Diagnosis and Management of Anemia in Patients With the Myelodysplastic Syndrome

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While not appropriate for all patients with the myelodysplastic syndrome, recombinant erythropoietin (EPO) is a possible alternative to red blood cell transfusion. Specific factors such as the presence of cytopenias, the bone marrow blast percentage, and cytogenetic findings determine which patients are good candidates for treatment with EPO.

Diagnosis of the Myelodysplastic Syndromes

Myelodysplastic syndrome (MDS) is composed of a group of diseases that for decades have been challenging to diagnose and manage.[1,2] MDS is a clonal disease of the bone marrow. The pathologic manifestation of morphologic abnormalities (dysplasia) include ringed sideroblasts, megaloblastic changes, pseudo-Pelger cells, and micromega and multinucleated megakaryocytes. The clinical spectrum ranges from a mild anemia to pancytopenia and acute leukemic evolution.

Pathogenesis of Myelodysplastic Syndrome

A major advance in the understanding of the pathogenesis of MDS has been the recognition of accelerated programmed cell death (apoptosis) in this disease.[3,4] The demonstration of both increased apoptosis by in situ end-labeling of DNA and increased cell proliferation by bromodeoxyuridine in vivo labeling distinguishes these disorders from acute myeloid leukemia (AML). To some extent, these observations reconcile the seemingly opposing findings of marrow hypercellularity seen in the majority of bone marrows of patients with MDS and the presentation of pancytopenia. This may be related to the levels of the apoptosis-related oncogene products such as c-*myc*, which enhances programmed cell death, and *bcl*-2, which has the opposite effect.[5] Other cytokines identified as playing a role include tumor necrosis factor alpha, transforming growth factor beta, and interleukin-1 beta-converting enzyme. Potential therapies to block the common lipid signaling pathways shared by these cytokines include the use of pentoxifylline, lisophylline, and ciprofloxacin.

Presenting Symptoms

Most patients with MDS do not have specific abnormalities on physical examination. The exception is the proliferative phase of chronic myelomonocytic leukemia. Twenty percent of patients present with gum hypertrophy and splenomegaly or hepatomegaly. The most common presentation in a patient over the age of 65 years is the discovery of anemia or pancytopenia without any other explanation. The incidence of MDS is similar to that of AML (ie, approximately five cases per 100,000 and rising to 30 cases per 100,000 in patients over age 70 years).[6]

Before proceeding with a bone marrow aspirate and biopsy in a patient suspected of having MDS, the possibility of the following conditions should be considered: vitamin B12 or folate deficiency, exposure to heavy metals, recent cytotoxic chemotherapy (including patients receiving methotrexate and other immunosuppressive agents for autoimmune disorders), chronic liver diseases, and human immunodeficiency virus (HIV) infection (Table 1). Once these conditions have been excluded, the bone marrow examination becomes of value. Both an aspiration and a biopsy are recommended (the latter to assess the cellularity, the presence of fibrosis, and islands of immature cells). The presence of significant dysplasia in any one of the major three cell lines (erythroid, granulocytic, or megakaryocytic), usually defined as 10% of cells affected, confirms the diagnosis.[7] To further classify the type of MDS, an accurate blast percentage must be determined (eg, less than 5%; 5% to 10%; 11% to 20%; 21% to 30%). An iron stain is necessary to subdivide the under 5% group into greater or less than 15% abnormal sideroblasts. Prognosis is inversely related to the percentage of blasts and has been confirmed in many studies.[8] For example, patients with refractory anemia with ringed sideroblasts have a median survival of five years, whereas patients with refractory anemia with excess blasts in transformation have a median survival of less than one year.

