Circulating Erythropoietin Levels After Bone Marrow Transplantation: Inappropriate Response to Anemia in Allogeneic Transplants

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We studied 24 recipients of autologous bone marrow transplantation (ABMT) or allogeneic BMT (BMT) to determine whether impaired erythropoietin (Epo) response to anemia could delay full erythropoietic recovery. Observed Epo levels were compared with predicted levels based on the relationship between Epo and hematocrit in 125 control subjects. Circulating Epo levels were normal during conditioning and the early posttransplant period. Between days 21 and 180, Epo levels remained normal in ABMT patients but were inappropriately low for the degree of anemia in BMT patients. Median time to full erythropoietic engraftment was longer in BMT than in ABMT recipients. Circulating Epo returned to appropriate levels after day 180, except in patients with active cytomegalovirus infection. We conclude that impaired Epo response to anemia can contribute to delayed erythropoietic recovery after allogenic BMT. Renal toxicity of ciclosporin, interaction between host and donor marrow, and cytomegalovirus infection might play a role. This study could support the use of recombinant human Epo to accelerate erythropoietic engraftment after BMT.

ALLOGENEIC BONE MARROW transplantation (BMT) or autologous BMT (ABMT) has become a successful treatment modality for selected patients with leukemia, lymphoma, and other hematopoietic disorders. Delayed platelet recovery has often been recognized as a potential problem after autografting. After BMT, recovery of granulocytes and platelets usually occurs within 2 to 3 months, while complete engraftment of erythrocytes may be more delayed. Late engraftment and recurrent myelosuppression can be because of reduced marrow stem cell reserve, chemoradiotherapy-induced damage of the hematopoietic microenvironment, cytotoxic drugs, excess production of inhibitory cytokines, or defective production of hematopoietic growth factors.

In the present study, we investigated whether defective erythropoietin (Epo) production could contribute to delayed erythropoietic engraftment after BMT, using sensitive radioimmunoassays that have been developed to evaluate serum Epo levels.[1-3] We performed serial measurements of immunoreactive circulating Epo levels in 24 patients in relation to their degree of anemia, and correlated Epo levels and engraftment with type of transplant, conditioning regimen, graft-versus-host disease (GVHD), and cytomegalovirus (CMV) infection.

PATIENTS AND METHODS

Patients. Twenty-four patients, 7 females and 17 males, aged 3 to 54 years, were studied for periods ranging from 106 to 1,920 days after BMT for various hematologic disorders. Their pretransplant characteristics are shown in Table 1. There were 12 patients with acute nonlymphocytic leukemia (ANLL), five with high-risk (leucocytosis $>30,000/\mu L$, extramedullary disease, and/or B-cell phenotype) acute lymphocytic leukemia (ALL), one with chronic myelogenous leukemia (CML), three with lymphoma (LS), one with Hodgkin's disease (HD), and two with severe aplastic anemia (AA). Except for a child who received busulfan (BU; 4 mg/kg/d for 4 days) and cyclophosphamide (CY; 60 mg/kg/d for 2 days), leukemic patients were conditioned with cytarabine (ara-C; 3 g/m^2 twice daily on 2 consecutive days), CY (60 mg/kg/d for 2 days), and total body irradiation (TBI; 8.0 Gy single fraction). Except for a patient who received etoposide (VP16, 400 $mg/m^2/d$ for 2 days), CY (60 mg/kg/d for 2 days), and TBI (8.0 Gy), patients with LS or HD were prepared with VP16 (250 $mg/m^2/d$) and CY (1,500 $mg/m^2/d$) for 4 days, and carmustine (BCNU; 300 mg/m^2) once. AA patients received CY (50 mg/kg/d for 4 days) and total lymphoid irradiation (TLI; 6.0 Gy). Ten patients received an autologous transplant and 14 an allogeneic transplant from an identical twin (n = 2), an HLA-identical sibling (n = 7), a phenotypically HLA-identical (n = 2), or a one mismatch family member (n = 3). Ciclosporin (CSP) with (n = 11) or without (n = 1) methotrexate (MTX; on days 1, 3, 6, and 11) was administered for 180 days to prevent GVHD. Fifteen transplants were performed in CMV-positive pairs (serological evidence of prior exposure of recipient and/or donor to CMV) and nine in CMV-negative pairs. Informed consent was obtained from the patients to undergo the procedure.

