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Erythropoietin and GM-CSF Following Autologous Bone Marrow Transplantation

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INTRODUCTION

IN THE stimulation of erythropoiesis by erythyropoietin, the amount of circulating erythropoietin is regulated by a feedback loop that includes oxygen sensors and erythropoietin production in the kidney. We have known since Winearls' pivotal study in 1986 [1] that exogenously administered erythropoietin (r-HuEPO) can correct the chronic anaemia resulting from renal failure.

Although erythropoietin's known effect is on red blood cell production, there are suggestions that it may also influence megakaryopoiesis. Some patients with iron deficiency anaemia—which stimulates high serum erythropoietin levels—also develop thrombocytosis [2]. Some renal failure patients treated with exogenous erythropoietin exhibit an increase in platelet count as well as in haemoglobin [3]. Both aspects are of potential value in patients treated with autologous bone marrow transplantation (ABMT), as this patient group is vulnerable to anaemia and haemorrhage, as well as to infection.

In ABMT, the patient is first given standard chemotherapy to achieve complete, or nearly complete, remission. Then the bone marrow is harvested. After harvesting and any necessary treatment, the bone marrow is frozen and the patient is given supralethal therapy, either chemotherapy alone or in combination with radiotherapy. Following that, the bone marrow is returned to the patient. Then one must wait for this transfused bone marrow to achieve adequate production of erythrocytes, white cells and platelets.

Recovery of erythropoiesis after ABMT is often delayed despite normal, or even high, levels of serum erythropoietin. Anaemia during this recovery phase has not been considered a major problem, however, because of the ease of erythrocyte (Ec) transfusion (which might be needed for several months). The agranulocytosis and thrombocytopenia that occur place the patient at risk for infections and haemorrhage. The recovery of myelopoiesis usually takes between 20 and 50 days, whereas the time needed for sufficient recovery of megakaryopoiesis can be up to 6 months, during which time patients have to be transfused.

Erythropoietin acts on erythrocyte precursors at different developmental levels. Early precursors are much less sensitive to this hormone than are late precursors [4]. Stimulation of early burst forming unit erythrocytes requires a 10 times greater concentration of erythropoietin than stimulating mature colony forming unit erythrocytes does [5]. For our concerns, an essential fact is that therapeutic intervention earlier, rather than later, in the evolutionary sequence of development has a more profound effect on outcome.

Because r-HuEPO must be used in significantly greater concentration to influence the more primitive, less differentiated cells, we wanted to see if high doses of r-HuEPO in patients treated with ABMT might have some effect, not only on erythropoiesis, but also on megakaryopoiesis. The safety of high doses was suggested by Winearls' basic study [1], which indicated that increased dosage in the setting of renal failure was not associated with possible adverse effects.

We initially worked with r-HuEPO on a compassionate use basis in patients experiencing partial or complete graft failure following ABMT. Daily use of this agent for several months, at dosage levels ranging from 150 U/kg to 250 U/kg, was extremely helpful in restoring erythropoiesis and correcting graft failure. The key to successful therapy seemed to be in giving sufficient erythropoietin for a long enough time.

Following these initial encouraging experiences, we carried out a controlled pilot study administering r-HuEPO in combination with granulocyte-macrophage colony stimulating factor (GM-CSF) therapy soon after bone marrow transplantation in an attempt to accelerate haematological reconstitution by simultaneously influencing all three blood cell lines.

PATIENTS AND METHODS

6 patients received the experimental treatment of r-HuEPO combined with GM-CSF, and 7 patients formed the control group. One-third of the patients in each group had either non-Hodgkin lymphoma, solid tumours, or acute leukaemia. The treatment and control groups were also roughly comparable in terms of stage of disease and conditioning regimen.

