COMMENTARY

Myelodysplastic Syndromes—Many New Drugs, Little Therapeutic Progress

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Myelodysplastic syndromes (MDS) constitute a form of blood cancer that primarily affects the elderly and is characterized by anemia (or other cytopenias) and a high risk of leukemic transformation.[1] The World Health Organization (WHO) system has formally classified MDS as 1 of 5 myeloid malignancies that also include acute myeloid leukemia (AML) and myeloproliferative neoplasms.[2] All myeloid malignancies, including MDS, are clonal stem cell diseases. Unlike the case with *BCR-ABL1*-positive chronic myelogenous leukemia,[3] the disease-causing mutation in MDS is currently unknown. It is generally believed that the MDS phenotype is additionally affected by secondary mutations, genetic haploinsufficiency, epigenetic changes, and altered host response that result in cytokine, immune, and bone marrow stromal changes.[1] Unfortunately, none of this information has successfully been translated into a robust pathogenetic framework or effective targeted therapy.

In routine clinical practice, MDS are suspected when an otherwise unexplained anemia is associated with other cytopenias, increased mean corpuscular volume, or increased red cell distribution width. The peripheral blood smear in MDS shows oval macrocytes, a dimorphic red blood cell population, or hyposegmented/hypogranulated neutrophils. Diagnosis requires bone marrow examination and cytogenetic studies. The consensual minimum criterion for diagnosis is the presence of erythroid, granulocyte, or megakaryocyte dysplasia in 10% or more of informative cells.[2] In this regard, one must exclude the possibility of erythroid dysplasia associated with vitamin B_{12}/folate/copper deficiency, viral infections, chemotherapy, or lead/arsenic poisoning. The detection of an abnormal karyotype confirms the morphologic diagnosis of MDS.[4] The WHO system further subclassifies MDS into 6 subcategories depending on the percentage of blasts in the bone marrow or peripheral blood, presence or absence of bone marrow multilineage dysplasia, or excess ring sideroblasts: refractory cytopenia with unilineage dysplasia, refractory anemia with ring sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess of blasts, MDS associated with isolated 5q–, and MDS unclassifiable.[2]

Myelodysplastic syndromes are rare in young people, with an estimated incidence rate of less than 1 per 100,000 before age 50 years and approximately 2 per 100,000 between ages 50 and 60 years; however, the incidence rises significantly after age 60 years: approximately 8 per 100,000 between ages 60 and 70 years and greater than 20 per 100,000 after age 70 years.[5] In 2004, close to 10,000 new US cases of MDS were registered, and approximately 7000 cases occurred in patients older than age 70 years.[5] Prognosis is poor for patients with MDS, with 3-year survival rates estimated at less than 50%.[5] The standard prognostic tool in MDS is the International Prognostic Scoring System (IPSS), which classifies patients into low-, intermediate-1, intermediate-2, and high-risk categories on the basis of the percentage of bone marrow blasts, the karyotype, and the number of cytopenias; the respective median survival rates are estimated at 8, 5.3, 2.2, and 0.9 years.[6,7] Although additional IPSS-independent prognostic variables have since been described, their added practical value has been modest.[8] From the standpoint of both disease biology and prognosis, it is important to distinguish primary MDS from therapy-related MDS; the latter is closely related to therapy-related AML and develops in the setting of prior exposure to chemotherapy (eg, alkylating agents, topoisomerase II inhibitors), radiotherapy, radiation accidents, benzene, or other toxins and is prognostically worse than primary MDS.[9]

Current management in MDS includes supportive care (eg, red blood cell transfusions), drug therapy, and allogeneic hematopoietic cell transplant (allo-SCT). Currently, allo-SCT is the only treatment modality for MDS with curative potential. However, because most patients with MDS are older than age 70 years,[5] they are not good candidates for allo-SCT, and the value of allo-SCT in younger patients is undermined by the substantial risk of treatment-related death and morbidity.[10-12] Furthermore, *cure* is not necessarily essential in the presence of drug therapy that can effectively control disease symptoms and prevent disease-related mortality.[13,14] Unfortunately, drug therapy for MDS has had limited success, which reflects our inadequate insight into disease pathogenesis. Regardless, 4 new drugs (azaciti-

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dine, decitabine, lenalidomide, and deferasirox) were recently approved by the Food and Drug Administration for use in certain types of MDS. In the following sections, I comment on their true value in current practice.

