Risk-Based Management of Myelodysplastic Syndrome

By David P. Steensma, MD [4] and Ayalew Tefferi, MD [5]

Most adult patients with hematopoietic failure due to myelodysplastic syndrome (MDS) are treated with supportive care measures, including hematopoietic growth factors (epoetin alfa, darbepoetin alfa, filgrastim, pegfilgrastim, sargramostim), red blood cell or platelet transfusions, and antimicrobial agents. Allogeneic stem cell transplantation can be curative, but only a small subset of patients are eligible for transplantation, and until recently there were few options other than supportive care for transplant-ineligible patients. Since 2004, the US Food and Drug Administration (FDA) has approved three new therapies specifically for the indication of MDS: two DNA methyltransferase inhibitors (azacitidine and decitabine) and an immunomodulatory agent (lenalidomide). Several other drugs are used by clinicians for treatment of patients with MDS, but are not specifically FDA-approved for this indication. With several therapeutic options available, yet none of them effective in the majority of cases, it can be challenging for clinicians to choose the most appropriate treatment for an individual patient. Here we discuss a risk-based management approach to MDS that incorporates recent data regarding these new therapies. While many questions remain about the optimal use of newer agents, the long-standing perception of MDS as a syndrome where therapeutic nihilism is the only realistic approach is slowly beginning to change.

For many years, there were few attractive treatment options for patients diagnosed with a form of myelodysplastic syndrome (MDS) beyond supportive and palliative care or, for a small number of younger patients with good performance status and a suitable human leukocyte antigen (HLA)-matched donor, allogeneic hematopoietic stem cell transplantation.[1-4] Chemotherapy regimens similar to those administered to patients with acute myeloid leukemia (AML) are generally too toxic for routine use in the typical older patient with MDS (median age at diagnosis: ~65 years), and many patients never recover hematopoiesis after such aggressive cytoreductive therapy. Furthermore, MDS patients who achieve a complete hematologic remission after antileukemic chemotherapy usually relapse within a few months. A number of pilot studies were conducted in the 1980s and 1990s to try to improve this grim situation (e.g., with retinoic acid, amifostine [Ethyol]), but most such clinical trials showed little benefit.

In the past 3 years, the US Food and Drug Administration (FDA) has approved three disease-modifying therapies specifically for use in patients with MDS.[5,6] Additionally, several investigators have described their experiences in the MDS setting with drugs approved for other indications. While it is questionable whether a substantial improvement in the natural history of the disease has truly been achieved, it is clear that some patients benefit from these therapies.[5,7] The expanding repertoire of available treatments for MDS means that choosing the right therapy for a newly diagnosed patient is becoming increasingly challenging. Here, we discuss the agents most commonly used for MDS therapy at present, and outline a strategy for management based on an assessment of an individual patient’s risk for cytopenia-related complications, disease progression, and death. For patients who are disinclined to pursue newer therapies or cannot afford them, good palliative and supportive care is still a reasonable option.

Accurate Assessment of Risk
The conditions grouped together as MDS are as diverse as the patients suffering from them.[8] Some patients with this diagnosis progress rapidly to AML or die from cytopenia-related complications within just a few months of diagnosis, while others do well for many years with a simple strategy of observation and "watchful waiting." In view of this heterogeneity, predicting the risk the disease confers to an individual patient is critically important, especially since all of the therapies currently used for MDS carry the potential for serious adverse effects. Given that the only curative therapy for MDS remains stem cell transplantation, it is important to ensure that the adverse effects of any other proposed treatment—where the goal is not cure—are unlikely to be greater than the morbidity of the disease itself. Unfortunately, the current prognostic methods for MDS are rather blunt tools, and accurate risk assessment remains a long way off.[9]

