

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Clara D. Bloomfield, MD

Advances in MDS

Charles A. Schiffer, MD
Professor of Medicine and Oncology
Leader, Multidisciplinary
Leukemia/Lymphoma Group
Barbara Ann Karmanos Cancer Institute
Wayne State University School of Medicine
Detroit, Mich.

H&O What are the characteristics of myelodysplastic syndromes (MDS)?

CS The use of the word “syndromes,” reminds us that MDS represents a spectrum of clinical behavior with many heterogeneous disorders included within this categorization. MDS is usually diagnosed after a bone marrow aspirate and biopsy are done to evaluate the cause of peripheral blood cytopenias, most commonly macrocytic anemia. MDS is initially characterized morphologically using the World Health Organization (WHO) classification system, which superseded the earlier French-American-British categorization. In addition to the severity of the cytopenias, the number of blasts and type and complexity of cytogenetic abnormalities assist in determining prognosis. Not surprisingly, patients who do most poorly are those with the lowest blood counts, most abnormal cytogenetics, and highest number of blasts. Scoring systems based on these parameters, such as the IPSS (International Prognostic Scoring System), which was recently refined with the recognition that patients requiring red blood cell (RBC) transfusions have a poorer prognosis, are widely used to provide estimates of expected survival and the likelihood of progression to acute myeloid leukemia (AML). Although these scores can be helpful in evaluating the prognosis of individual patients and allow comparisons between papers describing the results of treatment, they provide no insight into the biology of MDS.

H&O What is the status of research into the molecular pathogenesis of MDS?

CS Remarkably little is known about the molecular pathogenesis of MDS. This is the situation even in the subtypes of MDS that are most clearly defined clinically and cytogenetically, such as the so-called “5q- syndrome,” a disorder characterized by refractory anemia, thrombocytosis, chromosome deletion at 5q31-33, and female gender. It is generally accepted that MDS is a clonal hematopoietic stem cell disorder that can occur following exposure to exogenous toxins, including therapeutic radiation or chemotherapy. Usually, however, there is no obvious exposure to which the disease can be attributed. The incidence in the United States seems to be increasing, in part probably reflecting increasing diagnostic testing as well as changes in population demography with increasing numbers of older individuals. Because of the supposition that MDS is due to cumulative damage to hematopoietic stem cells, there is considerable interest in the role of inherited polymorphisms affecting the ability of individuals to metabolize genotoxins to which they are naturally exposed as well as to repair damaged DNA.

H&O Could you discuss lenalidomide for the treatment of MDS?

CS Lenalidomide (Revlimid, Celgene) is an analog of thalidomide that was approved by the US Food and Drug Administration (FDA) for the treatment of RBC transfusion-dependent anemia in patients with IPSS low- or intermediate-1-risk MDS associated with a chromosome deletion 5q (5q-) cytogenetic abnormality, with or without additional cytogenetic abnormalities. Almost all were refractory to treatment with erythropoietin. Approximately 70% of patients became RBC transfusion independent, most within the first 4–6 weeks of treatment, often with normalization of hemoglobin levels. Lenalidomide is administered orally and is generally well tolerated, although careful monitoring of patients is required because there is often very rapid reduction in previously safe platelet and neutrophil counts because of suppression of hematopoiesis from the 5q- clone, with delays in return of normal hematopoiesis. Dose reduc-

tions are frequently required and patients are at risk for infections and hemorrhage while neutropenic and thrombocytopenic. Importantly, and unique among other treatments for MDS, hematologic response is associated with complete or partial cytogenetic remission in most patients, indicating a major cytotoxic effect against the malignant clone. Lenalidomide is continued in responders with a median duration of response of approximately 2 years. The response rate in 5q- patients who have more advanced MDS is not known as the original clinical trials included only patients with relatively normal platelet and neutrophil counts. Trials are currently in progress to see if the remarkable results in lower-risk patients are seen in 5q- patients with more advanced disease, including those with AML.

Lenalidomide can also be of benefit for some lower-risk IPSS patients who do not have the 5q- chromosomal abnormality. Approximately 25% of these patients experience substantial increases in hemoglobin, although the median rise in hemoglobin is less than in the 5q- patients and the median response duration is shorter at 41 weeks. Lenalidomide has pleiotropic mechanisms of action, and the mechanism of response is not known. Gene expression comparisons of 5q- and non-5q- responding patients might be informative in this regard.

H&O What other treatments are available for MDS?

CS Treatment with erythropoietin can produce increases in hemoglobin level with reduction or sometimes elimination of the need for RBC transfusion in a minority of patients with refractory anemia and lower-risk IPSS scores. Responses are much more likely in patients with lower than expected endogenous levels of erythropoietin (<250–500 IU), more recent onset of the RBC transfusions, and a lower transfusion requirement at the initiation of erythropoietin. There may be benefit from the addition of low doses of granulocyte-colony stimulating factor in patients with refractory anemia with ringed sideroblasts. Therapy should be stopped in nonresponders or when patients become refractory to erythropoietin administration.

