Anemia in Multiple Myeloma and Its Management

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Anemia is a common feature of multiple myeloma. Its causation is multifactorial, but some patients benefit from recombinant human erythropoietin (rHuEpo).

Etiology of Anemia in Multiple Myeloma

Anemia is a frequent finding in patients with myeloma, second only to skeletal lytic lesions. Approximately 70% of patients have anemia at diagnosis with a median hemoglobin of approximately 10.5 g/dL. The severity of anemia is important in determining the stage and prognosis of disease as determined by the Durie and Salmon staging criteria. Like anemia of chronic disease, the anemia of myeloma is generally normochronic and normocytic, and it is characterized by shortened erythrocyte survival with failure of the bone marrow to compensate by increased red cell production. This depressed red cell production is multifactorial and includes the following factors: (1) impaired availability of storage iron, (2) inadequate erythropoietin response to the level of anemia, and (3) overproduction of cytokines that are capable of inhibiting erythropoiesis. In addition to direct inhibitory effects on erythropoiesis, these cytokines (including tumor necrosis factor, interleukin-1, and interleukin-6) may decrease reutilization of iron stores from reticuloendothelial cells and may interfere with erythropoietin production by the kidney.

Although many mechanisms contribute to the development of anemia in patients with multiple myeloma, the main mechanism is related to defective red cell production by the bone marrow. Reasons for defective erythropoiesis include marrow replacement with myeloma cells and cumulative marrow suppression from chemotherapy. However, the main mechanism of reduced erythropoiesis is related to defective production of erythropoietin or impaired erythroid marrow response to erythropoietin. Beguin et al reported that serum erythropoietin levels were low in approximately 25% of all patients with myeloma. This number increased to 50% of patients with stage III disease and 60% of those with renal impairment. In addition to being the primary growth factor for erythroid precursors, erythropoietin is also a survival factor and prevents apoptosis or programmed cell death of proerythroblasts. Therefore, reduced levels of erythropoietin results in both reduced red cell production and shortened red cell survival. Based on these findings, the use of recombinant human erythropoietin (rHuEpo) may be helpful in the treatment of anemia associated with myeloma.

The Role of rHuEpo

Following the molecular cloning of erythropoietin in 1985, rHuEpo was first found to be effective in the treatment of anemia associated with renal failure. In a study of patients with myeloma receiving hemodialysis, rHuEpo appeared to be effective in treating anemia, but the required doses appeared higher compared with those of patients with other causes of renal failure. This finding suggested that in addition to reduced serum erythropoietin levels found in myeloma patients, the marrow response to rHuEpo may be attenuated in myeloma patients compared with other patients with anemia. The distinction between deficient erythropoietin levels and marrow unresponsiveness may be important in the treatment of anemia of myeloma. Presumably, replacement doses of rHuEpo may be sufficient to induce a response in patients with low serum erythropoietin levels, but higher doses may be necessary in patients with a blunted marrow response.

In 1990, Ludwig et al first reported results using rHuEpo for treatment of anemia associated with multiple myeloma. Treatment with incremental doses of rHuEpo starting at 150 U/kg three times per week for six months resulted in an improvement in 11 of 13 patients. Increases in hemoglobin were associated with a significant improvements in quality of life and sense of well being. In a similar phase II trial, Barlogie and Bega reported their experience in treating patients with 150 U/kg three times per week and observed a response rate of 78%. These investigators also found that pretreatment serum erythropoietin levels greater than 100 U predicted lack of response to exogenous rHuEpo.

In 1995, Cazzola et al reported the results of a randomized, controlled, multicenter study conducted in Europe in which 146 patients were randomized to either placebo or four different dosages of rHuEpo, 100, 200, 400, or 600 U/kg, administered subcutaneously three times per week for six weeks. Of the 10 patients receiving placebo, none had a complete response, two had a partial response, and eight were nonresponders. In contrast, the response rates were between 20% and 30% for patients with pretreatment values above the cutoff points. These investigators concluded that the decision to use rHuEpo in a patient with anemia associated with myeloma should be based on pretreatment serum levels.

Essentially all studies have shown that rHuEpo is effective and safe in patients with anemia associated with myeloma. Response rates range from 55% to 85%, and its use reduces the need for multiple blood transfusions. Patients who respond have improved quality of life and are not exposed to the risks associated with repeated blood transfusions. The drug appears safe, and hypertension or hyperviscosity syndromes have not been a significant problem. Questions remain, however, regarding...
**Which patients with multiple myeloma should receive rHuEpo?** Patients who have a hemoglobin level of less than 11 g/dL may benefit from the use of rHuEpo. Waiting until the patient becomes overtly symptomatic from anemia is not advised. Patients who are symptomatic from anemia may need blood transfusions before beginning rHuEpo. As stated in the study by Garton et al., newly diagnosed myeloma patients who have anemia as the only manifestation of their disease (ie, have no lytic bone disease) may benefit from rHuEpo as the sole initial treatment of their disease. In this subset of patients, anemia represents the only symptomatic problem, and correction of the problem with rHuEpo may delay the need for chemotherapy until the disease progresses. In contrast to this situation, patients with more advanced disease may have improvement in their anemia when treated with chemotherapy. Patients whose hemoglobin levels remain below 11 g/dL despite chemotherapy may benefit from the use of rHuEpo. A baseline serum erythropoietin level should be obtained before beginning rHuEpo. Although no data are available from the current clinical trials, patients with normal serum erythropoietin levels may need a higher dose of rHuEpo to obtain a response compared to patients with low levels of serum erythropoietin.