### Classification Systems

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Total Score</th>
<th>Median Survival ≤ 60 yr old (n = 205)</th>
<th>Median Survival &gt; 60 yr old (n = 611)</th>
<th>Time Until 25% of Surviving Patients in Category Developed Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7 yr</td>
<td>11.8 yr</td>
<td>9.4 yr</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>0.5 or 1.0</td>
<td>3.5 yr</td>
<td>5.2 yr</td>
<td>3.3 yr</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.5 or 2.0</td>
<td>1.2 yr</td>
<td>1.8 yr</td>
<td>1.1 yr</td>
</tr>
<tr>
<td>High</td>
<td>2.5 or greater</td>
<td>0.4 yr</td>
<td>0.3 yr</td>
<td>0.5 yr</td>
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Most clinicians have become comfortable using the simple 1997 International Prognostic Scoring System (IPSS) for assessment of the likelihood of AML transformation or death in de novo MDS (Table 1).[10] The IPSS takes three key factors into account—the proportion of undifferentiated blasts in the patient's blood and marrow (as measured by the manual aspirate differential, not by flow cytometry, which tends to overestimate blast numbers), the cytogenetic risk profile, and the number of cytopenias that the patient has—in order to come up with a four-category prognostic assessment. However, while the IPSS was an important step forward, it is not perfect: As illustrated in Figure 1, any given IPSS category is associated with a broad range of clinical outcomes.
The 2001 MDS classification system of the World Health Organization (WHO) divides MDS into eight categories (Table 3).[11] Although intended as a clinicopathologic classification system rather than a rigorous prognostic tool, the WHO schema does help clinicians perform risk assessment.[12] For instance, forms of MDS that are limited to erythroid dysplasia are now recognized as carrying a better prognosis than forms where marrow dysplasia involves multiple cell lineages; also, patients with excess blasts (> 5%, and especially > 10%) in their bone marrow have a worse outlook than those with a normal blast count. The best outcomes are for patients with classic 5q- syndrome, who enjoy a median survival on the order of 8 to 10 years.[13] A recent proposal to integrate the IPSS with the WHO classification into a "World Health Organization Prognostic Scoring System (WPSS)" (Table 4 and Figure 2) is currently being independently evaluated.[14]
### Table 3

#### 2001 World Health Organization Classification of Myelodysplastic Syndrome

<table>
<thead>
<tr>
<th>Disease Subtype</th>
<th>Common Abbreviation</th>
<th>Typical Blood Findings</th>
<th>Typical Marrow Findings</th>
<th>Median Survival</th>
<th>Median time Until 25% of Patients Develop AML</th>
<th>Estimated Proportion of Newly Diagnosed MDS cases&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia</td>
<td>RA</td>
<td>Anemia, &lt;1% blasts</td>
<td>Erythroid dysplasia</td>
<td>108 mo</td>
<td>-105 mo</td>
<td>10%–15%</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts</td>
<td>RARS</td>
<td>Same as RA</td>
<td>Same as RA but ≥15% ringed sideroblasts</td>
<td></td>
<td></td>
<td>5%–10%</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>Bicytopenia or pancytopenia, &lt;1% blasts</td>
<td>Dysplasia in &gt;10% of cells in 2 or 3 cell lines, &lt;9% blasts</td>
<td>49 mo</td>
<td>-35 mo</td>
<td>25%–30%</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ringed sideroblasts</td>
<td>RCMD-RS</td>
<td>Same as RCMD</td>
<td>Same as RCMD but ≥15% ringed sideroblasts</td>
<td></td>
<td></td>
<td>10%–15%</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts type I</td>
<td>RAEB-I</td>
<td>Cytopenias, &lt;5% blasts</td>
<td>5%–9% blasts</td>
<td>-36 mo</td>
<td>-20 mo</td>
<td>20%</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts type II</td>
<td>RAEB-II</td>
<td>Cytopenias, 5%–19% blasts</td>
<td>10%–19% blasts</td>
<td>-20 mo</td>
<td>-6 mo</td>
<td>20%</td>
</tr>
<tr>
<td>5q- syndrome</td>
<td>Del(5q)</td>
<td>Anemia, normal or elevated platelet count</td>
<td>Hypolobated megakaryocytes, isolated chromosome 5q31 deletion</td>
<td>107 mo</td>
<td>Never reached</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MDS, unclassifiable</td>
<td>MDS-U</td>
<td>Cytopenias</td>
<td>Granulocyte or megakaryocyte dysplasia without erythroid dysplasia, or other atypical features</td>
<td>?</td>
<td>?</td>
<td>Variable</td>
</tr>
</tbody>
</table>