Samples. Four hundred sixty-five samples were collected from the 24 patients at various times before and after transplantation. The follow-up of these patients was divided into four consecutive periods: a pretransplant period (from 30 days before to the day of transplant), as well as an early (day 1 through 21), an intermediate (day 22 through 180), and a late (>180 days) posttransplant periods.

Samples were also obtained from 84 adult normal subjects who had not donated blood in the last 3 months, and from 82 patients with hypoplastic/aplastic, hemolytic, dyserythropoietic, or iron-deficient anemia, who had not received red blood cell (RBC) transfusions in the preceding week. The hematocrit (Hct) of these control subjects ranged from 15% to 57%, but only those with Hct between 20% and 43% (n = 125) were used in calculations because all values in transplant patients fell between these limits. We also studied two nontransplant patients with aplastic anemia and an additional ABMT patient who received ciclosporin for 3 months. Permission to draw blood for the study was obtained from patients and normal subjects.

Epo assay. Circulating Epo levels were measured by two different radioimmunoassays (RIA). The first RIA is a modification of an assay previously described in details,[1] and the second

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Table 1. Pretransplant Patient Characteristics

Patient No.	Sex/Age	Disease	Previous Therapy	Conditioning	Donor	GVHD Prophylaxis	CMV Status (Rec/Don)
1	F/44	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	1 Mismatch	CSP + MTX	Pos/Pos
2	F/41	ANLL, relapse	DNR, araC	HD – araC + CY + TBI	1 Mismatch	CSP + MTX	Neg/Neg
3	M/38	ANLL, 2nd CR	DNR, araC, AMSA, azacytidine, VP16, DHAD	HD – araC + CY + TBI	1 Mismatch	CSP + MTX	Neg/Pos
4	M/41	AA	None	CY + TLI	Phenot. ident.	CSP + MTX	Neg/Neg
5	M/54	ANLL, 1st CR	DNR, araC, VP16, DHAD	HD – araC + CY + TBI	Phenot. ident.	CSP + MTX	Pos/Neg
6	M/13	CML, CP	Hydroxyurea	HD – araC + CY + TBI	Genot. ident.	CSP + MTX	Pos/Neg
7	F/39	AA	None	CY + TLI	Genot. ident.	CSP	Pos/Pos
8	M/34	ALL, 1st CR	ADR, PDN, VCR, CY, ASP, araC	HD – araC + Cy + TBI	Genot. ident.	CSP + MTX	Pos/Pos
9	M/17	ALL, 1st CR	ADR, PDN, VCR, CY, ASP, araC	HD – araC + CY + TBI	Genot. ident.	CSP + MTX	Neg/Neg
10	M/21	LS, 3rd relapse	ADR, PDN, VCR, CY, ASP, araC, MTX	VP16 + CY + TBI	Genot. ident.	CSP + MTX	Neg/Neg
11	M/33	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	Genot. ident.	CSP + MTX	Pos/Pos
12	M/47	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	Genot. ident.	CSP + MTX	Pos/Pos
13	M/12	ANLL, 1st CR	DNR, araC, VCR	HD – araC + CY + TBI	Identical twin		Neg/Neg
14	M/31	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	Identical twin		Pos/Pos
15	F/26	ALL, 1st CR	ADR, PDN, VCR, CY, ASP, araC	HD – araC + CY + TBI	Autologous		Neg
16	M/31	ALL, 1st CR	ADR, PDN, VCR, CY, ASP, araC	HD – araC + CY + TBI	Autologous		Pos
17	M/43	HD, 4th CR	MOPP, ABVD, MTX, araC, VP16, Ifosfamide inverted Y and involved field XRT	CY + BCNU + VP16	Autologous		Pos
18	F/41	LS, 2nd CR	ACVBP, MTX, mantle XRT	CY + BCNU + VP16	Autologous		Pos
19	M/30	ALL, 2nd CR	ADR, PDN, VCR, CY, ASP, araC	HD – araC + Cy + TBI	Autologous		Neg
20	M/35	LS, 1st CR	ACVBP, MTX	CY + BCNU + VP16	Autologous		Pos
21	F/3	ANLL, 1st CR	DNR, araC, VP16, DHAD, VCR, 6-TG	BU + Cy	Autologous		Neg
22	M/53	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	Autologous		Neg
23	M/30	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	Autologous		Pos
24	F/54	ANLL, 1st CR	DNR, araC	HD – araC + CY + TBI	Autologous		Pos

