AML patients (11%), while SRSF2 mutations were most frequently noted in patients with MDS/myeloproliferative neoplasms (24%), particularly in chronic myelomonocytic leukemia. The U2AF1 mutations appeared to be most commonly associated with ASXL1 and TET2 mutations, whereas SF3B1 show a co-presence with the RUNX1 mutation. It has been reported that MDS patients with SF3B1 mutations have higher neutrophil and platelet counts, fewer bone marrow blasts, and longer event-free survival than patients

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**Table 5. MDACC Classification for Patients with Low-Risk Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>Adverse Factor</th>
<th>Assigned Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable cytogenetics</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Platelets &lt;50 x 10^9/L</td>
<td>2</td>
</tr>
<tr>
<td>Platelets 50–200 x 10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>Bone marrow blasts ≥4%</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk category: 1 (score 0–2); 2 (score 3–4); 3 (score >5).

*Diploid and 5q only were favorable cytogenetics; all others were considered as unfavorable cytogenetics.


**Table 6. MDACC Classification for Patients with High-Risk Myelodysplastic Syndromes**

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Category</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>&gt;2</td>
<td>2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60–64</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>2</td>
</tr>
<tr>
<td>Platelets (x 10^9/L)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>30–49</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>50–199</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt;12.0</td>
<td>2</td>
</tr>
<tr>
<td>Bone marrow blasts (%)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5–10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>11–29</td>
<td>2</td>
</tr>
<tr>
<td>White blood cell count (&lt; x 10^9/L)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Chromosome 7 abnormality or complex (≥3 abnormalities)</td>
<td>3</td>
</tr>
<tr>
<td>Prior transfusion</td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

Score: Low 0 – 4; Intermediate-1 5 – 6; Intermediate-2 7 – 8; High >9.

who do not have SF3B1 mutations.\textsuperscript{30} The SF3B1 mutations also have an independent association with superior OS ($P = 0.025$) and lower risk of evolution to AML ($P = 0.049$).\textsuperscript{30}

Mutational analyses are not yet ready for routine clinical use, and more studies are needed to allow for these molecular mutations to be used in the clinical setting for risk stratification and prognostication. In the future this may allow for more individualized treatment of MDS with improved outcomes.

### INTERMEDIATE-1-RISK MDS

#### CASE SCENARIO 1

A 67-year-old woman presents for evaluation of anemia. She has been complaining of progressive shortness of breath and fatigue for the past 3 to 4 months. Pallor is noted on exam and no other abnormalities are detected. No splenomegaly or organomegaly is noted. Complete blood count (CBC) shows a white blood cell (WBC) count of 6500/\(\mu\)L, hemoglobin of 7.5 g/dL, and a platelet count of 420,000/\(\mu\)L. The mean corpuscular volume is 110 \(\mu\)m\(^3\). Routine tests ordered by the patient’s primary care physician, including vitamin B12, folic acid, and iron studies, are all normal. A colonoscopy and an esophagastroduodenoscopy are normal. A bone marrow biopsy shows dyserythropoiesis and dysgranulopoiesis with 3\% blasts. Cytogenetic analysis reveals a normal female karyotype at 46,XX.

The patient has intermediate-1-risk MDS by the IPSS.

#### TREATMENT OPTIONS FOR LOW/INTERMEDIATE-1-RISK MDS

Several treatment options are available for patients with low- or intermediate-1-risk MDS. Therapy options include blood transfusion support with or without iron chelation therapy, erythropoiesis-stimulating agents with or without granulocyte-colony stimulating factors (G-CSF), lenalidomide, immunosuppressive therapy, and hypomethylating agents. For patients in whom anemia is the main problem, growth factor support or blood transfusions alone may be considered. The main risk of frequent blood transfusions is iron overload.