<sup>a</sup> From Harris et al.[107] as summarized in Cazzola and Malcovati[93] and Malcovati et al[12]

<sup>b</sup> From Komrokji and Bennett[106]

AML = acute myeloid leukemia; MDS = myelodysplastic syndromes.
It is important to note that the IPSS is based on 816 patients with de novo MDS. Patients with known secondary MDS (i.e., prior exposure to chemotherapy with alkylating agents or topoisomerase inhibitors, therapeutic or accidental exposure to ionizing radiation, or both) have a very high risk of AML progression and should probably be considered similarly to the highest IPSS risk group.\[15\] Additionally, there are many cytogenetic and molecular genetic risk categories that are not accounted for by the IPSS, because many of the less common MDS-associated karyotypes were represented by only a few patients in the 1997 analysis, resulting in inadequate statistical power to detect the difference between these small groups in outcome.\[16-18\] However, small cohort studies have suggested that some patients with certain uncommon but recurrent karyotypic changes (e.g., abnormalities of chromosome 17p that involve the \textit{TP53} gene) do particularly poorly.\[16,19,20\] These factors need to be considered when deciding on a particular therapeutic course for an individual patient.
Role of Allogeneic Stem Cell Transplantation
The only therapy that is curative for MDS remains allogenic stem cell transplantation.[21] Therefore, any patient with a potential transplant option should be evaluated by a transplant physician. Although the transplant-eligible group has traditionally comprised the minority of MDS patients, the "outer bound" for transplant eligibility in terms of advanced age and presence of serious comorbidities is continually being moved forward.[22,23] Therefore, an opinion from an up-to-date, experienced transplant specialist can be valuable in defining the full range of a patient's options and the risks involved.

One of the most difficult questions with respect to stem cell transplantation relates to the optimal timing.[24] Because this procedure still carries substantial morbidity and mortality (in most series, more than 25% of patients die within the first 100 days of stem cell infusion, and only about 30% are alive and disease-free at 3 years), it is prudent to avoid immediate transplantation in patients who might have several years of a good quality of life with less drastic interventions. However, it is now clear that the highest-risk patients should be referred for immediate transplantation.

In 2004, a Markov decision model that analyzed data from the International Bone Marrow Transplant Registry was published.[25] This study supported the idea that watchful waiting is still appropriate for transplant-eligible MDS patients with IPSS low- or intermediate-1-risk category disease, whereas immediate transplantation is more appropriate for intermediate-2- and high-risk patients. The Markov transplant analysis took place before the FDA approval and widespread use of azacitidine (Vidaza), decitabine (Dacogen), and lenalidomide (Revlimid), which may change the outlook for certain groups of patients. However, it is important to share with patients early on that a cure should not be expected with such agents, even if major improvement in blood counts and even cytogenetic complete remission are achieved.

DNA Methyltransferase Inhibitors
Azacitidine
The first medication FDA-approved for the specific indication of treatment of MDS was azacitidine (5-aza-deoxycytidine), in 2004.[26] This nucleoside analog is incorporated into RNA and DNA in the cell, and irreversibly binds to the enzyme DNA methyltransferase (DNMT), thereby inhibiting DNMT activity as cells proceed through subsequent cell cycles.[27] DNMT-mediated DNA methylation of cytosine in CpG dinucleotides throughout the mammalian genome is an epigenetic modification that can be associated with gene silencing, which can downregulate expression of key tumor-suppressor genes when excessive methylation is present in neoplastic cells.[28,29] Treatment of cells with azacitidine in vitro can result in DNA hypomethylation and reactivation of gene expression.[30] In 2002, the Cancer and Leukemia Group B (CALGB) reported the results of a 191-patient
randomized trial of a monthly 7-day 75 mg/m^2 subcutaneous azacitidine treatment regimen, compared with best supportive care, for patients with any French-American-British (FAB) category of MDS.[31,32] In the CALGB 9221 study, patients randomized to azacitidine had hematologic improvements that met criteria for complete or partial remission (CR or PR) by International Working Group (IWG) standards in 11% of patients, and there were more modest hematologic improvements of unclear importance in 36% of patients.[33] The combined endpoint of leukemia progression or death was delayed by 8 months in the patients that received azacitidine, and quality of life was significantly better, but overall survival was not clearly improved. The survival endpoint might have looked better if patients had not been allowed to cross over from the supportive care arm to the active treatment arm when they exhibited disease progression; most patients in the study did indeed cross over, precluding a robust assessment of azacitidine’s effects on overall survival in MDS. Median duration of response was 12 months. The importance of DNA hypomethylation vs other mechanisms of action of azacitidine in vivo is unclear, as published studies have been inconsistent.[34]