Abbreviations: Rec, recipient; Don, donor; DNR, daunorubicin; DHAD, mitoxantrone; ADR, doxorubicin; PDN, prednisolone; VCR, vincristine; ASP, asparaginase; VDS, vindesine; AMSA, amsacrine; 6-TG, 6-thioguanine; MOPP, nitrogen mustard + vincristine + procarbazine + prednisolone; ABVD, doxorubicin + bleomycin + vinblastine + dacarbazine; ACVBP, doxorubicin + cyclophosphamide + vindesine + bleomycin + prednisolone; CR, complete remission.

RIA is commercially available (Incstar Corp, Stillwater, MN). Both use recombinant human Epo (rhuEpo) for tracer and standards. Samples are incubated with rabbit anti-Epo serum for 3 days at 4°C (RIA no. 1) or 2 hours at room temperature (RIA no. 2) before Epo tracer is added. After overnight incubation, goat antirabbit serum is added. After centrifugation, the unbound tracer is removed by decantation and the pellet is counted. One hundred-microliter samples were run in duplicate but several samples had to be diluted 1:10. All samples obtained from a particular patient were assayed simultaneously. Epo levels in normal controls were 15.4 ± 6.4 mU/mL and 15.3 ± 4.8 mU/mL, respectively, with the first and second RIA. Thirty samples, with Epo concentrations ranging from 10 to 200 mU/mL, were measured by the two RIAs and no significant difference was found. Twelve control samples were run in each assay, with a between-assay coefficient of variation ranging from 10.3% to 14.1%.

Statistical methods. Log-transformed Epo values were used in all statistical analyses. Student's *t*-tests, with pooled or separated variances as appropriate, were used to compare two groups. Analysis of variance (ANOVA), with Snedecor's F-test or Welch's test as appropriate, was used to compare more than two groups. The *R* correlation coefficient between Hct and log (Epo) was computed.

RESULTS

Control subjects. In 125 nontransplant patients whose Hct was between 20% and 43%, Epo levels ranged from 10 to 538 mU/mL. The following regression ($R = .88$, $P = .0000$) was obtained between Epo (mU/mL) and Hct (%): log(Epo) = 3.967 − (0.0695 Hct). Based on this formula, a predicted log(Epo) value was derived for each sample and the O/P ratio of observed/predicted log(Epo) ranged from 0.76 to 1.33. Consequently, O/P ratios in transplant patients were considered abnormal if lower than 0.76, which corresponds to a minimum of 44% (for Hct = 43%) to 76% (for Hct = 20%) reduction in absolute Epo values. Although their mean serum creatinine rose respectively from 52, 77, and 86 μmol/L before treatment, to 78, 92, and 123 μmol/L on ciclosporin, the two nontransplant patients with aplastic anemia and the ABMT patient had appropriate levels throughout treatment with CSP.