The therapy for other subtypes of MDS can be more problematic. Decitabine (Dacogen, MGI Pharma) and azacitidine (Vidaza, Pharmion) are available for the treatment of all stages of MDS, although the randomized “pivotal” trials resulting in FDA approval were relatively small, and it is not possible to have confidence about the response rates in any of the IPSS subgroups. These agents are structurally similar and are cytotoxic when given at higher doses. At lower doses, they can produce DNA hypomethylation, resulting in re-expression of genes epi-

genetically silenced by DNA hypermethylation, although it is not certain that this is the mechanism by which they exert their effect in MDS. It is also not known which genes are activated and why these agents would “selectively” activate genes associated with improvement rather than worsening of the MDS. Decitabine and azacitidine are administered parenterally, azacitidine either subcutaneously or intravenously and decitabine intravenously (there has been research into delivering it subcutaneously as well). In comparison to lenalidomide, it takes longer to assess whether the treatment is of benefit, and often 3–5 monthly courses are required before a clinician can determine whether a patient is responding. Although both are generally given as outpatient regimens, blood counts tend to worsen before they improve, with attendant risks of neutropenia and thrombocytopenia. Unfortunately, the complete response rates are less than 10%, with durations generally measured in months, although perhaps a third of patients will have rises in other blood counts that can be clinically meaningful.

Comparative data to help decide which of these two agents to choose for a given patient are nonexistent, although there are anecdotal reports of patients responding to one but not the other. There is a non-data-driven perception that the hypomethylating agents are more suited to patients with advanced MDS, particularly those who are preleukemic. There is less systematic information on the use of these agents in patients with lower IPSS scores.

H&O What are the defining characteristics of preleukemic MDS?

CS The WHO classification requires more than 20% blasts in the bone marrow to diagnose AML, but I believe that decisions about treatment must be individualized and consider more than the number of blasts and the pathologic diagnosis. Clearly, when a patient’s blood counts decrease and the number of blasts increases, it is necessary to decide whether to administer more aggressive therapy. However, there are many patients in whom blast count increases occur slowly without worsening of their clinical condition, and therapy is not mandatory simply because they cross the “threshold” to AML. This is particularly true in older people with comorbidities that would predict poor tolerance of therapy. Conversely, there are many younger patients with pancytopenia in whom therapy should be considered independent of blast counts. In patients who are candidates for treatment, the choice is essentially between conventional intensive induction chemotherapy for AML, azacitidine or decitabine, or clinical trials evaluating newer agents. It should also be determined whether allogeneic transplantation should be

offered as initial therapy in suitable patients. There are no comparative trials, however. The complete remission rate following AML induction therapy is approximately 30–40% overall, decreasing with increasing patient age and more complex cytogenetic findings. These remissions are usually measured in months, and induction therapy requires hospitalization for approximately 1 month. Decitabine or azacitidine can be given to outpatients but may require months to produce a response. The decision about whether to treat and with which approach is one of the more difficult problems in the management of advanced MDS and would become simpler if more effective treatments are identified in the future.

H&O Could you discuss the International Working Group response criteria for myelodysplasia?

CS In 2000 and again in 2006, an International Working Group (IWG) proposed standardized response criteria for defining clinically significant responses in MDS. If complete remissions were common, then the traditional AML response definitions would suffice. In MDS, however, count improvements short of complete remission, and particularly rises in hemoglobin, are clearly of symptomatic benefit and had to be quantified in a standardized fashion to permit comparisons between treatments and results of clinical trials. Therefore, the IWG attempted to codify the language clinicians would be using so that risks of exaggerating or underestimating a response were reduced. Of note is that the newer IWG criteria set a higher requirement for a minimal absolute increase in the hemoglobin level to qualify as a response, rather than relying solely upon a more subjective criterion based on a reduction in the number of transfusions.

H&O Could you discuss other approaches to treating MDS now in research?

CS Combining hypomethylating agents with histone deacetylase inhibitors represents one rational investigative approach to the management of MDS. Both of these classes of drugs are intended to restore gene expression, although by different mechanisms. If restoring gene expression is, in fact, of importance, combining these agents makes sense, and interesting trials are now under way. Other agents, such as the farnesyltransferase inhibitor tipifarnib (Johnson & Johnson) have produced real, but very low, response rates in MDS. What is interesting is not the response rate per se but rather the possibility that careful molecular/cellular pharmacologic analyses of these responders could provide potential unique insights into the biology of the disease and how it interacts with particular therapies.

H&O When is stem cell transplantation indicated in MDS?

CS Despite the risks associated with this procedure, allogeneic stem cell transplantation is the only curative therapy available for MDS. Allogeneic transplantation should certainly be considered in younger, otherwise healthy patients with more advanced IPSS stages. In these patients, treatment failure is a consequence of both transplant-related complications and relapse. In contrast, relapse is very uncommon in patients with earlier stage disease, and transplantation should be considered in selected younger patients in whom there is evidence of unremitting RBC transfusion requirements and/or persistent life-threatening cytopenias that have not responded to other therapies. Studies using reduced-intensity conditioning regimens are in progress in the hope that the transplant option can be safely extended to older individuals. An unanswered question is whether the relapse rate will be higher following reduced-intensity conditioning transplantation, offsetting the benefit of decreased transplant-related deaths.

H&O What future avenues of research do you foresee in this setting?

CS We clearly require a better understanding of the fundamental biology (or biologies) of the disease(s). MDS can be difficult to study in the laboratory because it is probably necessary to focus on the small subpopulation of the malignant stem cells, rather than the entire population of cells. This creates a number of significant technical issues, but methodology is now evolving that can measure molecular parameters in small, selected groups of cells.

Suggested Readings

- Bernasconi P, Klersy C, Boni M, et al. World Health Organization classification in combination with cytogenetic markers improves the prognostic stratification of patients with de novo primary myelodysplastic syndromes. *Br J Haematol.* 2007;137:193-205.
- Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood.* 2006;108:419-425.
- Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1998;91:1100.
- Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106:1794-1803.
- List A, Dewald G, Bennett J, et al; Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355:1456-1465.
- Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol.* 2005;20:23:7594-7603.
- Silverman LR, McKenzie DR, Peterson BL, et al; Cancer and Leukemia Group B. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol.* 2006;20:24:3895-3903.