#### treatment response assessment

The International Working Group (IWG) criteria for response in MDS were developed in order to standardize response criteria in MDS. These criteria defined 2 different types of response in patients with MDS. First are disease-modifying responses such as complete response (CR), partial response (PR), and progressive disease. The second set of criteria includes hematologic improvement (HI), in which patients achieve benefit from therapy with improvement in quality of life. These guidelines were first developed in 2000\textsuperscript{31} and later updated in 2006 (modified IWG)\textsuperscript{32} to address some of the shortcomings of the IWG-2000 criteria (Table 7 and Table 8).

#### Iron Chelation Therapy

Iron chelation therapy is currently recommended for patients with low-risk MDS with a ferritin level above 1000 ng/mL or who have received more than 20 to 30 blood transfusions. However, the indication for iron chelation remains controversial.

#### Erythropoiesis-Stimulating Agents

Several erythropoiesis-stimulating agents are available, such as epoetin alfa, epoetin beta, epoetin zeta, and darbepoetin. Only darbepoetin and epoetin alfa
are currently approved by the Food and Drug Administration and available in the United States. Single-agent recombinant human erythropoietin (rhEPO) has a response rate ranging from 24% to 36.8%. Factors predictive of response to therapy were low-risk MDS, a low percentage of blasts, and no prior transfusions. The combination of rhEPO and G-CSF was evaluated in multiple phase II and III trials. In a small randomized phase III trial, patients who received both rhEPO and G-CSF had a better response rate when compared to those who received rhEPO alone (40% vs 73.3%). In another phase III trial, 110 patients were randomized to best supportive care (BSC) alone versus rhEPO with or without G-CSF. The response rate was 36% versus 9% for patients receiving rhEPO plus G-CSF versus BSC only. There was no difference in OS between patients receiving rhEPO and G-CSF or BSC only, but patients who had a response had an improvement in OS. However, 2 other large randomized trials did find a survival benefit for patients who received rhEPO. In a study by Jädersten et al, the long-term outcome of 121 patients treated with rhEPO plus G-CSF was compared to 225 untreated patients. The erythroid response rate in the rhEPO plus G-CSF group was 20% and the median response duration was 23 months. In multivariate analysis, rhEPO plus G-CSF was associated with improved OS.

In a study by the Groupe Francophone des Myelodysplasies (GFM), 403 patients with MDS who had received rhEPO with or without G-CSF were analyzed. The overall erythroid response rate was 62% and the median response duration was 24 months according to the IWG-2006 criteria. This group of patients was compared to an untreated MDS historical cohort included in the International MDS Risk Analysis Workshop (IMRAW) database that was used to define IPSS. Only patients with low and intermediate-1 MDS by the IPSS and with a hemoglobin level less than 10 g/dL were included in the analysis. The 5-year OS was superior in the French-EPO group when compared to the IMRAW untreated cohort (64% vs 39%). In multivariate analysis, rhEPO therapy was independently associated with improved survival. Patients with a low erythropoietin level (<100 mIU/mL) and need for fewer than 2 transfusions in 1 month are most likely to respond to rhEPO therapy. Darbepoetin was evaluated in multiple phase II and retrospective trials. Erythroid response rates varied from 45% to 71% depending on the study inclusion criteria. The addition of G-CSF to darbepoetin appeared to be beneficial in patients who did not respond to darbepoetin alone.

The current European Leukemia Network (ELN) guidelines suggest that rhEPO therapy should be

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**Table 8. Modified International Working Group Response Criteria for Altering Natural History of MDS**

<table>
<thead>
<tr>
<th>Category</th>
<th>Response Criteria (responses must last at least 4 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission (CR)</td>
<td>Bone marrow: ≤5% myeloblasts with normal maturation of all cell lines</td>
</tr>
<tr>
<td></td>
<td>Persistent dysplasia will be noted</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin ≥11 g/dL</td>
</tr>
<tr>
<td></td>
<td>Platelets ≥100 × 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Neutrophils ≥1.0 × 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Blasts 0%</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>All CR criteria if abnormal before treatment except:</td>
</tr>
<tr>
<td></td>
<td>Bone marrow blasts decreased by ≥50% over pretreatment but still &gt;5%</td>
</tr>
<tr>
<td></td>
<td>Cellularity and morphology not relevant</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood: if HI responses, they will be noted in addition to marrow CR</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Failure to achieve at least PR, but no evidence of progression for &gt;8 wks</td>
</tr>
<tr>
<td>Failure</td>
<td>Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td>Complete: disappearance of the chromosomal abnormality without appearance of new ones</td>
</tr>
<tr>
<td></td>
<td>Partial: at least 50% reduction of the chromosomal abnormality</td>
</tr>
</tbody>
</table>

