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Myelodysplastic Syndromes: Therapy and Outlook

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ABSTRACT

Myelodysplastic syndromes (MDS) are a diverse group of hematopoietic disorders characterized by dysplasia, peripheral cytopenias, and risk of progression to acute myeloid leukemia and death. In patients who are ineligible for potentially curative hematopoietic stem cell transplantation (HSCT), approved therapies such as lenalidomide, azacitidine, and decitabine are available for those who previously would have received supportive care alone. Each treatment can achieve hematologic improvement and enhance quality of life. Azacitidine is the only treatment to show a significant survival advantage in patients with higher-risk MDS compared with conventional care regimens. The treatment panorama has been further enhanced with immunosuppressive agents, growth factor support, and biologic response modifiers. Initial treatment decisions are based around HSCT eligibility and when best supportive care becomes insufficient. Transfusion dependence is associated with adverse outcomes and is an indication for possible treatment escalation.

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KEYWORDS: Azacitidine; Bone marrow transplantation; Myelodysplastic syndromes; Transfusion dependence

Treatment of the myelodysplastic syndromes (MDS) has progressed considerably in recent years. The emergence of Food and Drug Administration (FDA)-approved agents in the United States such as lenalidomide, azacitidine, and decitabine in particular has provided significant advances, resulting in patients who are ineligible for hematopoietic stem cell transplantation (HSCT) now being able to receive individualized treatment aimed at improving quality of life and changing the natural history of disease. Prior to these therapies becoming available, supportive care measures consisting of blood and platelet transfusions, hematopoietic growth factor support, and antimicrobials were the only available treatments. This review examines the goals of treatment in International Prognostic Scoring System (IPSS)-defined lower- and higher-risk subgroups, suggests the appropriate time to initiate treatment, sets out the recommendations of the National Comprehensive Cancer Network (NCCN) MDS Panel, and presents approved and investigational treatments transforming the standard of care in MDS.

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THERAPEUTIC GOALS AND INITIATING TREATMENT

Management of MDS is based on expectations of treatment tolerability and quality of life, as well as on the risks imposed by the disease itself.[1] However, because MDS differs from many hematologic malignancies in terms of its chronic nature and in the morbidity and mortality associated with cytopenias, alleviating disease-related symptoms is an important therapeutic goal.[2] Therapy should be optimized for each patient based on his or her IPSS risk category as well as age, performance status, and comorbidities, all of which determine the likelihood of a patient tolerating treatments of different intensities.[3] In making objective treatment decisions, physicians have come to rely on the major IPSS risk groups of "lower-risk" disease that encompasses Low- and Intermediate (Int)-1-risk categories, and "higher-risk" MDS that incorporates those patients with Int-2-and High-risk disease.[3,4] These risk groups allow stratification of patients according to survival and progression to acute myeloid leukemia (AML).[4] In the case of lower-risk MDS, the goals of therapy are hematologic improvement, transfusion independence, quality of life, and delay of progression. In contrast, for patients in the higher-risk group, alteration of disease natural history is of paramount importance.[2,3]

Even though a diagnosis of MDS is often suspected from the blood count and careful examination of the peripheral