Table 1. -- Diagnostic Evaluation for MDS

Establish serum folate, vitamin B12, ferritin, erythropoietin, serum Fe/total iron-binding capacity
Determine complete blood count, reticulocyte count, red blood cell indices
Rule out renal disorder, thyroid dysfunction, occult bleeding
Evaluate bone marrow and biopsy (percentage of blasts, degree of dysplasia, iron stain for iron stores, and percentage of abnormal sideroblasts)

Bone marrow cytogenetics are obtained at the time of the marrow procedure. Several abnormal karyotypes have been described in as high as 60% of primary MDS and as high as 85% in secondary MDS caused by treatment or known toxic exposure. Patients with abnormalities including 5q– or 20q– have a good prognosis, whereas monosomy 7 or complex abnormalities carry a worse prognosis.[9]

Over the years, many features of MDS have been studied in an attempt to better clarify the overall survival of patients with MDS. These features include degrees of dysplasia, the degree of cytopenia, lactic dehydrogenase levels, bone marrow blast percentage, presence of abnormal localization of immature precursors on the bone marrow biopsy, marrow immunophenotype (presence of CD34, for example), and marrow cytogenetics. An International Prognostic Scoring System (IPSS)[8] was recently published that used only three variables: cytopenias, percentage of marrow blasts, and marrow cytogenetics. More than 800 patients with primary MDS made up this large data base. Four risk groups were identified with median survivals: (1) low risk, 5.7 years, (2) intermediate-1 risk, 3.5 years, (3) intermediate-2 risk, 1.2 years, and (4) high risk, 0.4 years. An additional stratification for age less than or greater than 60 years provides an even better separation for the first two groups, doubling the median survival for the younger cohort in the low and intermediate-1 groups. It is hoped that this new type of risk assessment will permit a better

comparison of therapies by different study groups.

Management of Anemia in Myelodysplastic Syndromes

Until the availability of recombinant EPO, patients were arbitrarily given transfusions upon becoming symptomatic. After determining that B12 and folate levels were normal, alternative interventions (eg, pyridoxine or prednisone) were attempted, but very few patients responded. Transfusions would start at an approximate hemoglobin level of 9 g/dL and then be administered at a rate of two units every three to four weeks. Since each unit of blood yields 250 mg of elemental iron and the body has no way to excrete excess iron, patients who were given transfusions developed an increased risk of secondary hemosiderosis and possibly hemochromatosis and its associated phenomena.

Recombinant Erythropoietin

Recombinant erythropoietin (EPO) has provided an attractive alternative to red cell transfusion for a wide range of anemic patients but not all (Table 2). A recent publication[8] has provided a new prognostic index for patients with MDS. Utilizing the presence of cytopenias, bone marrow blast percentage, and cytogenetic findings, four distinctive groups were identified as defined previously. Patients with an IPSS score in the high-risk and intermediate-2 risk groups have a short median survival of one year or less, and they usually are candidates for intensive chemotherapy rather than EPO. Patients with IPSS scores in the low-risk to intermediate-1 risk groups are excellent candidates for EPO.

Table 2. -- Guidelines for Treating MDS With Erythropoietin
Hematocrit <30 OR hemoglobin <10.0 g/dL
Transfusion requirement
Endogenous EPO level <500 I.U./dL

Studies with EPO have been numerous and varied. In more than 40 published papers on the use of EPO from the mid-1990s to the present, endogenous EPO levels prior to the administration of exogenous EPO were widely divergent, and in some studies, endogenous EPO levels were not measured. Studies included patients who had transfusions as well as those who never received a transfusion, and EPO was used either alone or with other growth factors -- most often G-CSF and GM-CSF. Most trials included patients with ringed sideroblasts/refractory anemia and a few cases of refractory anemia with excess blasts.

EPO dosages also ranged widely, from a low of 80 U/kg to as high 1,000 to 10,000 U/kg. Schedules have been intravenous or subcutaneous and daily to three times a week. The duration of treatment has ranged from as little as 12 weeks to longer than a year.

The numbers in each of these individual studies are small, and some demonstrated remarkable success while others showed trivial or no success. One of the most notable studies with EPO was published by Rose and colleagues.[10] It employed a compassionate use protocol approved by the Food and Drug Administration and recombinant EPO provided by Ortho Biotech, Inc. Patients had to be significantly anemic; those who were likely to move on quickly to AML were excluded. EPO levels in patients accepted into the study were not to be above 500, although some subjects had higher levels. Other criteria were reasonably normal creatinine and correction of overt hemolysis and iron deficiency. More than 80% of patients had fewer than 5% blasts, providing an opportunity to observe the effects of EPO over a longer period of time. Ten percent of patients demonstrated a rise of at least 6 hematocrit points, and an additional 18% had a 50% decrease in transfusion requirements. The median serum EPO levels of these patients was 134; 86% of the responding cases had EPO levels of 100 or less.