considered in low/intermediate-1-risk (by IPSS) MDS patients with hemoglobin <10 g/dL, serum erythropoietin level <500 mIU/mL, and a requirement of fewer than 2 PRBC transfusions per month. G-CSF should be added to rhEPO if there is no response to rhEPO alone after 8 weeks of treatment. One should be mindful of the associated side effects and risk of thrombosis associated with the use of the rhEPO.

**Immunosuppressive Therapy**

Immunosuppressive therapy is indicated for the treatment of patients with hypoplastic MDS. Hypoplastic MDS is a distinct entity characterized by marrow hypoplasia, macrocytosis, severe leukopenia, and thrombocytopenia, with a low incidence of progression to AML. It has marrow cellularity that is low for age. Hypoplastic MDS is usually unresponsive to conventional therapy and represents approximately 15% of all MDS cases. It is not yet recognized as a separate disease according to the WHO classification. The median age of onset is the same as classic MDS, but hypoplastic MDS is seen more commonly in females. The bone marrow shows fewer dysplastic features and more hypocellularity. There is a higher incidence of refractory anemia (66.7%) and chromosome 7 abnormalities as compared to normo-/hypercellular MDS. Hypoplastic MDS is often thought to have similarities with aplastic anemia in its pathogenesis. The presence of dysplasia, increased percentage of blasts, and abnormal karyotype favor the diagnosis of hypoplastic MDS over aplastic anemia, and there is an aberrant CD34+ clone present in the bone marrow along with an elevated hemoglobin-F-containing erythroblast population. The suppression of hematopoiesis is not only due to the presence of abnormal clones, but also due to immunological suppression. An abnormal T-cell clone is usually detected, which usually disappears with immunosuppressive therapy. The immunomedi­ated pathophysiology hypothesis is further supported by evidence that the HLA-DR15 allele is overrepresented in patients with refractory anemia when compared to healthy controls.

Various immunosuppressive agents have been studied in an attempt to optimize the treatment of this variant of MDS. In a randomized phase III trial, 45 patients with MDS, refractory anemia with or without sideroblasts, RAEB-1, and hypoplastic MDS were randomized to receive either horse antithymocyte globulin (ATG, 15 mg/kg for 5 days) and oral cyclosporine (for 180 days) or BSC. At 6-month follow-up, 13 (29%) of 45 patients achieved a hematologic response (CR+PR) in the ATG plus cyclosporine arm, whereas 4 (9%) of 43 patients in the BSC arm achieved a hematologic response ($P = 0.0156$). Response at 6 months was favored in patients with a hypoplastic marrow, low blast counts, hypoplastic MDS, and the ATG plus cyclosporine treatment. No significant differences were noted among the arms in treatment-free survival, leukemia-free survival, and OS. However, crossover was allowed, which may have impacted these results.

The National Heart, Lung and Blood Institute proposed a scoring system using HLA-DR15, age, and duration of PRBC transfusion dependence to identify those MDS patients who are most likely to respond to immunosuppression. However, in a review by Sloand et al, age was the strongest predictive factor for response. The 2013 ELN guidelines recommend consideration of immunosuppressive therapy with ATG with 6 months of oral cyclosporine for transfusion-dependent, young (<60 years) patients with less than 5% marrow blasts and normal cytogenetics.