Decitabine

Decitabine (5-aza-2’-deoxycytidine), another DNMT inhibitor that was FDA-approved for use in MDS in May 2006, has distinct in vitro properties compared to azacitidine or cytarabine.[35,36] For instance, decitabine is not incorporated into cellular RNA to the same degree as azacitidine, is activated by deoxycytidine kinase (like cytarabine) rather than uridine-cytidine kinase (like azacitidine), and does not block cell-cycle progression at the G1-S checkpoint to the same degree as cytarabine or azacitidine.[37-39] The clinical importance of these differences, if any, is unknown. A 170-patient multicenter randomized trial (D-0007) showed that a 9-dose, 3-day, every-6-week intravenous decitabine regimen (45 mg/m^2/d, 135 mg/m^2 per treatment cycle) was associated with a 17% overall CR+PR rate by IWG criteria in the active therapy arm—similar to the CR/PR response rates seen with azacitidine in the CALGB 9221 trial—with 13% of patients having more modest hematologic improvements.[40] This regimen is detailed on the decitabine package insert and generally requires hospital admission for administration.

A lower-dose, 5-day 20 mg/m^2/d (100 mg/m^2 per treatment cycle) intravenous outpatient decitabine schedule is currently being explored, with preliminary reports claiming a CR rate by IWG criteria of 39%.[41] This suggests that dose and schedule may be critically important for optimizing the use of DNA-hypomethylating agents, and alternative doses and schedules of azacitidine are also now being pursued.[42] A European analysis claimed that decitabine was particularly effective in thrombocytopenic patients.[43] Median duration of clinical response to decitabine is about 10 months.[40]

With respect to leukemia progression or death, azacitidine and decitabine seem to be most effective at delaying this combined endpoint in IPSS High- and Intermediate-2-risk category patients.[27,44,45] In contrast, lower-risk patients, although they may benefit from these agents by manifesting a salutary hematopoietic response, have a higher risk-benefit ratio, so this class of drugs should be used in such patients only after careful consideration.[46] Many clinicians reserve these drugs for patients who either are transfusion-dependent or have excess blasts in their bone marrow. The major adverse-effects of both agents include worsening of cytopenias, which is troublesome but may be partly overcome with myeloid growth factors.

Unanswered Questions

From a practical standpoint, a number of important clinical questions have yet to be answered with respect to the use of DNMT inhibitors in patients with MDS. First, is it important to stay "on schedule" and treat patients with these agents every 4 to 6 weeks, even when blood counts have not recovered from the previous cycle of therapy? Some clinicians do not wait until full restoration of normal blood counts before proceeding with another cycle of these agents, but do withhold treatment if there is evidence of frankly aplastic marrow or as long as the cytopenias remain profound without any sign of hematopoietic recovery. This approach seems reasonable but needs to be validated in careful clinical trials before it can be generally adopted.

Second, how long should patients be treated with hypomethylating agents without apparent results before the agent is declared a failure? The median time to a response to azacitidine and decitabine has been between three and six cycles in published studies, and there are anecdotal reports of patients not responding until much later.[33] With azacitidine, 75% of patients respond by four cycles and 90% respond by six cycles.[33] The need for cells to go through the cell cycle before the epigenetic modifications induced by these drugs are likely to have any effect suggests that prolonged treatment is likely to be necessary for most patients, if they indeed work via epigenetic mechanisms. However, this needs to be balanced against the inconvenience of therapy and the risk of prolonged cytopenias.
Third, how long should therapy with DNMT inhibitors be continued after a clinical response is achieved? While practical considerations often dictate patients taking a "drug holiday," it is now clear that responding patients who do not receive some form of maintenance therapy with azacitidine or decitabine will relapse. However, it is not clear to what extent further therapy helps prevent such a relapse.

