Red Cell Disorders

Efficacy of recombinant human erythropoietin therapy started one month after autologous peripheral blood stem cell transplantation

On day 30 after autologous peripheral blood stem cell transplantation (PBSCT), 20 patients were randomized to receive either erythropoietin at a dose of 500 U/kg/week s.c. (Epo group) or no treatment (control group). After 3 weeks, hemoglobin (p<0.0001) and serum transferrin receptor (p<0.0001) concentrations were higher in the Epo group. Hb response (+2 g/dL) was achieved in 100% vs 28% (p<0.0001) and Hb correction (≥13 g/dL) in 70% vs 10% (p=0.0238) of the patients, respectively. This is the first randomized study showing an efficacy of erythropoietin therapy on Hb levels after autologous PBSCT.

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After high-dose chemotherapy and autologous hematopoietic cell transplantation, endogenous erythropoietin (Epo) remains elevated for 1-3 weeks, then returns to appropriate[1] or low levels[2,3] in marrow or peripheral blood stem cell recipients, respectively. Although some pilot studies,[4] but not others,[5] have suggested that recombinant human erythropoietin (rHuEpo) can be beneficial in this context, all randomized trials using huge doses of rHuEpo starting on day 1 post-transplant have shown no advantage.[6-8] In a recent phase II trial, we started rHuEpo one month after autologous peripheral blood stem cell transplantation (PBSCT).[2] Hemoglobin (Hb) concentration was corrected to ≥13 g/dL in 87% of the patients, compared to 14% of an untreated historical group. The next step was to confirm the effectiveness of rHuEpo on Hb levels in a prospective randomized trial. Confirmation of effectiveness would then justify a larger randomized trial powered for evaluation of transfusion requirements and quality of life. Based on our phase II trial,[2] we calculated that only 20 patients were necessary to demonstrate Hb response and correction with rHuEpo. The protocol was approved by the Ethics Committee of the University of Liège and written informed consent from the patients was obtained on the day of randomization (day 30). Ten patients were randomized to receive rHuEpo (Neorecormon®) 500 U/kg s.c. once weekly starting on day 30 post-transplant (Epo group), and 10 others to no rHuEpo (control group). None had received rHuEpo in the preceding 3 months or was transfusion-dependent before transplantation. Red blood cell and platelet transfusions were given when Hb concentration and platelet count were below 8 g/dL and 15×10^9/L, respectively. The primary endpoint was the proportion of patients achieving Hb correction (Hb ≥13 g/dL) before day 100. The dose of rHuEpo was then reduced to the lowest that maintained Hb at 12-14 g/dL. Patients with functional iron deficiency (transferrin saturation <20%) in the Epo group (n=3) received 3 doses of 200 mg i.v. iron saccharate (Venofer®). The groups were well balanced for clinical characteristics (Table 1). The levels of serum soluble transferrin receptor (sTfR) (a quantitative measure of erythropoietic activity) as well as Epo (and observed/predicted (O/P) Epo ratio) were measured as previously reported.[2] Groups were compared by unpaired Student's t-tests (with Welsh's correction in case of unequal variance) and Wilcoxon's rank tests, as appropriate. Prior to day 30, erythropoiesis and Hb levels (Figure 1) and speed of erythroid engraftment (Table 1) were strictly comparable in the two groups. Before starting rHuEpo, mean±SD O/P Epo ratio was 0.76±0.13 (<1 in 95% of the patients). Whereas sTfR and Hb remained stable between days 30-

Table 1. Patients' characteristics prior to rHuEpo treatment.

	Control group	*Epo group*
Number of patients	10	10
Age (M±SD), years	56±9	57±7
Gender		
Males	10	10
Females	0	0
Disease		
Acute myeloid leukemia	1	1
Non Hodgkin's lymphoma	2	3
Multiple myeloma	7	6
Disease status		
Complete remission	6	3
Not in complete remission	4	7
Prior autologous HCT		
Yes	7	6
No	3	4
Conditioning regimen		
Melphalan	7	6
Cyclophosphamide+TBI	2	2
Cyclophosphamide+Ara-C+TBI	1	1
BEAM	0	1
Graft manipulation		
None	10	10
Serum creatinine (mg/L) on day 30	10.6±4.1	11.5±5.7
Graft composition (mean ± SD)		
CD34$^+$ cells ×10^6/kg	7.16±3.34	12.67±8.23
BFU-E ×10^4/kg	164.7±132.3	162.2±130.2
Days to 1% reticulocytes (median)	12	13
Hb levels at day 30 (mean)	9.7 ± 1.2	9.3 ± 1.2
RBC transfusions (days 0-30)	1.9±3.1	2.7 ± 2.3
Days to last RBC transfusion (median)	11	12
Days to unsupported platelet count of 20×10^9/L (median)	11	11
Days to unsupported platelet count of 100×10^9/L (median)	33	37
Days to last platelet transfusion (median)	6	9
Days to 0.5×10^9/L neutrophils (median)	8	8
Days to 1×10^9/L neutrophils (median)	9	9
Number of days of G-CSF (mean±SD)	10±2	10±2

TBI: total body irradiation; BFU-E: burst-forming unit-erythroid; G-CSF: granulocyte colony-stimulating factor; None of the comparisons between rHuEpo and control groups was statistically significant.