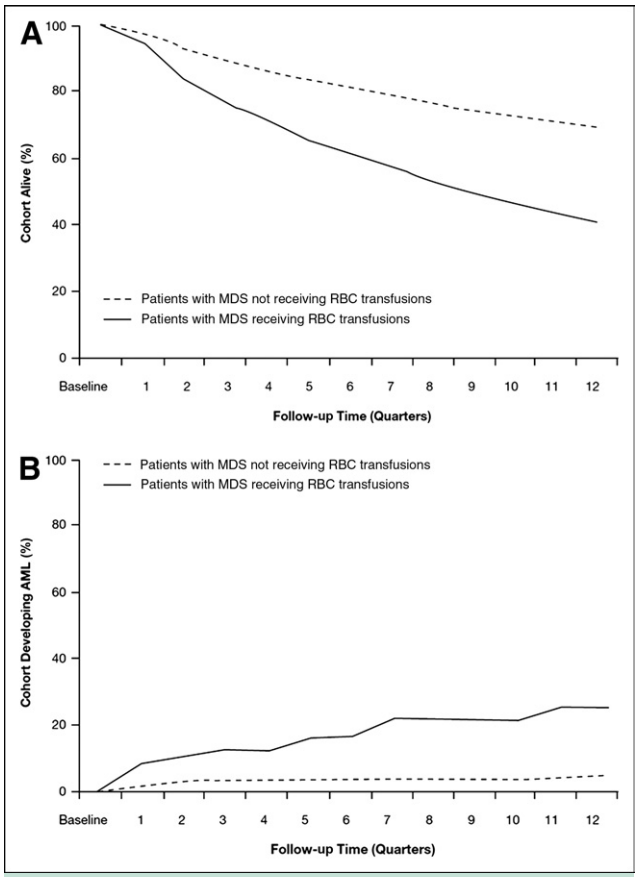

Figure 1 Patients with myelodysplastic syndromes (MDS) who are red blood cell (RBC)-transfusion-dependent are at increased risk of (*A*) shortened survival and (*B*) progression to acute myeloid leukemia (AML). (Reprinted with permission from *J Clin Oncol.*[6] © 2010 by the American Society of Clinical Oncology. All rights reserved.)

blood smear, along with exclusion of other common causes of low blood counts, treatment should not be initiated without a definitive diagnosis. Physicians can use the pace of disease progression and symptoms as indicators to determine when treatment will likely be needed, and a bone marrow aspiration, biopsy, and chromosomal analysis must be undertaken for definitive diagnosis. A "watch and wait" approach is generally recommended for patients with lower-risk disease, a hemoglobin level >10 g/dL, and with no transfusion needs.[5] Higher-risk patients usually require treatment immediately.[5] Given that HSCT is the only potentially curative treatment for MDS,[2] any initial decision must be made around the eligibility of the patient for transplantation. A key consideration in any patient with MDS is the need to avoid chronic transfusion dependency, because this is associated with iron overload and its attendant potential risk of organ damage and dysfunction.[5,6] Transfusion dependency also affects quality of life and predicts shortened survival (**Figure 1**).[6-8] Best supportive care for all patients includes clinical monitoring, red blood cell (RBC) and platelet transfusions for symptomatic anemia or thrombocytopenia, psychosocial support, and quality-of-life assessments.[3] Daily iron chelation with subcutaneous deferoxamine or oral deferasirox should be considered to decrease iron overload in patients receiving >20 to 30 RBC transfusions.[3] In addition, hematopoietic growth factor support, such as erythropoietin, granulocyte colony-stimulating factor, or granulocyte/macrophage colony-stimulating factor, should be considered for symptomatic cytopenias that are unresponsive to correction of all other identifiable causes of the low blood counts.[3] Also, the physician must determine when best supportive care is insufficient and what further treatment is indicated in those patients considered ineligible for transplantation.

Transfusion dependency impacts on quality of life and predicts shortened survival, reinforcing the need for definitive diagnosis and treatment in such patients.

THERAPEUTIC ALGORITHM FOR MYELODYSPLASTIC SYNDROMES

A therapeutic algorithm adapted with minor modifications from the 2010 MDS guidelines of the NCCN is shown in **Figure 2**.[3] Although most patients who are eligible for HSCT are aged <55 years,[9] any patient with good performance status may be considered subject to the availability of a suitable donor.[3] In this regard, allogeneic HSCT from an HLA-matched sibling donor or matched unrelated donor with nonmyeloablative conditioning is the preferred approach in older patients, particularly for those with higher-risk disease.[3]

Among patients with lower-risk disease who are not transplantation candidates, those with deletion of the long arm of chromosome 5 [del(5q)] abnormality and symptomatic anemia generally receive lenalidomide in the United States.[3] Patients with lower-risk disease should receive erythroid growth factor support for refractory symptomatic anemia with an erythropoietin level of ≤500 mU/mL.[3] Some patients will respond to immunosuppressive therapy; nonresponders can be included in a clinical trial, proceed to hypomethylating agents, or be considered for allogeneic HSCT.[3] Patients with thrombocytopenia or neutropenia should receive hypomethylating agents or may be included in a clinical trial, and nonresponders may receive immunosuppressive therapy.[3]