Fourth, should the dose of the drug be reduced during maintenance therapy, or during induction therapy in patients who have not fully recovered blood counts? It is not clear that there is a dose-response curve with hypomethylating agents, but the answer to this question is simply unknown.

Fifth, what is the optimal schedule for these agents, and can other drugs be used in combination? The role of combination therapy, especially with other epigenetic-modifying agents, is currently being explored in a number of clinical trials. Practical considerations such as accessibility to chemotherapy units on weekends often dictate deviation from the FDA-approved schedule (eg, the 7-day schedule on the azacitidine label, which is frequently modified to a 5-day schedule or to a 5-day plus 2-day schedule, since many chemotherapy administration units in the United States are closed on weekends).

Finally, is there a role for azacitidine and decitabine either in maintaining remission after induction therapy similar to that given to AML patients, or post-stem cell transplantation? Again, there is hope that these agents will play a role in the post-intensive therapy or posttransplant setting, but their precise role has yet to be defined by well-designed clinical trials. Both drugs are associated with responses in AML.[47,48]

**Lenalidomide: An 'Immunomodulatory' Agent**

The therapeutic success with thalidomide (Thalomid) in patients with multiple myeloma or other clonal hematopoietic disorders led to clinical trials of this mysterious agent in MDS.[49] While objective hematopoietic improvements were observed, adverse effects of thalidomide led to high rates of study subject dropout in early trials.[50-52] Lenalidomide (CC-5013) is a drug chemically related to thalidomide that was engineered to retain the beneficial effects of thalidomide while minimizing some of the toxicity, and is associated with reduced rates of neuropathy and possibly a lower teratogenic potential.[53]

Lenalidomide treatment in MDS has been particularly promising in patients with chromosome 5q31 deletion, regardless of the karyotypic complexity. In a pilot study, 10 of 12 patients (83%) enjoyed a partial or complete cytogenetic response and a reduction or complete resolution of the need for red cell transfusion.[54] The median time to achievement of clinical response has been about 4 to 5 weeks. In a follow-up study of 148 patients with interstitial chromosome 5 deletions that included band q31, 112 patients (76%) had a reduced need for red cell transfusions, and 99 patients (67%) did not require any transfusions at all for the duration of the study.[55] The median duration of transfusion independence was not reached after 2 years of follow-up, and the median hemoglobin rise was a striking 5.4 g/dL. Cytogenetic improvement was observed in 62 of 85 evaluable patients (73%), and 38 (45%) had complete cytogenetic remission. Additionally, 38 of 106 patients (36%) had complete resolution of morphologic abnormality in their bone marrow.

On the negative side, neutropenia was present in 55% of patients and thrombocytopenia in 44% in the lenalidomide del(5q) study.[55] This, in addition to the high cost and substantial logistical problems associated with prescribing the drug, has been the chief barrier to using lenalidomide in MDS. Myeloid growth factors can help with the neutropenia, but thrombocytopenia is more difficult to deal with. Thrombocytopenia at baseline is the most important variable associated with reduced probability of hematologic or cytogenetic response; patients in published studies have had a platelet count of 50,000 or above at baseline and an absolute neutrophil count of 500/mm³ or above. Thus, the usefulness of lenalidomide in the severely pancytopenic patient with MDS who happens to have a 5q31 deletion is less clear. Lenalidomide does have favorable effects in some patients who have normal cytogenetic results, and there may turn out to be other karyotypes that also predict a beneficial response to lenalidomide.[56] Only further experience with this drug will help define such groups.