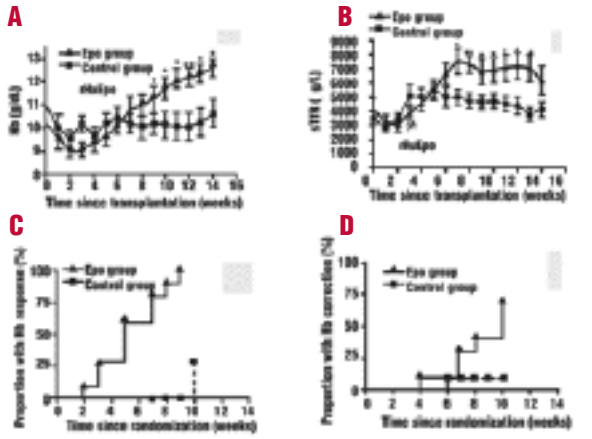

Figure 1. Randomized comparison of a group of 10 patients receiving rHuEpo (Epo group) and 10 patients receiving no treatment (control group). *p* values: *<0.05, **<0.01. A. Evolution of Hb levels from the day of transplantation. B. Evolution of sTfR levels from the day of transplantation. C. Kaplan-Meier plot of time to Hb response (increment >2 g/dL) from day 30 post-transplant ($p<0.0001$). D. Kaplan-Meier plot of time to Hb correction (Hb >13 g/dL) from day 30 post-transplant ($p = 0.0238$)

100 in the control group, both increased rapidly in the Epo group (Figures 1 A-B) to become significantly higher ($p<0.0001$) after day 49 or 63, respectively. The Kaplan-Meier probabilities of achieving a Hb increment of at least 2g/dL at 3, 6 or 10 weeks after starting rHuEpo were 30%, 60% and 100%, respectively, in the Epo group, versus 0%, 0% and 28%, respectively, in the control group (Figure 1C, $p<0.0001$). The probability of achieving Hb values of 12 or 13g/dL before day 100 (Figure 1D) were 90% and 70% in the Epo group versus 40% ($p=0.0058$) and 10% ($p=0.0238$) in the control group, respectively. The median times to Hb response (+ 2 g/dL) or Hb correction in the Epo group were 5 weeks and 10 weeks, respectively (not reached in control group). Two patients in each group (0.9±0.8 in controls vs 0.3±0.2 in Epo group, $p=0.4755$) received RBC transfusions between days 30-100.

rHuEpo is unlikely to increase red blood cell production when endogenous Epo is elevated and nearly all Epo receptors on erythroid progenitors and precursors are saturated, particularly early post-transplant when there are relatively few of these cells.[9] Therefore it is not surprising that all previous randomized trials starting rHuEpo on the day of transplantation were unsuccessful.[6-8] In this study, we took a more physiological approach by providing rHuEpo 30 days after transplantation, when endogenous Epo is low and erythroid precursors are proliferating fully.[2] We had previously shown in pilot phase II studies that a similar strategy was effective in both allogeneic[10] and autologous[2] hematopoietic stem cell transplantations. We therefore carried out a prospective randomized trial to confirm that this approach can indeed increase Hb levels after autologous PBSCT. The trial was not powered to show an effect on transfusions. This is the first randomized trial demonstrating the efficacy of rHuEpo therapy given after autologous hematopoietic stem cell transplantations. These results have led to the development of an ongoing large multicenter trial investigating the impact of rHuEpo therapy with or without intravenous iron supplementation on quality of life and transfusion requirements after autologous PBSCT.

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Reference

1. Beguin Y, Clemons GK, Oris R, Fillet G. Circulating erythropoietin levels after bone marrow transplantation: inappropriate response to anemia in allogeneic transplants. Blood 1991; 77: 868-73.
2. Baron F, Frere P, Fillet G, Beguin Y. Recombinant human erythropoietin therapy is very effective after an autologous peripheral blood stem cell transplant when started soon after engraftment. Clin Cancer Res 2003;9:5566-72.
3. Beguin Y, Baron F, Fillet G. Influence of marrow erythropoietic activity on serum erythropoietin levels after autologous hematopoietic stem cell transplantation. Haematologica 1998; 83:1076-81.
4. Olivieri A, Scortechini I, Capelli D, Montanari M, Lucesole M, Gini G, et al. Combined administration of α-erythropoietin and filgrastim can improve the outcome and cost balance of autologous stem cell transplantation in patients with lymphoproliferative disorders. Bone Marrow Transplant 2004;34:693-702.
5. Locatelli F, Zecca M, Pedrazzoli P, Prete L, Quaglini S, Comoli P, et al. Use of recombinant human erythropoietin after bone marrow transplantation in pediatric patients with acute leukemia: effect on erythroid repopulation in autologous versus allogeneic transplants. Bone Marrow Transplant 1994;13:403-10.
6. Chao NJ, Schriber JR, Long GD, Negrin RS, Catolico M, Brown BW, et al. A randomized study of erythropoietin and granulocyte colony- stimulating factor (G-CSF) versus placebo and G-CSF for patients with Hodgkin's and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. Blood 1994;83:2823-8.
7. Link H, Boogaerts MA, Fauser AA, Slavin S, Reiffers J, Gorin NC, et al. A controlled trial of recombinant human erythropoietin after bone marrow transplantation. Blood 1994;84:3327-5.
8. Vannucchi AM, Bosi A, Ieri A, Guidi S, Saccardi R, Lombardini L, et al. Combination therapy with G-CSF and erythropoietin after autologous bone marrow transplantation for lymphoid malignancies: a randomized trial. Bone Marrow Transplant 1996;17:527-31.
9. Beguin Y, Oris R, Fillet G. Dynamics of erythropoietic recovery after bone marrow transplantation: role of marrow proliferative capacity and erythropoietin production in autologous versus allogeneic transplants. Bone Marrow Transplant 1993; 11:285-92.
10. Baron F, Frere P, Beguin Y. Once weekly recombinant human erythropoietin therapy is very efficient after allogeneic peripheral blood stem cell transplantation when started soon after engraftment. Haematologica 2003;88:718-20.