Azacitidine and Decitabine

Epigenetic alteration of gene expression is usually facilitated by DNA methylation (eg, CpG-island hypermethylation) or posttranscriptional histone modification (eg, methylation, acetylation). In MDS, epigenetic mechanisms might contribute to altered transcription of tumor suppressor genes and lead to clonal expansion and disease progression.[15] On the basis of such assumptions, 2 classes of anti-epigenetic drugs are currently being evaluated: histone deacetylase inhibitors (eg, depsipeptides, vorinostat, panobinostat, valproic acid) and DNA methyltransferase inhibitors (eg, azacitidine, decitabine). Azacitidine (5-azacitidine) and decitabine (5-aza-deoxycytidine, ie, the deoxy derivative of 5-azacitidine) are cytosine nucleoside analogues, as is cytarabine. All 3 drugs are proapoptotic and cytotoxic at "high" doses. At lower doses, azacitidine and decitabine have been shown to induce DNA hypomethylation.[16] However, there is currently no good evidence to suggest that this underlies their mechanism of action in patients.[17]

Controlled studies of MDS using subcutaneous 5-azacitidine (75 mg/m^2/d for 7 days every 28 days)[18] or intravenous decitabine (15 mg/m^2 over 3 hours every 8 hours for 3 days every 6 weeks)[19] have shown that the 2 drugs are associated with response rates similar to those of subcutaneous low-dose cytarabine[20]: complete remission (CR) rates of 9%, 7%, and 20.3% and partial remission rates of 8%, 16%, and 11.9%, respectively. The respective median survivals were 21 months for patients receiving azacitidine (vs 14 months for patients receiving supportive care only), 14 months for those receiving decitabine (vs 15 months for patients receiving supportive care only), and 19 months for patients receiving low-dose cytarabine (vs 15 or 20 months for patients receiving low-dose cytarabine in combination with granulocyte-macrophage colony-stimulating factor or interleukin 3). Two more recent studies comparing either azacitidine or decitabine with "best" alternative care in patients with high-risk MDS showed a survival advantage for the former (median survival of 24.5 vs 15 months)[21] but not the latter (10 vs 9 months).[22]

How does one interpret the aforementioned information? First, it is important to underscore the fact that the studies involved patients with primarily high- or intermediate-2 risk MDS or AML, and therefore, it is inappropriate and potentially dangerous (both drugs cause severe myelosuppression) to extrapolate the results to patients with IPSS low- or intermediate-1 risk disease. Second, in regard to higher-risk MDS, the results are confounded by the inclusion of patients with AML or chronic myelomonocytic leukemia. For example, in the 2 randomized studies involving azacitidine,[18,21] the WHO-defined diagnosis in 31% to 38% of the patients was AML or chronic myelomonocytic leukemia. Third, and most importantly, it is unclear whether the overall treatment outcome with azacitidine or decitabine is truly superior to that of either low-dose cytarabine or AML-like induction chemotherapy. For example, the latter has been shown to induce CR rates of approximately 50% in patients with MDS,[23,24] whereas subcutaneous low-dose cytarabine (20 mg twice a day for 10 days every 4 to 6 weeks), compared to hydroxyurea, has been shown to improve survival in patients with AML or high-risk MDS.[25]