BMT patients. Mean Epo level in transplant patients (71 ± 92 mU/mL, range 8 to 745) did not differ from that obtained in control subjects but the O/P ratio was lower (0.90 ± 0.21 *v* 1.00 ± 0.13, $P < .001$). Mean Epo level was 122 ± 127 mU/mL pretransplant, whereas levels were 100 ± 84, 58 ± 89, and 35 ± 41 mU/mL in early, intermediate, and late posttransplant periods, respectively. With corresponding Hct of 30.8% ± 3.5%, 30.9% ± 3.0%, 30.2% ± 3.3%, and 33.5% ± 4.1%, mean O/P ratios were 1.03 ± 0.20, 1.03 ± 0.16, 0.82 ± 0.20, and 0.85 ± 0.19, respectively. In the pretransplant period, there was no difference between samples drawn before, during, or immediately after conditioning.

Epo levels (106 ± 108 *v* 55 ± 80 mU/mL, $P < .001$) and O/P ratio (1.01 ± 0.20 *v* 0.84 ± 0.20, $P < .001$) were higher in autologous than in allogeneic BMT. However, the lower O/P ratios observed in allogeneic BMT were restricted to

the intermediate (0.75 ± 0.17) and late (0.79 ± 0.16) posttransplant periods, whereas in the early period (0.99 ± 0.16) they were comparable to the pretransplant period (0.99 ± 0.19). For each patient, the intermediate and late posttransplant periods were termed normal or abnormal according to whether the majority of Epo levels decreased below the 95% confidence limit of the control regression. After BMT (Fig 1), Epo levels were abnormal in 11 of 12 and 4 of 10 patients during the intermediate and late periods, respectively. The figures were 1 of 2 and 0 of 2 in twin BMT, and 1 of 10 and 1 of 10 in autologous BMT (Fig 2). As shown in Fig 3, the inverse relationship between log(Epo) and Hct was weak ($R = -.29, P < .0001$) and the regression line had a reduced slope ($P < .001$ for difference with controls) in BMT: log(Epo) = 2.522 − (0.0321 Hct). The relationship was strong and the regression normal (slope and y-intercept not different from controls) in ABMT ($R = -.51$, $P < .0001$) and in twin BMT ($R = -.64, P < .0001$): log(Epo) = 3.667 − (0.0589 Hct); and log(Epo) = 3.606 − (0.0630 Hct), respectively.

Data on occurrence of GVHD, CMV infection, engraftment, and disease and survival status are shown in Table 2. Complete engraftment was defined as neutrophils (PMN) ≥1,000/μL, platelets (PLT) ≥100,000/μL, and hemoglobin (Hb) ≥10 without transfusion. Median time to complete engraftment for PMN, PLT, and RBC were 29, 126, and 180 days after BMT, and 56, 360, and 120 days, respectively, after ABMT. Acute GVHD occurred in seven patients but Epo levels remained normal in two of them (patient no. 1 who failed to engraft, and patient no. 15 who received an autologous BMT). Among engrafted BMT patients, Epo levels were lower in those with acute GVHD (O/P ratio 0.66 *v* 0.78, $P < .05$). Chronic GVHD occurred in four patients but had no apparent effect on Epo levels. Shorter use of CSP in patient no. 9 failed to correct Epo levels before day 180, while its longer use in patient no. 5 did not delay Epo recovery after day 180. The patient who did not receive MTX had the same pattern of defective Epo production as those who received MTX. There was no correlation between individual values of trough CSP levels and O/P ratios. Table 3 shows data on serum creatinine levels and mean O/P ratios in individual patients. Mean serum creatinine increased 19% in ABMT and 59% in BMT patients ($P < .01$) in the intermediate posttransplant as compared with the pretransplant period. However, neither in the intermediate nor in the late posttransplant period, was there a significant correlation between mean creatinine and mean O/P ratio in either BMT, ABMT, or all transplant patients. Serologic evidence (fourfold or greater increase in titer of antibody to CMV, either by complement fixation or by enzyme-linked immunosorbent assay [ELISA] for CMV IgM) of active CMV infection was present in eight

