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Once weekly recombinant human erythropoietin therapy is very efficient after allogeneic peripheral blood stem cell transplantation when started soon after engraftment

We enrolled 13 recipients of an allogeneic peripheral blood stem cell transplant (PBSCT) in a trial of recombinant human erythropoietin (rHuEpo) therapy (500 U/kg/wk once weekly) started on day 30 after PBSCT. Ten patients who did not receive rHuEpo served as controls. The overall probability of achieving a hemoglobin level >13g/dL was 91% in rHuEpo-treated patients versus 14% in controls (p=0.0001).

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We recently showed that recombinant human erythropoietin (rHuEpo) therapy was very efficient when the therapy was started 35-1444 days after an allogeneic hematopoietic stem cell transplant.[1] In this study, we first studied endogenous erythropoietin production in a cohort of 10 allogeneic peripheral blood stem cell transplant (alloPBSCT) recipients (control group) with the aim of defining the best time to start rHuEpo therapy after alloPBSCT. We then enrolled 13 alloPBSCT recipients in a trial of recombinant human erythropoietin (rHuEpo group) therapy at a dose of 500 U/kg/wk, given once a week (qw) starting on day 30 after PBSCT (Table 1) with the aim of achieving hemoglobin levels of 13 g/dL (complete response). Results were compared with those in a group of 13 similar patients[1] receiving rHuEpo at the same dose given thrice weekly starting on day 35 after PBSCT (historical group).

The trigger for packed red blood cell transfusions was a hemoglobin (Hb) 8 g/dL for all patients receiving rHuEpo and 8 g/dL (N=6) or 9 g/dL (N=4) for patients included in the control group. One of 13 patients in the rHuEpo group, 2/13 in the historical group (p=NS) and 4/10 in the control group (p=NS) had a major ABO incompatibility with their donor. Once the target Hb had been achieved, the dose of rHuEpo was reduced so as to use the lowest dose capable of maintaining the Hb between 12 and 14 g/dL. Laboratory as well as statistical analyses were carried out as previously reported.[2-5]

After PBSCT, serum erythropoietin levels peaked on day 0 with a mean observed-to-predicted (O/P) erythropoietin[6] of 1.15±0.09 (p=0.03 compared with O/P Epo in 31 healthy donors) (Figure 1A) but became inappropriately low for at least 6 months thereafter.

After two weeks of treatment, transfusion independence was achieved in 12/13 (92%) patients in the rHuEpo group, 11/13 (85%) in the historical group (p=NS) and 5/10 (50%) patients in the control group (p=0.05). Eleven of 13 patients in the rHuEpo group, 7/13 in the historical group (p=NS) versus 3/10 patients in the control group (p=0.0131) did not require red blood cell transfusions between days 50 and 150 after the transplant. Hb values of 12 and 13 g/dL as well as a 2 g/dL Hb increment were achieved after a median of 3, 7 and 3 weeks in the rHuEpo group, 6 (p=NS), 8 (p=NS) and 3 (p=NS) weeks in the historical group, and >>15 (p<0.001), >>15 (p<0.001), >> 15 (p=0.002) weeks in the control group. The overall actuarial 150-day probability of achieving a complete response was 91% in the rHuEpo group, 90% in the historical group versus 14% (p<0.001) in the control group (Figure 1B).

Table 1. Characteristics of the patients.

Patient number	Diagnosis	Age (years)	Sex	Source of stem cells	Type of donor	ABO Rhesus (Recipient/donor)	Acute GVHD (stage)
Control group							
1	MDS	56	M	PBSC	Sibling, HLA_{id}	A+/A+	II
2	AML	46	M	PBSC	Sibling, HLA_{id}	A+/A+	II
3	CML	36	M	PBSC	Sibling, HLA_{id}	O+/A+	II
4	AA	16	F	PBSC	Sibling, HLA_{id}	O^-/B+	0
5	MDS	45	F	PBSC	Sibling, HLA_{id}	O+/A+	0
6	NHL	13	M	PBSC	Sibling, 1 mismatch	O^-/A^-	0
7	CML	43	M	PBSC	Sibling, 1 mismatch	A+/O+	II
8	AML	47	F	PBSC	Daughter, 1 mismatch	A+/O+	I
9	AML	4	F	PBSC	Sibling, HLA_{id}	O+/O+	0
10	MDS	8	M	PBSC	Sibling, HLA_{id}	A+/A+	0
rHuEpo group (once weekly)							
11	AML	42	F	PBSC	Sibling, HLA_{id}	O+/O+	0
12	ALL	26	M	PBSC	Sibling, HLA_{id}	A+/A+	0
13	AML	37	F	PBSC	Sibling, HLA_{id}	A+/O+	0
14	MDS	43	M	PBSC	Unrelated, HLA_{id}	O+/A^-	0
15	ALL	31	M	PBSC	Sibling, HLA_{id}	AB+/B+	0
16	AML	24	M	PBSC	Sibling, HLA_{id}	O+/O+	II
17	CML	39	F	PBSC	Sibling, HLA_{id}	A+/A+	0
18	AA	16	M	PBSC	Sibling, HLA_{id}	O+/O+	0
19	ALL	9	M	PBSC	Unrelated, HLA_{id}	A+/O^-	0
20	NHL	27	M	PBSC	Father, 1 mismatch	B+/O+	I
21	AML	52	M	PBSC	Sibling, HLA_{id}	O^-/O+	0
22	AML	26	M	PBSC	Sibling, HLA_{id}	A+/A+	0
23	AML	52	F	PBSC	Sibling, HLA_{id}	O+/O+	0

AML: acute myeloid leukemia; NHL: non-Hodgkin's lymphoma; CML: chronic myeloid leukemia; AA: aplastic anemia; MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; ET: essential thrombocythemia; M: male; F: female; PBSC: peripheral blood stem cells; BM: bone marrow; HLA_{id}: HLA identical.