**What dose of rHuEpo should be used?** Most studies have demonstrated that a starting dose of 150 U/kg given subcutaneously three times per week is a sufficient starting dose. For those patients who respond to rHuEpo, benefit usually is seen by eight weeks of therapy. (A complete response is defined as a hemoglobin level of 13 g/dL or greater, and a partial response is an incremental increase of $>2$ g/dL.) If a response is not seen by eight weeks, then the dose may be increased to 300 U/kg three times weekly for one month. As mentioned above, higher doses of rHuEpo may be required for patients with normal or high baseline levels of serum erythropoietin. If no response is seen following four additional weeks of an increased rHuEpo dose, a response is unlikely and the drug should be discontinued.

**What is the role of maintenance rHuEpo therapy following a response?** Once a satisfactory response has been obtained with rHuEpo, the dose should be reduced by half to try to maintain the response. In some cases, the rHuEpo may be discontinued, but careful observation is necessary to ensure that the patient does not develop recurrent anemia.

**What side effects can be anticipated?** Generally, rHuEpo is well tolerated when administered subcutaneously at a dose of 150 U/kg three times weekly. Potential side effects in the myeloma patient include hypertension and hyperviscosity syndrome; however, these are uncommon and should be treated in the usual fashion.

**References**


**DR SPIVAK**

Several of the studies had only a small number of patients. Also, patients who go to the Mayo Clinic have to be well enough to get there, so this is a preselected population. In addition, if you want a rationale for whom you are going to treat, show me a patient with a high erythropoietin level who has anemia, and more times than not, I will show you a patient who will not respond to EPO. The levels vary with the disease, of course.

My highest cutoff level for EPO treatment -- 1,000 -- is in myelodysplasia, but I have seen patients with EPO levels of 800 who have responded to EPO. There is some literature support for using a level that high. In studies in HIV-infected patients, it was 500.

My experience in myelodysplasia is that some of these patients have EPO levels that are elevated out of proportion to their anemia. In other words, there is no correlation between serum EPO and hemoglobin in myelodysplasia patients. With these patients, you are in a different paradigm.

**DR DALTON**
My own anecdotal experience is that I have had patients with EPO levels in the hundreds who have responded. Even though I think the Italian study is a good one, my concern is with the algorithm they set: if no response was seen by two weeks, patients are taken off at week 3. If they had continued to treat them at higher doses and beyond the initial three weeks, they might have responded.

**DR BENNETT**

I agree that the Mayo Clinic study suffers from small numbers and that the power calculations for data error are nonexistent in looking at differences in EPO levels. I think this should be ignored. However, this paper does show positive results, so you have to pay attention to that.

**DR ZUCKERMAN**

Regarding the cutoffs with serum EPO levels at 50 and 70 mIU/mL, there are two separate issues here. First, is there a significant difference in response at 50 vs 70, and second, is it worthwhile, in any individual patient, to give EPO? Even if there is a statistically significant difference in the response rate -- for example, if 60% respond if they have EPO levels less than 70, and 28% respond if they have EPO levels above 70 -- would you say that you would not go for that 28% response rate? What is the cutoff in determining that the chance of response is not high enough to try it?

**DR CRAWFORD**

Regarding viscosity, there is a direct relationship between plasma viscosity and plasma volume. The higher the plasma viscosity, the larger the plasma volume; therefore, there is a dilutional component that functions as a compensation to avoid much of the hyperviscosity. This explains why we do not see as much of the hyperviscosity syndrome as we might otherwise. Most people with myeloma have a plasma viscosity in the 2 to 3 range; those above 4 classically have the hyperviscosity syndrome.

I worry about hematocrit levels that get too high, particularly in patients with large M-spikes or high or high-normal viscosities. I believe that, in the lung cancer model, if patients return to a hemoglobin of 15 or 16, fine; that is what they started out with and I am not too worried. However, the level in myeloma might be a problem. We might see some complications that might not normally occur in myeloma. I would favor some sort of graded dose. I would hope we do not get into the situation that dialysis patients have, ie, stopping therapy when a certain target level is achieved and then reinstituting it, because once therapy is stopped, you are just going to be back down to where you were, and you will have to start again.

**DR DALTON**

The issue of plasma viscosity, while important, is something I have rarely dealt with, even in patients with IgA or IgG-3 myeloma.

**DR SPIVAK**

I would not measure plasma viscosity because that is not going to change. Complications will be dependent on the myeloma protein and its characteristics. The whole blood viscosity has to be measured, which will prevent problems. You could argue to any third-party carrier that you are trying to avoid the need for blood transfusions in these patients.

**DR CRAWFORD**

I discussed plasma viscosity because there are established clinical numbers for it. In this country, there are no numbers for whole blood viscosity, but there are good data from Europe where viscosities are routinely measured instead of sedimentation rates to correlate with various disease states.

**DR DALTON**

My own practice with myeloma is to begin antitumor treatment, and if I do not see a response within three months and the patient remains anemic, I start EPO. This is dependent on what is used for treatment. If melphalan/prednisone (MP) is used, it can take four or five months before a response is seen. However, with vincristine, doxorubicin, and dexamethasone (VAD), the response is usually prompt. If I use VAD and the anemia has not improved in a couple of months, the patient will receive EPO.

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