Lenalidomide

Lenalidomide is a second-generation thalidomide analogue with a broad cytokine modulatory activity that includes inhibition of tumor necrosis factor α.[26] Lenalidomide is more potent than thalidomide in its anti-angiogenic, anti–tumor necrosis factor α, and T-cell costimulatory activity.[27] Two relatively large studies of MDS with[28] or without[29] 5q– karyotype provide the evidence for lenalidomide (10 mg/d or closely similar schedule) use in MDS. Both studies involved patients with primarily low or intermediate-1 risk MDS who were transfusion-dependent at baseline. Lenalidomide use led to transfusion independence in 67% (with 5q–) and 26% (without 5q–) of the patients with a remission duration of approximately 2 years (with 5q–) and 9 months (without 5q–). Grade 3/4 neutropenia and thrombocytopenia occurred in 55% and 44% of patients with 5q– and 30% and 25% of patients without 5q–, respectively. Cytogenetic CR was documented in 45% (with 5q–) and 9% (without 5q–) of informative patients, all occurring among hematologic responders. Lenalidomide (10 mg/d) was also useful in high- or intermediate-2 risk MDS associated with isolated 5q– karyotype, especially in the presence of greater than 100×10^9/L platelet count.[30] Regardless, all 3 of the aforementioned studies involving singe-agent lenalidomide suffer from lack of a control group, which makes it difficult to appreciate the impact of the drug on survival and its true value in patients without 5q– karyotype.

Deferasirox

Deferasirox is an oral iron-chelating agent that is approved by the Food and Drug Administration for use in transfusional hemosiderosis associated with hemoglobinopathies, rare anemias, and MDS. However, the value of iron chelation therapy for MDS is dubious because complications of iron overload develop after many years of target organ exposure that commences early in life; in more

than 85% of patients with MDS, the diagnosis is made after they are older than 60 years, and the 3-year survival rate is only 35%.[31] Some have argued that such treatment might be appropriate for a subset of patients with MDS who have a long life expectancy and who are identified by the presence of less than 5% bone marrow blasts and absence of multilineage dysplasia and high-risk cytogenetic abnormalities.[32] What is often overlooked is the fact that transfusion-dependent patients with MDS do not have a long life expectancy and that transfusion need in MDS is a marker of biologically aggressive disease with inferior overall and leukemia-free survival.[32] Two major Mayo Clinic studies have demonstrated the detrimental effect of transfusion dependency, but not serum ferritin, on the survival of patients with otherwise "low-risk" MDS including RARS[33] and "MDS associated with isolated 5q–."[34] Similar observations were made in patients with myelofibrosis.[35,36]

Despite the aforementioned studies, the literature is full of weak attempts to overstate the danger of iron overload in patients with MDS and the unproven value of iron chelation therapy.[37-42] Most of these studies inappropriately used serum ferritin as the surrogate for both clinically relevant disease and treatment effect, and some have even flirted with retrospective comparison of patients who have or have not received iron chelation therapy. The fact is that physicians are more likely to administer iron chelation therapy to patients in whom a longer life expectancy is anticipated, and, therefore, nothing short of a prospective randomized study can provide the information needed to justify the use of a potentially toxic and officially expensive form of treatment.[43-45]

Conclusion

The genius of Henry S. Plummer has enabled the establishment of a robust Mayo Clinic health record system.[46] Using such records with approval of the institutional review board, Mayo Clinic investigators have published several retrospective studies, including those in MDS.[33,34] However, we will be the first ones to admit that, when it comes to treatment recommendations, such studies cannot substitute for properly designed prospective studies with primary end points that signify meaningful health outcome. Current recommendations for the use of iron chelation therapy for MDS are (1) not evidence-based, (2) economically irresponsible, (3) usually organized and sponsored by drug companies, and (4) not consistent with the essence of clinical excellence in academia.[47,48]

I am also underwhelmed by the overall therapeutic impact of hypomethylating agents in patients with MDS. In general, I find the risk/benefit balance of using azacitidine or decitabine in IPSS low- or intermediate-1 risk MDS unfavorable. In IPSS high- or intermediate-2 risk disease, my first preference is allo-SCT; if this is not possible, I favor clinical trial participation over the currently available therapeutic options. Otherwise, in the presence of a 5q– karyotype associated with symptomatic disease, it is reasonable to start with a treatment trial that includes lenalidomide. In all other instances, AML-like induction chemotherapy and low-dose cytarabine, azacitidine, or decitabine are equally reasonable to use, and a properly designed randomized study, not data massaging, is needed to choose one over the other.

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