Mean Hb levels were significantly higher in the rHuEpo and historical groups than in the control group from day 60 after the transplant (Figure 1C). Average soluble transferrin receptor TfR levels remained at the lower end of normal values in patients not receiving rHuEpo (Figure 1D). However, they rapidly increased above the upper normal limit with rHuEpo therapy but progressively decreased when the dose of rHuEpo was reduced.

In this study, we first show that endogenous erythropoietin levels were adequate or inappropriately high for the degree of

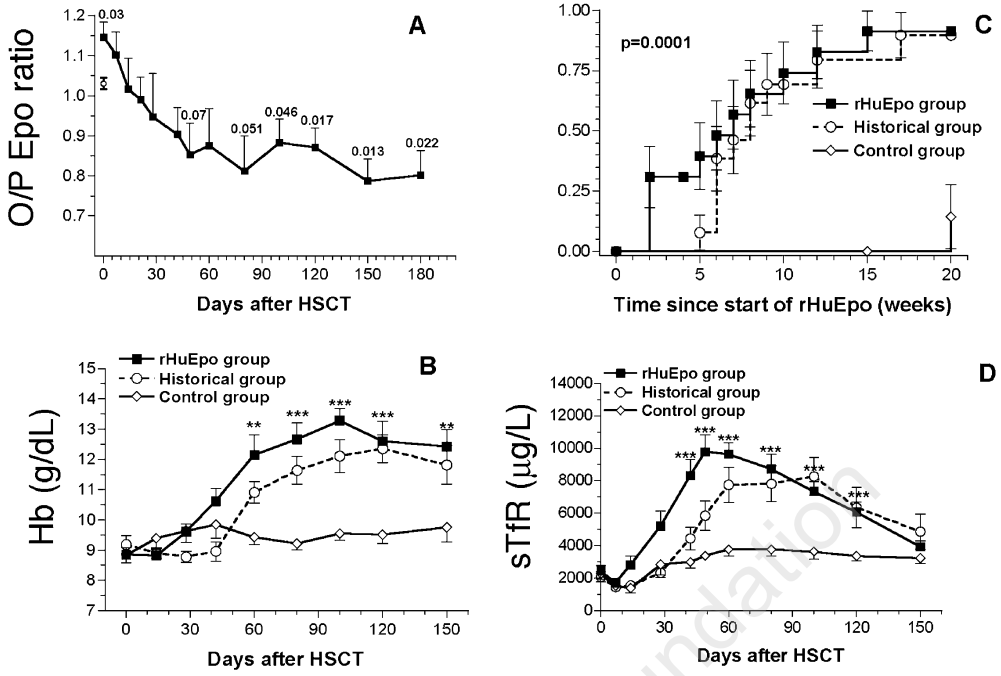

Figure 1. (A) Endogenous erythropoietin production after peripheral blood stem cell transplantation, as assessed by O/P erythropoietin ratios (Mean + SEM). The mean value in 31 normal donors is also shown (open circle). (B) Kaplan-Meier plots of time to a Hb > 13 g/dL. (C-D) Hb (C) and sTfR (D) from day of transplantation (HSCT). *p* values are given for comparisons of the rHuEpo group with the control group : (*) <0.05, (**) <0.01, (***) <0.001.

anemia from day 0 to day 28 after the transplant, but became inappropriately low for at least 6 months thereafter. This observation after alloPBSCT transplants is similar to that made in our previous investigation of recipients of an allogeneic marrow transplant,[7,8] indicating that the source of stem cells does not significantly affect the development of erythropoietin deficiency. In addition, this supports the notion that providing rHuEpo more than 28 days after the transplant is a more physiological approach than starting therapy in the recovery phase of the transplant.

We then confirmed, in a second cohort of patients, the high efficacy of rHuEpo therapy at a dose of 500 U/kg/wk when started about day 30 after the transplant. Moreover, we demonstrated that rHuEpo therapy administered once weekly after a myeloablative allogeneic transplant is as effective as the same dosage given in 3 divided doses[9] in terms of stimulation of erythropoiesis and Hb response. Similar findings were recently reported in anemic patients with lymphoproliferative malignancies.[10]

In conclusion, rHuEpo 500 U/kg/wk administered once weekly is very efficient in the setting of allogeneic hematopoietic stem cell transplantation when started about day 30 after the transplant. The probability of rapidly normalizing Hb values exceeds 90%. These results must be confirmed in prospective, randomized studies.

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