For patients with higher-risk disease who are ineligible for HSCT, current evidence supports the use of hypomethylating agents or treatment in a clinical trial.[3] With its attendant high-risk of treatment-related morbidity and mortality, many patients are ineligible for high-intensity therapy owing to age, performance status, and comorbid conditions. Patient preference is often a factor in selecting a suitable therapy in this higher-risk group.[3]

Barriers to enrollment in a clinical trial include socioeconomic status and geographical location.[10,11] Primary care physicians are encouraged to refer their patients to a specialist with an interest in MDS when contemplating this option.

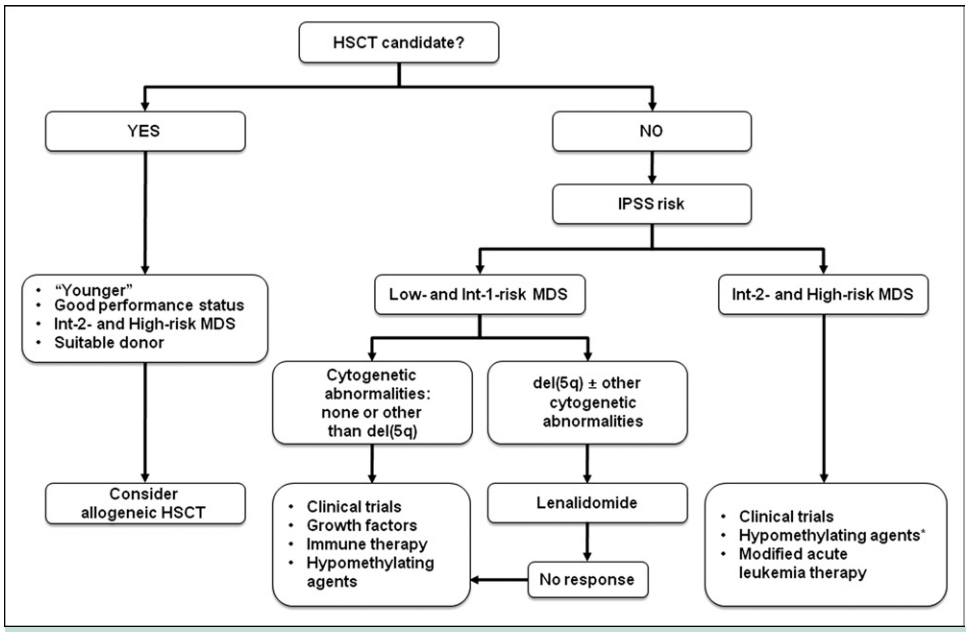

Figure 2 Therapeutic algorithm for the myelodysplastic syndromes. Supportive care is suggested as an adjunct to treatment for all patients. *Preferred treatment: azacitidine. del(5q) = deletion of long arm of chromosome 5; HSCT = hematopoietic stem cell transplantation; Int = intermediate; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes. (Adapted from NCCN Clinical Practice Guidelines in Oncology.[3])

APPROVED TREATMENTS

The management of MDS has improved in recent years with the availability of several active treatments that can alter the natural history of the disease and improve quality of life. Much progress has been made in the management of cytopenias. In the case of symptomatic anemia, increased response rates to erythropoiesis-stimulating agents are observed when patients are selected based on hematocrit levels of <36% together with adequate iron stores and serum erythropoietin levels at a maximum of 500 mU/mL.[3] In patients with symptomatic anemia, refractory thrombocytopenia, or neutropenia, immunosuppressive therapy with antithymocyte globulin, with or without cyclosporine, is potentially underutilized. However, it is associated with a good probability of response in patients with lower-risk disease aged ≤60 years, or in those with HLA-DR15 histocompatibility type, bone marrow hypoplasia, normal cytogenetics, and/or evidence of a paroxysmal nocturnal hemoglobinuria clone.[3,12] Neutropenia, in particular, may not respond to other interventions.

The disease management of MDS has improved in recent years with the availability of several active treatments that can alter the natural history of the disease and improve quality of life.