**Hypomethylating Agents**

Hypomethylating agents have also been evaluated in patients with low-risk MDS, although fewer studies have been conducted in low-risk than in high-risk MDS. In the first randomized trial of azacitidine versus BSC by Silverman et al, patients with all-risk MDS were randomized to receive either azacitidine (75 mg/m$^2$/day subcutaneously [SQ] for 7 days every 28 days) or BSC. For patients randomized to the BSC arm, crossover was allowed after 4 months for patients whose disease was worsening. Responses were seen in 60% of patients in the azacitidine arm (7% CR, 16% PR, 37% HI) compared with 5% (HI) in the BSC arm ($P < 0.001$). Median time to leukemic transformation or death was 21 months for azacitidine versus 13 months for BSC ($P = 0.007$). Because of the crossover design, there was no difference in OS between the groups. Of the 99 patients enrolled on the azacitidine arm, 28% had low/intermediate-1-risk MDS and 24% had refractory anemia/RARS. There was no difference in response rates across all MDS subtypes.

More recently, a prospective phase II study of azacitidine in patients with low/intermediate-1-risk MDS was done. Patients were allowed in the study if they had a low probability of responding to rhEPO or did not respond to rhEPO and had significant thrombocytopenia or neutropenia. Of the 32 patients enrolled, the overall response rate (ORR) was 47% (CR 16%, HI 31%) and the median OS from the time of starting azacitidine was 28.5 months. Decitabine is another hypomethylating agent that has shown promise in the treatment of MDS.
the ADOPT trial, Steensma et al demonstrated that decitabine 20 mg/m² by intravenous infusion daily for 5 consecutive days every 4 weeks was a viable option for treatment of MDS, with an ORR of 32%; the overall improvement rate was 51%, which included 18% HI.60 In that study, 54% of patients had low/intermediate-1-risk MDS. Similar response rates were observed in all FAB subtypes and IPSS risk categories. Decitabine was investigated in a randomized phase II study at a lower dose. Patients with low/intermediate-1-risk MDS were randomized to receive decitabine 20 mg/m² SQ on days 1, 2, and 3 of a 28-day cycle or 20 mg/m² on days 1, 8, and 15 of a 28-day cycle. The ORRs were 23% in both arms, and 16% of patients receiving the 3-consecutive day schedule achieved CR. These results suggest that decitabine administered SQ at a lower dose may be as effective as other regimens in this group of patients with low-risk MDS.61 Renal precautions should be followed while using decitabine and the renal function monitored for dose adjustment.

5Q-DELETION SYNDROME

CASE SCENARIO 2

A 67-year-old woman presents for evaluation of anemia. Her CBC shows a WBC count of 6500/µL, hemoglobin of 7.5 g/dL, and a platelet count of 420,000/µL. A gastrointestinal work-up was negative and no other cause of anemia has been elucidated. A bone marrow biopsy shows 3% blasts with micromegakaryocytes. FISH and cytogenetics detect a 5q abnormality. The patient has low-risk MDS associated with isolated 5q deletion (del(5q)).

DEFINITION

The traditional 5q-deletion syndrome was characterized by macrocytic anemia, erythroid hypoplasia, normal or elevated platelet count, hypoproliferative megakaryocytes, and isolated del(5q) as an isolated chromosomal abnormality. However, not all cases of del(5q)-associated MDS variants fit into this original description, and only 5% patients met the classical description of the 5q− syndrome.68 Subsequently, MDS with isolated del(5q) was recognized as a separate entity in the 2008 WHO classification of myeloid neoplasms and acute leukemia. This entity was defined by an isolated del(5q), macrocytic anemia, less than 5% bone marrow blasts, less than 1% peripheral blasts, no Auer rods, and normal to increased megakaryocytes with hypolobated nuclei without specification of erythroid abnormalities.22