Experimental patients received daily treatment with 300 U/kg of r-HuEPO by intravenous (iv) push (Eprex provided by Cilag AG, Schaffausen, Switzerland) and 250 μg/m² GM-CSF as a 4-h iv infusion (Leucomax, provided by Sandoz AG, Bern, Switzerland) from day 10 after transplantation either until the level of 500 granulocytes was reached or until day 35, whichever occurred first. The 10-day delay in instituting therapy was chosen based both on our earlier experience with GM-CSF, and on previous studies of this haemopoietic growth factor following allogeneic bone marrow transplantation [6]. These latter studies documented a small increase in leukocyte production appearing after 2 weeks, followed by a rebound effect after discontinuing GM-CSF administration.

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The parameters assessed to evaluate recovery of granulopoiesis were: number of days to hospital discharge; number of days in isolation; number of days on antibiotics; and number of days to reach >100 granulocytes and >500 granulocytes. The parameters reflecting erythropoiesis recovery were: number of days to reach haemoglobin >10 g/l and >12 g/l; total number of transfusions needed; number of transfusions needed after day 35 following transplantation; and serum erythropoietin level. Parameters associated with recovery of megakaryopoiesis included total number of platelet transfusions needed; number of platelet transfusions needed after day 35 following transplantation; and number of days to reach 20 000 platelets and 50 000 platelets.

Because the number of patients in each group in this pilot study is too small to permit any meaningful statistical analysis, the tables present values for the individual patients.

RESULTS

There was no apparent influence on granulopoiesis, as the values for variables reflecting recovery are similar in the treated and untreated groups (Table 1). Two experimental patients (numbers 11 and 13) developed a fever which was thought to result from the administration of GM-CSF itself. In each case the drug was discontinued, and the fever then disappeared.

Erythropoiesis appeared to show some effect from treatment (Table 2). Although the number of red cell transfusions needed in each group was very similar both overall and in the period after 35 days post-transplantation, the average time needed to reach 12 g/l of haemoglobin was reduced from over 150 days in the untreated group to just over 100 days in the group given r-HuEPO + GM-CSF therapy. In the untreated group of 7 patients, 1 never reached this goal and 3 took more than 180 days to reach it, while only 1 treated patient took more than 180 days. Only 1 untreated patient attained this goal in less than 100 days, while 3 of the treated patients did so.

A positive effect was also observed on megakaryopoiesis (Table 3). The average total number of platelet transfusions was 25% less in the treated group (15, as opposed to 20 in the untreated group). The average time required to reach 50 000 platelets was approximately 100 days in the untreated group, and approximately 70 days for treated patients.

CONCLUSIONS

In treating one group of ABMT patients with a combination of r-HuEPO and GM-CSF, we had chosen r-HuEPO in an attempt to facilitate the resumption of erythropoiesis and megakaryopoiesis, and selected GM-CSF hoping to promote the return of granulopoiesis. Our data suggest a possible stimulation of erythropoiesis as well as megakaryopoiesis in those patients treated with these two agents, although no effect on granulopoiesis was seen.

In speculating as to the mechanism(s) underlying the observed effects on erythropoiesis and megakaryopoiesis, the graph of serum erythropoietin levels assessed for the first 5 weeks after bone marrow transfusion (Fig. 1) may be informative. The control group showed a slightly elevated serum level following bone marrow transplantation, which fell to a stable level between 50 and 100 U/l. In the r-HuEPO-treated patients, however, the serum level rose to between 500 and 2000 U/l, then dropped after stopping treatment.

*Table 1. Recovery of granulopoiesis**

Patient	In hospital	On isolation	On antibiotics	To reach Gc >100	To reach Gc >500
Control					
1	39	30	17	28	31
2	43	30	0	15	36
3	26	22	23	22	27
4	25	19	0	14	23
5	23	22	17	14	25
6	59	41	48	48	65
7	33	21	23	15	43
Average	35.4	26.4	18.3	22.3	35.7
Treatment					
8	33	29	22	27	45
9	33	26	26	26	>180
10	24	18	16	14	20
11	22	18	16	12	20
12	25	17	12	16	19
13	36	27	31	18	39
Average	28.8	22.5	20.5	18.8	53.8

*Data for each parameter reflect number of days, with transplantation as day 0.