Data from Hellström-Lindberg[11] suggest that patients who have ringed sideroblasts have a response rate to EPO of less than 10%. Using a meta-analysis approach, responses were seen in 21% of patients with other types of MDS, with somewhat higher responses when patients received no transfusions or only occasional transfusions and had low EPO serum levels (under 200 U). A more recent study[12] by this group, including American investigators, has combined EPO with G-CSF. The dosages of EPO ranged between 5,000 to 10,000 U per day SC and G-CSF at 1.0 µg/kg per day SC to double the pretreatment granulocyte count. Thirty-six percent of patients showed a response, and no difference occurred among morphologic subgroups, but the highest responses were again noted in patients who had the lowest EPO levels (<100 U) and fewer than two transfusions per month (74% response rate). The investigators noted that it may take up to two to three months before responses occur. The duration of the responses is at least one year, with much variability in maintenance regimens. Verification of these results is being undertaken by the Eastern Cooperative Oncology Group, but it will be several years before more information becomes available.

Quality-of-Life Studies

The ECOG trial is also studying issues involving quality of life. Its trial design will enable investigators to discern quality of life with improvement of hemoglobin levels vs quality of life with or without transfusions. Results will reveal whether simply raising the hematocrit will materially affect other parameters of general well being. Overall, fewer transfusions are safer and more comfortable for the patient, and those receiving transfusions are still at risk for complications such as hepatitis, HIV, viral infection, transfusion reactions, longer hospital stays, and iron overload.

Conclusions

Patients with MDS clearly have an abnormal clone. This situation stands in contrast with the majority of solid tumor patients who are currently receiving EPO in whom the bone marrow stem cell is not primarily affected. Whether there is a residual normal clone in MDS patients or whether we are taking advantage of erythroid precursors that retain some sensitivity to EPO is currently unknown. Today, the entire therapeutic armamentarium is designed either to modulate the clone with the use of cytokines and hormones or to destroy the clone in patients who are suitable for therapeutic assault with an allogeneic transplant or with intensive chemotherapy.

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DR DALTON

Have studies on red cell survival been performed, both before and after receiving EPO? The question comes up because EPO increases production, but some in vitro studies also show that EPO may actually be an antiapoptotic hormone. This may be important in this particular disease.

DR ZUCKERMAN

It would not be an issue of apoptosis in the mature, circulating red cells. The apoptosis issue would come in the erythroid precursors in the marrow, and that is what EPO appears to do: reduce the apoptosis. Of course, once you have a nonnucleated erythroid cell, apoptosis does not come into play.

DR BENNETT

If you are referring to chromium-labeled studies on red cell survival, I am not aware that any studies have been done. As far as alterations in apoptosis, the answer is yes. Eva Hellström has shown that before and after the administration of EPO and G-CSF, there is a marked decrease in apoptosis. Therefore, I believe that there is some evidence that one is having an impact on the balance between c-*myc* and *bcl*-2, and other factors. Peter Greenberg and his group at Stanford have a paper that studies *bcl*-2 evolution. As the disease evolves, with increasing percentages of blast proliferation and a decrease in apoptosis, the status of *bcl*-2 increases, as measured on a paraffin model.

DR CRAWFORD

I know of a couple of mechanisms by which you might see that effect of G-CSF synergy with EPO. The effects of GM-CSF on early stem cells are well known. In addition, however, G-CSF has an anti-inflammatory effect of reducing TNF-alpha and IL-1.

DR BENNETT

In addition to looking at an effect of erythropoiesis, which would be measured by looking at stool and urinary protoporphyrins, it would be interesting to know if a study has been done on the surviving non- nucleated red cells in the peripheral blood to show whether they have a shortened red cell survival. For example, do they have a shortened survival in pernicious anemia or folic acid deficiency?