Lenalidomide is FDA-approved only for patients in the low or intermediate-1 IPSS risk category who are unlikely to respond to recombinant erythropoietin (ie, have a serum erythropoietin level of greater than 500 U/L, or have previously failed epoetin alfa [Epoegen, Procrit] or darbepoetin alfa [Aranesp] therapy). However, the role of this drug in the MDS therapeutic armamentarium is potentially broader than that, and there have even been case reports of favorable responses in patients with MDS transformed to AML.[57] The narrow wording of the FDA approval of lenalidomide and the serious cost issues mentioned above may restrict the access of such patients to the drug.
Antithymocyte Globulin and Immunosuppressive Agents
Some patients with MDS may respond to immunosuppressive therapy directed at potentially autoreactive T-cell clones, a strategy that has been quite successful in treating the bone marrow failure associated with aplastic anemia. Antithymocyte globulin (horse-derived ATG [Atgam], rabbit-derived ATG [Thymoglobulin]) and antilymphocyte globulin (ALG, no specific preparation available in the United States) have resulted in hematologic responses, mostly partial, in about 20% to 40% of patients with MDS.[58-61]
The most common adverse event associated with these agents is serum sickness, which can be mitigated to some degree with corticosteroid coadministration. The source of the ATG (ie, rabbit vs horse) does not seem to affect outcome.[62] In one study, younger patients with short duration of red cell transfusion and HLA-DR15 (DR2) had a better likelihood of response.[63] However, a European group did not find the HLA-DR15 association with positive response in their more recent multicenter study.[61] Better methods of predicting response in individual patients are clearly needed before ATG can find its niche in MDS therapy.
Other approaches have used different immunosuppressive and immunomodulatory agents, including cyclosporine and antibodies against tumor necrosis factor-alpha.[64-67] The chief obstacle with these drugs, again, is in selecting appropriate patients. While some clinicians limit immunosuppressive treatment to patients with hypoplastic MDS (ie, a hypocellular bone marrow) by analogy with aplastic anemia, other groups have not found that hypoplasia of the bone marrow consistently predicts response to immunosuppressant therapy in MDS.[68,69] Most clinicians reserve these agents for patients who have lower-risk disease and do not have an excess of blasts. If hematopoietic impairment is associated with a cyto-genetically abnormal clone and accumulation of undifferentiated myeloblasts in the marrow, the likelihood that immune suppression will result in clinical improvement is small.
Arsenic Trioxide, Valproate, and Other Histone Deacetylase Inhibitors
Eukaryotic DNA is wrapped around nucleosomes and tightly packaged in chromatin, and the regional acetylation status of the eight histone subunits that comprise the core of the nucleosomes determines how accessible a particular area of DNA is to transcription.[70] Accessibility of DNA to transcription, in turn, determines the level of expression of key tumor suppressors and other genes. Histone acetylation is controlled by the enzyme histone deacetylase (HDAC), and HDAC inhibitors with high potency are currently in clinical trials in MDS and other diseases.[71]
At least three drugs that are approved by the FDA for other indications possess some HDAC inhibitory activity: arsenic trioxide (Trisenox), valproic acid (Depakene), and, most recently, vorinostat (SAHA [Zolinza]), which was approved by the FDA in late 2006 for treatment of patients with refractory cutaneous T-cell lymphoma. Preliminary trials have shown occasional responses (mostly hematologic improvement, rather than CR or PR) with each of these agents in MDS, but these responses are generally not robust or durable.[34,72-75] Arsenic trioxide has peculiar issues with respect to cardiotoxicities such as QT-interval prolongation, and it requires careful monitoring during use, dampening enthusiasm for its role outside of the clinical trial setting.[76] This class of agents may be more useful as part of a combination regimen, or when used in different doses or schedules than those explored to date.
Supportive Care
Erythropoietic Growth Factors

Sluggish erythropoiesis in patients with MDS can often be encouraged with the use of supraphysiologic doses of recombinant human erythropoietin. This may result in hemoglobin levels improving, a decrease in red cell transfusion needs, and potentially augmentation of quality of life.[77,78] Epoetin alfa (Epogen, Procrit) and epoetin beta (not available in the United States) have been used for MDS-associated anemia since the early 1990s, and in most series, response rates in unselected patients have been between 15% and 25%. [79,80] Work by the Nordic MDS group suggests that the patients who are most likely to benefit are those with endogenous erythropoietin level less than 500 U/L, and patients who require less than 2 units of packed red blood cells per month to maintain physiologic hemoglobin levels. [80] If patients have both a high endogenous erythropoietin level and heavier transfusion needs, their likelihood of response to recombinant erythropoietin supplementation is less than 10%, whereas if they have neither of these adverse factors, it is greater than 70% (Table 6). [80]
A preliminary study of very high doses of epoetin in the early 1990s did not show any improvement over the response rate observed using more typical doses of 40,000 to 60,000 U/wk.[81] However, this question is being revisited, because several studies incorporating darbepoetin administered at doses higher than those typically used for cancer-associated anemia resulted in substantial erythropoietic responses higher than that previously seen with typical doses of epoetin. For instance, a French study using 300 µg of darbepoetin weekly showed a 71% red cell response rate (77% of those responses were considered "major"), an Italian study using varying doses of darbepoetin (most commonly 150 µg weekly) described a 45% erythropoietic response rate, and another European trial of 150 µg of darbepoetin weekly (restricted to low and intermediate—1 IPSS risk category patients) reported a 40.5% red cell response rate.[82-84] Ongoing trials of epoetin alfa at higher doses in MDS will address whether this effect is drug-specific or merely a matter of dosage.