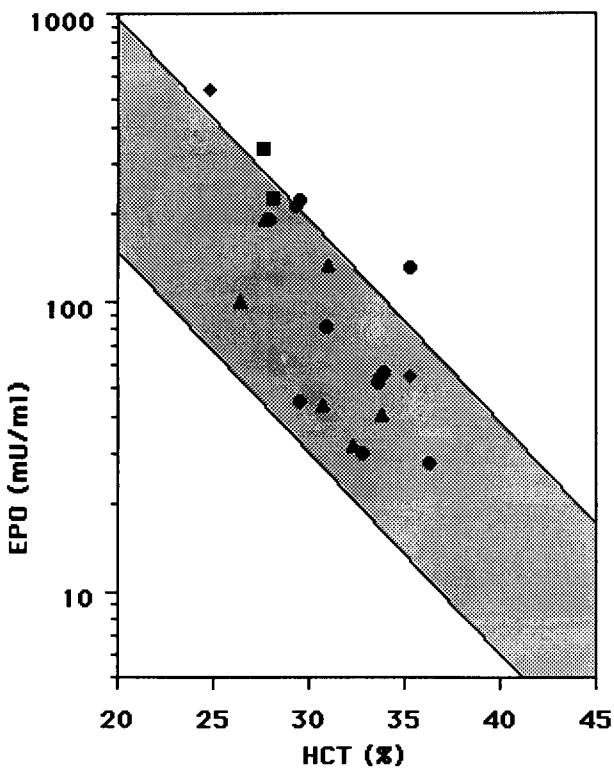

Fig 1. Relationship between Epo levels and Hct in a patient undergoing an autologous transplant. Control subjects are represented by their 95% confidence limits (shaded area). Pretransplant (◆), as well as early (■), intermediate (●), and late (▲) posttransplant periods are shown separately. Epo production in response to anemia is normal.

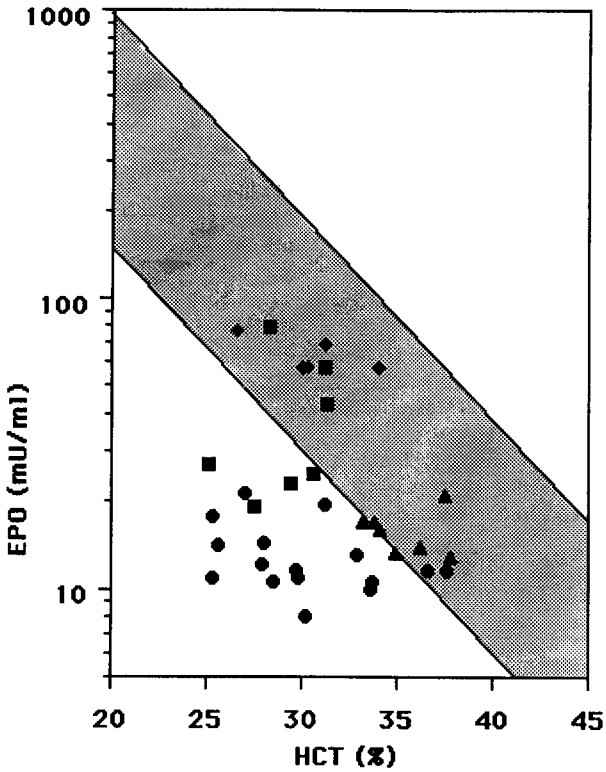

Fig 2. Relationship between Epo levels and Hct in a patient undergoing an allogeneic transplant. Control subjects are represented by their 95% confidence limits (shaded area). Pretransplant (◆), as well as early (■), intermediate (●), and late (▲) posttransplant periods are shown separately. Increased Epo production in response to anemia is not observed.

