

CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

Treating Low-risk Myelodysplastic Syndromes in the Community Setting

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H&O How are low-risk myelodysplastic syndromes defined?

LC The traditionally accepted definition of low-risk myelodysplastic syndromes (MDS) implies that transfusion dependence for red blood cells is the major clinical issue. Low-risk MDS does not necessarily raise the concern of death due to disease complications or of disease transformation into acute leukemia. Many clinicians thus believe that the goal of treatment of patients with low-risk MDS is to reduce or eliminate the need for red blood cell transfusions. If this goal is feasible in a given patient, reasonably positive outcomes can be expected. Once the International Prognostic Scoring System (IPSS) became commonly accepted, however, many clinicians began to note two important features of what is considered low-risk MDS: first, survival of 5–10 years in the average 60-year-old is not ideal; second, there may be subgroups within the low-risk classification, such as patients with thrombocytopenias, who have suboptimal outcomes. It is therefore becoming apparent in the community that there is a tension in the approach to patients with low-risk disease because it may not be wholly accurate to think of their risk as “low”; rather, this risk may simply be lower than that of other patients for whom transformation to acute myeloid leukemia, or death, is likely in the first few years. As such, does the community need to begin thinking about treatments that will potentially lead to improvement in survival? Moreover, is the mortality associated with low-risk MDS underestimated?

H&O What is the effect on risk of deletion of chromosome 5q31?

LC In general, deletion of chromosome 5q31 from a prognostic standpoint would be viewed as a neutral-to-favorable finding, according to the IPSS. The 5q- syndrome typically occurs in older women who have had macrocytic anemia and a high platelet count. Patients with 5q- syndrome have traditionally been thought to have essentially undiminished survival.

H&O What are the challenges relating to the decision to treat a patient with low-risk MDS?

LC In my opinion, there are three principal challenges. First, and this may be underappreciated by those of us interested in developing new drugs for the treatment of MDS, is the difficulty in diagnosing low-risk MDS. For people over 65 years of age in the United States, the prevalence of anemia may peak at 10–20%. Of these anemic individuals, it is possible to discern the cause in approximately 75% by classic diagnostic approaches, such as testing serum iron and transferrin levels. In the remainder, traditional evaluations for anemia do not provide a diagnosis. The potentially diagnostic finding of dysplasia in the marrow is, however, subjective and sometimes subtle. Therefore, the community struggles with the diagnosis of anemic patients without significant dysplasia in the marrow and who have no or minimal abnormalities in their white blood cell or platelet counts. Could the anemia be an unrecognized phenomenon of aging or is it actually low-risk MDS? Second, there is a group of patients with an anemia that may be symptomatic but who do not require frequent, or sometimes any, transfusions. In the absence of diagnostic morphologic or cytogenetic findings, should we diagnose these individuals as having MDS? These patients typically receive an erythropoiesis-stimulating agent (ESA) and achieve

a good response. Interestingly, this response may create a sense that the ESAs are more active in low-risk MDS than clinical trial data indicate. Third, the community agrees that transfusions are burdensome in terms of costs, patient convenience, and quality of life, and the benefits accrued from transfusions are transient. Also, iron overload is potentially a clinically significant complication of transfusions in people with low-risk MDS.

In my view, it is reasonable to use serum erythropoietin level to guide initial treatment decisions. The closer the serum erythropoietin level is to 500 mIU/ μ L or higher, the lower the likelihood of a response to an ESA. When the level is closer to 200 mIU/ μ L, the likelihood of a response is quite high. The highest response rates are observed in patients who require no or infrequent transfusions and who have a lower serum erythropoietin level. If a patient does not receive an ESA or does not respond, the available treatment options are the hypomethylating agents azacitidine (Vidaza, Pharmion) and decitabine (Dacogen, MGI Pharma), the immunomodulatory agent lenalidomide (Revlimid, Celgene), or a clinical trial of an experimental therapy. I think we are learning whether the likelihood of benefiting from any one agent is worthwhile given the perception that survival in low-risk MDS is "good" and that transfusions may not be too burdensome.

H&O Could you discuss the calculus involved in deciding which approach to use?

LC The convenience of an oral agent makes lenalidomide highly attractive, provided a patient's insurance plan covers it. The response rate in transfusion-dependent patients (~25%) is notable and, in my opinion, undervalued. Responders tend to experience response of almost 1 year. The potential for myelosuppression must be monitored, but this toxicity is not, in my opinion, significant. Data suggest that the erythroid response to hypomethylating agents in terms of transfusion independence is approximately 40%. The inconvenience of a weekly series of injections for many months and the uncertainty of the duration of administration needed both complicate the treatment paradigm for these agents. A question clinicians face is whether lifelong administration of a hypomethylating agent is necessary. Alternately, should administration occur intermittently based on red blood cell response and subsequent loss of response? Practically, when I consult a patient with transfusion-dependent anemia secondary to MDS, who is otherwise doing well, it is difficult to recommend indefinite therapy. However, I do not believe clinicians should be hesitant to recommend hypomethylating agents. The rate of transfusion independence and the

potential for a survival gain are respectable. Finally, clinical trials should be made available to most patients.

H&O In the community setting, what disease characteristics help guide the choice of therapy?

LC If a patient with low-risk, transfusion-dependent MDS characterized by a high serum erythropoietin level has what the treating clinicians consider significant neutropenia or thrombocytopenia in addition to anemia, a hypomethylating agent should be the treatment of choice. In such patients, avoiding the myelosuppression associated with lenalidomide is likely to be beneficial. Patients who respond to hypomethylating agents may have a response that encompasses all three cell lines, whereas the response to lenalidomide is typically more erythroid in nature.

H&O What research is ongoing to improve the treatment options available to patients with low-risk MDS?

LC New agents are currently under development for low-risk MDS. The combination of a hypomethylating agent and lenalidomide is under investigation to elucidate whether this combination benefits more patients than either agent alone and to assess what the duration of response would be. However, the financial burden of treating low-risk MDS with such a combination may be prohibitive. Additionally, there are newer analogs of thalidomide under research, with the hope that one may prove potent in patients with MDS without the deletion of chromosome 5q31 anomaly. In younger patients with low-risk MDS, nonmyeloablative stem cell transplantation is being considered earlier in the clinical course by some institutions.

H&O How is the decision to pursue stem cell transplantation made?

LC I think it is better to educate all patients about this option rather than trying to select a patient with whom to discuss transplantation. I suspect that younger patients with a greater transfusion burden are more willing to accept the short-term risks for the potential long-term benefit. From our standpoint, they are good candidates for nonmyeloablative or reduced-intensity conditioning stem cell transplantation. The expected survival in patients with low-risk MDS probably appears less acceptable to a patient in his or her 50s than to a patient in his or her 70s. Nonmyeloablative conditioning regimens have enabled us to consider stem cell transplantation for more people than I would have thought possible a decade ago.

At my institution, we begin to discuss the option of transplantation with a patient in the first year after diagnosis. If we are able, from an insurance standpoint, we search for sibling and, as necessary, unrelated donors. For a patient with low-risk MDS, we monitor transfusion frequency, the pattern of blood counts (eg, is the patient developing neutropenia?), and reassess the marrow aspirate and cytogenetics periodically for evidence of progression. If the disease is stable, we continue to discuss the risks versus the benefits. If there is evidence of progression, we encourage the patient to proceed to stem cell transplantation.

Suggested Readings

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