Lenalidomide, a second-generation oral immunomodulating agent, is approved for the treatment of anemia in RBC-transfusion-dependent patients with IPSS-defined Low- or Int-1-risk MDS and a del(5q) cytogenetic abnormality, with or without additional abnormalities.[3,13,14] The del(5q) abnormality is the most common chromosomal deletion in MDS, with 5% to 6% of patients having the sole karyotypic abnormality and 10% to 20% of patients having del(5q) plus ≥1 additional abnormality.[4] In these patients, who often present with severe refractory anemia and thrombocytosis, treatment with lenalidomide 5 mg and 10 mg resulted in RBC-transfusion independence for ≥26 weeks in 43% and 56% of patients, respectively, compared with 6% of patients who received placebo in a large randomized phase 3 study (P <0.001 for both lenalidomide groups versus placebo).[15] Furthermore, 25% and 50% of these treated patients, respectively, showed a reverse of cytogenetic abnormalities compared with 0% of patients in the placebo group (P <0.001 for both lenalidomide groups versus placebo).[15] Despite the impressive remissions seen in many of these patients, over time lenalidomide resistance may develop owing to recurrence or expansion of the del(5q) clone; however, this has not been shown in a prospective study with appropriate controls.[16] It should also be noted that patients with MDS and del(5q) abnormality who are treated with lenalidomide can remain transfusion-independent for extended periods even after discontinuation of treatment and, in some cases, despite persistence or reoccurrence of the del(5q) clone.[17,18] Lenalidomide is generally well tolerated; however, it can cause grade 3 or 4 neutropenia and thrombocytopenia, which require intervention.[15]

Azacitidine and decitabine are cytosine nucleoside analogs with a mechanism of action that involves hypo-

methylation of DNA by inhibition of methyltransferase activity. This results in restoration of normal growth control and differentiation to mature hematopoietic cells.[19-21] In addition, azacitidine, but not decitabine, has a cytotoxic effect resulting from its incorporation into RNA.[19] The US FDA has approved azacitidine and decitabine for the treatment of all MDS subtypes.

Unlike standard chemotherapy, both azacitidine and decitabine are associated with a slow onset of response. In the case of azacitidine, first response is seen on average by the second or third course of treatment, with 91% of responders achieving their first response by 6 cycles of treatment and 48% of responders having a further improvement in the quality of response with continued treatment.[21-23] Each drug has demonstrated significant rates of hematologic improvement and remission compared with supportive care in large randomized phase 3 studies.[20,24] A total of 50% of patients treated with azacitidine showed hematologic improvement and 27% achieved remission, compared with 31% and 5% of patients, respectively, who received supportive care ($P < 0.01$ for both).[24] Decitabine treatment led to hematologic improvement or remission in 30% of patients compared with 7% of patients who received supportive care ($P < 0.001$).[20] However, continued treatment beyond first response may be needed to achieve optimal response to both drugs.[20-24] Azacitidine is the only hypomethylating agent to demonstrate significantly prolonged overall survival in patients with higher-risk MDS compared with conventional care regimens.[24] Remarkably, the survival benefit for azacitidine was apparent irrespective of the presence of several risk factors, including poor-risk cytogenetics, high bone marrow blast percentage, MDS subtype, and IPSS-defined high-risk disease. Moreover, complete or even partial response to azacitidine is not required for improved overall survival.[25] Myelosuppression in patients receiving azacitidine is readily managed with dose modifications and administering blood product transfusions.[26] The FDA-approved administration schedule for azacitidine is 75 mg/m^2 per day on days 1 to 7 of each 28-day cycle. Recent results suggest that patients with lower-risk MDS respond well to alternative 5-day dosing strategies, which permit dose flexibility by avoiding weekend administration.[22] This study did not investigate survival as an endpoint.[22] Patients with higher-risk MDS may have similar outcomes with the 5-day and 7-day regimens; however, there are no prospective randomized, controlled studies that have directly compared these regimens.[27]

The survival data for decitabine have been disappointing. Two phase 3 studies have failed to demonstrate a significant survival advantage for decitabine compared with supportive care in patients with MDS.[20,28] Imperfect study design and short treatment duration may account for the absence of survival benefit. However, both azacitidine and decitabine are associated with significant quality-of-life improvements when compared with supportive care.[20,29]