Table 2. Recovery of erythropoiesis

Patient	Days† to reach Hb >10g/l	Days† to reach Hb >12g/l	No. red blood cell transfusions After 35 days†	No. red blood cell transfusions Total
Control				
1	55	160	4	29*
2	75	>180	4	10
3	87	>180	0	8
4	54	54	2	9
5	>180	>180	34	44
6	NR	NR	8	16
7	36	160	2	10
Average	81.2	152.3	7.7	18.0
Treatment				
8	61	96	2	15
9	>180	>180	20	24
10	47	54	2	13
11	24	ED	0	13
12	60	65	6	14
13	36	120	2	12
Average	68.0	103.0	5.3	15.2

NR = Not reached. ED = Early death (occurring postdischarge, 90 days post-transplant). *Patient developed haemolytic uraemic syndrome. †Days post-transplant.

Table 3. Recovery of megakaryopoiesis

Patient	Days to reach platelet count >20 000	Days to reach platelet count >50 000	No. platelet transfusions After 35 days	No. platelet transfusions Total
Control				
1	45	55	4	24
2	50	>180	5	11
3	39	53	1	8
4	25	44	0	8
5	>180	>180	26	36
6	NR	NR	15	27
7	46	64	10	26
Average	64.2	96.0	8.7	20.0
Treatment				
8	45	45	3	12
9	>180	>180	30	39
10	26	33	0	5
11	28	28	0	6
12	46	65	3	16
13	35	48	2	11
Average	60.0	66.5	6.3	14.8

NR = Not reached.

Patients with chronic anaemia and polycythaemia vera maintain a very low serum erythropoietin level [7]. Even though other kinds of anaemias generate an inverse relationship between haemoglobin and serum erythropoietin levels, especially in iron-deficiency anaemia, the serum level seldom rises above 500 units [8]. Since the serum level rose much higher in our treated patients, we speculate that our higher dosage achieved this concentration of erythropoietin and that this concentration, in turn, stimulated erythropoiesis and possibly megakaryopoiesis as well. The high levels observed in these patients could theoretically exert a switch on pluripotent stem cells, which in turn could explain the missing effect of concomitant GM-CSF on granulopoiesis. Thus, there is the possibility that a high dose of r-HuEPO could exert an inhibitory effect on granulopoiesis.

We do not yet know, however, if the faster recovery of megakaryopoiesis is due solely to the high serum levels of erythropoietin that are likely to have resulted from r-HuEPO administration, or to a synergistic effect of GM-CSF and these high serum levels. Further controlled, systematic work is required to determine whether or not GM-CSF is a critical ingredient in the possible improvement in stimulation of platelet production.

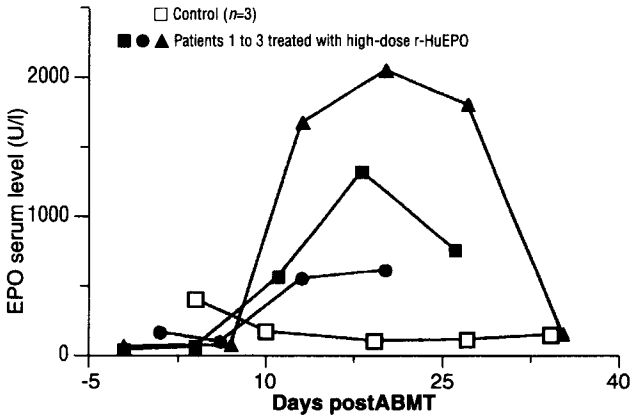

Fig. 1. Serum erythropoietin levels after ABMT. Patients 1 to 3 were treated with the combination of high-dose r-HuEPO and GM-CSF. The mean values for 3 control patients are also presented.

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