If no response is observed after erythropoietin therapy is initiated, it is not clear how long clinicians should wait before deciding such treatment has been ineffective. Evidence-based guidelines suggest increasing the erythropoietic agent's dose if no response has been observed after 4 to 8 weeks, and discontinuing therapy if there has been no response after 8 to 12 weeks.[4,85] In the absence of any information to the contrary, these recommendations seem reasonable.

Myeloid Growth Factors
Granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]), when used alone, may improve the white blood cell count in MDS patients but do not change the overall survival or rate of disease progression.[86] These agents are most often combined with red cell factors, and they do improve the erythropoietic response rate from 15%-20% to 35%-40%.[77,87] In the United States, however, logistical concerns (particularly Medicare reimbursement rules regarding self-injection) limit the use of these agents.

Nevertheless, it is reasonable, in IPSS low- and intermediate-1-risk patients with anemia that has not responded to erythropoietin alone, to add G-CSF at a dose of 0.3 to 3 µg/kg/d, or comparable doses of GM-CSF. The use of pegfilgrastim (Neulasta) should be approached cautiously in MDS: Splenic ruptures and leukemoid reactions have been reported in this setting when the standard 6-mg postchemotherapy dose is used.[88]

Platelet Growth Factors
Clinical responses to interleukin-11 (IL-11, oprelvekin [Neumega]) in MDS have been modest and transient.[89] Although chronic use would be required in MDS, it is difficult to use this agent long-term, even in low doses, because of the potential for fluid accumulation, with associated atrial distention/dysrhythmia risk and peripheral edema.
Initial clinical trials of recombinant human thrombopoietins in the 1990s were halted because of the immunogenicity of these compounds.[90] Several newer thrombopoietin receptor-stimulating agents that do not appear to be immunogenic are currently in clinical trials. These include AMG531 and eltrombopag (SB-497115). Neither agent is FDA-approved for any indication as of this writing, but the response rates of these agents in MDS will be of great interest, as thrombocytopenia is often a major issue in the quality of life of patients with MDS.

Iron Chelation

In the past, most clinicians did not aggressively pursue transfusional iron overload in patients with MDS.[91] In part, this was because deferoxamine, the only iron chelator available in the United States prior to 2005, had to be administered parenterally for a prolonged period (8 to 12 hours), typically 5 to 7 nights per week, to be effective. Biochemically apparent iron overload is common in red cell transfusion-dependent patients with MDS: After receiving 20 to 25 units of packed red cells, most patients have a ferritin level approaching or exceeding 1,000 ng/mL.[92,93] This is especially true in patients with sideroblastic anemia, who in general have higher levels of iron stores at baseline than patients with other forms of MDS, and may also be true in those with hemochromatosis-associated HFE polymorphisms. However, the frequency of clinically relevant iron overload is generally likely to be much lower in MDS.

In 2005, a multivariate analysis of MDS risk factors by Malcovati and colleagues in Italy suggested that a ferritin level greater than 1,000 ng/mL was associated with an increased risk of death.[12] This information, combined with the availability of a new oral iron chelator (deferasirox, ICL670 [Exjade]) that is usually well tolerated by patients with good baseline kidney function, is now leading clinicians to revisit issues of iron chelation in MDS.[94] Unfortunately, most patients with IPSS Intermediate-2- or High-risk category disease will not live long enough for iron chelation to become a major clinical problem.