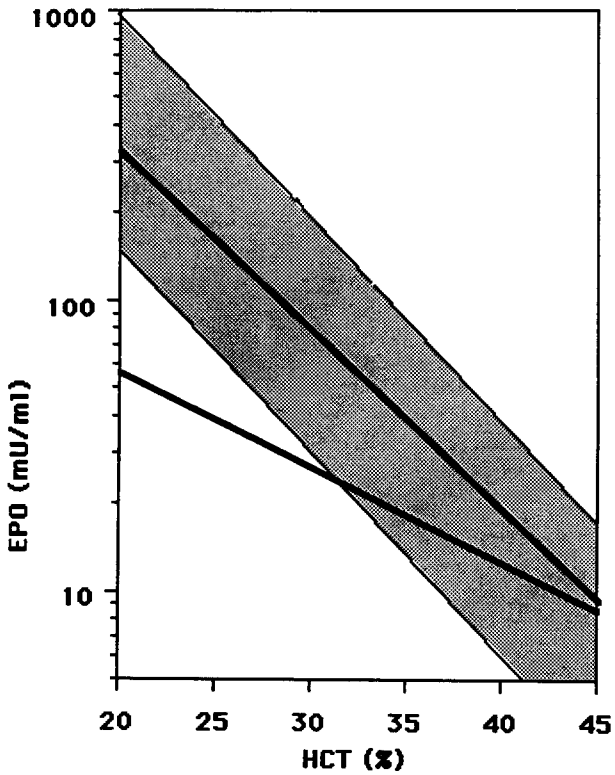

Fig 3. Regression of Epo levels versus Hct in autologous (upper regression line) and allogeneic (lower regression line) transplants. All samples from each period are included. Control subjects are represented by their 95% confidence limits (shaded area). Epo production in response to anemia is normal in ABMT but insufficient in BMT patients.

patients. Seven (five allogeneic, one twin, and one autologous) had low Epo levels until day 180 and four (three allogeneic and one autologous) beyond day 180. Among the 16 patients without CMV infection, only six (six allogeneic) had low Epo levels before and none after day 180. Only one patient (allogeneic) had abnormal Epo levels pretransplant; he had active CMV infection at that time. One patient relapsed after BMT and normalized Epo levels at that time.

DISCUSSION

As compared with normal individuals, marrow stem cell reserve has been shown to be reduced after BMT,[4,5] and even more so after ABMT.[6] On the other hand, growth-promoting activity for megakaryocyte and granulocyte-macrophage but not for erythrocyte progenitors has been observed in plasma samples obtained from BMT recipients.[7] In our study, whereas platelet and granulocyte recovery were faster in BMT than in ABMT recipients, full erythrocyte engraftment was slower after allogeneic transplantation. Thus, despite higher erythroid burst forming unit (BFU-E) numbers,[6] recovery of normal peripheral RBC counts appeared to be exceedingly delayed, suggesting the possibility of a selective defect in maturation and differentiation of erythroid precursors. Epo stimulates erythropoiesis by inducing proliferation and differentiation of late erythroid progenitors (erythroid colony forming unit [CFU-E]), while BFU-E are less dependent on Epo and more on burst-promoting activity of interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF).[8]

Table 2. Posttransplant Data on GVHD, CMV Infection, Engraftment, and Current Status