DR ZUCKERMAN

It would also be interesting to know whether, during the course of erythroid maturation, EPO produces hardier red cell that might survive longer. I am unaware of any studies in any EPO trials for any disease in which that has been addressed.

DR BENNETT

That could be studied quickly in MDS patients. Data on red cell survival could be determined prior to the introduction of EPO; then, following treatment, determine if there is a normal red cell survival or a high-normal red cell survival of longer than 28 days.

DR ZUCKERMAN

The cleanest study might actually be in the renal failure patients, where there is simply an EPO deficiency disorder and little else impacting on red cell survival.

DR CRAWFORD

Regarding desferal, do you supplement iron because these people are not mobilizing it, or do you give them desferal and then EPO? Are these questions being addressed in either direction?

DR BENNETT

The ECOG trial gives no recommendations for supplementing iron. The statement is that patients cannot be iron-deficient, based on ferritin levels and iron stains in the bone marrow, as well as serum iron and total iron-binding capacity (TIBC). Anecdotally, we saw a dramatic phenomenon with EPO in a 40-year-old woman with

chronic lymphocytic leukemia. She completed a trial with fludarabine and reversed her neutrophil/lymphocyte ratio perfectly. She became profoundly anemia as part of this process. Previously, she had hematocrits in the mid-30s and went down to hematocrit as low as 24 with no evidence of blood loss. We started recombinant EPO, and she became iron-deficient, with a mean corpuscular volume that plummeted to approximately 65. A serum iron at that point was 5, although it previously had been normal. She had not responded to EPO. She had not become more anemic; her hematocrit remained around 22. We began iron and kept her on EPO, and her hematocrit at six weeks later was 40. She recovered 5 to 6 hematocrit points every 10 days, while one would expect about 3 hematocrit points every 10 days. We stopped the EPO and continued only with iron. This is the first time I have seen surreptitious iron deficiency being provoked by the administration of EPO. I believe it is critical to be sure that a patient is not borderline iron-deficient; if so, iron should be given. However, as a standard recommendation for patients receiving EPO, we do not normally recommend iron therapy.

DR LEE

We used EPO without ferrous sulfate when we gave chemoradiation therapy to non-small-cell lung cancer patients. Our idea was that if the patient was not iron-deficient, there was normal storage in the bone marrow. However, the mobilization and utilization of iron may not be normal in patients with cancer. We found that without ferrous sulfate supplement, our patients with lung cancer developed anemia despite the therapy with EPO, but when ferrous sulfate was added, only one developed anemia. Even in the patient population with MDS who have much iron storage in the bone marrow, iron supplements will be required for the erythropoiesis.

DR BENNETT

There is no reliable information about giving supplemental iron to patients with malignancies, exclusive of MDS, whose iron stores you expect to be reasonably normal. Whether the recommendation should be to do a quick survey of iron stores is, I suppose, open-ended. Many patients with Hodgkin's disease, for example, present with a picture that mimics iron deficiency. They can have low serum iron but usually low-to-normal TIBCs, and sometimes low-normal or elevated ferritin levels. Whether they will respond to oral iron is unclear; traditionally, they have not, but they might with EPO administration.

Regarding a leukemia-triggering phenomenon, I believe there is no evidence to support a potential role for EPO in that. The evidence for other growth factors is marginal at best. In the few randomized trials in which patients were administered growth factor vs no growth factor, the evolution of AML was identical. Some early reports of growth factor that triggered AML were published, but those investigators agree that the patients were at high risk for evolution to AML and probably were in the process of developing AML when the growth factor was prescribed.

In patients with MDS who are receiving growth factors, we see changes in the character of the early precursors, ie, more promyelocytes and more late myeloblasts. Thus, you can become alarmed as to whether they actually are evolving. However, if you leave them alone (or stop the growth factor, if you are really concerned), the appearance reverses. There is little evidence that these growth factors will trigger an AML evolution in MDS.

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