ROLE OF LENALIDOMIDE IN MDS

Lenalidomide is a second-generation thalidomide analogue with immunomodulatory properties that has been shown to be effective in the treatment of del(5q)-associated MDS. Lenalidomide has multiple mechanisms of action, including stimulation of erythropoiesis, immunomodulation, and antineoplastic effects via antiangiogenic and antiproliferative activity.64,65 In addition to the standard treatment options for MDS, lenalidomide is specifically used in the treatment of del(5q) MDS. Lenalidomide appears to work in del(5q) MDS by suppressing the del(5q) clone,66,67 while in non-del(5q) MDS it works by restoring the efficacy of erythropoietin-induced activation of the STAT5 pathway.68

Experience from the dose finding study (MDS-001) and the deletion 5q registration trial (MDS-003) suggested the mechanism of action of lenalidomide in MDS is karyotype-dependent. In the landmark MDS-001 trial, List et al conducted a randomized phase III study of lenalidomide versus placebo in 43 RBC transfusion–dependent patients with low/intermediate-1-risk MDS. These patients either had had no response to rhEPO or had a high endogenous erythropoietin level. Of these, 24 patients (56%) had a response, with 20 achieving transfusion independence (TI), and 3 had a more than 50% reduction in transfusion requirements. The response rate was highest among patients with a clonal interstitial deletion involving chromosome 5q and among patients with lower prognostic risk. At a median follow-up of 81 weeks, the median duration of TI had not been reached.69

The MDS-002 trial evaluated the role of lenalidomide in transfusion-dependent non-del(5q) patients. In this trial, Raza et al evaluated patients with IPSS low-/intermediate-1-risk MDS and transfusion-dependent anemia with normal or abnormal karyotypes without del(5q).70 A total of 114 patients initiated treatment on the 21-day schedule, and 100 patients received continuous daily dosing. Of these, 26% patients achieved TI and 17% had a 50% or greater decrease in transfusion requirements. Among patients who achieved TI, 90% became transfusion independent by 16.9 weeks, 95% by 26 weeks, and 100% by 39 weeks. The median duration of TI was 41 weeks.

In the MDS-003 trial, List et al evaluated the benefit of lenalidomide in 148 patients with del(5q31) alone or with other cytogenetic abnormalities. Patients had lower intermediate-1-risk disease according to the IPSS. A total of 46 patients received 10 mg of lenalidomide over 21 days and 102 patients received 10 mg of lenalidomide daily. Of these patients, 76% had a response to treatment, with 67% achieving TI by week 24. The
remaining patients had a 50% or greater reduction in transfusion requirement. The median time to achievement of TI was 4.6 weeks (1–49 weeks). At a median follow-up of 104 weeks, 53 of 99 patients who became transfusion independent remained free of transfusion needs. After 24 weeks of treatment, there was complete resolution of cytologic dysplasia in all hematopoietic lineages in 38 of the 106 patients (36%). In this trial, patients with baseline platelets greater than 100,000/µL and absolute neutrophil count (ANC) greater than 500/µL, and who experienced profound neutropenia and thrombocytopenia during the first weeks of treatment had a higher rate of TI.71

Fenaux et al conducted a phase III, randomized double-blind study to evaluate the efficacy of lenalidomide in 139 RBC transfusion–dependent patients with low/intermediate-1-risk del(5q31) MDS (the MDS-004 trial). Patients were randomized to receive lenalidomide 10 mg daily for days 1 through 21 versus lenalidomide 5 mg daily for days 1 through 28 versus placebo. According to the IWG-2000 criteria, TI rates achieved were (≥8 weeks) 61.0% with lenalidomide 10 mg, 51.1% with lenalidomide 5 mg, and 7.8% with placebo; 48.8% patients achieved a response during cycle 1 (all dose groups combined). At a median follow-up of 1.55 years, the median duration of erythroid response was not reached. The median OS was 44.5 months in the 10 mg group, more than 35.5 months in the 5 mg group, and 42.4 months in the placebo group. The 3-year OS for the lenalidomide groups was 56.5%.72

