REGULATION OF ENDOGENOUS ERYTHROPOIETIN LEVELS IN ANEMIA ASSOCIATED WITH MYELODYSPLASTIC SYNDROMES

To the Editor:

Myelodysplastic syndromes (MDS) are a group of hematopoietic disorders characterized by ineffective hematopoiesis and refractory cytopenias. Recently, we and others have used recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) in an attempt to overcome bone marrow failure in patients with MDS. Neutropenia was corrected in nearly all patients treated; however, erythroid responses were observed in only a fraction of the patients after multiple cycles of treatment. Therefore, additional strategies are necessary to more uniformly overcome the anemia associated with MDS.

One approach might be to combine GM-CSF with another growth or regulatory factor that could serve to enhance the erythropoietic response. One possible candidate agent is erythropoietin (EPO), a hematopoietic growth factor that promotes the growth and maturation of late erythroid precursors, which has been shown to help overcome anemia in patients with compromised EPO production (eg, end-stage renal disease). However, the rationale for the use of EPO in MDS requires understanding whether the anemia in this disease is associated with an altered regulation of EPO or is related to a deficiency in responsive erythroid target cells. Since our GM-CSF clinical trial yielded both red blood cell responders and nonresponders, this provided a unique opportunity to study the regulation of EPO in this disease, as well as the impact of GM-CSF treatment on the erythroid progenitor cell pool.

Serum EPO levels were determined using a sensitive competitive radioimmunoassay (SmithKline Beecham Biologicals, King of Prussia, PA). Bone marrow cells were obtained before and after two cycles of GM-CSF treatment and in remission. Assays for erythroid progenitor cells (BFU-E) were done as described previously. Comparison of serum EPO levels before and after GM-CSF treatment were done using Student’s t test. The relationship between serum EPO levels and hematocrit values was determined using a linear correlation analysis.

Of the 16 patients treated with GM-CSF, three patients showed an erythropoietic response. The patients exhibiting a red blood cell response were not distinct in FAB class, karyotype, or pretreatment serum EPO levels (Fig 1). Baseline serum EPO levels were markedly elevated (median, 435 mIU/mL; range, 63 to 3,700 mIU/mL) in all 14 patients studied (Fig 1). After two cycles of GM-CSF treatment, serum EPO levels remained elevated (median, 600 mIU/mL; range, 66 to 4,700 mIU/mL) in all 11 patients who had no red blood cell response (Fig 1). In contrast, in all three patients who had an erythropoietic response, serum EPO levels had dropped markedly (P < .05) after two cycles of treatment with GM-CSF, from a baseline median of 580 mIU/mL (range, 370 to 800 mIU/mL) to a post-treatment median of 48 mIU/mL (range, 33 to 69 mIU/mL) (Fig 1). The serum EPO levels in these three erythroid responders continued to decline further with rises in hematocrit levels, until they normalized in two of the three patients and achieved near-normal levels in the third patient (range, 16 to 43 mIU/mL).

Overall, a significant correlation was found between serum EPO levels and hematocrit concentrations (r = .690, P < .001, data not shown). The slope of the correlation line was similar to that reported previously for simple iron deficiency anemia and other anemias not associated with chronic disorders. Thus, the EPO levels in MDS patients appeared to be appropriate for their degree of anemia.

To better understand the biologic basis for anemia and the nature of response to GM-CSF, we examined the growth pattern of bone marrow erythroid progenitor cells before and after GM-CSF treatment. Bone marrow erythroid progenitor cell (BFU-E) growth was.

Fig. 1. Serum EPO levels before (baseline) and after (post-treatment) two cycles of GM-CSF treatment in 14 patients with MDS (three patients with [—] and 11 patients without [—] a red blood cell response). The shaded area represents the upper portion of the normal range, which extends from 4 to 26 mIU/mL.
extremely low or absent in all seven patients studied before GM-CSF treatment (ie, day 14 BFU-E, 0 [n = 6] to 2 [n = 1] colonies per 10⁹ cells plated) compared with that observed from normal donors (ie, day 14 BFU-E, 15 to 85 colonies per 10⁹ cells plated [n = 20]). While BFU-E levels remained unchanged in the red blood cell nonresponders, they increased in all three red blood cell responders (day 14 BFU-E: 57, 3, and 31 colonies per 10⁹ cells) during remission. Curiously, the duration of erythropoietic response after discontinuation of the GM-CSF treatment appeared to be related to the degree of BFU-E expansion while on treatment (greater than 2.5 years, 20 weeks, and 1 year in the three respective patients). These findings suggested that the degree of expansion of erythroid progenitor pools might be an important component for the duration of response.

In summary, our findings demonstrate that serum EPO levels are markedly elevated in patients with MDS, and these levels appear to be appropriate for their degree of anemia. Furthermore, serum EPO levels declined in all three red blood cell responders, indicating that EPO levels are under physiologic regulation and that the hematocrit-EPO feedback loop is intact in these disorders. These results suggest that recombinant human EPO might not play a major therapeutic role in MDS patients who exhibit extremely high endogenous EPO levels. Whether pharmacologic doses of recombinant human EPO in patients with moderately elevated EPO levels can override ineffective erythropoiesis remains to be determined and is currently under investigation. However, our findings that BFU-E growth is extremely poor or absent and that GM-CSF can expand this pool and correct anemia in few patients suggest that hematopoietic regulators acting at the primitive progenitor-cell level might help expand the erythroid progenitor-cell pool and augment erythropoietic response in these disorders.

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REFERENCES

Regulation of endogenous erythropoietin levels in anemia associated with myelodysplastic syndromes [letter]

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