Patient No.	Acute GVHD	Chronic GVHD	CMV Infection	Last RBC Transfusion (d)	Day of PLT/μL		Day of PMN/μL		Current Status		
					50,000	100,000	500	1,000	Disease	Survival	(d)
1	IV	Severe	0	Cont'd	No	No	100	104	CR	Dead	(106)
2	0	Subclinical	Hepatitis	305	305	365	34	38	CR	Alive	(545)
3	II	Moderate	Gastroenteritis	270	46	152	26	27	CR	Alive	(980)
4	I	0	0	100	16	42	24	27	CR	Alive	(625)
5	I	Mild	0	135	34	45	24	31	CR	Alive	(605)
6	0	0	Subclinical	135	80	100	38	45	CR	Alive	(655)
7	I	0	Subclinical	150	21	24	13	17	CR	Alive	(638)
8	0	0	0	180	25	30	26	27	CR	Alive	(385)
9	0	0	0	180	160	No	29	36	CR	Alive	(330)
10	0	0	0	Cont'd	57	No	24	27	Relapse	Dead	(145)
11	0	0	Subclinical	Cont'd	56	No	28	31	CR	Alive	(115)
12	I	0	0	140	32	97	20	23	CR	Alive	(180)
13	0	0	0	83	19	25	17	25	CR	Alive	(1,920)
14	0	0	Subclinical	19	45	59	13	15	CR	Alive	(655)
15	I	0	0	80	113	360	48	50	CR	Alive	(370)
16	0	0	0	300	230	355	54	94	CR	Alive	(405)
17	0	0	Subclinical	Cont'd	190	No	49	56	Relapse	Alive	(495)
18	0	0	Subclinical	115	24	32	27	29	CR	Alive	(440)
19	0	0	0	300	No	No	33	64	CR	Alive	(335)
20	0	0	0	75	33	42	32	46	CR	Alive	(150)
21	0	0	0	83	70	120	39	56	CR	Alive	(305)
22	0	0	0	90	52	No	29	33	CR	Alive	(585)
23	0	0	0	120	120	270	39	59	CR	Alive	(565)
24	0	0	0	106	48	86	27	43	CR	Alive	(125)

Abbreviations: Cont'd, denotes current continuation of transfusions; No, indicates that level has not yet been achieved.

Table 3. Data on Renal Function and Mean O/P Ratios in Individual Patients

Patient No.	Serum Creatinine Level (μmol/L)				Mean O/P Ratio			
	Pre-BMT	Day 21	Days 22-180*	Days > 180†	Pre-BMT	Days 1-21	Days 22-180	Days > 180
1	86	232	130	—	1.05	1.07	1.14	—
2	60	86	114	91	1.20	1.03	0.79	0.85
3	69	86	129	162	0.81	0.81	0.67	0.56
4	95	95	160	126	1.18	1.02	0.64	0.94
5	60	52	125	79	1.30	1.22	0.69	0.99
6	60	52	100	89	1.03	0.98	0.78	0.73
7	86	95	149	122	0.97	0.79	0.59	0.79
8	86	86	124	108	0.92	1.03	0.73	0.84
9	95	103	100	83	0.88	0.91	0.75	0.80
10	86	112	105	—	0.90	1.01	0.72	—
11	86	120	138	—	0.74	0.99	0.78	—
12	103	86	144	—	1.06	1.00	0.73	—
13	52	52	89	69	0.92	1.17	0.92	0.88
14	69	52	62	79	0.88	0.88	0.72	0.84
15	77	95	87	93	1.11	1.02	0.98	0.82
16	86	77	97	117	1.20	1.04	1.12	1.11
17	95	95	96	92	1.20	1.30	1.07	0.99
18	60	60	68	69	0.93	0.92	0.64	0.73
19	52	60	71	83	0.96	1.16	1.06	0.93
20	69	86	89	—	1.16	1.11	0.84	—
21	34	34	49	—	1.04	1.23	0.82	—
22	77	69	88	91	1.24	1.08	0.88	0.92
23	77	60	74	86	1.35	—	1.06	1.29
24	69	52	71	—	1.01	1.09	1.05	—

*Mean of 12 to 16 serum creatinine values.
†Mean of 6 to 9 serum creatinine values.

Epo originates mainly in the kidney, which responds to hypoxia by increasing Epo production. Circulating Epo levels are best expressed in relation to the Hct.[1] We found an excellent correlation between Epo levels and Hct in 125 subjects with various forms of anemia. Therefore, Epo levels measured in transplant patients could be related to predicted values calculated from the Hct, and were considered normal if falling within the predicted range.