Based on the above data, patients with MDS with del(5q), low/intermediate-1-risk disease and platelet count >100,000/µL who are PRBC transfusion–dependent should be considered for therapy with lenalidomide 10 mg daily for 21 days of every 28-day cycle. Therapy should be continued for a minimum of 8 to 12 weeks before considering switching therapy. Lenalidomide should be continued as long as the patient is responding and tolerating therapy well. Dose modifications may be needed based on side effects, especially cytopenias, and tolerance to the medication.73

RISK OF TRANSFORMATION

In the MDS-004 trial, the reported cumulative risk of AML for the lenalidomide-dose groups combined was 16.8% at 2 years and 25.1% at 3 years. In contrast, the rate of AML transformation in the placebo group who crossed over to lenalidomide was reported to be 30.4%. Hence, there seems to be no increase in the rate of leukemic transformation with the use of lenalidomide.72

The GFM evaluated 95 transfusion-dependent patients with lower-risk MDS with del(5q) who were treated with lenalidomide (10 mg/day) and found that 6 (6.3%) of these patients progressed to AML. They compared this cohort of 95 lenalidomide-treated patients to a historical control cohort of 99 lower-risk MDS patients with del(5q) who never received lenalidomide. Interestingly, the 4-year estimated cumulative incidence of AML was 9% in patients treated with lenalidomide and 15.8% in controls who did not receive lenalidomide which was not statistically different (P = 0.16).74 Hence, there is no apparent increase in the risk of leukemic transformation with the use of lenalidomide in patients with low-risk del(5q) MDS.

PROGNOSIS

According to the revised IPSS scoring system, patients with del(5q) have a favorable prognosis, with an expected median survival of 4.8 years and a 25% risk of evolution to AML at 9.4 years.24 In a Mayo Clinic study, 88 patients who met the definition of MDS with isolated del(5q) by the 2008 WHO criteria were evaluated. The median OS was 66 months. The median follow-up was over 33 months and the rate of leukemic transformation was 5.7%. In this study, age ≥70 years, red blood cell transfusion need, and the presence of blood marrow dysgranulopoiesis were identified as independent predictors of inferior survival. Risk groups were defined according to the presence of these 3 risk factors. The presence of 0 (low risk), 1 (intermediate risk), or ≥2 (high risk) risk factors corresponded to median survivals of 102, 52, and 27 months, respectively. Four of the 5 patients with leukemic transformation had additional cytogenetic abnormalities at the time of transformation, including del(7q).75

HIGH-RISK MDS WITH DEL(5Q)

CASE SCENARIO 3

A 67-year-old woman presents for evaluation for anemia. Her CBC shows a WBC count of 6500/µL, hemoglobin 7.5 g/dL, and a platelet count of 60,000/µL. A bone marrow biopsy shows 11% blasts. FISH and cytogenetics show del(5q). The patient has IPSS high-risk MDS associated with isolated del(5q).

MANAGEMENT

Patients with high-risk MDS and del(5q) carry a poor prognosis and, unlike patients with low/intermediate-1-risk MDS with del(5q), have low response rates with lenalidomide. Although response rates with hypomethylating agents are low, this remains the treatment of choice for these patients.76
In a phase II study by Ades et al, 47 patients with del(5q) high-risk MDS received lenalidomide 10 mg daily (days 1–21). In this group, 19% had isolated del(5q), 23% had 1 additional chromosomal abnormality, and the remaining 58% had more than 1 additional chromosomal abnormality. Thirteen (27%) achieved a response according to IWG 2006 criteria, including 7 (15%) CRs, 2 marrow CRs, and 4 HI-erythroid. At a median follow-up of 330 days, median OS was 272 days. Median survival was 169 days in patients who failed to respond as compared to 560 days in patients who achieved a hematologic response. The median survival was not reached in patients who achieved a hematologic CR (P < 0.01). In the whole cohort, CR was achieved in 67% of patients (6 of 9 patients) with isolated del(5q), 9% (1 of 11) with single additional abnormality, and none of the 27 patients with more than 1 additional abnormality (P < 0.001).

