

Erythropoietin and granulocyte colony-stimulating factor as a treatment of myelodysplastic syndrome anemia

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The heterogeneous group of clonal myeloid disorders called the myelodysplastic syndromes (MDS) is characterized by abnormal bone marrow proliferation and differentiation of hematopoietic stem cells.

A high number of patients associate different levels of anemia. Some arise the idea that the therapy with erythropoietin (EPO) and granulocyte-stimulating factor (G-CSF) improves erythroid responses in a portion of MDS patients not responding to EPO alone.

Between December 1997 and June 2004, 110 patients with MDS had been enrolled into this phase 3 prospective randomized trial, with a median follow-up period of 5.8 years (range, 0.8-9.6 years).

The primary objective was to compare the benefits of EPO treatment versus supportive care (SC) for correcting the patients' anemia and to evaluate whether adding G-CSF or increasing the EPO dose enhanced the erythroid response in patients whose disease initially failed to respond to lower doses of EPO. The secondary objective was to compare the incidence of acute myeloid leukemia (AML) and overall survival, in patients between the study arms.

Patients were randomly assigned to receive SC alone (arm A) or EPO 150 U/kg daily subcu-

taneously plus SC (arm B) for 4 months (step 1). Patients crossed over from arm A to arm B and moved to step 2 after the initial 4-month period of observation if there was absence of erythroid response.

For nonresponders at steps 1 or 2, G-CSF (1 µg/kg per day) was added (step 3). Step 3 responders continued this treatment, and nonresponders received increased EPO doses (300 U/kg per day) plus G-CSF (step 4). The response rates in the EPO versus SC alone arms were 36% versus 9.6% ($p=0.002$), respectively, at the initial treatment step, 47% in the EPO arm, including subsequent steps.

Adding the G-CSF to the treatment has no significant effect. No differences were found in overall survival of patients in the EPO versus SC arms (median, 3.1 vs 2.6 years) or in the incidence of transformation to acute myeloid leukemia (7.5% vs. 10.5% patients). Increased survival was demonstrated for erythroid responders versus nonresponders (median, 5.5 vs 2.3 years, $p=0.004$).

In conclusion, this trial has demonstrated that a major portion of patients with MDS and symptomatic anemia had substantial clinical benefit from treatment with EPO with or without G-CSF, but no impact on mortality, except for erythroid responders. ■

Comment on a paper:

Greenberg PL, Sun Z, Miller KB et al – Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). *Blood* 2009; 114:2393-2400