Most Epo levels were normal before transplant and remained so in the first 3 weeks posttransplant. Although we did observe in many patients elevated Epo levels during or immediately after conditioning, the increase remained appropriate for the degree of anemia. No particular chemoradiotherapy regimen could be identified as an independent stimulatory factor for Epo production by the kidney.[9] Only patient no. 1 had inappropriately high Epo levels, developing late after BMT in the context of graft rejection, and possibly triggered by hypoxia and hepatic injury.[10] Others[11] have also found appropriate increases in Epo levels after conditioning and inadequately low levels on day 28, but did not compare BMT with ABMT patients.

Between days 21 and 180, Epo levels were basically normal after ABMT (Fig 1) and inappropriately low after BMT (Fig 2). ABMT patients appeared to be responding normally to anemia (Figs 1 and 3), whereas most BMT patients seemed not to increase Epo production at lower Hct levels (Figs 2 and 3). Renal function was significantly more impaired after BMT than ABMT. This result is not likely to originate from a direct kidney injury provoked by TBI or chemotherapy, as the same conditioning regimens were used for BMT and ABMT. Two problems are specific to BMT patients, ie, occurrence of GVHD and use of CSP and MTX to prevent it. Theoretically, CSP could stimulate Epo production through its vasoconstrictive action in the kidney, or reduce it as part of its tubular toxicity,[12] but no correlation between CSP and Epo levels has been found after renal transplantation.[13] In the present study, Epo production did not correlate with the blood CSP levels nor the duration of CSP therapy. The correlation between mean serum creatinine and mean O/P ratio of individual patients in a given period was not significant. Despite alteration in renal function, the nontransplant patients with aplastic anemia and an ABMT patient retained normal Epo production throughout treatment with CSP. However, even if the magnitude of defective Epo production did not correlate with the degree of renal impairment, it seems reasonable that long-term kidney injury by CSP plays a role as a causative agent, and this should be further investigated in larger groups of patients. Another study[14] has found lower Epo levels at 0.5, 1, and 2 months post-BMT in patients given CSP as compared with those receiving T-cell–depleted marrow, but the investigators failed to relate Epo levels to the Hct. On the other hand, although Epo levels were less reduced in BMT patients without acute GVHD, defective Epo production was not restricted to patients with GVHD. This finding seems to indicate that if interaction between donor and recipient is responsible for inadequate Epo production, this might not be generated

through the same mechanisms as those involved in GVHD. CMV infection was identified as another independent cause of defective Epo production. CMV infection was the only apparent explanation for insufficient Epo levels before transplant (n = 1) or beyond day 180 (n = 4), as well as after ABMT (n = 1).

The mechanisms by which donor-host interaction and CMV infection can impair Epo production remains to be determined. Both GVHD[5,7] and CMV infection[15] have been associated with delayed neutrophil and/or platelet recovery after BMT, but not much attention has been given to erythrocyte recovery. Macrophage-derived and T-cell–derived cytokines, such as IL-1, IL-2, interferon-γ, and tumor necrosis factor, have been shown to inhibit the growth of erythroid progenitors in vitro.[16-18] Inhibition of erythropoiesis in BMT patients could thus be mediated by overproduction of certain cytokines in response to infection or donor-versus-host reaction. Cytokines could act by decreasing Epo production by the kidney and/or by accelerating Epo catabolism.[19] Certain cytokines could also inhibit the action of Epo on erythroid progenitors[17] or exert a direct suppressor effect on them.[16,18]

rhuEpo has now become available for the treatment of the anemia of end stage renal disease.[20,21] As with other cytokines now under clinical investigation in this setting, replacement therapy with rhuEpo could be devised as an alternative therapeutic option to RBC transfusions in selected patients undergoing BMT.

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