Additionally, it is currently not clear to what degree iron overload alone contributes to excess mortality or morbidity in MDS, even among those patients with lower-risk disease (ie, life expectancy > 5 years).[91] Even if iron overload itself is responsible for the correlation between a markedly elevated ferritin and an increased hazard of death in low-risk MDS, one would have to demonstrate, in a controlled fashion, whether or not intervention with iron chelation alters the complication rates from iron overload. Until then, since iron chelation therapy is quite expensive, it should only be used after a detailed discussion of the uncertainties with the patient.

Special Disease Subtypes

Pure Sideroblastic Anemia

Idiopathic acquired sideroblastic anemia, first described in 1956, was considered a form of MDS by the 1970s.[95,96] However, there is a clear distinction between patients who have sideroblasts and only erythroid-lineage dysplasia, vs those with sideroblasts in association with multilineage dysplasia or excess blasts.[97,98] The former have a particularly indolent course with a median survival exceeding 10 years and rare leukemic transformation, whereas the latter have a poorer outlook.[99] Patients with pure sideroblastic anemia often are given a brief trial of pyridoxine (vitamin B6) at a dose of 100 mg/d. This is reasonable because some patients do have late-onset pyridoxine-responsive forms of sideroblastic anemia.[100] While pyridoxine is quite inexpensive, patients with trilineage dysplasia almost never respond to this intervention, and in these patients it may be little more than a waste of time. It is important to evaluate patients with pure sideroblastic anemia for other causes of sideroblastic anemia, such as copper deficiency, mutations in ALAS2 (if mean corpuscular volume is low), and sideroblastogenic drugs.[101]

Chronic Myelomonocytic Leukemia

Patients with the MDS/myeloproliferative disease overlap syndrome, chronic myelomonocytic leukemia (CMML), are a heterogeneous and distinct group who present difficult challenges. Some patients with CMML have more proliferative features (organomegaly, leukocytosis) and require cytoreductive therapy, whereas others have an MDS-like course dominated by marrow failure associated with a mild relative monocytosis, and may benefit from interventions focused on improving hematopoiesis.[102,103] Rare patients with gene rearrangements involving the platelet-derived growth factor receptor-beta chain—eg, t(5;12)(q33;p13)—are generally offered imatinib mesylate (Gleevec), but these unfortunately represent only a tiny minority of CMML patients.[104]

Etoposide and hydroxyurea were compared head-to-head in CMML in a 1995 French-led study, with hydroxyurea proving superior (60% vs 36% overall response rate, 20 vs 9 months median survival) but both agents performing relatively poorly.[105] More recently, the M.D. Anderson group reported clinical responses with decitabine in patients with CMML,[41] and salutary responses have also been
reported with azacitidine,[106] but the numbers of patients treated with these agents thus far have been small. Independent confirmation of these findings in larger groups of patients are necessary. CMML patients with a high white blood cell count are often excluded from MDS clinical trials, such as the recent studies of lenalidomide, and need to be approached on an individualized basis, as there are few data to help determine how to treat these patients.

Summary Recommendations

Even in view of the introduction of new therapies for MDS, certain core treatment principles remain unchanged.[3] Because overall outcomes remain poor, patients with MDS should be offered clinical trial participation whenever possible. In addition, all patients with MDS should receive the best possible supportive care with transfusion support and antimicrobial agents as needed. Patients who potentially are stem cell transplantation candidates should be referred for an opinion from a transplant center.

Anemic patients, regardless of karyotype, who have an endogenous erythropoietin level less than 500 U/L should undergo a trial of an erythropoietic agent, either epoetin or darbepoetin for at least 8 to 12 weeks, using adequate doses. Patients with chromosome 5q31 deletions, regardless of karyotype complexity, should be considered for lenalidomide therapy. Intermediate to high-risk MDS patients or secondary MDS patients who do not have a transplant option can be considered for azacitidine or decitabine. Patients with symptomatic or transfusion-dependent anemia who do not have an excess of blasts can be offered immunosuppressive agents. Finally, whether or not iron chelation therapy results in a meaningful health outcome in patients with MDS is currently being studied in a controlled clinical trial, and until results are available therapy should be individualized.

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