Although full-dose cytarabine-based therapy has been standard for higher-risk MDS, it is associated with poor results, especially in patients aged >70 years, in those with poor performance status, or in those with adverse karyotypes.[30,31] Allogeneic HSCT is the only treatment able to induce long-term remission in patients with MDS, but considering its high rate of treatment-related mortality (about 39% of patients at 1 year), suboptimal disease-free survival (about 29% of patients at 5 years), and chronic graft-versus-host disease (about 15% of patients at 1 year),[32] it is recommended as first-line treatment only for patients with Int-2 or high-risk disease as defined by the IPSS criteria.[33] Moreover, only a small minority of patients are eligible for HSCT, with the findings of 1 physician survey suggesting that <5% of patients receive HSCT.[34] More than 50% of these cases underwent myeloablative transplantation despite 3-year leukemia-free survival rates of 23% to 36%, depending on age group, reported for nonmyeloablative HSCT.[35] Many physicians consider "older age" as a barrier to HSCT; however, a recent analysis in 1,080 patients with MDS or AML in first complete remission, who underwent HSCT using reduced intensity conditioning, showed no impact of age on outcome.[36] Indeed, it is becoming increasingly apparent that it is the comorbidities associated with increasing age, rather than age itself, that are the primary patient-specific factors associated with HSCT outcomes.[37]

NOVEL THERAPIES

Several investigational therapies are currently being evaluated for MDS. Among these are the immune thrombocytopenic purpura–like treatments for thrombocytopenia. Immune thrombocytopenic purpura–like treatments reflect the understanding that some patients with MDS with immunologically mediated cytopenias could benefit from immunosuppressive therapies.[38,39] Such treatments include corticosteroids, intravenous immunoglobulin, danazol, the anti-CD52 monoclonal antibody alemtuzumab, and the thrombopoietin receptor analog romiplostim.[40-43] Clofarabine, the purine nucleoside antimetabolite, has recently been evaluated in patients with higher risk MDS and has achieved a response rate of 43%.[44] As our understanding of the epigenetic changes that characterize MDS improves, other classes of agents, such as the histone deacetylase inhibitors, are likely to play a greater role.[45] As with other malignancies, angiogenesis is involved in the pathogenesis of higher risk MDS, indicating a potential role for angiogenesis inhibitors.[1,46] Given the recent success of azacitidine, efforts are underway to improve disease management with an oral formulation for ease of administration.[47,48] Preliminary data of maintenance therapy using azacitidine have shown maintenance in higher risk disease is feasible and associated with prolonged remissions with mild side effects.[49] Finally, the success of agents such as lenalidomide, azacitidine, and decitabine suggests that novel combination regimens may also be a way forward in the management of MDS. The use of lenalidomide in patients with higher-risk MDS is under investigation.[50,51] The early results of a phase 1 study of lenalidomide plus azacitidine in higher-risk

treatment-naive patients with MDS suggest this novel combination is well tolerated, with a response rate that at least equals that of either agent used alone in this setting.[50] Combinations currently under investigation in lower-risk MDS include romiplostim plus lenalidomide, and azacitidine plus romiplostim.[52,53]

SUMMARY

There is a range of treatment options available in MDS to alleviate symptoms, improve quality of life, and extend survival. The range of therapies enables treatment to be tailored to the individual, with therapeutic goals aligned to IPSS-defined risk category, disease classification, age, and performance status. Quality of life is a major consideration in any treatment decision and should be heavily weighted when discussing options with the patient. In lower-risk MDS where the goal is to reduce transfusion dependency, improve quality of life, and delay disease progression, possible treatments include growth factor support, immunosuppressive therapy, and hypomethylating agents. However, in the subgroup of patients with symptomatic anemia and del(5q) abnormality, with or without other cytogenetic abnormalities, lenalidomide is the initial treatment of choice. In higher-risk MDS where the goal is to extend survival, HSCT remains the only potentially curative therapy. For the majority of patients who are ineligible for HSCT, azacitidine is the only treatment shown to prolong survival compared with conventional care.

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