In this study, the absence of cytogenetic abnormalities in addition to del(5q) and baseline platelet count greater than 100,000/µL were significant predictors of achieving a CR.

Response to hypomethylating patients is also poor in this group of patients. In a small study of 38 patients with del(5q) and high-risk MDS treated with azacitidine, the ORR including HI-erythroid was 15%. The median OS for the whole group was 9 months and was even lower in patients with complex cytogenetics and del(5q) (7 months).

Since patients with chromosome 5 abnormalities in high-risk MDS have poor outcomes but have some response to lenalidomide, increasing doses of lenalidomide were evaluated to determine whether any improvement in response could be achieved. In a phase II study, 28 patients received 25 mg lenalidomide daily for 16 weeks. Of these, 16 had AML and 12 had intermediate-2/high-risk MDS. Three patients had isolated del(5q), 6 had del(5q) plus one additional aberration, 14 had del(5q) and a complex karyotype, 4 had monosomy 5, and 1 had del(5q) identified by FISH only. The ORR in the MDS patients was 36%. Patients with isolated del(5q) and those with additional aberrations had similar response rates. However, none of the patients with TP53 mutations responded.

**HIGH-RISK MDS**

**CASE SCENARIO 4**

A 67-year-old woman presents for evaluation of anemia. Her CBC shows a WBC count of 6500/µL, hemoglobin 7.5 g/dL, and platelet count of 130,000/µL. A gastrointestinal work-up was negative and no other cause of anemia has been elucidated. A bone marrow biopsy shows 5% blasts with erythroid and megakaryocytic dysplasia. FISH and cytogenetics detect monosomy 5 and monosomy 7. The patient has high-risk MDS.

**PROGNOSIS**

Patients with select recurrent cytogenetic abnormalities are recognized to have a presumed diagnosis of primary MDS according to the 2008 WHO classification. These include monosomy 5 and 7, among others. Based on the R-IPSS, this patient falls in the very high risk category with an expected survival of 0.8 years.

**MANAGEMENT**

Patients with high-risk MDS need to be treated aggressively as they have a high rate of progression to AML and a short expected survival. Therapy is dictated largely by the patient’s performance status. If the patient is “older” in age and has a poor functional status, supportive care may be offered with or without hypomethylating therapy. In younger patients with a good performance status, hypomethylating agents followed by hematopoietic cell transplantation (HCT) is the recommended therapy.

**Hypomethylating Agents**

In a phase III randomized trial (AZA-001) conducted by Fenaux et al in patients with high-risk MDS, patients were randomized to receive azacitidine (75 mg/m² daily for 7 days every 28 days) or conventional care (CCR, consisting of BSC, low-dose cytarabine, or intensive chemotherapy as selected by investigators before randomization). At a median follow-up of 21.1 months, the median OS was 24.5 months (9.9 – not reached) for the azacitidine group versus 15.0 months (5.6–24.1 months) for the CCR group (P = 0.0001). Azacitidine was given for a median of 9 cycles (4–15), and 86% of the patients who received azacitidine remained on 75 mg/m² per day throughout the study with no dose adjustments. In patients with −7/del(7q), the median OS was 13.1 months (3.9–24.5 months) in the azacitidine group (n = 30) compared with 4.6 months in the CCR group. The median time to AML transformation was 17.8 months in the azacitidine group compared with 11.5 months in the CCR group (P < 0.0001). The duration of hematologic response (CR, PR, and any hematologic improvement) was also significantly longer in the azacitidine group (median 13.6 months) than in the CCR group (5.2 months; P = 0.0002). Median duration of CR plus PR in the azacitidine
group was 3.2 months versus 3.0 months ($P = 0.48$) in the CCR group. Factors affecting survival in that study were performance status, presence of circulating blasts, RBC transfusion $\geq$ 4 units in 8 weeks, and cytogenetics. Based on these 4 factors, patients were subdivided into low-, intermediate-, and high-risk groups with median survival of not reached, 15 months, and 6.1 months, respectively.\(^8\) A survival benefit was seen in all subgroups analyzed, including patients with stable disease, and with the exception of those with progressive disease on treatment. This confirmed that treatment with azacitidine prolongs OS and lowers the risk of progression to AML in patients with higher-risk MDS compared with treatment with CCR including AML chemotherapy.

Decitabine was evaluated in 2 large phase III trials.\(^8\),\(^8\) In the first study, 170 patients were randomly assigned to receive either BSC or decitabine 15 mg/m$^2$ 3 times daily for 3 days repeated every 6 weeks. The ORR for patients receiving decitabine was 30% (9% CR, 8% PR, and 13% HI).\(^8\) Using a similar decitabine schedule, Lübbert et al reported an ORR of 34% (CR 13%, PR 6%, and HI 15%).\(^8\) However, in both studies there was no difference in OS in patients receiving decitabine on this schedule when compared to BSC. In order to better define the best dose schedule for decitabine, Kantarjian et al randomized patients with MDS to 1 of 3 decitabine schedules: 20 mg/m$^2$ IV daily for 5 days, 20 mg/m$^2$ SQ daily for 5 days, and 10 mg/m$^2$ IV daily for 10 days.\(^8\) In this study, patients randomized to receive 20 mg/m$^2$ IV daily for 5 days had the highest CR rate (39%) and this was chosen as the basis for a multicenter phase II study, the ADOPT trial,\(^8\) in which decitabine 20 mg/m$^2$ was administered to 99 patients with MDS. The ORR was 51% (17% CR, 15 marrow CR, and 18 HI). Most responses were seen after 2 cycles (82%), and the median duration of response was 10 months. The 1-year survival was 66% and the median OS was 19.4 months.

The outcomes in patients with high-risk MDS in whom azacitidine therapy fails are poor.\(^8\) Prêbet et al evaluated 435 patients with high-risk MDS who had stopped responding to azacitidine and found that the median OS was 15 months and the 2-year survival probability was 15%. Hence, efforts are being made to improve the responses to azacitidine by adding various other agents such as lenalidomide, idarubicin, and deferasirox.

**Hematopoietic Stem Cell Transplantation**

The only potentially curative option for MDS is an allogeneic HCT. The estimated OS for patients with MDS following HCT is 30% to 40%. In 2 large registry studies by the Center for International Bone Marrow Transplant Registry (CIBMTR) and EBMT, age had no impact on the outcome of HCT.\(^8\),\(^8\) Despite this data, few patients older than 65 years undergo HCT. This was evident in a study by McClune et al where only 10% of patients undergoing HCT were older than 65. There are several reasons why older patients do not receive HCT including comorbidities, donor status, and reluctance of both the patient and physician to consider HCT. In addition, coverage of HCT for MDS by the US Centers for Medicare and Medicaid Services (CMS) depended on local coverage determinations. In 2010 CMS approved a study proposed by the CIBMTR for coverage with evidence development. Since approval of that study, the number of older patients undergoing HCT has markedly increased,\(^8\) though the results of this study are pending. Two large studies in the United States and Europe will soon be launched to compare the outcome of patients with MDS treated with HCT versus non-HCT therapies.\(^8\)

**SUMMARY**

Treatment of patients with MDS needs to be individualized according to their risk stratification. Patients with low-risk MDS may be treated with supportive care alone including transfusions, iron chelation therapy, growth factors, lenalidomide, immunosuppressive therapy, or hypomethylating agents. Patients with high-risk MDS and good performance status should be referred for evaluation for an allogeneic HCT. Therapy with hypomethylating agents prior to HCT is recommended. Molecular prognostic factors may further refine the classification of risk status of patients with MDS. Several ongoing studies are evaluating the role of combination therapies in the treatment of patients with high-risk MDS. In addition, 2 large studies in both the United States and Europe are evaluating the role and timing of HCT in this patient population.

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